# Toxicological Profile for 1,2-Dichloroethane

July 2024

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

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# FOREWORD

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

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

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

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.

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

*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 |
|---|---|
| July 2024 | Final toxicological profile released |
| January 2022 | Draft for public comment toxicological profile released |
| September 2001 | Final toxicological profile released |

# CONTRIBUTORS & REVIEWERS

## CHEMICAL MANAGER TEAM

Carolyn Harper, Ph.D. (Lead)
Hana Pohl, M.D., Ph.D.

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

Ryan Klein, Ph.D.
Adriana Antezana, M.S.
Kerry Diskin, Ph.D.
Hannah Derrick, B.S.
Sara Sokolinski, B.S.
AJ Casner, B.S.
Meghan Lynch D.Sc.

Abt Associates, Cambridge, MA

Claire Heit, Ph.D.
Heather Carlson-Lynch, M.S., D.A.B.T.
Julie Klotzbach, Ph.D.
Julie Melia, Ph.D., D.A.B.T.
Ramsey Hanna, Ph.D.
Mario Citra, Ph.D.

SRC, Inc., North Syracuse, NY

## REVIEWERS

### Interagency Minimal Risk Level Workgroup:

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

### Additional reviews for science and/or policy:

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

## PEER REVIEWERS

1. Jordan N. Smith, Ph.D.; Joint Appointment, Department of Environmental and Molecular Toxicology (EMT); Oregon State University (reviewed Draft for Public Comment Profile)

2. John C. Lipscomb, Ph.D., D.A.B.T, F.A.T.S; Lipscomb and Associates, PLLC; Sherwood, Arkansas (reviewed Draft for Public Comment Profile)

3. James V. Buckner, Ph.D.; Professor Emeritus of Pharmacology and Toxicology; Department of Pharmaceutical & Biomedical Sciences; College of Pharmacy; University of Georgia; Athens, Georgia (reviewed Draft for Public Comment Profile and MRLs in the Post-Public Comment Profile)

4. David C. Dorman, DVM, Ph.D., DABVT, DABT; Professor of Toxicology; North Carolina State University; College of Veterinary Medicine; Department of Molecular Biomedical Sciences; Raleigh, North Carolina (reviewed MRLs in the Post-Public Comment Profile)

5. Ivan Rusyn, M.D., Ph.D.; University Professor; KC Donnelly Professor of Veterinary Physiology and Pharmacology; Chair, Interdisciplinary Faculty of Toxicology; Director, Superfund Research Center; Texas A&M University; College Station, Texas (reviewed MRLs in the Post-Public Comment Profile)

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-Dichloroethane, also called ethylene dichloride, is a colorless oily liquid. It is primarily used in the production of vinyl chlorides, which are used to make a variety of plastic and vinyl products including polyvinyl chloride (PVC) pipes and other construction materials. 1,2-Dichloroethane is also used as a solvent in organic synthesis. 1,2-Dichloroethane is produced by chlorination of ethylene using a catalyst.

1,2-Dichloroethane is released to the environment during its production and use, with the vast majority of the fugitive emissions going into the air. Vapor-phase 1,2-dichloroethane goes through photochemical degradation in the atmosphere, with an estimated reaction half-life of 65–73 days; the primary degradation products are carbon dioxide and hydrochloric acid (Arnts et al. 1989; Atkinson 1986; Kwok and Atkinson 1995). If released to soil, 1,2-dichloroethane is not expected to adsorb strongly and may leach into groundwater. Volatilization is expected to be an important environmental fate process for 1,2-dichloroethane in soil and bodies of water due to its Henry's law constant of $1.18 \times 10^{-3}$ atm-$m^3$/mol at 25°C. Biodegradation is expected to occur slowly in both water and soil surfaces. Hydrolysis and photolysis are not expected to be important fate processes in aqueous and soil environments, and the potential for bioconcentration in aquatic organisms appears to be low.

The general population is exposed to 1,2-dichloroethane primarily from inhalation of ambient air, particularly near point sources. Other potential routes of exposure for the general population include ingestion of 1,2-dichloroethane in contaminated drinking water or food items and dermal absorption. In addition, inhalation exposure may occur from 1,2-dichloroethane that has volatilized from water during activities such as cooking, bathing, showering, and dishwashing, if 1,2-dichloroethane is in the water supply. Children are expected to be exposed to 1,2-dichloroethane by the same routes as adults. In the past, 1,2-dichloroethane was detected in human milk, but more recent data showing 1,2-dichloroethane in breast milk were not located. Occupational exposure to 1,2-dichloroethane occurs through inhalation and dermal contact with the compound at workplaces where it is produced or used.

Median daily atmospheric concentrations of 1,2-dichloroethane are typically in the 0.01–0.1 ppb range for urban, suburban, rural, and remote sites, and higher near point sources such as factories, wastewater treatment plants, and hazardous waste sites. Populations residing near hazardous waste disposal sites or municipal landfills may be subject to higher-than-average levels of 1,2-dichloroethane in ambient air and drinking water since 1,2-dichloroethane is volatile and is mobile in soil and may leach into drinking water supplies.

## 1.2 SUMMARY OF HEALTH EFFECTS

Acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) health effects can result from inhalation, oral, or dermal contact with 1,2-dichloroethane. There are a limited number of epidemiological studies on the health effects in humans, as well as numerous case reports of people who died following acute-duration exposure to high levels by inhalation or ingestion. Studies in animals exposed by inhalation, oral, and dermal routes were evaluated. As illustrated in Figure 1-1, reproductive, respiratory, neurological, hepatic, immunological, and cancer endpoints are the most sensitive targets of 1,2-dichloroethane inhalation exposure. As shown in Figure 1-2, renal, gastrointestinal, body weight, immunological, and cancer endpoints are the most sensitive targets of 1,2-dichloroethane oral exposure. Animals exposed to 1,2-dichloroethane for chronic durations also had high mortality.

Figure 1-1 identifies the sensitive targets of inhalation exposure to 1,2-dichloroethane in animals and Figure 1-2 identifies the sensitive targets of oral exposure in animals. For oral exposure studies in animals, there are differences between gavage exposure and drinking water/feed exposure. Generally, effects are observed at lower doses in gavage studies compared to drinking water or feed studies. For example, in intermediate-duration studies, the lowest gavage dose producing death was 240 mg/kg/day (NTP 1991), compared to 4,926 mg/kg/day in a drinking water study (NTP 1991). The differences in response may be due to saturation of the detoxification/excretion mechanism due to bolus gavage dosing. When biotransformation processes are saturated, higher levels of 1,2-dichloroethane circulate throughout the body and conjugate with glutathione resulting in reactive intermediates and toxic effects rather than being detoxified and eliminated.

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

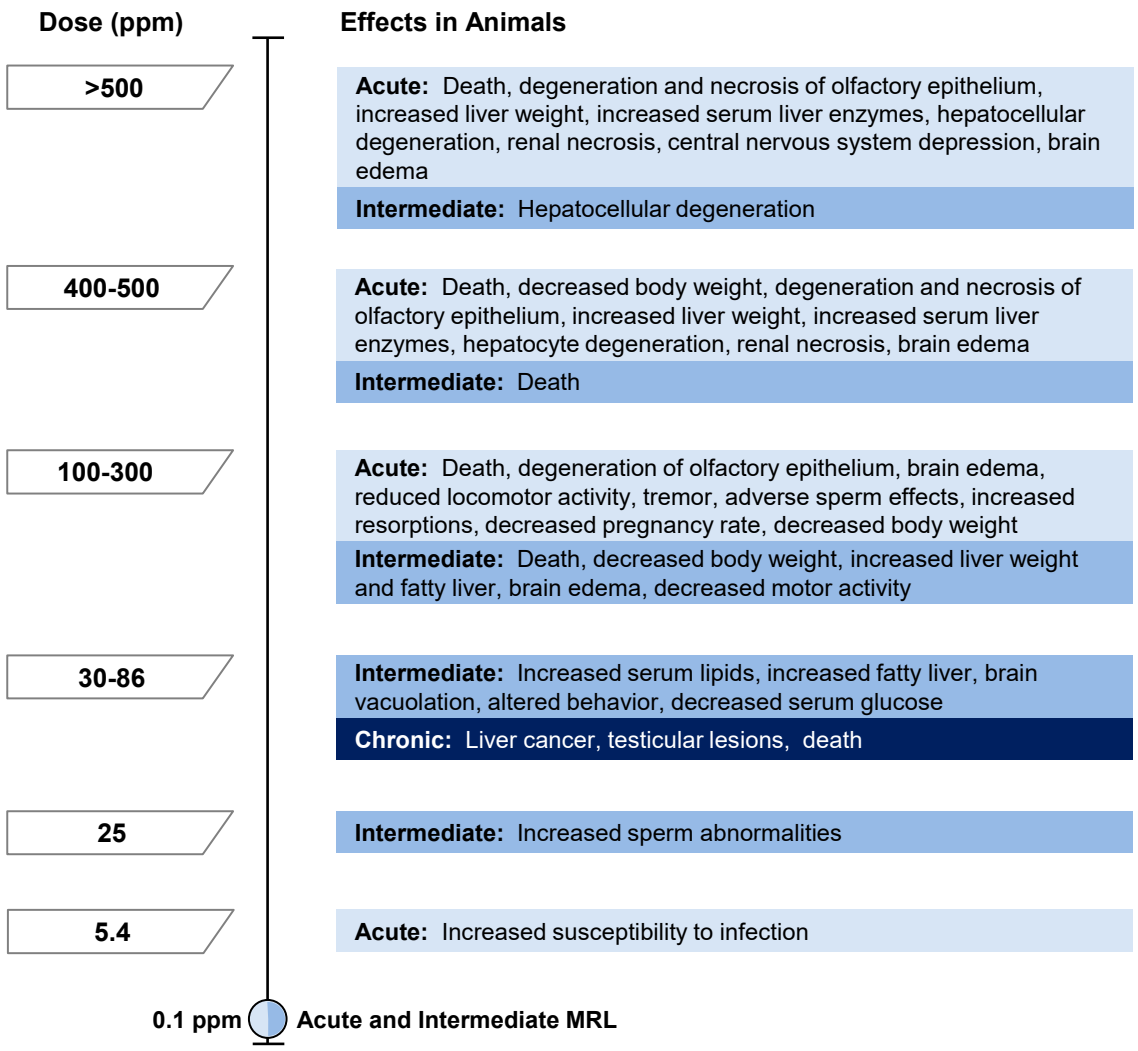
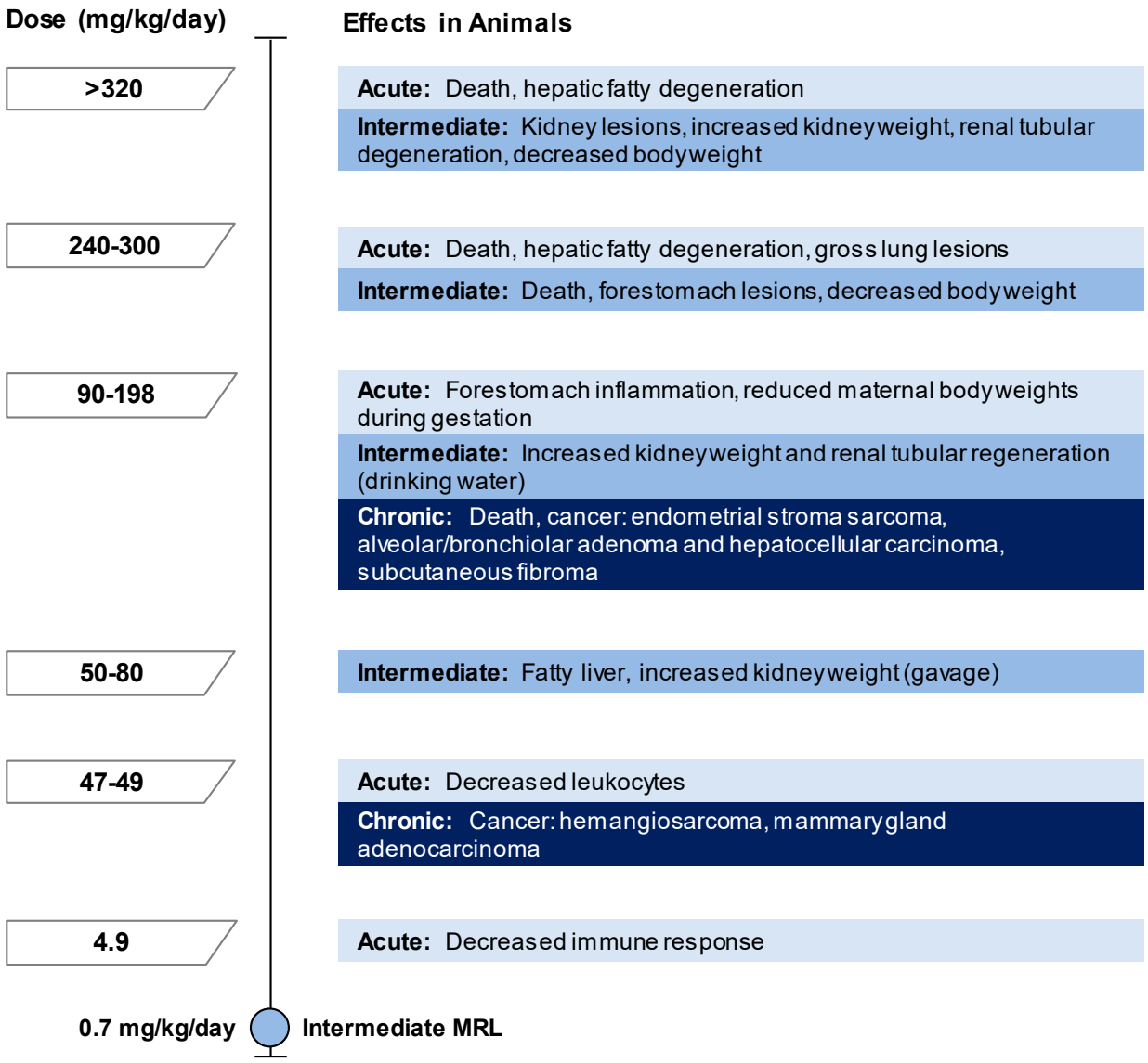


**Figure 1-2. Health Effects Found in Animals Following Oral Exposure to 1,2-Dichloroethane**




***Respiratory Effects.*** 1,2-Dichloroethane produces adverse respiratory effects in humans following both inhalation and ingestion. Respiratory effects observed in individuals who died following acute high-level oral exposure were respiratory distress, lung congestion, pulmonary edema, dyspnea, and bronchitis (Hubbs and Prusmack 1955; Hueper and Smith 1935; Lochhead and Close 1951; Martin et al. 1969; Nouchi et al. 1984; Yodaiken and Babcock 1973). Experimental animal studies demonstrated nasal olfactory degeneration/necrosis and regeneration, pulmonary congestion, and pulmonary edema after acute-duration inhalation or gavage exposure (Heppel et al. 1945; Hotchkiss et al. 2010; Salovsky et al. 2002). Intermediate- and chronic-duration inhalation and oral studies did not result in respiratory effects

(Daniel et al. 1994; Morgan et al. 1990; NCI 1978; NTP 1991; van Esch et al. 1977). A 26-week dermal study (using transgenic mice susceptible to early tumorigenesis) produced hyperplasia and tumors in the lungs of female mice (Suguro et al. 2017).

***Hepatic Effects.*** Liver effects have been observed in cases of humans who died following acute-duration inhalation or ingestion of 1,2-dichloroethane. Hepatotoxicity was indicated by elevated serum markers used to assess liver injury, enlarged liver, and vacuolation and extensive centrilobular necrosis at autopsy in case studies (Chen et al. 2015; Cheng et al. 1999; Hubbs and Prusmack 1955; Martin et al. 1969; Przezdziak and Bakula 1975; Schönborn et al. 1970). Evidence from animal studies supports the conclusion that the liver is a target organ for inhalation exposure to 1,2-dichloroethane. Hepatic effects in animals exposed via inhalation included increased levels of serum markers of liver injury, increased liver weight, and histopathological changes of macrophage aggregation and hepatocellular degeneration (Brondeau et al. 1983; Heppel et al. 1946; Hotchkiss et al. 2010; Pang et al. 2018; Spencer et al. 1951; Wang et al. 2017). No hepatic effects were observed after chronic-duration inhalation exposure; however, liver tumors were observed (Cheever et al. 1990; Nagano et al. 2006). Studies of animals exposed orally have not shown adverse hepatic effects of 1,2-dichloroethane (Alumot et al. 1976; Aragno et al. 1992; Daniel et al. 1994; Danni et al. 1992; Munson et al. 1982; NCI 1978; NTP 1991).

***Renal Effects.*** 1,2-Dichloroethane is acutely nephrotoxic in humans following both inhalation and ingestion. Renal effects observed in individuals who died following acute-duration, high-level exposure were diffuse necrosis, tubular necrosis, and kidney failure (Hubbs and Prusmack 1955; Hueper and Smith 1935; Lochhead and Close 1951; Nouchi et al. 1984; Schönborn et al. 1970; Yodaiken and Babcock 1973). Renal effects seen in experimental animals include increased kidney weight and tubular degeneration and regeneration with oral (Daniel et al. 1994; Morgan et al. 1990; NTP 1991; van Esch et al. 1977) and dermal exposure (Suguro et al. 2017). No renal effects were observed following chronic-duration oral exposure (NCI 1978). Inhalation studies have shown renal effects only at high concentrations (Heppel et al. 1946; Hotchkiss et al. 2010; Spencer et al. 1951).

***Gastrointestinal Effects.*** 1,2-Dichloroethane induced nausea and vomiting in case studies of humans exposed by inhalation (McNally and Fostvedt 1941; Nouchi et al. 1984; Wirtschafter and Schwartz 1939) and in occupational studies (Liu et al. 2010; Zhan et al. 2011; Zhou et al. 2015). Gastrointestinal effects including nausea, vomiting, diarrhea, gastritis, and hemorrhages of the gastrointestinal tract have been noted in humans after ingestion of 1,2-dichloroethane (Garrison and Leadingham 1954; Hubbs and Prusmack 1955; Hueper and Smith 1935; Lochhead and Close 1951; Martin et al. 1969; Schönborn et al.

1970; Yodaiken and Babcock 1973). Animal studies of oral exposure have reported gastrointestinal inflammation and hyperplasia (Daniel et al. 1994; Morgan et al. 1990; NCI 1978; NTP 1991). The gastrointestinal effects were observed in gavage studies; in studies in which 1,2-dichloroethane was administered via drinking water, no gastrointestinal effects were noted at much higher doses (NTP 1991).

***Immunological and Lymphoreticular Effects.*** Information pertaining to immunological effects in humans exposed to 1,2-dichloroethane is limited to a report of splenic congestion and hemorrhage in one case report of ingestion (Hubbs and Prusmack 1955). In mice, immunosuppressive effects were observed following both acute-duration inhalation exposure and acute-duration oral exposure. A single 3-hour inhalation exposure to low levels of 1,2-dichloroethane increased susceptibility of mice to bacterial infection, although no changes in bactericidal activity or other immune function endpoints were found in rats after single inhalation exposures with longer durations and higher concentrations (Sherwood et al. 1987). Effects observed in mice following acute-duration gavage administration of 1,2-dichloroethane included reduced humoral immunity (immunoglobulin response to sheep red blood cells) and decreased cell-mediated immunity (delayed-type hypersensitivity response to sheep erythrocytes) (Munson et al. 1982). However, an intermediate-duration oral study of drinking water exposure failed to corroborate the results of the gavage study by the same study authors (Munson et al. 1982). Leukocyte counts were not affected in intermediate-duration drinking water and gavage studies in rats, and intermediate- and chronic-duration oral exposures did not produce histological changes in immune system tissues in rats and mice (Daniel et al. 1994; Morgan et al. 1990, NCI 1978; NTP 1991). Immune function has not been evaluated in intermediate- or chronic-duration inhalation studies nor in chronic-duration oral studies of 1,2-dichloroethane.

***Neurological Effects.*** Neurological symptoms and signs in people exposed to high levels of 1,2-dichloroethane by inhalation or ingestion included headache, dizziness, irritability, drowsiness, tremors, partial paralysis, and coma (Chen et al. 2015; Dang et al. 2019; Hubbs and Prusmack 1955; Liu et al. 2010; Lochhead and Close 1951; Nouchi et al. 1984; Wirtschafter and Schwartz 1939; Yodaiken and Babcock 1973; Zhan et al. 2011). Autopsies of people who died after acute-duration exposure revealed effects in the brain including hyperemia, hemorrhage, myelin degeneration, diffuse changes in the cerebellum, shrunken appearance and pyknotic nuclei in the Purkinje cell layer of the cerebellum, and parenchymatous changes in the brain and spinal cord (Nouchi et al. 1984). Toxic encephalopathy, primarily characterized by cerebral edema, has been observed in workers exposed to 1,2-dichloroethane for longer periods of time (Chen et al. 2015; Dang et al. 2019; Liu et al. 2010; Zhan et al. 2011). Additionally, neuronal necrosis, demyelination and toxic leukoencephalopathy were noted in case studies

(Zhan et al. 2011; Zhou et al. 2015), and neuropsychological impairment was reported in workers in an occupational study (Bowler et al. 2003).

The results of experimental animal inhalation studies confirm that the central nervous system is a target of 1,2-dichloroethane, with exposure leading to clinical signs such as tremors, abnormal posture, uncertain gait, and narcosis, along with brain edema and increased brain water weight (Heppel et al. 1945; Jin et al. 2018a; Spencer et al. 1951; Zhang et al. 2011; Zhong et al. 2020). Neurobehavioral changes indicative of central nervous system depression have been observed in animals after inhalation exposure to 1,2-dichloroethane (Hotchkiss et al. 2010; Wang et al. 2013). In addition, clinical signs of neurotoxicity and mild necrosis in the cerebellum were found in rats administered 1,2-dichloroethane by gavage for 13 weeks (Morgan et al. 1990; NTP 1991). In contrast, no clinical signs or neurological lesions were seen in rats or mice exposed through their drinking water at higher concentrations for 13 weeks (NTP 1991), and no brain lesions were seen in rats exposed orally for 2 years (NCI 1978). The effects seen in the gavage study might be attributable to the method of dosing. As noted above, the differences in response may be due to saturation of the detoxification/excretion mechanism due to bolus gavage dosing.

***Reproductive Effects.*** A single epidemiological study on reproductive effects of exposure to 1,2-dichloroethane in humans is suggestive of a reduction in gestation duration, but co-exposure to other chemicals occurred in most cases, and the adequacy of the study design could not be evaluated because of reporting deficiencies (Zhao et al. 1989). A study in mice reported reproductive toxicity after intermediate-duration inhalation exposure to 1,2-dichloroethane; effects included significant pathological changes in the testes; vacuolar degeneration of germ cells in the testes; decreased sperm concentration, motility, and progressive motility; and increased abnormalities of the sperm head, body, and tail (Zhang et al. 2017). A well-designed study of reproductive toxicity found no adverse effects on the fertility, gestation, or survival of the pups of rats exposed by inhalation to 150 ppm of 1,2-dichloroethane for 60 days pre-mating, then throughout mating, gestation, and lactation in a one-generation reproduction study (Rao et al. 1980). One- and two-generation reproductive toxicity studies found no chemical-related effects on fertility indices in long-term oral studies in mice and rats, but exposure to higher oral doses caused increases in non-surviving implants and resorptions in rats that also experienced maternal toxicity (Lane et al. 1982; Payan et al. 1995). Histological examinations of the testes, ovaries, and other male and female reproductive system tissues were performed in other intermediate- and chronic-duration inhalation and oral animal studies with negative results, but reproductive function was not evaluated (Alumot et al. 1976; Cheever et al. 1990; Daniel et al. 1994; Morgan et al. 1990; NCI 1978; NTP 1991; van Esch et al. 1977).

***Cancer.*** Epidemiological studies that have investigated associations between occupational or oral exposure to 1,2-dichloroethane and increased incidences of cancer are inadequate for assessing carcinogenicity in humans because studies did not adequately assess confounding by co-exposures to various other chemicals (Austin and Schnatter 1983a, 1983b; Benson and Teta 1993; Goldberg et al. 1995; Hansen 2000; Hogstedt et al. 1979; Isacson et al. 1985; Reeve et al. 1983; Teta et al. 1989; Waxweiler et al. 1983). There have been mixed results in animal studies of tumor incidence after 1,2-dichloroethane exposure via inhalation. While Cheever et al. (1990) and Maltoni et al. (1980) failed to find carcinogenic effects after chronic-duration exposure, Nagano et al. (2006) found dose-dependent increases in benign and malignant tumors in rats of both sexes and female mice after chronic-duration inhalation exposure to 1,2-dichloroethane. The former studies were limited by use of a single exposure concentration (that was lower than the concentration resulting in tumors in the study by Nagano et al. [2006]) and by early mortality, respectively. 1,2-Dichloroethane induced a clear positive carcinogenic response in animals after gavage administration, resulting in statistically significant increases in forestomach squamous cell carcinomas, hemangiosarcomas, and subcutaneous fibromas in male rats; mammary gland adenocarcinomas and hemangiosarcomas in female rats; hepatocellular carcinomas and alveolar/bronchiolar adenomas in male mice; and alveolar/bronchiolar adenomas, mammary carcinomas, and endometrial tumors in female mice (NCI 1978). Other animal bioassays provide supportive evidence for the carcinogenicity of dermal contact with 1,2-dichloroethane. Van Duuren et al. (1979) showed compound-related increases in lung tumors following lifetime dermal exposure of female mice, and Suguro et al. (2017) reported an increase in bronchioloalveolar adenomas and adenocarcinomas in transgenic (genetically modified for increased susceptibility to cancer) mice after intermediate-duration dermal exposure.

The Department of Health and Human Services (HHS) has determined that 1,2-dichloroethane may reasonably be anticipated to be a human carcinogen. The International Agency Research on Cancer (IARC) has placed 1,2-dichloroethane in Group 2B (possibly carcinogenic to humans), and the U.S. Environmental Protection Agency (EPA) has classified 1,2-dichloroethane as a Group B2 carcinogen (probable human carcinogen).

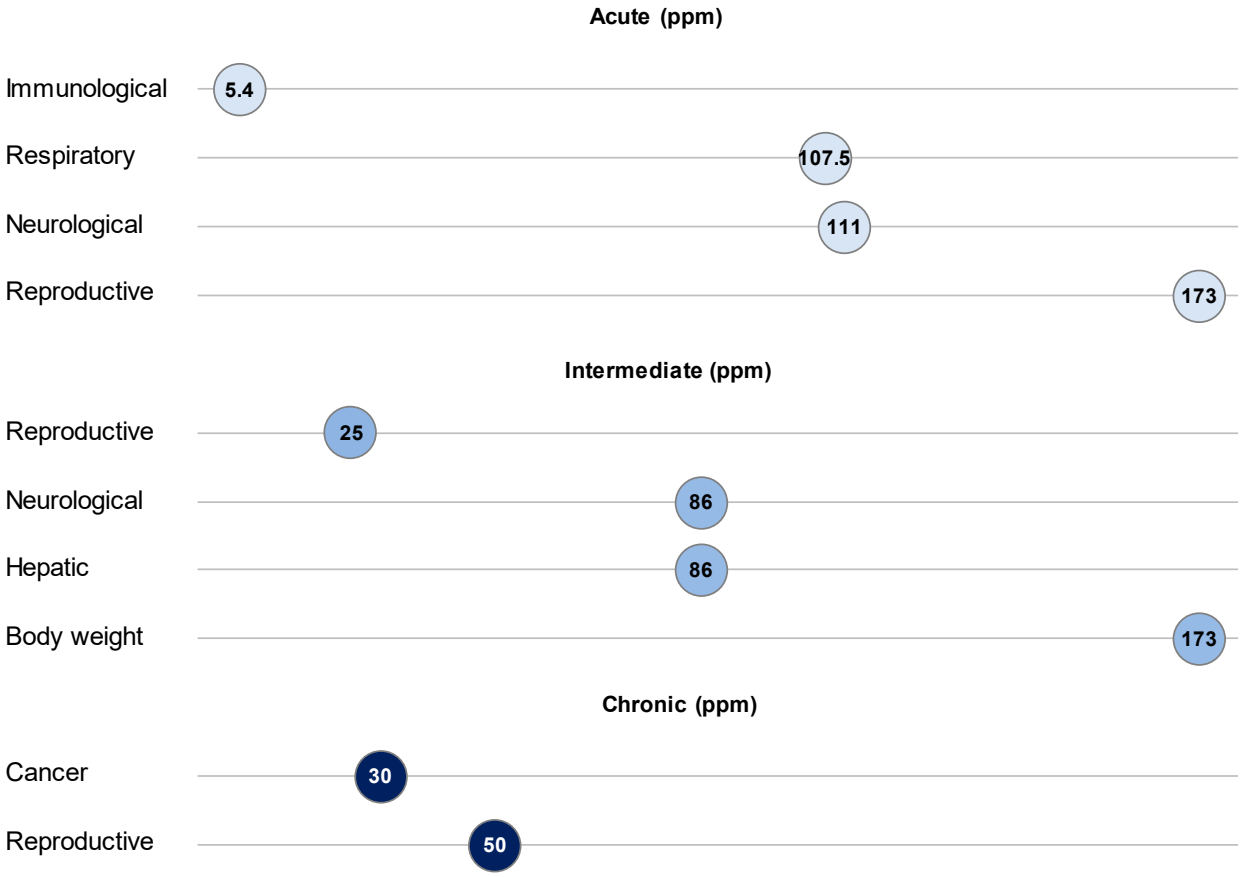
## 1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was considered adequate for derivation of an acute- and intermediate-duration inhalation MRL for 1,2-dichloroethane. A chronic-duration inhalation MRL was not derived because

available studies identified effect levels (LOAELs and NOAELs) for noncancer effects that are higher than both the point of departure (POD) for the acute-duration inhalation MRL (36.28 ppm) and the serious LOAEL for intermediate-duration inhalation exposure (25 ppm), precluding derivation of an MRL. It is ATSDR's practice to not derive MRLs from serious LOAELs. The respiratory tract was the most sensitive target following acute-duration inhalation exposure to 1,2-dichloroethane. Other sensitive endpoints of inhalation exposure include immunological, neurological, and reproductive effects, as demonstrated in Figure 1-3. The oral database was considered adequate for derivation of an intermediate-duration oral MRL for 1,2-dichloroethane, and inadequate for derivation of acute- and chronic-duration oral MRLs. Data were insufficient to derive an acute-duration oral MRL due to uncertainty about the validity of results at the lowest effect level based on differences in effect between gavage doses and drinking water doses. Briefly, there is a notable difference in toxicokinetics between gavage and drinking water administration. With gavage administration, bolus dosing leads to saturation of the detoxification/ excretion mechanism and exacerbates toxicity (see Section 3.1). This is described in more detail in Appendix A. Data were insufficient for the derivation of a chronic-duration oral MRL as the most sensitive endpoint was represented by a serious effect. As presented in Figure 1-4, immunological, gastrointestinal, body weight changes, and the kidney are sensitive targets of 1,2-dichloroethane toxicity. In the figure, LOAELs obtained from gavage studies are shown as circles, while LOAELs obtained from drinking water or dietary studies are shown as squares. The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

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

**Reproductive, respiratory, neurological, hepatic, immunological, and cancer endpoints are the most sensitive targets of 1,2-dichloroethane inhalation exposure.**
Numbers in circles are the lowest LOAELs for all health effects in animals.
No reliable dose-response data were available for humans.



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

**Renal, gastrointestinal, body weight, immunological, mortality, and cancer endpoints are the most sensitive targets of 1,2-dichloroethane oral exposure.**

Numbers in circles are the lowest LOAELs from gavage studies for all health effects in animals.
Numbers in squares are the lowest LOAELs from drinking water or dietary studies.
No reliable dose-response data were available for humans.

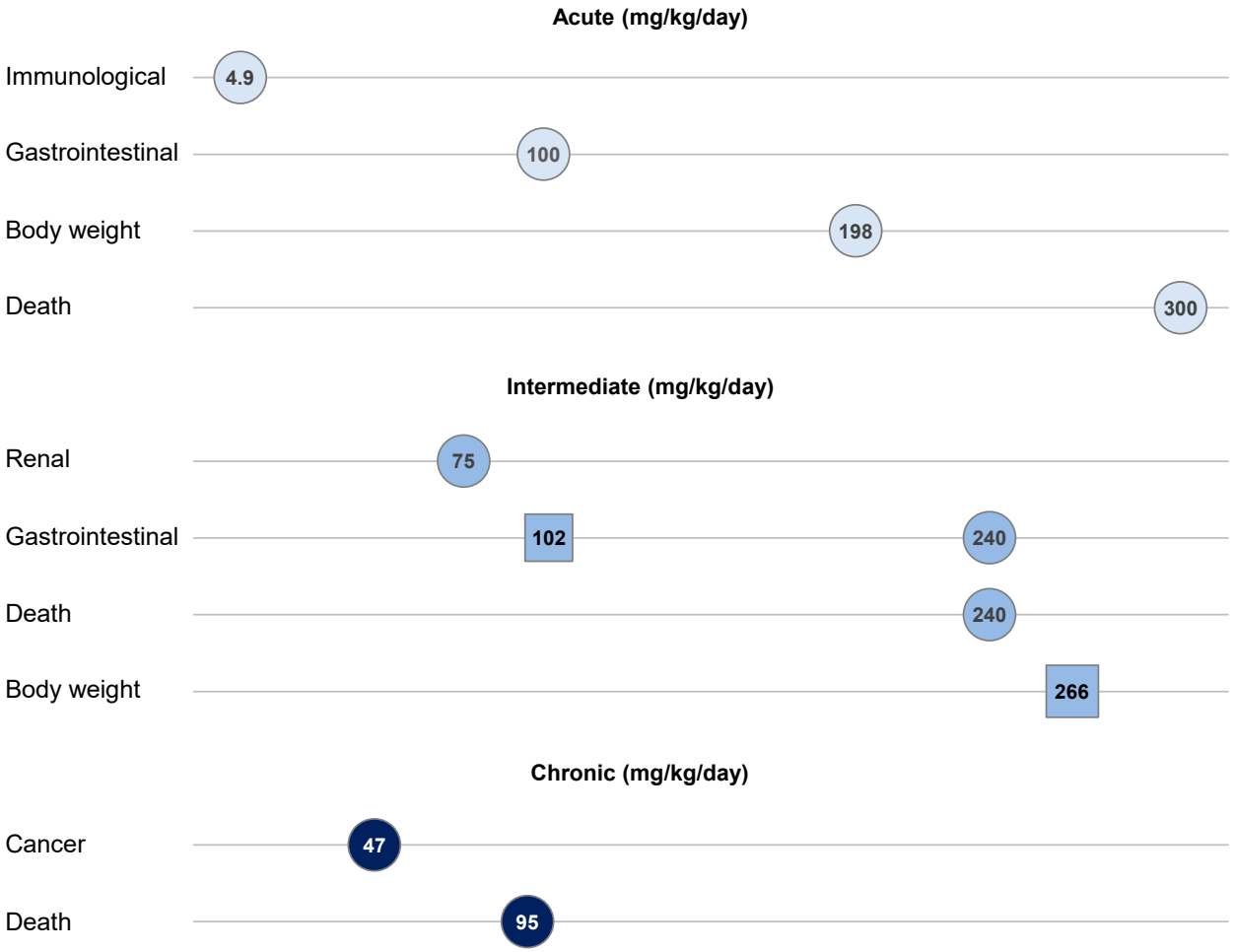


**Table 1-1. Minimal Risk Levels (MRLs) for 1,2-Dichloroethane[a]**

| Exposure route | Exposure duration | MRL | Critical effect | POD type | POD value | Uncertainty/ modifying factor | Reference |
|---|---|---|---|---|---|---|---|
| Inhalation | Acute | **0.1 ppm** (0.4 mg/m$^3$) | Degeneration with necrosis of olfactory epithelium | $BMCL_{HEC}$ | 3.84 ppm | UF: 30 | Hotchkiss et al. 2010 |
| | Intermediate | **0.1 ppm** (0.4 mg/m$^3$) | Neurobehavioral changes (altered performance in open field test) | $BBMCL_{1SD\text{-}HEC}$ | 3.70 ppm | UF: 30 | Zhong et al. 2022 |
| | Chronic | None | – | – | – | – | – |
| Oral | Acute | None | – | – | – | – | – |
| | Intermediate | **0.7 mg/kg/day** | Kidney tubule regeneration, increased kidney weight | $BMDL_{10}$ | 70.1 mg/kg/day | UF: 100 | Morgan et al. 1990; NTP 1991 |
| | Chronic | None | – | – | – | – | – |

[a]See Appendix A for additional information.

$BBMCL_{1SD}$ = Bayesian benchmark response of 1 standard deviation; BMCL = 95% lower confidence limit on the benchmark concentration; $BMDL_{10}$ = benchmark dose lower confidence limit for 10% extra risk benchmark response; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; POD = point of departure; UF = uncertainty factor

# CHAPTER 2. HEALTH EFFECTS

## 2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of 1,2-dichloroethane. 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-dichloroethane, but may not be inclusive of the entire body of literature.

Animal inhalation studies are presented in Table 2-1 and Figure 2-2 and animal oral studies are presented in Table 2-2 and Figure 2-3.

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.

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

As illustrated in Figure 2-1, the majority of the health effects data come from experimental animal studies. While there were 15 human studies, most were case studies. There were studies of comprehensive noncancer endpoints in animals exposed by inhalation and oral routes, and cancer was assessed in animals exposed by inhalation, oral, and dermal routes. The effects examined in most studies include death, body weight, hepatic, renal, respiratory, neurological, and reproductive endpoints. It should be noted that cytochrome P450 metabolism of 1,2-dichloroethane appears to be saturable in rats at gavage doses ~25 mg/kg and inhalation concentrations of ~150 ppm, both of which correspond to blood levels of 5–10 µg/mL.

The human and animal studies indicate that reproductive, respiratory, neurological, hepatic, immunological, and cancer endpoints are the most sensitive targets of inhaled 1,2-dichloroethane exposure, and renal, gastrointestinal, body weight, immunological, and cancer endpoints are the most sensitive targets of oral exposure to 1,2-dichloroethane..

- ***Immunological:*** 1,2-Dichloroethane exposure was associated with impaired immune response as evidenced by decreased leukocytes, reduced humoral immunity and cell-mediated immunity, and increased susceptibility to infection following one acute-duration inhalation study and one acute-duration gavage study in mice. However, a longer-term oral study of drinking water exposure did not observe adverse immunological effects.

- ***Respiratory:*** Inhalation exposure to 1,2-dichloroethane resulted in histopathological changes in the nasal cavity of rats (degeneration/regeneration and necrosis of the olfactory epithelium in the dorsal meatus) in one acute-duration study; chronic-duration exposure of rats to a lower concentration did not result in this effect.

- ***Neurological:*** The brain is a target for inhalation exposure to 1,2-dichloroethane as evidenced by symptoms and neuroimaging findings in human case reports of occupational exposure and by experimental animal studies that reported brain edema, increased brain water content, and vacuolation in the brain. Reduced locomotor activity and behavioral changes in open field have been observed in mice exposed by inhalation for acute and intermediate durations. Oral studies have suggested some neurological effects when 1,2-dichloroethane was administered by gavage, but not at higher doses administered in drinking water.

- ***Hepatic:*** Hepatic effects of 1,2-dichloroethane seen in some studies of animals after inhalation exposure include increased relative liver weights, increased serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and histopathological changes of macrophage aggregation and hepatocellular degeneration. High-quality studies of animals exposed orally have not shown effects of 1,2-dichloroethane on the liver.

- ***Renal:*** Increased kidney weight and histopathological changes (tubular regeneration) have been reported in rats and mice with oral exposure to 1,2-dichloroethane. Inhalation studies have not shown effects on the kidney except at very high concentrations.

- ***Reproductive:*** Inhalation exposure to 1,2-dichloroethane resulted in reproductive effects including decreased sperm concentration and motility and increased sperm abnormalities in mice exposed for acute and intermediate durations.

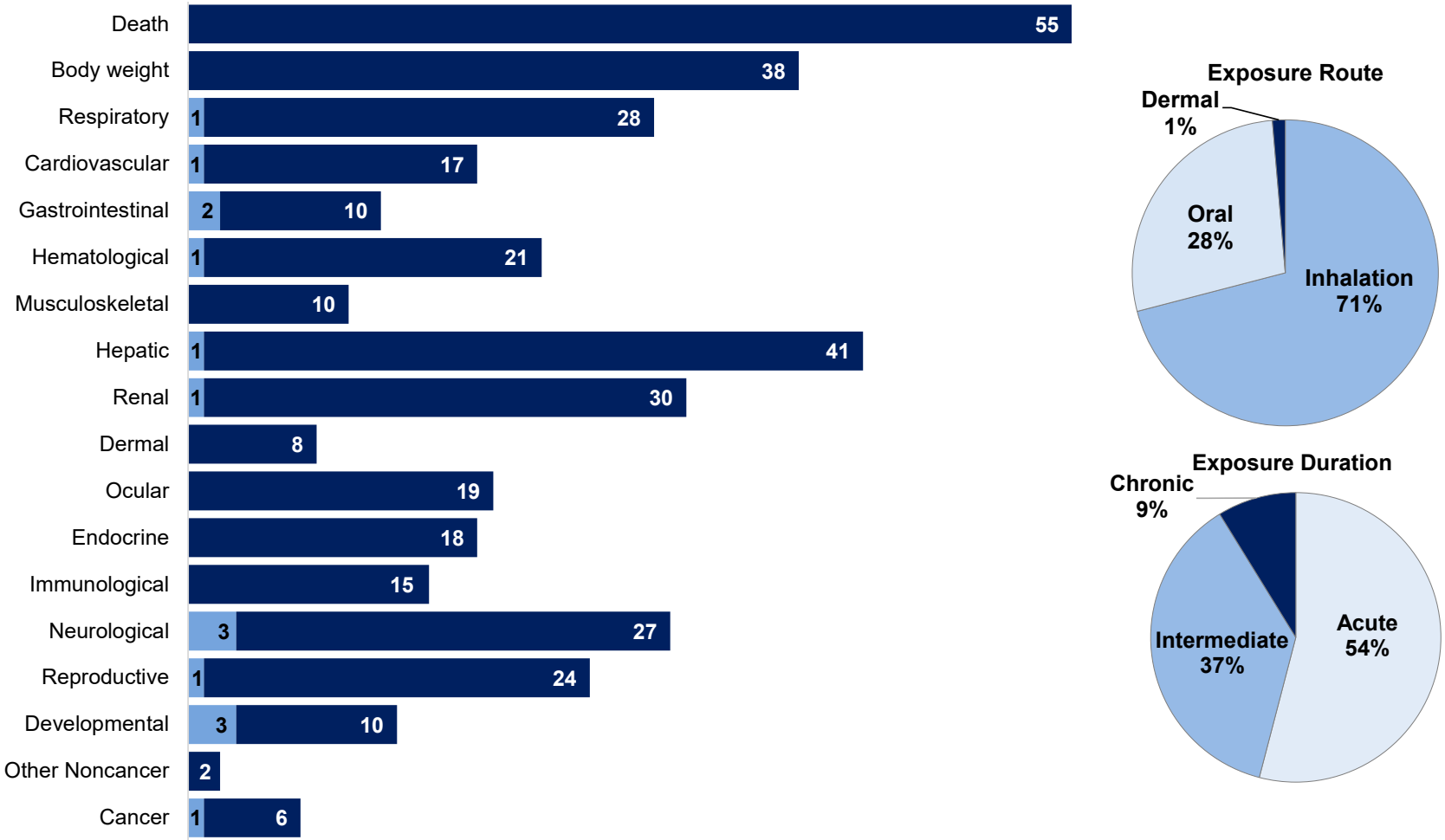
- ***Death:*** Mortality was observed in animals exposed by oral and inhalation routes. Administration by gavage results in death at much lower doses than administration in drinking water.

- ***Gastrointestinal:*** Gavage administration of 1,2-dichloroethane resulted in histopathological changes of hyperplasia and inflammation in the forestomach in one acute-duration study and one intermediate-duration study, but studies of exposure via drinking water at much higher doses did not show these changes.

- ***Cancer:*** Cancers, including hemangiosarcomas and mammary gland tumors in both rats and mice, subcutaneous fibromas and forestomach carcinomas in rats, and liver, lung, and endometrial tumors in mice, have been observed in chronic-duration studies of exposure to 1,2-dichloroethane via oral and/or inhalation routes.

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

**Most studies examined death, body weight, hepatic, renal, respiratory, neurological, and reproductive effects of 1,2-dichloroethane**
Fewer studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint)




*Includes studies discussed in Chapter 2. A total of 101 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

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

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses | Parameters monitored | Endpoint | NOAEL | Less serious LOAEL | Serious LOAEL | Effects |
|---|---|---|---|---|---|---|---|---|---|
| **ACUTE EXPOSURE** | | | | | | | | | |
| **Heppel et al. 1945** | | | | | | | | | |
| 1 | Rat 20 NS | 7 hours | 1,500, 3,000 | GN, HP, CS | Death | | | 1,500 | 4/20 deaths within 3 days after exposure |
| **Heppel et al. 1945** | | | | | | | | | |
| 2 | Rat (Wistar) 8 M, 21 F | 5 days 7 hours/day | 1,500 | GN, HP, CS | Death | | | 1,500 | All animals died within 5 days of exposure |
| **Heppel et al. 1946** | | | | | | | | | |
| 3 | Rat (NS) 26 NS | 2 weeks 5 days/week 7 hours/day | 1,000 | GN, HP, CS, LE | Death | | | 1,000 | 17/26 died by the 10th exposure |
| **Hotchkiss et al. 2010** | | | | | | | | | |
| 4 | Rat (Fischer-344) 5–10 M, 5–10 F | 4 hours | 0.0, 196.4, 607.8, 2,029 | BW, CS, GN, HP, LE, NX | Bd wt | 2,029 | | | |
| | | | | | Resp | 196.4 | 607.8 | | Very slight to slight bilateral, focal degeneration/regeneration and necrosis of the olfactory epithelium of the dorsal meatus |
| | | | | | Hepatic | 607.8 F 2,029 M | 2,029 F | | Very slight aggregates of macrophages/histiocytes in the centrilobular region; multifocal degeneration of hepatocytes |
| | | | | | Renal | 607.8 | 2,029 | | Females: very slight multifocal degeneration with necrosis of the outer stripe/outer zone of medulla Males: very slight basophilia and altered coloration of the basophilic outer stripe/outer zone of medulla |

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

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses | Parameters monitored | Endpoint | NOAEL | Less serious LOAEL | Serious LOAEL | Effects |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Neuro | 196.4 F<br>607.8 M | 607.8 F<br>2,029 M | | Females: decreased response to sharp noise and decreased motor activity<br>Males: decreased resistance to handling, decreased extensor thrust and decreased response to tail pinch and noise stimulus; increased palpebral closure, and urination and defecation |
| | | | | | Repro | 2,029 | | | |
| **Hotchkiss et al. 2010** | | | | | | | | | |
| 5 | Rat (Fischer-344)<br>5 M, 5 F | 8 hours | 0.0, 52.8, 107.5, 155.8 | CS, BW, HP, OW | Bd wt | 155.8 | | | |
| | | | | | Resp | 52.8 F<br>107.5 M | 107.5 F[b]<br>155.8 M | | Very slight degeneration with necrosis of the olfactory epithelium in the dorsal meatus |
| **Pang et al. 2018** | | | | | | | | | |
| 6 | Rat (Sprague-Dawley)<br>NS M | 5 days<br>6 hours/day (WB) | 0, 333, 557, 1,000 | BC, BI, OW, HP | Hepatic | 333 | 557 | | Increased relative liver weight, ~2-fold increase in serum ALT, increased total cholesterol, ultrastructural changes in liver |
| **Payan et al. 1995** | | | | | | | | | |
| 7 | Rat (Sprague-Dawley)<br>25–26 F | 14 days<br>GDs 6–20<br>6 hours/day | 0, 150, 194, 254, 329 | LE, BW, RX, DX | Bd wt | 254 | | 329 | 24% decreased body weight gain during GDs 6–21 |
| | | | | | Repro | 329 | | | |
| | | | | | Develop | 329 | | | |
| **Schlacter et al. 1979 (also reported in Rao et al. 1980)** | | | | | | | | | |
| 8 | Rat<br>16–30 F | 10 days<br>GDs 6–15<br>7 hours/day | 0, 100, 300 | BW, OW, FI, WI, CS, DX, RX, LE | Death | | | 300 | 10/16 died |
| | | | | | Bd wt | 100 | | | |
| | | | | | Repro | 100 | | 300 | Pregnancy rate decreased by 48% |
| | | | | | Develop | 100 | | 300 | 100% resorptions |

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

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses | Parameters monitored | Endpoint | NOAEL | Less serious LOAEL | Serious LOAEL | Effects |
|---|---|---|---|---|---|---|---|---|---|
| **Sherwood et al. 1987** | | | | | | | | | |
| 9 | Rat (Sprague-Dawley) 16 M | 5 hours | 0, 100, 200 | IX | Immuno | 200 | | | |
| **Sherwood et al. 1987** | | | | | | | | | |
| 10 | Rat (Sprague-Dawley) 16 M | 12 days 5 days/week 5 hours/day | 0, 10, 20, 50, 100 | IX | Immuno | 100 | | | |
| **Spencer et al. 1951** | | | | | | | | | |
| 11 | Rat (Wistar) 20 M, 20 F | 2–3 days 7 hours/day | 0, 400 | BW, OW, HP, BC | Death | | | 400 | 24/40 died |
| **Spencer et al. 1951** | | | | | | | | | |
| 12 | Rat (Wistar) 54 B | 0.1–8 hours | 300, 600, 800, 1,000, 1,500, 3,000, 12,000, 20,000 | CS, BC, LE, BW, GN, HP, OW | Death | | | 1,000 | $LC_{50}$ for an exposure duration of 7.2 hours |
| **Spencer et al. 1951** | | | | | | | | | |
| 13 | Rat 15 F | Up to 14 days 7 hours/day | 0, 400 | BW, OW, GN, HP, BC, CS | Death | | | 400 | All rats died |
| **Zhang et al. 2011** | | | | | | | | | |
| 14 | Rat (Sprague-Dawley) 48 M, 48 F | 6 hours | 0, 618, 1,235, 2,471 | HP | Neuro | 618 | | 1,235 | Increased water content in cortex, brain edema[c] |

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

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses | Parameters monitored | Endpoint | NOAEL | Less serious LOAEL | Serious LOAEL | Effects |
|---|---|---|---|---|---|---|---|---|---|
| **Zhang et al. 2011** | | | | | | | | | |
| 15 | Rat (Sprague-Dawley) 48 M, 48 F | 6 hours | 0, 2,471 | HP | Neuro | | | 2,471 | Increased cerebral cortex water content, consistent with cerebral edema[c], after 2 hours |
| **Zhong et al. 2020** | | | | | | | | | |
| 16 | Rat (Sprague-Dawley) 8–10 M, 8–10 F | 7 days 8 hours/day | 0, 137, 420 | BW, OW, HP | Bd wt | 137 | 420 M | 420 F | LOAEL:18% decrease in body weight in males<br>SLOAEL: 27% decrease in body weight in females |
| | | | | | Neuro | 137 M | | 137 F<br>420 M | Vacuolization in the cerebral cortex in females at ≥137 ppm and in males at 420 ppm |
| **Zhou et al. 2016** | | | | | | | | | |
| 17 | Rat (Sprague-Dawley) 30 M | 1.5 or 4 hours | 0, 988, 2,965 | | Neuro | | | 988 | Lesions with brain edema[c] in the white matter in both brain hemispheres |
| **Heppel et al. 1945** | | | | | | | | | |
| 18 | Mouse (NS) 19–20 NS | 7 hours | 1,500, 3,000 | GN, HP, CS, LE | Death | | | 1,500 | All mice died |
| **Heppel et al. 1945** | | | | | | | | | |
| 19 | Mouse 22 NS | 2 hours | 1,500, 3,000 | GN, HP, CS, LE | Death | | | 3,000 | All mice died |
| **Jin et al. 2018a** | | | | | | | | | |
| 20 | Mouse (Kunming albino) 5 F | 3 days 3.5 hours/day | 0, 296 | BW, NX, HP | Bd wt | | | 296 | 21% decrease in bodyweight |
| | | | | | Neuro | | | 296 | Brain edema[c]; body tremor and forelimb flexure seen after 2 days, and severe after 3 days |
| **Jin et al. 2018b** | | | | | | | | | |
| 21 | Mouse (albino) 5 F | 2 days 3.5 hours/day | 296 | NX, HP | Neuro | | | 296 | Increased water content of brain and increased blood:brain barrier permeability after 2 days |

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

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses | Parameters monitored | Endpoint | NOAEL | Less serious LOAEL | Serious LOAEL | Effects |
|---|---|---|---|---|---|---|---|---|---|
| **Jin et al. 2019** | | | | | | | | | |
| 22 | Mouse (albino) 5 F | 3 days 3.5 hours/day (WB) | 0, 253 | HP | Neuro | | | 253 | Brain edema[c]; vacuolization in the cerebral cortex |
| **Sherwood et al. 1987** | | | | | | | | | |
| 23 | Mouse 158–173 F | 3 hours | 0, 2.3, 5.4, 10.8 | IX | Immuno | 2.3 | 5.4 | | Increased susceptibility to infection |
| **Sherwood et al. 1987** | | | | | | | | | |
| 24 | Mouse (CD-1) 158 F | 5 days 3 hours/day | 0, 2.3 | IX | Immuno | 2.3 | | | |
| **Wang et al. 2013** | | | | | | | | | |
| 25 | Mouse (albino) 8 F | 10 days 3.5 hours/day | 0, 56, 111, 222 | BI, NX | Neuro | 56 | 111 | | Reduced locomotor activity |
| **Wang et al. 2014** | | | | | | | | | |
| 26 | Mouse (albino) 10 F | 3 days 3.5 hours/day | 0, 272, 296, 321 | HP | Death | | | 296 | 3/10 died |
| | | | | | Neuro | 272 | | 296 | Increased water content in cerebral tissues; morphological characteristics of brain edema[c] |
| **Yang et al. 2021** | | | | | | | | | |
| 27 | Mouse (albino) 5 F | 3 days 3.5 hours/day (WB) | 0, 247 | BW, CS, HP | Bd wt | 247 | | | |
| | | | | | Neuro | | | 247 | Brain edema[c]; vacuolization in the cerebral cortex |
| **Zhang and Jin 2019** | | | | | | | | | |
| 28 | Mouse (albino) 10 F | 3 days 3.5 hours/day (WB) | 0, 247 | LE, OW, HP, NX | Neuro | 247 | | | |

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

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses | Parameters monitored | Endpoint | NOAEL | Less serious LOAEL | Serious LOAEL | Effects |
|---|---|---|---|---|---|---|---|---|---|
| **Zhang et al. 2017** | | | | | | | | | |
| 29 | Mouse (Swiss-Webster) 10–15 M | 6 hours/day, 1 week | 0, 25, 86, 173 | BW, BC, RX, HP | Bd wt<br>Repro | 173<br>25 | | 86 | SLOAEL: Histopathological changes to the testes (vacuolar degeneration of germ cells in the seminiferous tubules, sloughing of spermatogenic cells into the lumen of the testes) |
| **Heppel et al. 1945** | | | | | | | | | |
| 30 | Guinea pig 12–16 NS | 7 hours | 1,500, 3,000 | GN, HP, CS, LE | Death | | | 1,500 | 6/12 died |
| **Heppel et al. 1945** | | | | | | | | | |
| 31 | Guinea pig 9 M | 4 days 7 hours/day | 1,500 | GN, HP, CS, LE | Death | | | 1,500 | 9/9 died |
| **Heppel et al. 1946** | | | | | | | | | |
| 32 | Guinea pig 16 NS | 4 days 7 hours/day | 1,000 | GN, HP, CS, LE | Death | | | 1,000 | All guinea pigs died |
| **Spencer et al. 1951** | | | | | | | | | |
| 33 | Guinea pig 8 M | 1–14 days 5 days/week 7 hours/day | 0, 400 | BW, OW, GN, HP, BC | Death | | | 400 | All guinea pigs died within 14 days |
| **Spencer et al. 1951** | | | | | | | | | |
| 34 | Guinea pig 8 M | 7 hours/day 5 days/week, up to 14 days | 0, 400 | BW, OW, GN, HP, BC | Death | | | 400 | All guinea pigs died within 14 days |
| **Heppel et al. 1945** | | | | | | | | | |
| 35 | Rabbit 4 F, 1 M | 5 days 7 hours/day | 1,500 | CS, LE | Death | | | 1,500 | 4/5 died |
| **Heppel et al. 1945** | | | | | | | | | |
| 36 | Rabbit 16 NS | 7 hours | 3,000 | GN, HP, CS | Death | | | 3,000 | 12/16 died within 3 days after exposure |

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

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses | Parameters monitored | Endpoint | NOAEL | Less serious LOAEL | Serious LOAEL | Effects |
|---|---|---|---|---|---|---|---|---|---|
| **Schlacter et al. 1979 (also reported as Rao et al. 1980)** | | | | | | | | | |
| 37 | Rabbit 19–21 F | 13 days GDs 6–18 7 hours/day | 0, 100, 300 | BW, OW, FI, WI, CS, NX, DX, LE, RX | Bd wt | 300 | | | |
| | | | | | Repro | 300 | | | |
| | | | | | Develop | 300 | | | |
| **INTERMEDIATE EXPOSURE** | | | | | | | | | |
| **Heppel et al. 1946** | | | | | | | | | |
| 38 | Rat (NS) 15 M, 1 F | Up to 14 weeks 5 days/week 7 hours/day | 0, 400 | GN HP CS | Death | | | 400 | 9/16 died within 12 weeks; 7/16 deaths occurred before the 5th exposure day |
| **Heppel et al. 1946** | | | | | | | | | |
| 39 | Rat (Wistar) 23 M, 16 F | 15 weeks 5 days/week 7 hours/day | 0, 100 | GN, HP, CS | Resp | 100 | | | |
| | | | | | Cardio | 100 | | | |
| | | | | | Hepatic | 100 | | | |
| | | | | | Renal | 100 | | | |
| | | | | | Endocr | 100 | | | |
| **Heppel et al. 1946** | | | | | | | | | |
| 40 | Rat (Osborne-Mendel) 12 M | 6 weeks 5 days/week 7 hours/day | 0, 200 | GN, HP, CS | Death | | | 200 | 8/12 died; 5 died after the first exposure |
| **Heppel et al. 1946** | | | | | | | | | |
| 41 | Rat (Wistar) 1 M, 11 F | 17 weeks 5 days/week 7 hours/day | 0, 200 | GN, HP, BC, UR, CS | Death | | | 200 | 7/12 died |
| **Rao et al. 1980** | | | | | | | | | |
| 42 | Rat (Sprague-Dawley) 20 M, 20 F | 1 generation 7 days/week 6 hours/day | 0, 25, 75, 150 | BW, OW, FI, GN, HP, RX | Bd wt | 150 | | | |
| | | | | | Hepatic | 150 | | | |
| | | | | | Renal | 150 | | | |
| | | | | | Repro | 150 | | | |

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

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses | Parameters monitored | Endpoint | NOAEL | Less serious LOAEL | Serious LOAEL | Effects |
|---|---|---|---|---|---|---|---|---|---|
| **Spencer et al. 1951** | | | | | | | | | |
| 43 | Rat (Wistar) 15 M,15 F | 198–212 days 5 days/week 7 hours/day | 0, 100, 200 | BW, OW, GN, HP, BC, CS | Bd wt | 200 | | | |
| | | | | | Resp | 200 | | | |
| | | | | | Cardio | 200 | | | |
| | | | | | Hemato | 200 | | | |
| | | | | | Hepatic | 200 | | | |
| | | | | | Renal | 200 | | | |
| | | | | | Endocr | 200 | | | |
| **Spencer et al. 1951** | | | | | | | | | |
| 44 | Rat 15 M, 15 F | 14–56 days 7 hours/day | 0, 400 | BW, OW, GN, HP, BC, CS | Death | | | 400 M | All rats died |
| **Heppel et al. 1946** | | | | | | | | | |
| 45 | Mouse 19 NS | 4 weeks 5 days/week 7 hours/day | 0, 100 | GN, HP, CS | Resp | 100 | | | |
| | | | | | Hepatic | 100 | | | |
| | | | | | Renal | 100 | | | |
| **Huang et al. 2020** | | | | | | | | | |
| 46 | Mouse (CD-1) 20 M | 28 days 7 days/week 6 hours/day (WB) | 0.06, 28.17, 90.96, 179.87 | BW, FI, HP, NX | Bd wt | 179.87 | | | |
| | | | | | Neuro | 90.96 | | 179.87 | Decreased activity in open field, damage to cerebellar granular cells (shrunken and hypereosinophilic cytoplasm, nuclear pyknosis, apoptosis) |
| **Liang et al. 2021** | | | | | | | | | |
| 47 | Mouse (Swiss) 10 M | 28 days 7 days/week 6 hours/day (WB) | 0, 25, 86, 173 | LE, BW, OW, HP | Bd wt | 173 | | | |
| | | | | | Neuro | 25 | 86 | | Vacuolization in the cerebral cortex |

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

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses | Parameters monitored | Endpoint | NOAEL | Less serious LOAEL | Serious LOAEL | Effects |
|---|---|---|---|---|---|---|---|---|---|
| **Wang et al. 2017** | | | | | | | | | |
| 48 | Mouse (Swiss-Webster) 10 M | 28 days 6 hours/day | 0, 86, 173 | BI, BC, BW, HP, OW | Bd wt | 86 | 173 | | 25% decrease in body weight gain after 28 days |
| | | | | | Hepatic | | 86 | | Increased liver weight; increased free fatty acids in liver; increased serum levels of triglycerides (296%) and free fatty acids (171%) |
| | | | | | Other noncancer | 86 | 173 | | Decreased blood glucose |
| **Zhang et al. 2017** | | | | | | | | | |
| 49 | Mouse (Swiss-Webster) 10–15 M | 28 days 6 hours/day | 0, 25, 86, 173 | BW, BC, HP, RX | Bd wt | 86 | | 173 | ~15% weight loss |
| | | | | | Repro | 25 | | 86 | SLOAEL: increased total sperm abnormalities and histopathologic changes to the testes (vacuolar degeneration of germ cells in the seminiferous tubules, sloughing of spermatogenic cells into the lumen of the testes) |
| **Zhong et al. 2020** | | | | | | | | | |
| 50 | Mouse (CD-1) 11–13M | 28 days 6 hours/day (WB) | 0.09, 30.78, 95.89, 193.08 | BW, HP | Bd wt | 193.08 | | | |
| | | | | | Neuro | 95.89 | | 193.08 | Brain edema[c], vacuolization in the cerebral cortex |
| **Zhong et al. 2022** | | | | | | | | | |
| 51 | Mouse (CD-1) 20 M | 28 days 6 hours/day (WB) | 0, 25, 86, 185 | LE, OW, HP, NX | Neuro | 25[d] | | 86 | Altered behavior in open field (decreased distance and time in central area); vacuolization and demyelination in the cerebral cortex |

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

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses | Parameters monitored | Endpoint | NOAEL | Less serious LOAEL | Serious LOAEL | Effects |
|---|---|---|---|---|---|---|---|---|---|
| **Heppel et al. 1946** | | | | | | | | | |
| 52 | Guinea pig 12 M, 2 F | 25 weeks 5 days/week 7 hours/day | 0, 200 | GN, HP, CS | Death | | | 200 | 5/14 died |
| **Heppel et al. 1946** | | | | | | | | | |
| 53 | Guinea pig 10 M, 2 F | 14 weeks 5 days/week 7 hours/day | 0, 400 | GN, HP, CS | Death | | | 400 | 7/12 died |
| **Spencer et al. 1951** | | | | | | | | | |
| 54 | Guinea pig 8 M, 8 F | 170–246 days 5 days/week 7 hours/day | 0, 100, 200 | BW, OW, GN, HP, BC, CS | Bd wt | 200 | | | |
| | | | | | Resp | 200 | | | |
| | | | | | Cardio | 200 | | | |
| | | | | | Hemato | 200 | | | |
| | | | | | Hepatic | | 100 | | Increased relative liver weight and fatty degeneration |
| | | | | | Renal | 200 | | | |
| | | | | | Endocr | 200 | | | |
| **Spencer et al. 1951** | | | | | | | | | |
| 55 | Guinea pig 8 F | 7 hours/day, 5 days/week, 14–32 days | 0, 400 | BW, OW, GN, HP, BC | Death | | | 400 | All guinea pigs died within 32 days |
| **Heppel et al. 1946** | | | | | | | | | |
| 56 | Dog 6 F | 9 weeks 5 days/week 7 hours/day | 1,000 | GN, HP, CS, BC, UR, LE | Death | | | 1,000 | 2/6 died |
| **Heppel et al. 1946** | | | | | | | | | |
| 57 | Rabbit 2 M, 3 F | 20 weeks 5 days/week 7 hours/day | 0, 400 | GN, HP, CS | Death | | | 400 | All rabbits died |

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

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses | Parameters monitored | Endpoint | NOAEL | Less serious LOAEL | Serious LOAEL | Effects |
|---|---|---|---|---|---|---|---|---|---|
| **Heppel et al. 1946** | | | | | | | | | |
| 58 | Rabbit<br>6 NS | 20 weeks<br>5 days/week<br>7 hours/day | 1,000 | GN, HP, CS | Death | | | 1,000 | 5/6 died |
| **Heppel et al. 1946** | | | | | | | | | |
| 59 | Cat<br>6 NS | 11 weeks<br>5 days/week<br>7 hours/day | 1,000 | GN, HP, CS, LE | Death | | | 1,000 | 2/6 died |
| **CHRONIC EXPOSURE** | | | | | | | | | |
| **Cheever et al. 1990** | | | | | | | | | |
| 60 | Rat (Sprague-Dawley)<br>50 M, 50 F | 2 years,<br>5 days/week,<br>7 hours/day | 0, 50 | LE, BW, OW, FI, WI, GN, HP, CS | Bd wt | 50 | | | |
| | | | | | Resp | 50 | | | |
| | | | | | Cardio | 50 | | | |
| | | | | | Gastro | 50 | | | |
| | | | | | Hemato | 50 | | | |
| | | | | | Musc/skel | 50 | | | |
| | | | | | Hepatic | 50 | | | |
| | | | | | Renal | 50 | | | |
| | | | | | Dermal | 50 | | | |
| | | | | | Ocular | 50 | | | |
| | | | | | Endocr | 50 | | | |
| | | | | | Immuno | 50 | | | |
| | | | | | Neuro | 50 | | | |
| | | | | | Repro | 50 F | 50 M | | Increased testicular lesions (not specified) |

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

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses | Parameters monitored | Endpoint | NOAEL | Less serious LOAEL | Serious LOAEL | Effects |
|---|---|---|---|---|---|---|---|---|---|
| **Nagano et al. 2006** | | | | | | | | | |
| 61 | Rat (Fischer-344) 50 M, 50 F | 104 weeks, 5 days/week, 6 hours/day 6 weeks of age | 0, 10, 40, 160 | BC, BW, CS, FI, HE, HP, LE, OW, UR | Bd wt | 160 | | | |
| | | | | | Hemato | 160 | | | |
| | | | | | Cancer | | | 160 | CEL: Increased incidence of subcutis fibromas and adenomas and fibroadenomas of the mammary gland |
| **Nagano et al. 2006** | | | | | | | | | |
| 62 | Mouse (B6D2F1) 50 M, 50 F | 104 weeks, 5 days/week, 6 hours/day 6 weeks of age | 0, 10, 30, 90 | BC, BW, CS, FI, HE, HP, LE, OW, UR | Bd wt | 90 | | | |
| | | | | | Cancer | | | 30 M | CEL: Increased incidence of liver hemangiosarcoma |

Studies selected for derivation of inhalation MRLs.

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive an acute-duration inhalation MRL of 0.1 ppm for 1,2-dichloroethane based on a $BMCL_{10}$ of 57.62 ppm converted to human equivalent concentration ($BMCL_{HEC}$) of 3.84 ppm and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability); see Appendix A for more detailed information regarding the MRL.
[c]Brain edema was measured by subtracting brain dry weight from brain wet weight.
[d]Used to derive an intermediate-duration inhalation MRL of 0.1 ppm for 1,2-dichloroethane based on a $BBMCL_{1SD}$ of 14.763 ppm, which was adjusted to continuous duration exposure (6 hour/24 hour) and converted to a $BBMCL_{1SD\text{-}HEC}$ of 3.69 ppm. The $BBMCL_{1SD\text{-}HEC}$ of 3.69 ppm was divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

ALT = alanine aminotransferase; B = both males and females; $BBMCL_{1SD}$ = Bayesian benchmark response of 1 standard deviation; BC = serum (blood) chemistry; Bd wt or BW = body weight; BI = biochemical changes; $BMCL_{10}$ = benchmark concentration lower confidence limit for 10% extra risk benchmark response; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; F = female(s); FI = food intake; GD = gestation day; GN = gross necropsy; HE = hematology; HEC = human equivalent concentration; Hemato = hematological; HP = histopathology; Immuno = immunological; IX = immune function; $LC_{50}$ = median lethal concentration; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OW = organ weight; Repro = reproductive; Resp = respiratory; RX = reproductive function; UR = urinalysis; (WB) = whole body; WI = water intake

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

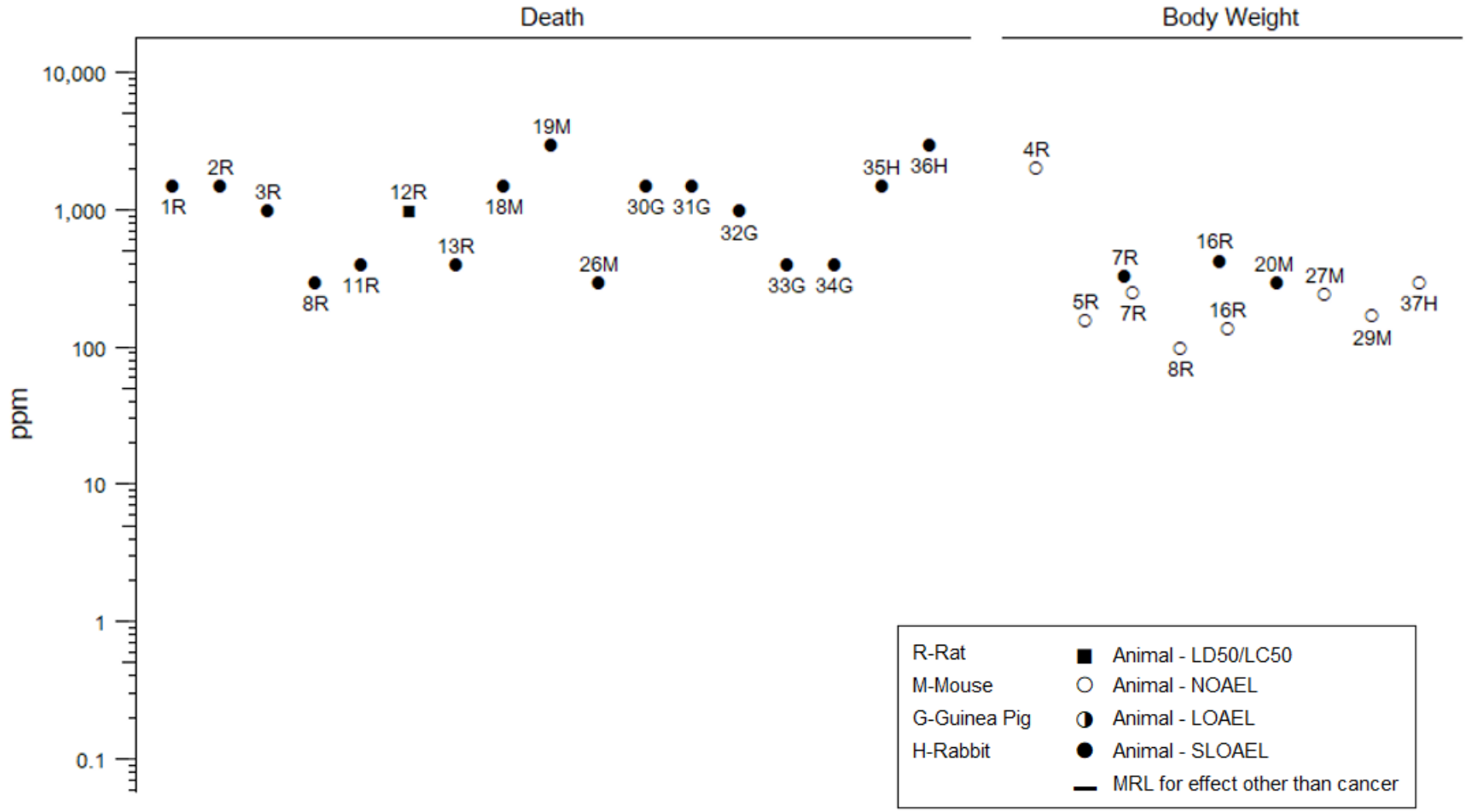


**Figure 2-2. Levels of Significant Exposure to 1,2-Dichloroethane – Inhalation**
Acute (≤14 days)

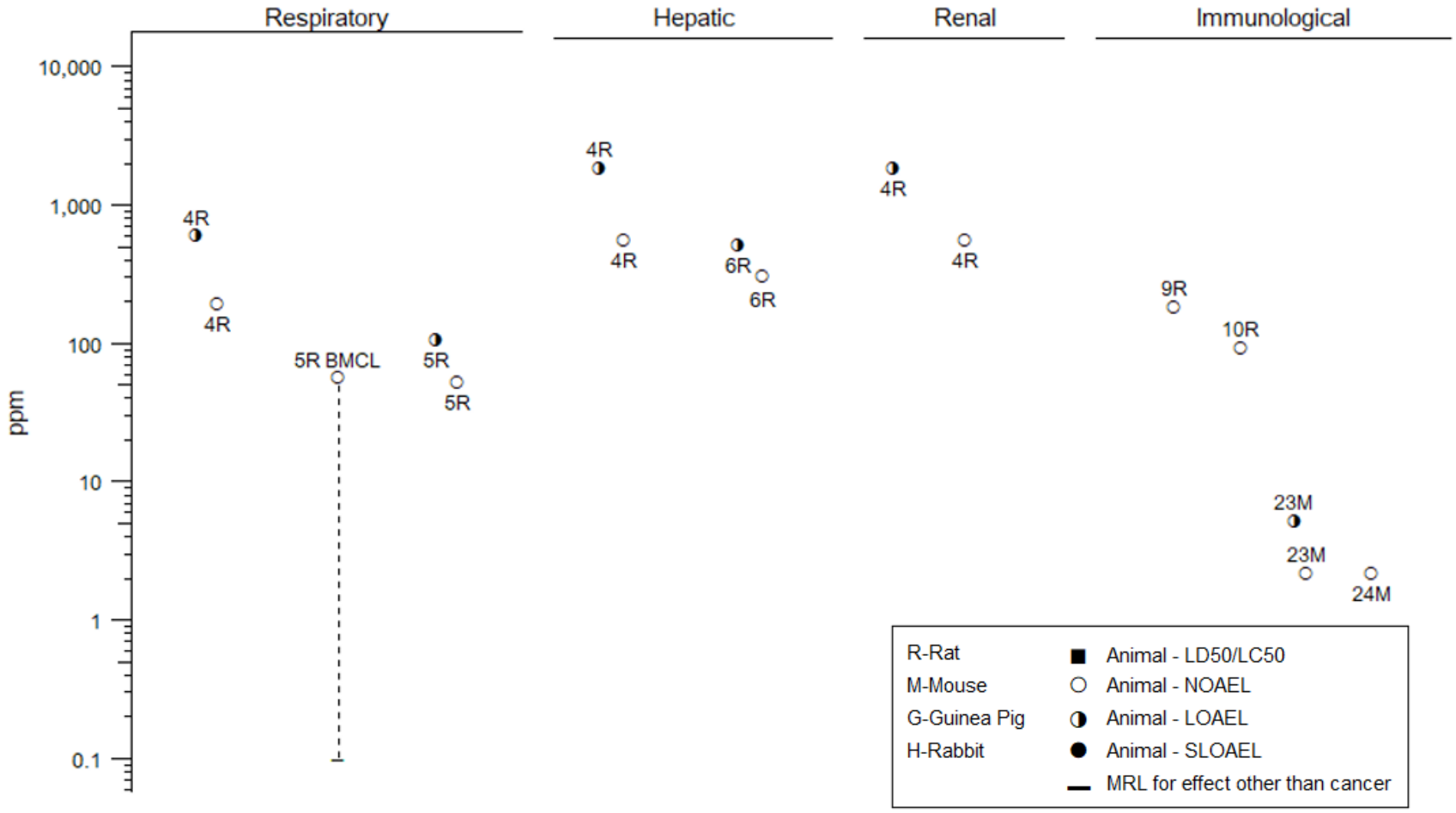


**Figure 2-2. Levels of Significant Exposure to 1,2-Dichloroethane – Inhalation**
Acute (≤14 days)

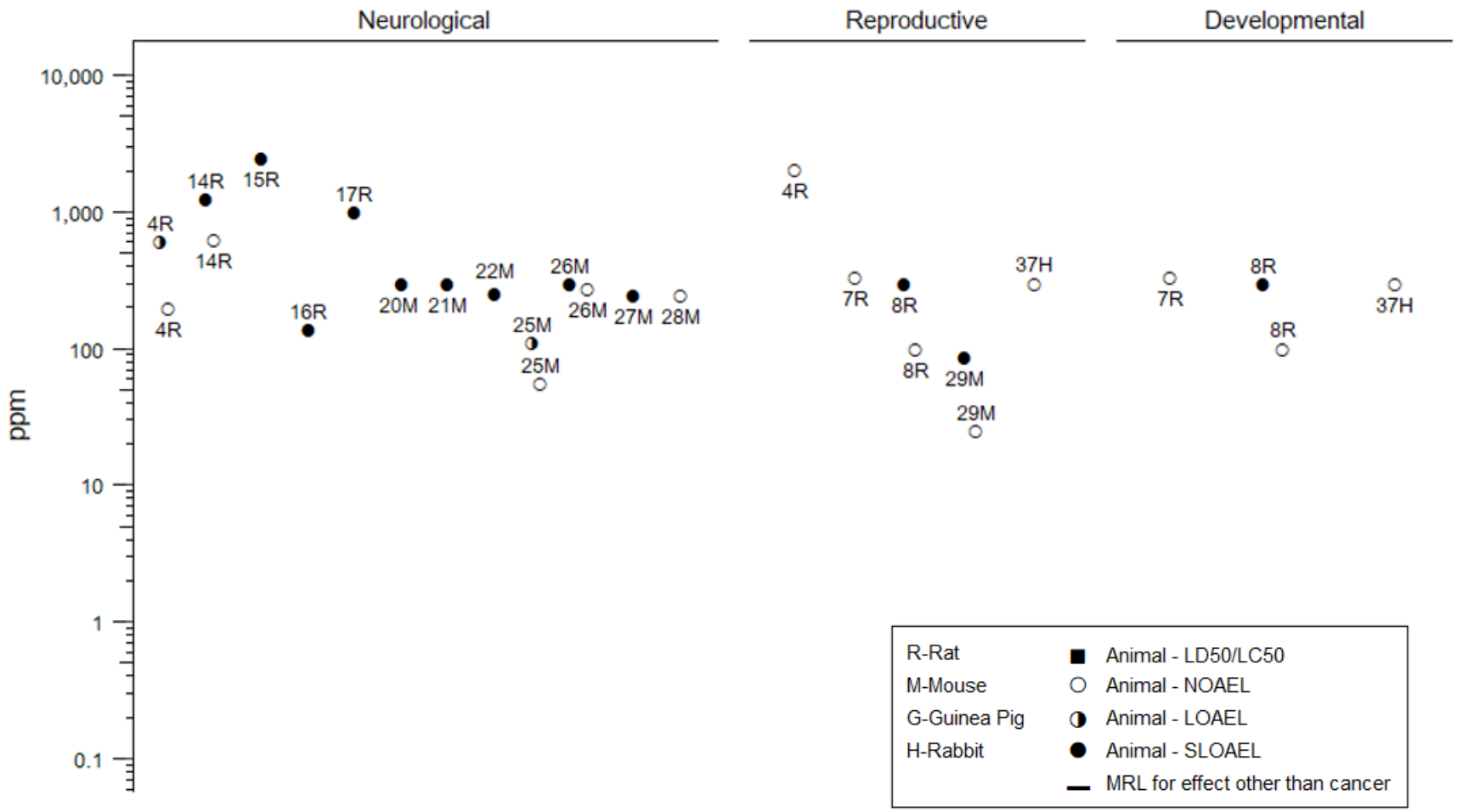


**Figure 2-2. Levels of Significant Exposure to 1,2-Dichloroethane – Inhalation**
Intermediate (15–364 days)

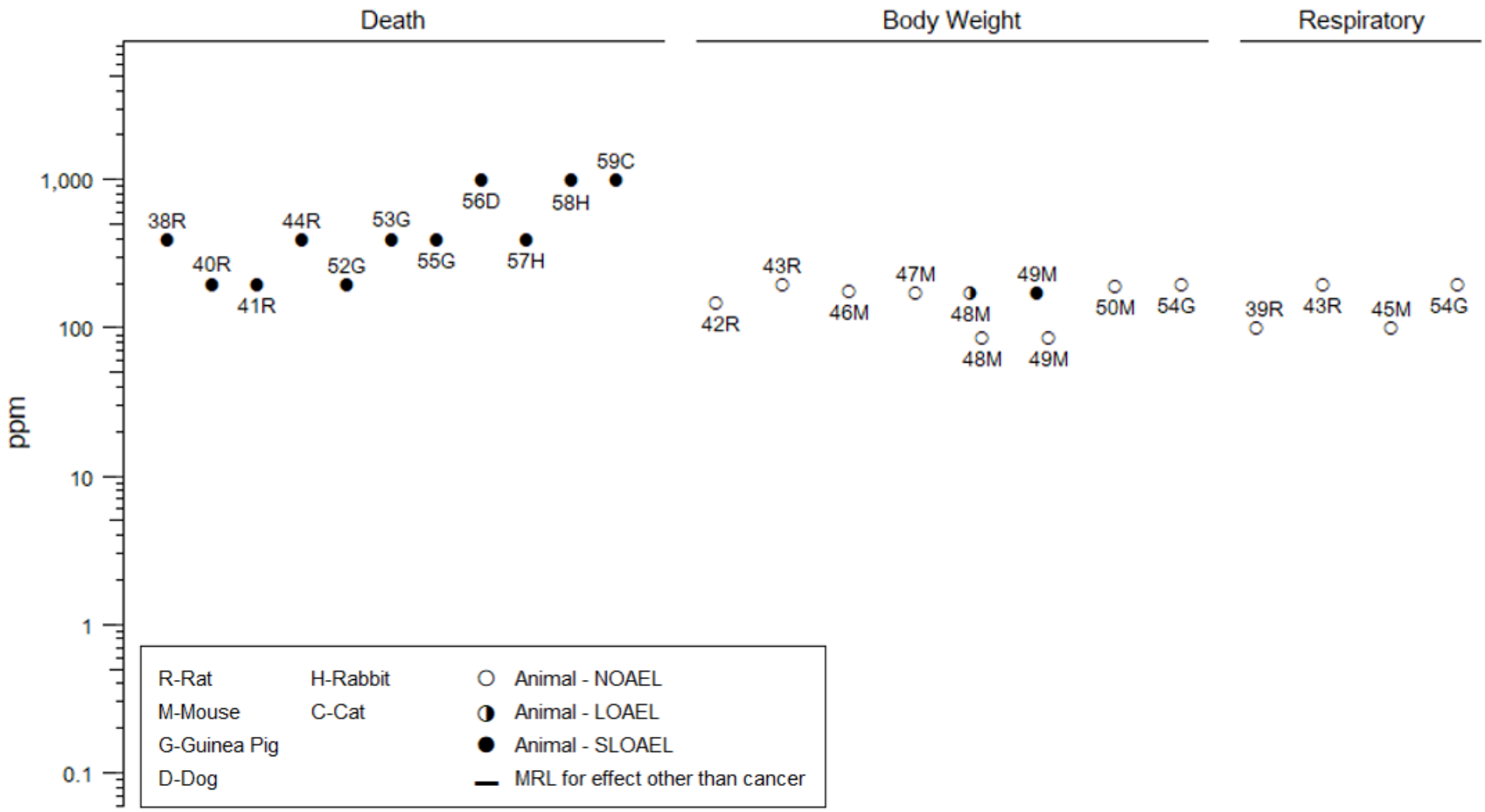


**Figure 2-2. Levels of Significant Exposure to 1,2-Dichloroethane – Inhalation**
Intermediate (15–364 days)

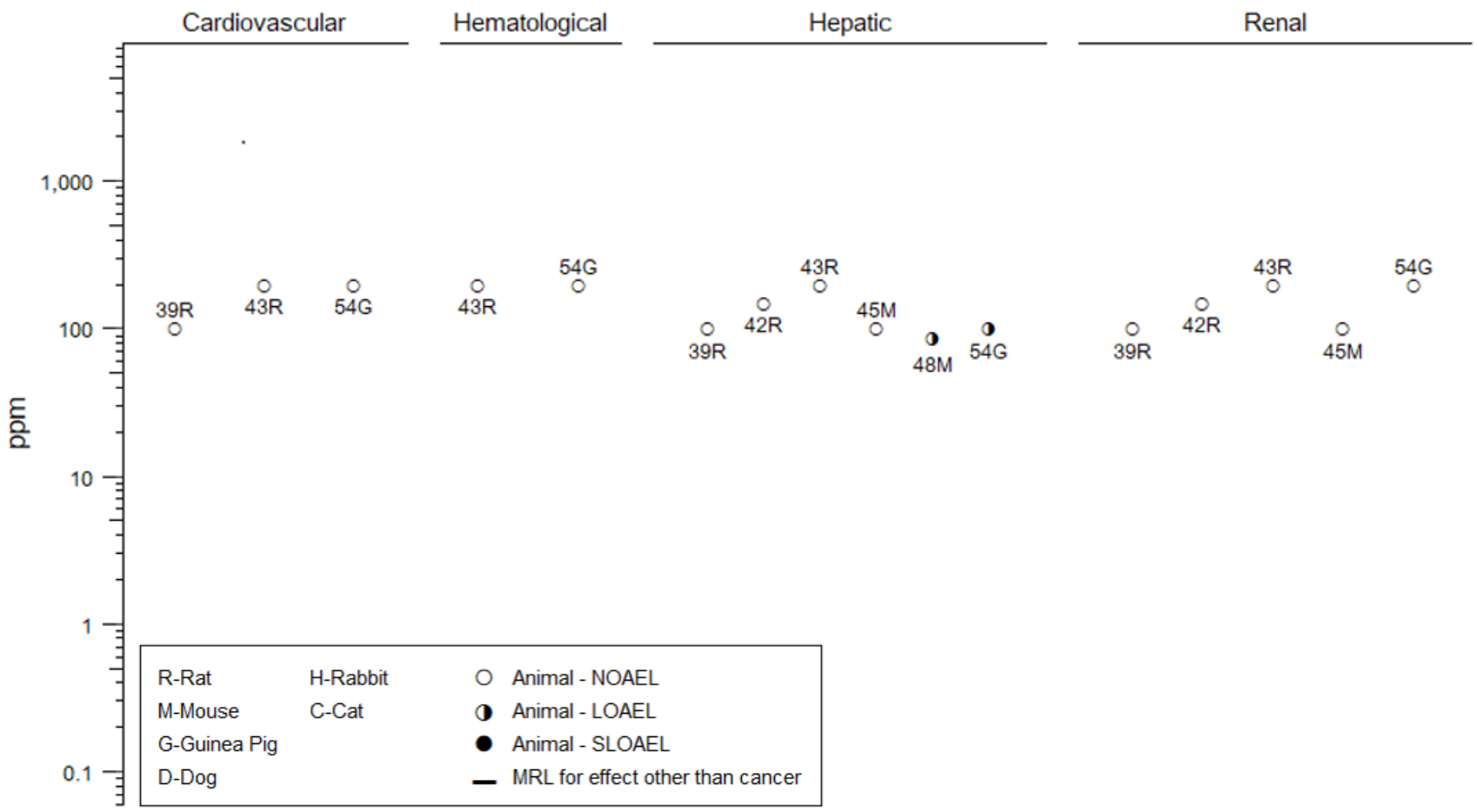


**Figure 2-2. Levels of Significant Exposure to 1,2-Dichloroethane – Inhalation**
Intermediate (15–364 days)

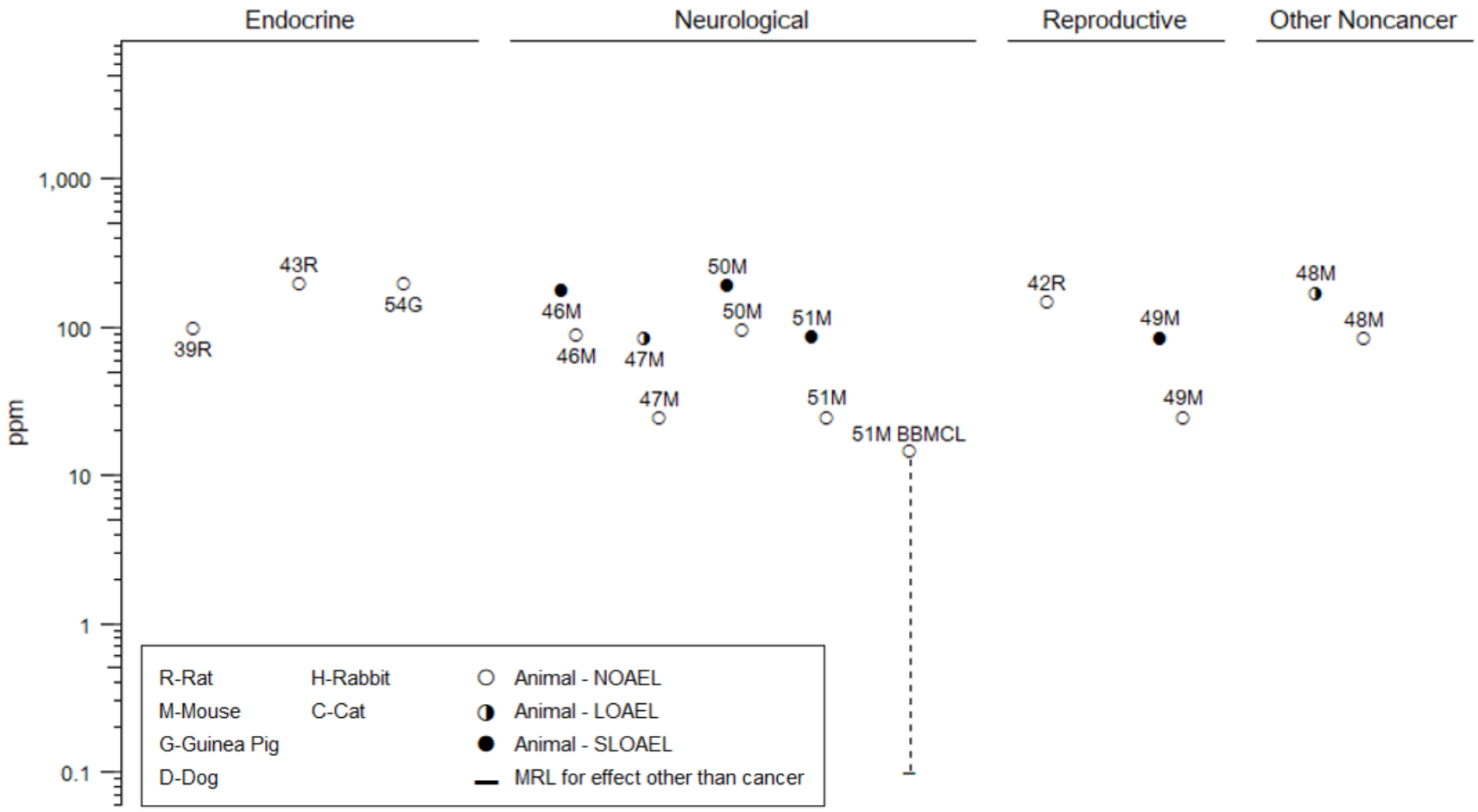


**Figure 2-2. Levels of Significant Exposure to 1,2-Dichloroethane – Inhalation**
Chronic (≥365 days)

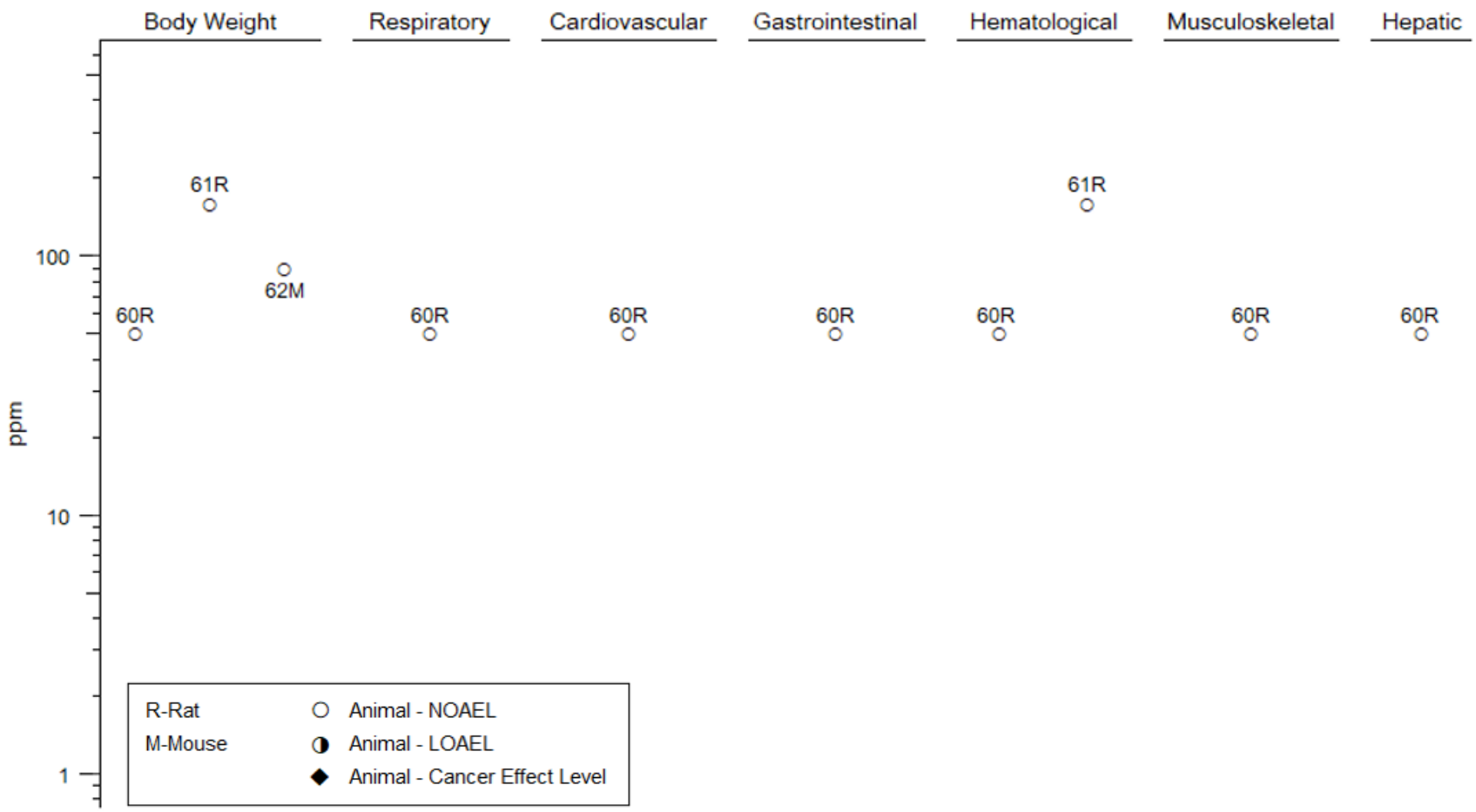
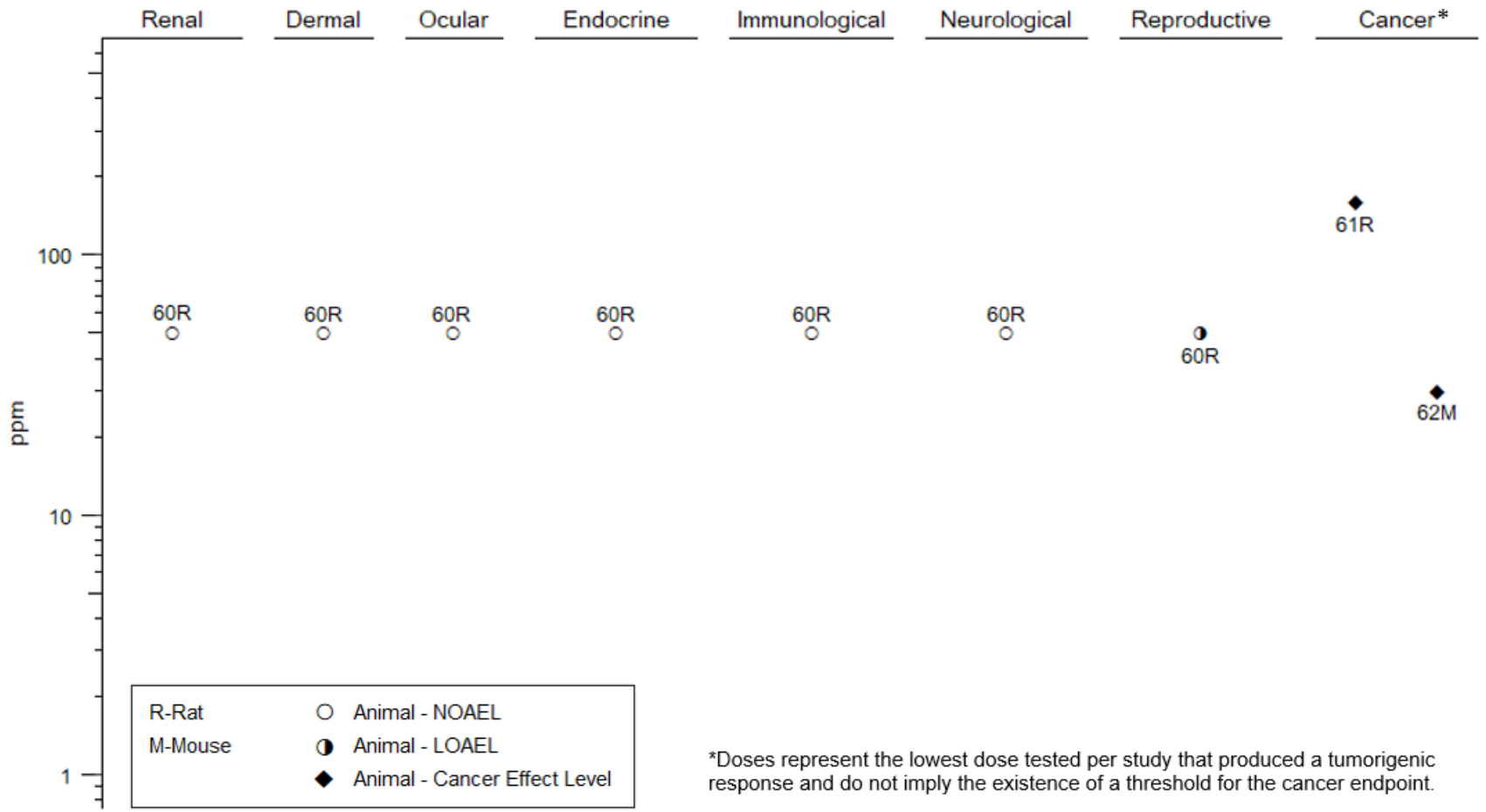


**Figure 2-2. Levels of Significant Exposure to 1,2-Dichloroethane – Inhalation**
Chronic (≥365 days)




*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer endpoint.

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

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses | Parameters monitored | Endpoint | NOAEL | Less serious LOAEL | Serious LOAEL | Effects |
|---|---|---|---|---|---|---|---|---|---|
| **ACUTE EXPOSURE** | | | | | | | | | |
| **Daniel et al. 1994** | | | | | | | | | |
| 1 | Rat (Sprague-Dawley) 50 M, 50 F | 10 days Once/day (GO) | 0, 10, 30, 100, 300 | BI, BW, CS, DX, GN, HE, HP, IX, LE, NX, OW | Death | | | 300 | 10/10 females and 8/10 males died |
| | | | | | Bd wt | 100 | | | |
| | | | | | Resp | 100 | 300 | | Reddening of lungs of rats that died |
| | | | | | Cardio | 100 | | | |
| | | | | | Gastro | 30 | 100 | | Minimal inflammatory changes in forestomach |
| | | | | | Hemato | 100 | | | |
| | | | | | Musc/skel | 100 | | | |
| | | | | | Hepatic | 100 | | | |
| | | | | | Renal | 100 | | | |
| | | | | | Dermal | 100 | | | |
| | | | | | Endocr | 100 | | | |
| | | | | | Immuno | 100 | | | |
| | | | | | Neuro | 100 | | | |
| | | | | | Repro | 100 | | | |
| **McCollister et al. 1956** | | | | | | | | | |
| 2 | Rat (albino) 80 B | 1 day (G) | NS | | Death | | | 680 | $LD_{50}$ |
| **Payan et al. 1995** | | | | | | | | | |
| 3 | Rat (Sprague-Dawley) 25–26 F | 14 days GDs 6–20 (GO) | 0, 119, 158, 198, or 238 | LE, BW, RX, DX | Bd wt | 158 | 198 | 238 | LOAEL: 30% decrease in absolute maternal weight gain (minus gravid uterus weight) and 22% decrease in weight gain on GDs 9–12 SLOAEL: 49% decrease in absolute weight gain and 73% decrease in weight gain on GDs 6–9 |

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

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses | Parameters monitored | Endpoint | NOAEL | Less serious LOAEL | Serious LOAEL | Effects |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Repro | 238 | | | |
| | | | | | Develop | 238 | | | |
| **van Esch et al. 1977** | | | | | | | | | |
| 4 | Rat (Wistar) 6 M | 14 days Once/day 5 days/week (GO) | 0, 3, 30, 100, 300 | BW, CS, DX, GN, HE, HP, IX, LE, NX, OW | Death | | | 300 | All rats died |
| | | | | | Bd wt | 100 | | | |
| | | | | | Resp | 100 | | | |
| | | | | | Hemato | 100 | | | |
| | | | | | Hepatic | 100 | 300 | | Fatty degeneration |
| | | | | | Renal | 100 | | | |
| | | | | | Endocr | 100 | | | |
| **Munson et al. 1982** | | | | | | | | | |
| 5 | Mouse (CD-1) 10–12 M | 14 days Once/day (G) | 0, 4.9, 49 | BC, BI, OW, BW | Bd wt | 49 | | | |
| | | | | | Hemato | 49 | | | Decreased leukocyte count |
| | | | | | Hepatic | 49 | | | |
| | | | | | Renal | 49 | | | |
| | | | | | Immuno | | 4.9 | | Decreased humoral and cell-mediated immune responses |
| **Munson et al. 1982** | | | | | | | | | |
| 6 | Mouse (CD-1) NS | 1 day (G) | NS | LE | Death | | | 413 489 | $LD_{50}$ |
| **INTERMEDIATE EXPOSURE** | | | | | | | | | |
| **Alumot et al. 1976** | | | | | | | | | |
| 7 | Rat 6 M, 6 F | 5–7 weeks 2 times/day (F) | 0, 15, 30, 80 | BW, OW, BI | Bd wt | 80 | | | |
| | | | | | Hepatic | 30 | 80 | | Increased fat content of liver |

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

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses | Parameters monitored | Endpoint | NOAEL | Less serious LOAEL | Serious LOAEL | Effects |
|---|---|---|---|---|---|---|---|---|---|
| **Charlap 2015** | | | | | | | | | |
| 8 | Rat (Sprague-Dawley) 27 M 27 F | 1-generation extended F0: 90–120 days F1: 90–120 days (W) | 0, 50, 150, 300 | LE, CS, BW, FI, WI, HE, BC, UR, GN, OW, HP, NX, RX, DX | Bd wt | 300 F 150 M | 300 M | | Decreased body weight by 10% |
| | | | | | Resp | 300 | | | |
| | | | | | Cardio | 300 | | | |
| | | | | | Hemato | 300 | | | |
| | | | | | Hepatic | 300 | | | |
| | | | | | Renal | 300 | | | |
| | | | | | Endocr | 300 | | | |
| | | | | | Neuro | 300 | | | |
| | | | | | Repro | 300 | | | |
| | | | | | Develop | 150 | 300 | | reduced F1 pup weight (up to 10.7% lower than controls between PNDs 4 and 21) |
| **Daniel et al. 1994** | | | | | | | | | |
| 9 | Rat (Sprague-Dawley) 10 M, 10 F | 90 days Once/day (GO) | 0, 37.5, 75, 150 | BI, BW, CS, DX, GN, HE, HP, IX, LE, NX, OW | Bd wt | 150 | | | |
| | | | | | Resp | 150 | | | |
| | | | | | Cardio | 150 | | | |
| | | | | | Gastro | 150 | | | |
| | | | | | Hemato | 75 F 150 M | 150 F | | Decreased erythrocyte count, hematocrit, and hemoglobin; increased leukocyte count |
| | | | | | Musc/skel | 150 | | | |
| | | | | | Hepatic | 150 | | | |
| | | | | | Renal | 37.5 | 75 | | Increase in relative kidney weight |
| | | | | | Dermal | 150 | | | |
| | | | | | Ocular | 150 | | | |
| | | | | | Endocr | 150 | | | |
| | | | | | Immuno | 150 | | | |

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

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses | Parameters monitored | Endpoint | NOAEL | Less serious LOAEL | Serious LOAEL | Effects |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Neuro | 150 | | | |
| | | | | | Repro | 150 | | | |
| **Morgan et al. 1990; NTP 1991** | | | | | | | | | |
| 10 | Rat (F344/N) 10–20 M, 10 F | 13 weeks (W) | M: 0, 49, 86, 147, 259, 515 F: 0, 58, 102, 182, 320, 601 | BW, OW, FI, WI, GN, HP, BC, CS | Bd wt | 601 | | | |
| | | | | | Resp | 601 | | | |
| | | | | | Cardio | 601 | | | |
| | | | | | Gastro | 601 | | | |
| | | | | | Hemato | 601 | | | |
| | | | | | Musc/skel | 601 | | | |
| | | | | | Hepatic | 601 | | | |
| | | | | | Renal | 58 F 515 M | 102 F[b] | | Tubular regeneration, increase in absolute and relative kidney weight |
| | | | | | Dermal | 601 | | | |
| | | | | | Ocular | 601 | | | |
| | | | | | Endocr | 601 | | | |
| | | | | | Immuno | 601 | | | |
| | | | | | Neuro | 601 | | | |
| | | | | | Repro | 601 | | | |
| **Morgan et al. 1990; NTP 1991** | | | | | | | | | |
| 11 | Rat (Sprague-Dawley) 10–20 M, 10 F | 13 weeks (W) | M: 0, 60, 99, 165, 276, 518 F: 0, 76, 106, 172, 311, 531 | BW, OW, FI, WI, GN, HP, BC, CS | Bd wt | 531 | | | |
| | | | | | Resp | 531 | | | |
| | | | | | Cardio | 531 | | | |
| | | | | | Gastro | 531 | | | |
| | | | | | Hemato | 531 | | | |
| | | | | | Musc/skel | 531 | | | |
| | | | | | Hepatic | 531 | | | |
| | | | | | Renal | 531 | | | |
| | | | | | Dermal | 531 | | | |
| | | | | | Ocular | 531 | | | |

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

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses | Parameters monitored | Endpoint | NOAEL | Less serious LOAEL | Serious LOAEL | Effects |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Endocr | 531 | | | |
| | | | | | Immuno | 531 | | | |
| | | | | | Neuro | 531 | | | |
| | | | | | Repro | 531 | | | |
| **Morgan et al. 1990; NTP 1991** | | | | | | | | | |
| 12 | Rat (Osborne-Mendel) 10–20 M, 10 F | 13 weeks (W) | M:0, 54, 88, 146, 266, 492 F:0,82, 126, 213, 428, 727 | BW, OW, FI, WI, GN, HP, BC, CS | Bd wt | 727 F 126 M | 266 M | | 12% decrease in terminal body weight of males |
| | | | | | Resp | 727 | | | |
| | | | | | Cardio | 727 | | | |
| | | | | | Gastro | 727 | | | |
| | | | | | Hemato | 727 | | | |
| | | | | | Musc/skel | 727 | | | |
| | | | | | Hepatic | 727 | | | |
| | | | | | Renal | 727 | | | |
| | | | | | Dermal | 727 | | | |
| | | | | | Ocular | 727 | | | |
| | | | | | Endocr | 727 | | | |
| | | | | | Immuno | 727 | | | |
| | | | | | Neuro | 727 | | | |
| | | | | | Repro | 727 | | | |
| **Morgan et al. 1990; NTP 1991** | | | | | | | | | |
| 13 | Rat (F344/N) 10–20 M, 10 F | 13 weeks 5 days/week Once/day (GO) | M: 0, 30, 60, 120, 240, 480 F: 0, 18, 37, 75, 150, 300 | BW, OW, FI, WI, GN, HP, BC, CS | Death | | | 300 F 240 M | 9/10 females died; 10/10 males died |
| | | | | | Bd wt | 150 | | | |
| | | | | | Resp | 150 | | | |
| | | | | | Cardio | 150 | | | |
| | | | | | Gastro | 300 F 120 M | 240 M | | Forestomach hyperplasia and inflammation |

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

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses | Parameters monitored | Endpoint | NOAEL | Less serious LOAEL | Serious LOAEL | Effects |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Hemato | 150 | | | |
| | | | | | Musc/skel | 150 | | | |
| | | | | | Hepatic | 150 | | | |
| | | | | | Renal | 37 F<br>120 M | 75 F | | Increase in absolute and relative kidney weight |
| | | | | | Dermal | 150 | | | |
| | | | | | Ocular | 150 | | | |
| | | | | | Endocr | 150 | | | |
| | | | | | Repro | 150 | | | |
| **van Esch et al. 1977** | | | | | | | | | |
| 14 | Rat (Wistar)<br>10 M, 10 F | 90 days<br>5 days/week<br>Once/day<br>(GO) | 0, 10, 30, 90 | BW, CS, DX, GN, HE, HP, IX, LE, NX, OW | Bd wt | 90 | | | |
| | | | | | Resp | 90 | | | |
| | | | | | Cardio | 90 | | | |
| | | | | | Gastro | 90 | | | |
| | | | | | Hemato | 90 | | | |
| | | | | | Musc/skel | 90 | | | |
| | | | | | Hepatic | 90 | | | |
| | | | | | Renal | 30 | 90 | | Increase in relative kidney weight |
| | | | | | Endocr | 90 | | | |
| | | | | | Neuro | 90 | | | |
| | | | | | Repro | 90 | | | |
| **Lane et al. 1982** | | | | | | | | | |
| 15 | Mouse (ICR Swiss)<br>10 M, 30 F | 49 weeks, 2-generation<br>*ad libitum*<br>(W) | 0, 5, 15, 50 | BW, WI | Repro | 50 | | | |
| | | | | | Develop | 50 | | | |

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

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses | Parameters monitored | Endpoint | NOAEL | Less serious LOAEL | Serious LOAEL | Effects |
|---|---|---|---|---|---|---|---|---|---|
| **Morgan et al. 1990; NTP 1991** | | | | | | | | | |
| 16 | Mouse (B6C3F1) 10 M, 10 F | 13 weeks (W) | M: 0, 249, 448, 781, 2,710, 4,207 F: 0, 244, 647, 1,182, 2,478, 4,926 | BW, OW, FI, WI, GN, HP, CS | Death | | | 4,926 F | 9/10 died |
| | | | | | Bd wt | 4,926 F | 4,207 M | | 16% decrease in terminal body weight |
| | | | | | | 2,710 M | | | |
| | | | | | Resp | 4,926 | | | |
| | | | | | Cardio | 4,926 | | | |
| | | | | | Gastro | 4,926 | | | |
| | | | | | Hemato | 4,926 | | | |
| | | | | | Musc/skel | 4,926 | | | |
| | | | | | Hepatic | 4,926 | | | |
| | | | | | Renal | 4,926 F | | | |
| | | | | | | 249 M | 448 M | | Tubular regeneration, increased absolute and relative kidney weight |
| | | | | | Dermal | 4,926 | | | |
| | | | | | Ocular | 4,926 | | | |
| | | | | | Endocr | 4,926 | | | |
| | | | | | Immuno | 4,926 | | | |
| | | | | | Neuro | 4,926 | | | |
| | | | | | Repro | 4,926 | | | |
| **Munson et al. 1982** | | | | | | | | | |
| 17 | Mouse (CD-1) 16 M | 90 days *ad libitum* (W) | 0, 3, 24, 189 | GN, BC, BW, WI | Resp | 189 | | | |
| | | | | | Hemato | 189 | | | |
| | | | | | Hepatic | 189 | | | |
| | | | | | Renal | 189 | | | |
| | | | | | Immuno | 189 | | | |

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

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses | Parameters monitored | Endpoint | NOAEL | Less serious LOAEL | Serious LOAEL | Effects |
|---|---|---|---|---|---|---|---|---|---|
| **NCI 1978** | | | | | | | | | |
| 18 | Mouse (B6C3F1) 5 M, 5 F | Once/day, 5 days/week, 6 weeks (GO) | 0, 159, 251, 398, 631, 1,000 | BW, LE | Death | | | 251 | 3/5 males and 1/5 females died |
| **CHRONIC EXPOSURE** | | | | | | | | | |
| **Alumot et al. 1976** | | | | | | | | | |
| 19 | Rat 18 M, 18 F | 2 years 2 times/day (F) | 0, 12.5, 25 | BW, FI, CS, BI | Bd wt | 25 | | | |
| | | | | | Hepatic | 25 | | | |
| | | | | | Renal | 25 | | | |
| | | | | | Repro | 25 | | | |
| | | | | | Develop | 25 | | | |
| **NCI 1978** | | | | | | | | | |
| 20 | Rat (Osborne-Mendel) 50 M, 50 F | 78 weeks 5 days/week Once/day (GO) | 0, 47, 95 | BW, GN, HP, CS | Death | | | 95 | 42/50 males and 40/50 females died |
| | | | | | Bd wt | 95 | | | |
| | | | | | Cancer | | | 47 | CEL: hemangiosarcoma (males and females), mammary gland adenocarcinoma (females), subcutaneous fibromas (males) |

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

| Figure key[a] | Species (strain) No./group | Exposure parameters | Doses | Parameters monitored | Endpoint | NOAEL | Less serious LOAEL | Serious LOAEL | Effects |
|---|---|---|---|---|---|---|---|---|---|
| **NCI 1978** | | | | | | | | | |
| 21 | Mouse (B6C3F1) 50 M, 50 F | 78 weeks 5 days/week Once/day (GO) | M: 0, 97 195 F: 0 149, 299 | BW, GN, HP, CS | Death | | | 299 F | 36/50 died |
| | | | | | Bd wt | 299 | | | |
| | | | | | Cancer | | | 149 F | CEL: Endometrial stromal sarcoma; alveolar/bronchiolar adenoma and hepatocellular carcinoma |
| | | | | | | | | 195 M | CEL: hepatocellular carcinoma, alveolar/bronchiolar adenoma |

Studies selected for derivation of oral MRLs.

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive an intermediate-duration oral minimal risk level (MRL) of 0.7 mg/kg/day for 1,2-dichloroethane based on $BMDL_{10}$ of 70.08 mg/kg/day and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability); see Appendix A for more detailed information regarding the MRL.

B = both males and females; BC = serum (blood) chemistry; Bd wt or BW = body weight; BI = biochemical changes; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; F = female(s); FI = food intake; (G) = gavage; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; (GO) = gavage in oil; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; IX = immune function; $LD_{50}$ = median lethal dose; LE = lethality; 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; OW = organ weight; Repro = reproductive; Resp = respiratory; RX = reproductive function; UR = urinalysis; (W) = drinking water; WI = water intake

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

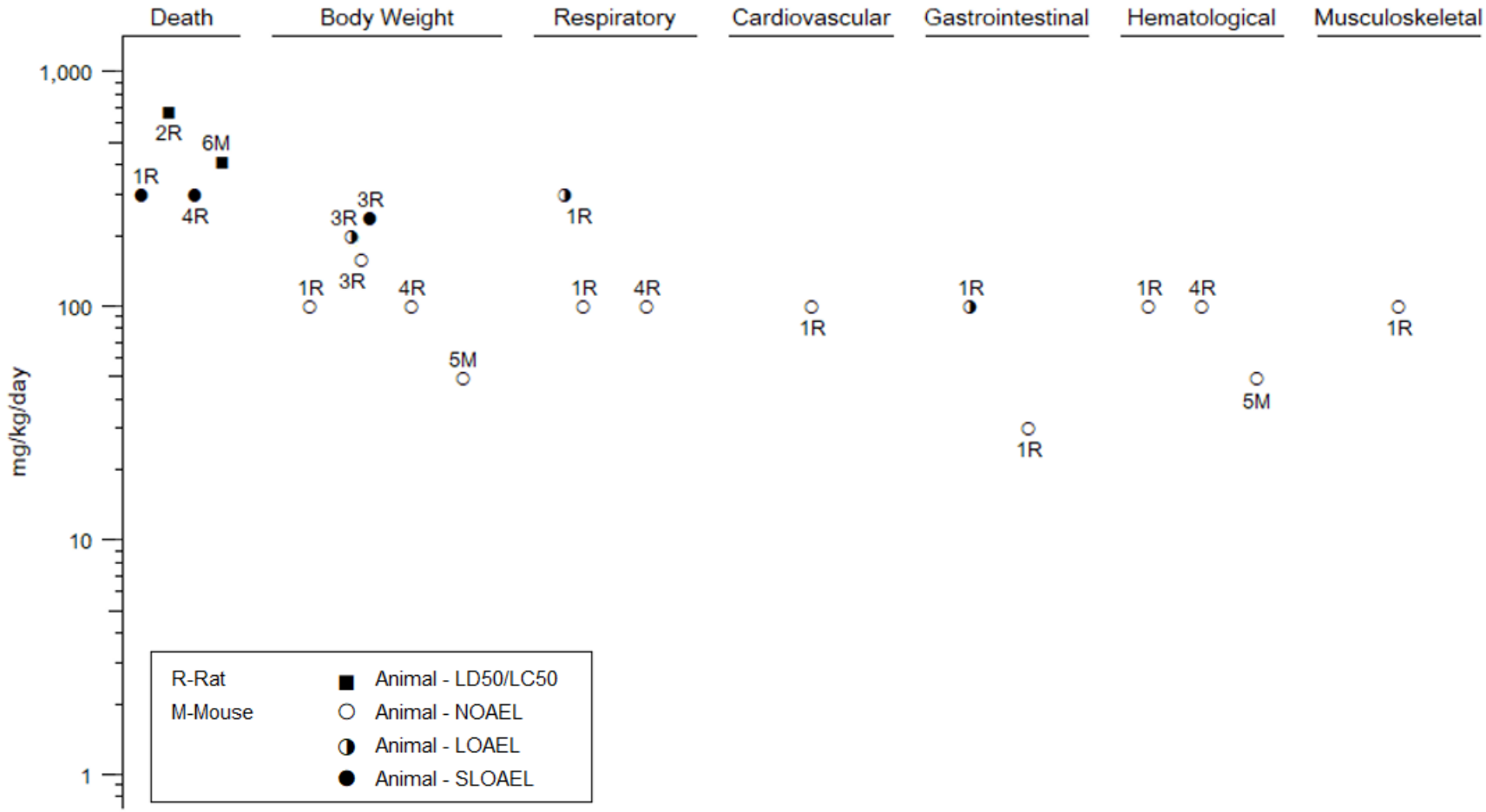


**Figure 2-3. Levels of Significant Exposure to 1,2-Dichloroethane – Oral**
Acute (≤14 days)

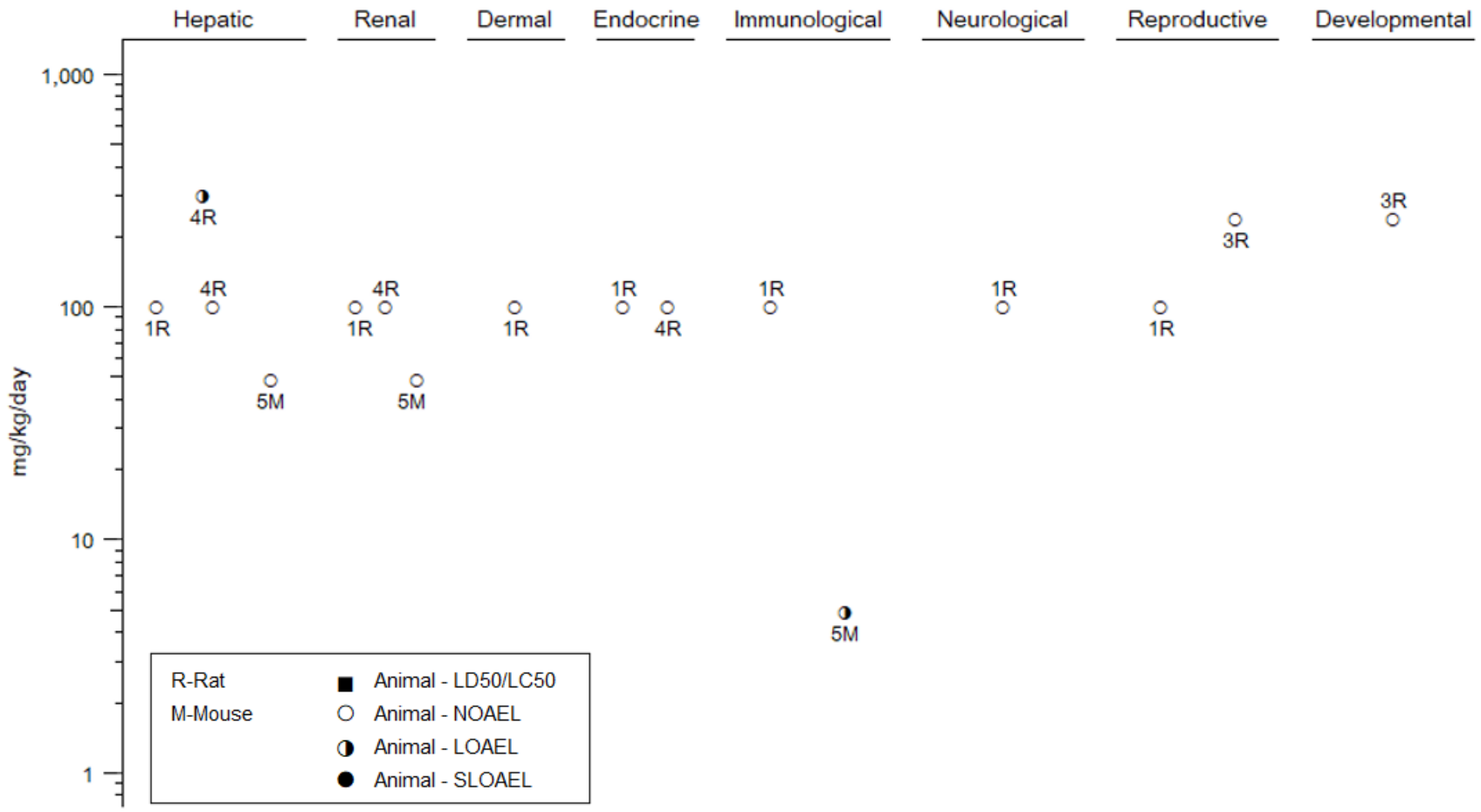


**Figure 2-3. Levels of Significant Exposure to 1,2-Dichloroethane – Oral**
Intermediate (15–364 days)

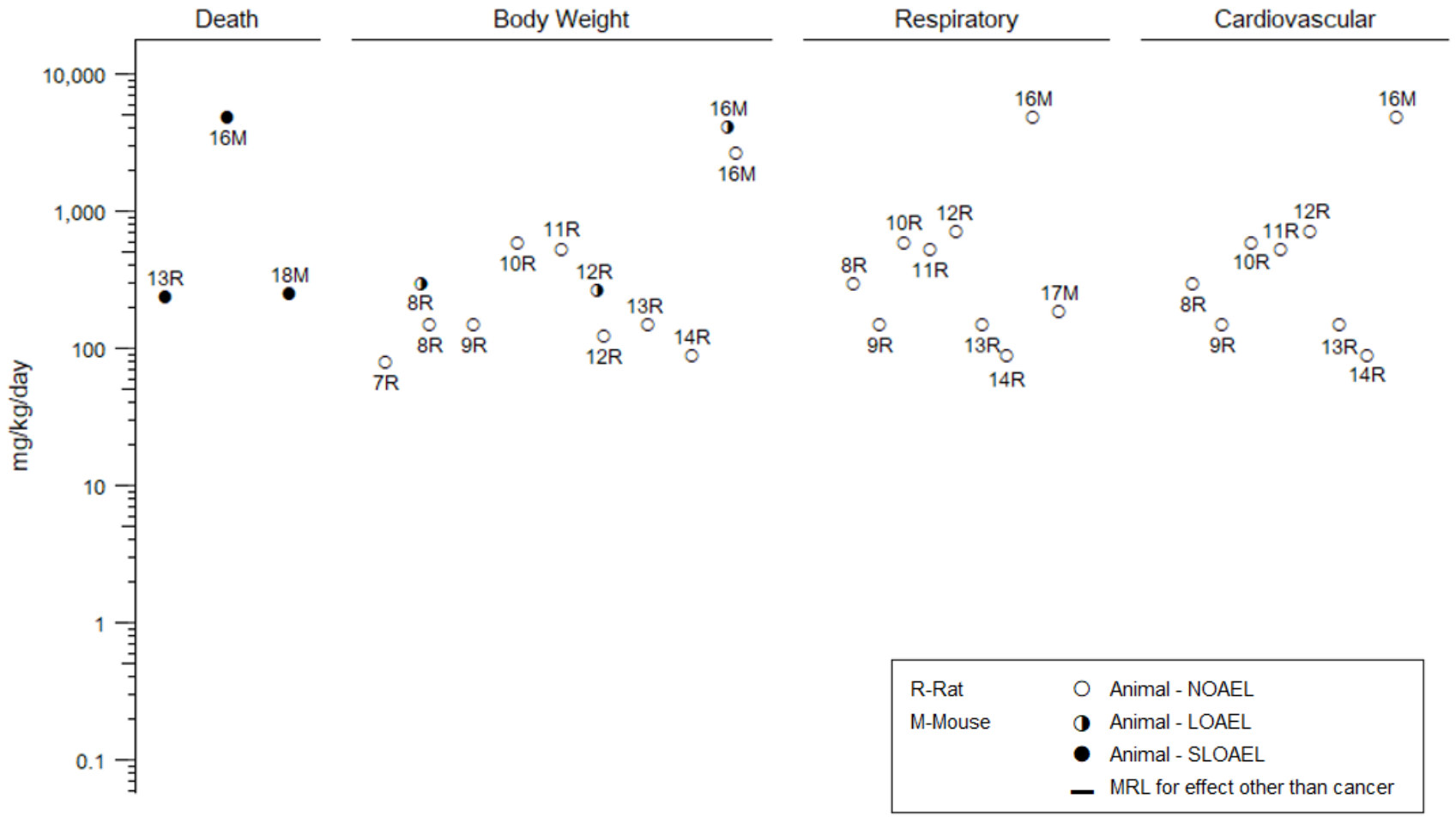


**Figure 2-3. Levels of Significant Exposure to 1,2-Dichloroethane – Oral**
Intermediate (15–364 days)

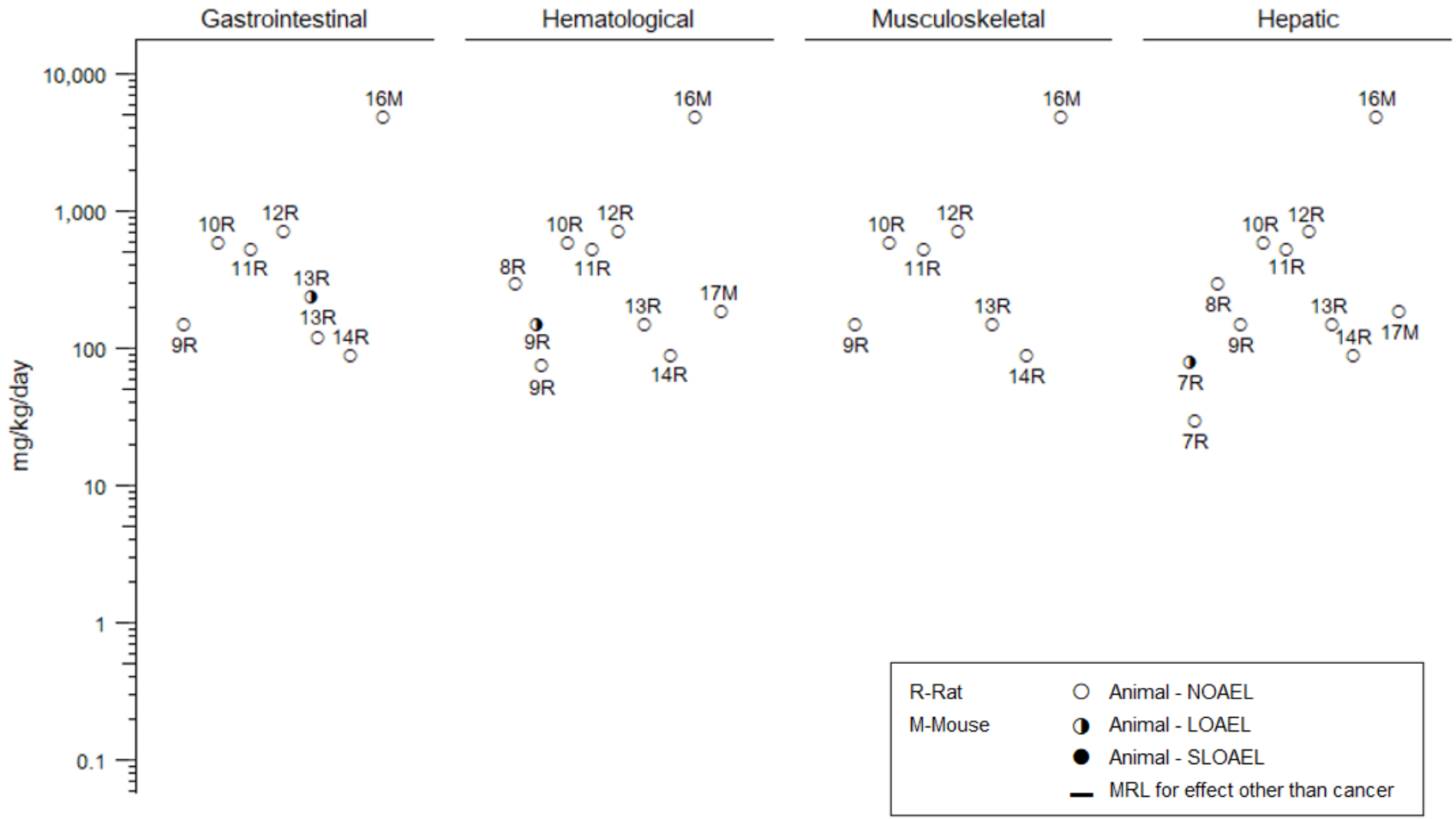


**Figure 2-3. Levels of Significant Exposure to 1,2-Dichloroethane – Oral**
Intermediate (15–364 days)

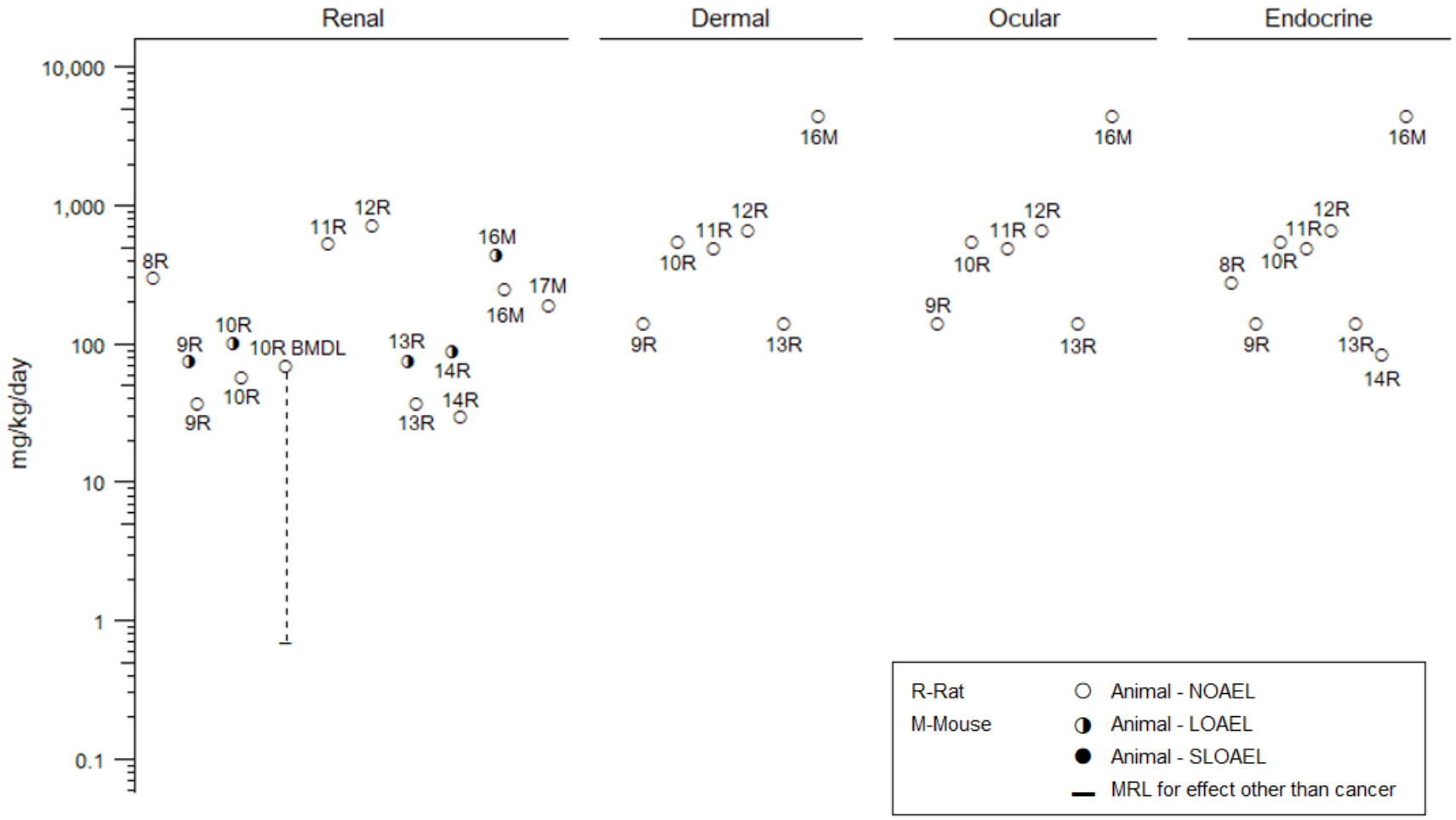


**Figure 2-3. Levels of Significant Exposure to 1,2-Dichloroethane – Oral**
Intermediate (15–364 days)

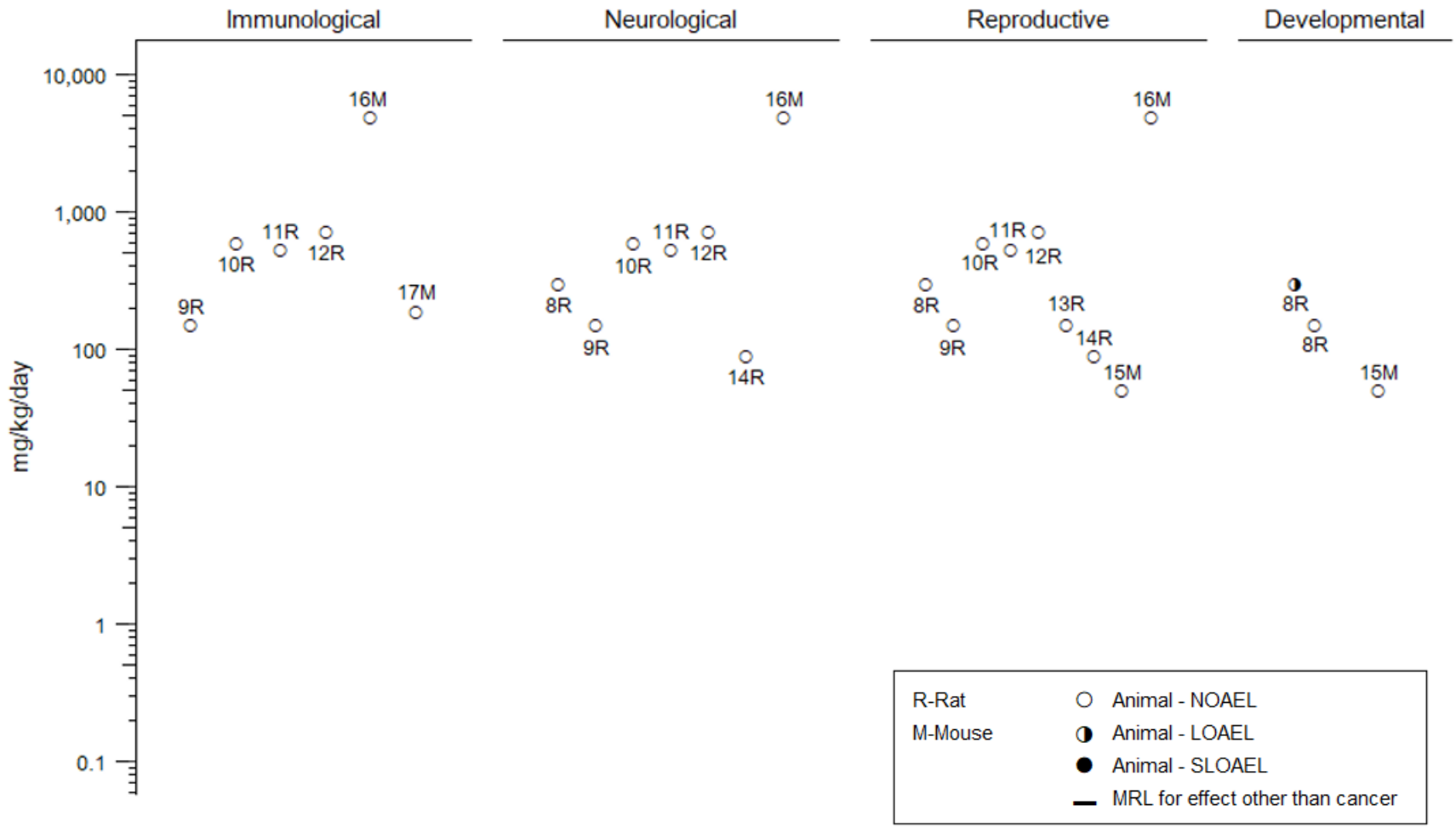
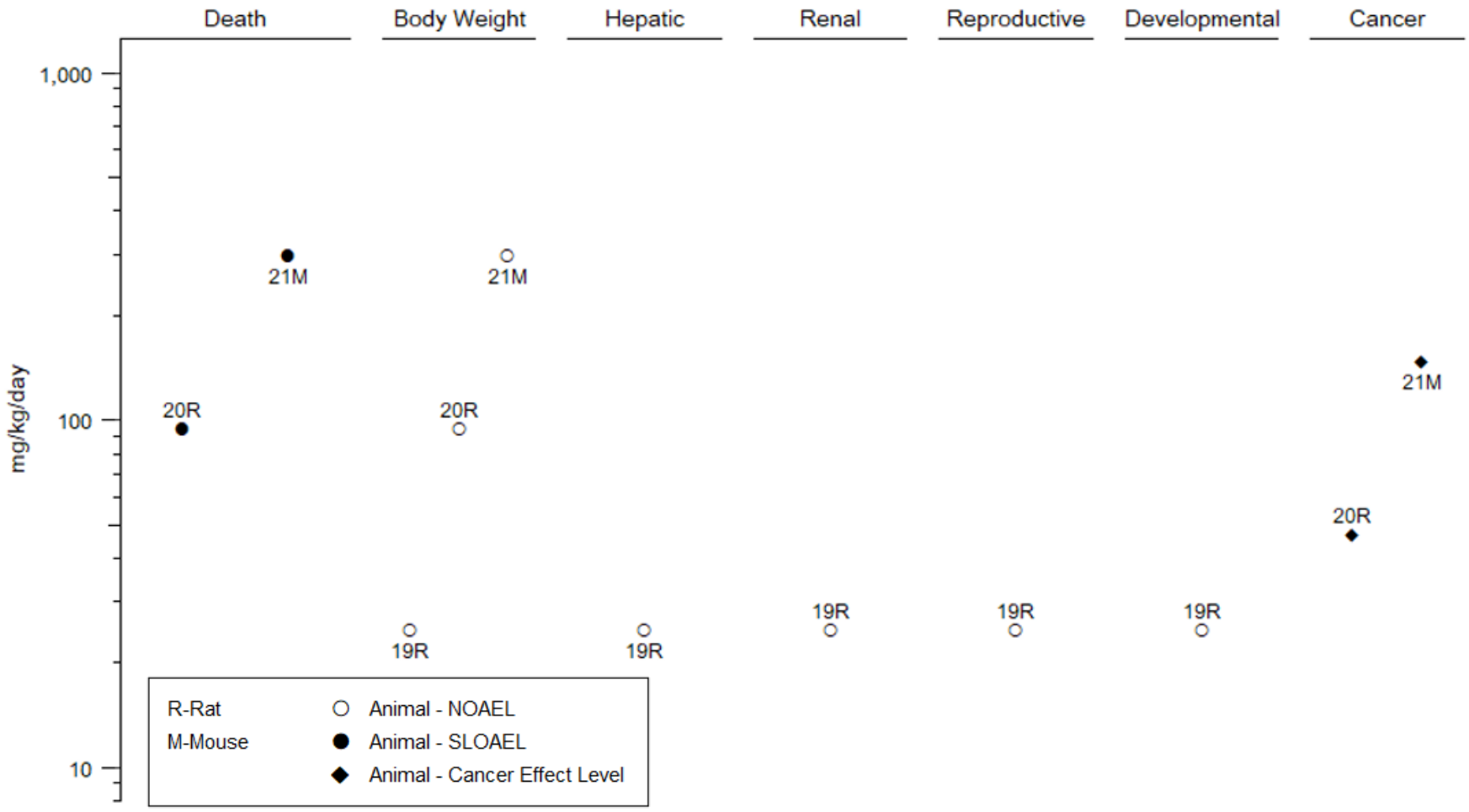


**Figure 2-3. Levels of Significant Exposure to 1,2-Dichloroethane – Oral**
Chronic (≥365 days)



## 2.2 DEATH

No studies were located regarding death in humans or animals after dermal exposure to 1,2-dichloroethane.

Several case reports show that inhalation of concentrated 1,2-dichloroethane vapor can be lethal to humans. A 51-year-old man who inhaled concentrated vapor (concentration not reported) for 30 minutes died 5 days later from cardiac arrhythmia (Nouchi et al. 1984). The vapor exposure concentration could not be determined, and it was described as a "thick vapor of dichloroethane." An autopsy revealed congestion of the lungs, degenerative changes in the myocardium, liver necrosis, renal tubular necrosis, and shrunken nerve cells in the brain. A 45-year-old female occupationally exposed to 1,2-dichloroethane in air at unknown concentrations for about 11 months was admitted to a hospital with headaches, dizziness, and visual disturbance (Liu et al. 2010). The patient died 6 months after discharge from pneumonia and respiratory failure.

Deaths in humans have occurred from ingestion of large amounts of 1,2-dichloroethane. Hueper and Smith (1935) reported a case in which a 63-year-old man accidentally swallowed approximately 2 ounces (60 mL) of 1,2-dichloroethane and died 22 hours later of circulatory failure. A 50-year-old man mistakenly ingested approximately 30 mL of 1,2-dichloroethane and died 10 hours later (Lochhead and Close 1951). A 14-year-old boy died 5 days after ingesting 15 mL of 1,2-dichloroethane (Yodaiken and Babcock 1973). A 30-year-old man ingested approximately 40 mL of 1,2-dichloroethane and died 28 hours later (Garrison and Leadingham 1954). Schönborn et al. (1970) reported a case of an 18-year-old man who became drowsy and cyanotic, and exhibited bradycardia after drinking approximately 50 mL of Marament (a pharmaceutical formulation), which was equivalent to 50 g of 1,2-dichloroethane (714 mg/kg, assuming 70 kg body weight); he died 17 hours later in a state of circulatory shock. A hospital patient accidentally ingested a "small" quantity of 1,2-dichloroethane and died 18 hours later after intensive supportive measures were taken; the immediate cause of death was not reported (Hubbs and Prusmack 1955).

In animals, acute-duration inhalation exposure to 1,2-dichloroethane also causes death. A median lethal concentration ($LC_{50}$) of 1,000 ppm was determined for an 8-hour exposure in rats; shorter exposure durations resulted in higher $LC_{50}$ values (Spencer et al. 1951). Necropsy of these rats revealed histopathological changes in the liver and kidney. Heppel et al. (1945, 1946) and Spencer et al. (1951) examined the toxic effects of inhaled 1,2-dichloroethane in a number of species. Acute, intermittent

exposure (~14 days) resulted in death in guinea pigs and rats at 400 ppm; in rabbits, mice, and dogs, death occurred at 1,500 ppm. These were the lowest exposure concentrations that produced death in animals. Gross observations at necropsy revealed liver and kidney effects ranging from increased organ weight to necrosis, pulmonary congestion, and fatty infiltration and degeneration of the myocardium (Heppel et al. 1945, 1946; Spencer et al. 1951). High mortality (10/16) was seen in rat dams exposed to 300 ppm for 7 hours/day during consecutive gestation days (GDs) 6–15 (Schlacter et al. 1979). No deaths were recorded for rats exposed to concentrations of 1,2-dichloroethane as high as 2,029 ppm for 4 hours, and as high as 155.8 ppm for 8 hours (Hotchkiss et al. 2010). Wang et al. (2014) reported 30% mortality at 296 ppm and 60% mortality at 321 ppm in female mice exposed on 3.5 hours/day for 3 days. No deaths occurred in rats exposed to up to 222 ppm for 3.5 hours/day for 10 days (Sun et al. 2016).

Intermediate-duration inhalation exposures (6–25 weeks) with a frequency of 7 hours/day, 5 days/week caused deaths in guinea pigs, rats, and mice exposed to 200 ppm; rats and rabbits exposed to 400 ppm; and dogs, cats, and monkeys exposed to 1,000 ppm (Heppel et al. 1946; Spencer et al. 1951). Necropsy of these animals showed liver, kidney, heart, and lung effects similar to those observed following acute-duration exposure. In a chronic-duration inhalation study, there was no exposure-related effect on survival in rats that were exposed to 50 ppm of 1,2-dichloroethane for 7 hours/day, 5 days/week, for 2 years (Cheever et al. 1990). Chronic-duration (2-year) inhalation exposure to 1,2-dichloroethane did not result in a significant difference in survival rates among rats and male mice exposed to concentrations as high as 160 and 90 ppm, respectively, compared to non-exposed groups (Nagano et al. 2006). Among female mice in this study, significant decreases in survival rates were seen at ≥30 ppm over 2 years; however, the deaths did not show a relationship with exposure concentrations and were attributed to malignant lymphomas unrelated to treatment.

Deaths were also observed in animals following oral exposure to 1,2-dichloroethane. An acute oral median lethal dose ($LD_{50}$) value of 680 mg/kg was reported for rats exposed by gavage (McCollister et al. 1956), but the dose levels and the time of death after administration were not reported. Munson et al. (1982) determined $LD_{50}$ values of 489 and 413 mg/kg for male and female mice, respectively for 1,2-dichloroethane administered by a single gavage dose; the mice died over a 48-hour period. Daily gavage doses of 300 mg/kg for 10–14 days caused 80–100% mortality in rats (Daniel et al. 1994; van Esch et al. 1977).

Intermediate-duration studies in animals indicate that the lethality of 1,2-dichloroethane is greater when administered by gavage than in drinking water. Death occurred in 3/5 male mice and 1/5 female mice at

251 mg/kg/day and all animals died at 398 mg/kg/day (male mice) or 631 mg/kg/day (female mice) when exposed to 1,2-dichloroethane by gavage for 6 weeks (NCI 1978). Similarly, in rats exposed by gavage for 6 or 13 weeks, doses ≥240 mg/kg/day caused deaths in all animals (Morgan et al. 1990; NTP 1991). All male rats died within 13 weeks at 240 mg/kg/day and within 3 days at 480 mg/kg/day (Morgan et al. 1990; NTP 1991). Compared with gavage administration, deaths occurred at much higher dose levels in drinking water. No deaths occurred among rats exposed to doses ≤727 mg/kg/day in drinking water for 13 weeks (Morgan et al. 1990; NTP 1991). Mice that were exposed to 1,2-dichloroethane in drinking water for 13 weeks experienced mortality only at the high dose of 4,930 mg/kg/day; mortality began to increase during the first 2 weeks of exposure, reaching 90% after 13 weeks (Morgan et al. 1990; NTP 1991).

Chronic-duration exposure to 1,2-dichloroethane by gavage reduced survival in rats and mice. Treatment for 78 weeks with 195 mg/kg/day resulted in 84% mortality in male rats compared to 50% in controls and 80% mortality in female rats, compared with 35% controls (NCI 1978). The mortality was seen as early as week 2 and became substantial after 15 weeks, whereas in controls, mortality wasn't noted until 50 weeks in males and 80 weeks in females. In mice, 72% mortality occurred in females exposed to 299 mg/kg/day by gavage for 78 weeks; mortality became evident after 10 weeks (NCI 1978).

## 2.3 BODY WEIGHT

No studies were located regarding effects on body weight in humans after oral or dermal exposure to 1,2-dichloroethane.

No studies were located regarding effects on body weight in humans after acute (duration of ≤14 days) inhalation exposure to 1,2-dichloroethane. A weight loss of 10 pounds was noted in a packing plant employee who was repeatedly exposed to unreported, but potentially high, air concentrations of 1,2-dichloroethane for 9 weeks, although the period over which the weight was lost relative to the exposure period was not specified (McNally and Fostvedt 1941).

Decreases in body weight were observed in rats acutely exposed to 296 ppm1,2-dichloroethane for 3.5 hours/day on 3 consecutive days (Jin et al. 2018a). In rats, a 7-day exposure to concentrations of 420 ppm 1,2-dichloroethane resulted in decreased body weight (Zhong et al. 2020). All rats, including controls, lost body weight after exposure to 0.0, 196.4, 607.8, and 2,029 ppm for 4 hours; while exposed animals lost more than controls and the loss was dose-related, the difference was not statistically

significant (Hotchkiss et al. 2010). Decreased body weight gain or weight loss occurred in maternal rats that were exposed to 300 or 329 ppm of 1,2-dichloroethane for 7 hours/day during gestation; these effects were not observed at 100 or 254 ppm (Payan et al. 1995; Schlacter et al. 1979). Several studies reported no changes in body weights in mice or rats acutely exposed to 1,2-dichloroethane (Spencer et al. 1951, Sun et al. 2016, Yang et al. 2021).

Intermediate-duration exposure to 1,2-dichloroethane via inhalation resulted in mixed results in body weights of mice. Mice exposed to ~173 ppm of 1,2-dichloroethane aerosol for 6 hours/day for 28 consecutive days had decreased body weight (Wang et al. 2017; Zeng et al. 2018). Zhang et al. (2017) found a mean body weight loss of 3.32 g in male mice (approximately 15% body weight loss relative to the beginning of exposure) in the 173-ppm exposure group under similar exposure conditions. However, no changes in body weight gain were caused by exposures to up to 193 ppm for 6 hours/day for 28 days in mice (Huang et al. 2020; Liang et al. 2021; Zhong et al. 2020); 200 ppm for 28–35 weeks in rats and guinea pigs (Spencer et al. 1951); 400 ppm for 33–35 weeks in rabbits (Spencer et al. 1951); 160 ppm for 104 weeks in rats (Nagano et al. 2006); and 90 ppm for 104 weeks in mice (Nagano et al. 2006). No changes in body weight gain were caused by chronic-duration exposures to 50 ppm for 2 years in rats (Cheever et al. 1990).

Acute-duration animal studies found no effects on body weight in rats administered ≤100 mg/kg/day by gavage for 10 or 14 days (Daniel et al. 1994; van Esch et al. 1977) or mice exposed to ≤49 mg/kg/day by gavage for 14 days (Munson et al. 1982). A gavage treatment in rats with 198 mg/kg/day (but not ≤158 mg/kg/day) for 14 days during pregnancy (GDs 6–20) caused a 30% reduction in maternal body weight gain (Payan et al. 1995). Reduced growth (10–30% decreases in body weight gain) has been observed in animals following intermediate- and chronic-duration oral exposures, including rats administered >90 mg/kg/day by gavage for 90 days (Daniel et al. 1994; Morgan et al. 1990; NTP 1991), rats and mice exposed to 259 and 4,210 mg/kg/day, respectively, in drinking water for 90 days (Morgan et al. 1990; NTP 1991), and mice administered 299 mg/kg/day by gavage for 78 weeks (NCI 1978). No effect on body weight was seen in rats administered up to 95 mg/kg/day by gavage for 78 weeks (NCI 1978) or up to 25 mg/kg/day for 2 years (Alumot et al. 1976).

In an intermediate-duration dermal carcinogenicity study (using transgenic mice for early detection of cancers), dorsal skin of transgenic mice was exposed to 126 mg of 1,2-dichloroethane in 200 µL of acetone, 3 times/week for 26 weeks resulting in decreased body weights in female mice beginning at

week 18 (Suguro et al. 2017). No significant changes in bodyweight were observed for male mice in the same study.

## 2.4 RESPIRATORY

Short-term exposure to concentrated 1,2-dichloroethane in air may produce adverse respiratory effects in humans. In a case report of a 51-year-old man, respiratory distress was reported 20 hours after the initial exposure to "thick vapor" of unknown concentration; autopsy revealed that the lungs were severely congested and edematous (Nouchi et al. 1984). Chronic bronchitis and a dry pharynx were reported in a packing plant employee following 5 months of repeated exposures to unreported air concentrations of 1,2-dichloroethane (McNally and Fostvedt 1941).

The respiratory effects exhibited by individuals who later died following acute-duration oral exposure to 1,2-dichloroethane included congestion, pulmonary edema (at 570 mg/kg/day), dyspnea, and bronchitis (Hubbs and Prusmack 1955; Hueper and Smith 1935; Lochhead and Close 1951; Martin et al. 1969; Yodaiken and Babcock 1973). The pulmonary edema reported in the case report by Yodaiken and Babcock (1973) may have been chemical pneumonitis due to aspiration of 1,2-dichloroethane.

Nasal tissue was the most sensitive target site following acute-duration inhalation exposure to 1,2-dichloroethane in rats. Treatment-related lesions consisting of regeneration of the olfactory mucosa were observed in rats 14 days after exposure to 196.4–2,029 ppm 1,2-dichloroethane for 4 hours (Hotchkiss et al. 2010). Exposure to ≥107.5 ppm 1,2-dichloroethane for 8 hours in rats resulted in degeneration and necrosis of the nasal olfactory epithelium (Hotchkiss et al. 2010). Nasal olfactory lesions were generally found bilaterally in symmetrical patterns in the mucosa lining the dorsal nasal meatus, nasal septum, and ethmoid turbinates; the more lateral and ventral aspects of the olfactory mucosa were not affected. In the affected sites, the nuclei of olfactory cells were slightly pyknotic and the amount of cytoplasm was decreased. Bronchoalveolar lavage performed 1 day after 1,2-dichloroethane exposure revealed no treatment-related effects on pulmonary inflammatory cells, no markers of lung injury, nor any changes in phagocytic activity of pulmonary alveolar macrophages (Hotchkiss et al. 2010).

In animals, acute-duration exposure to high concentrations of 1,2-dichloroethane was associated with pulmonary congestion. A single 7-hour exposure to 3,000 ppm of 1,2-dichloroethane resulted in death with accompanying pulmonary congestion in mice, rats, rabbits, and guinea pigs (Heppel et al. 1945).

Lower concentrations in single 7-hour exposures of 1,2-dichloroethane did not produce lung lesions. However, a series of six 7-hour exposures from the same study at 1,500 ppm produced death in mice with similar pulmonary congestion.

No pulmonary lesions were found by histological examination in rats and mice exposed to 100 ppm for 7 hours/day, 5 days/week for 4–15 weeks, rabbits and monkeys exposed to 200 ppm for 25 weeks, or dogs exposed to 400 ppm for 8 months (Heppel et al. 1946). A limited number of rabbits, monkeys, and dogs were exposed, and not all of these animals were histologically examined. Similarly, there were no histopathological changes in the lung following exposures to 200 ppm for 28–35 weeks in rats and guinea pigs or 400 ppm for 33–35 weeks in rabbits (Spencer et al. 1951). Chronic-duration exposure to 50 ppm of 1,2-dichloroethane for 7 hours/day, 5 days/week for 2 years caused no histological alterations in the respiratory tract (including nasal cavity and mucous membrane, lung, trachea, and larynx) of rats (Cheever et al. 1990).

In an acute-duration study, male rats were administered a single gavage dose of 136 mg/kg of 1,2-dichloroethane and bronchioalveolar lavage fluid (BALF) was examined on day 1, 5, 15, and 30 days after administration (Salovsky et al. 2002). Findings included increased lactate dehydrogenase, alkaline phosphatase, and acid phosphatase in the BALF on day 1 post treatment. Histological examination of the lung showed pneumonitis characterized by congestion, edema, and interstitial inflammatory changes on days 1 and 5 post treatment, with decreasing severity on day 15 or 30 post treatment. Additionally, increased lipid peroxidation (malondialdehyde) and elevated levels of key antioxidant enzymes (superoxide dismutase, catalase, and glutathione peroxidase) in lung tissue were seen at days 1 and 5 after exposure (Salovsky et al. 2002). Gross and histological examinations of rats treated with 100 mg/kg/day via gavage for 10 or 14 days showed no effects in the respiratory tract (Daniel et al. 1994; van Esch et al. 1977). Another study in mice found no changes in lung weight or gross appearance following exposure to 49 mg/kg/day by gavage for 14 days (Munson et al. 1982).

Gross and histological examinations of rats treated with 480 mg/kg/day via gavage for 90 days showed no effects in the respiratory tract (Daniel et al. 1994; Morgan et al. 1990; NTP 1991 van Esch et al. 1977). Similarly, no histopathological changes in the respiratory tract were found in rats and mice that ingested 1,2-dichloroethane in the drinking water at doses of 492 and 4,210 mg/kg/day, respectively, for 90 days (Morgan et al. 1990; NTP 1991). The histological examinations performed by NTP (1991) included the nasal cavity and turbinates in addition to the lungs and bronchi. Another study in mice found no changes in lung weight or gross appearance following administration of 189 mg/kg/day in drinking water for

90 days (Munson et al. 1982), but these results are limited by lack of histological examinations. Gross and histological examinations of rats and mice treated with 95 and 299 mg/kg/day, respectively, for 78 weeks showed no effects in the respiratory tract (NCI 1978).

In a shortened carcinogenicity study in RasH2 transgenic mice, dermal exposure to 1,2-dichloroethane in acetone for 26-weeks resulted in increased lung weights and histopathological changes in the lung characterized by bronchioloalveolar hyperplasia and discolored spots/areas or nodules in the lungs in female mice, but not male mice (Suguro et al. 2017).

## 2.5 CARDIOVASCULAR

No studies were located regarding effects on the cardiovascular system in humans and animals after dermal exposure to 1,2-dichloroethane.

Autopsy findings in a 51-year-old man who inhaled a “thick vapor” of unknown concentration of 1,2-dichloroethane for 30 minutes included diffuse degenerative changes of the myocardium such as fragmentation, loss of nuclei of myocardial fibers, and interstitial edema (Nouchi et al. 1984); death was attributed to cardiac arrhythmia. However, since Nouchi et al. (1984) did not report on the medical and behavioral history of the individual, data were insufficient to conclude that these cardiac effects were due exclusively to 1,2-dichloroethane. In occupational studies, blood pressure was normal in one shoe-making factory employee exposed to unreported air concentrations of 1,2-dichloroethane over 6 years and two packing plant employees exposed to unreported air concentrations of 1,2-dichloroethane for 2- or 5-month periods (Chen et al. 2015; McNally and Fostvedt 1941).

Clinical investigation of patients who died following acute ingestion of 1,2-dichloroethane determined that cardiovascular insufficiency and hemorrhage were major factors contributing to death (Garrison and Leadingham 1954; Hueper and Smith 1935; Martin et al. 1969; Schönborn et al. 1970). Numerous surficial petechial hemorrhages of the heart were observed at autopsy in a man who died from ingesting a “small” quantity of 1,2-dichloroethane (Hubbs and Prusmack 1955).

Cardiac effects have been reported in animals exposed by inhalation to 1,2-dichloroethane. Acute lethal concentrations produced myocarditis in rats, dogs, and monkeys (Heppel et al. 1946). Guinea pigs died following exposure to 200 ppm for 25 weeks and had fatty infiltration and degeneration of the heart (Heppel et al. 1946). Among animals that survived intermediate-duration exposure to 1,2-dichloroethane,

cardiac changes were observed only in monkeys. Fat droplets were found in the myocardium of two of two monkeys exposed to 200 ppm for 7 hours/day, 5 days/week for 25 weeks; no control animals were used (Heppel et al. 1946). No cardiovascular lesions were seen upon gross or microscopic examination in rats and mice exposed to 100 ppm for 4–15 weeks, in rabbits exposed to 200 ppm for 25 weeks, or in dogs exposed to 400 ppm for 8 months; all at a frequency of 7 hours/day, 5 days/week (Heppel et al. 1946). However, only two to six rabbits and three dogs per exposure level were tested, and histopathology was conducted on only a subset of animals. Similarly, there were no histopathological changes in the heart following exposures to 200 ppm for 28–35 weeks in rats and guinea pigs, or 400 ppm for 33–35 weeks in rabbits (Spencer et al. 1951). In a chronic-duration study, exposure to 50 ppm of 1,2-dichloroethane for 2 years failed to produce cardiovascular lesions in rats (Cheever et al. 1990).

Cardiovascular histopathological effects were not found in animals orally exposed to 1,2-dichloroethane, even at lethal doses. Histological examinations showed no cardiovascular effects following gavage exposure in rats treated with ≤100 mg/kg/day for 10 days (Daniel et al. 1994), rats treated with 480 mg/kg/day for 90 days (Daniel et al. 1994; Morgan et al. 1990; NTP 1991; van Esch et al. 1977), or rats and mice treated with 95 and 299 mg/kg/day, respectively, for 78 weeks (NCI 1978). Similarly, no histopathological changes in the heart were found in rats and mice that ingested 1,2-dichloroethane in the drinking water at doses of 492 and 4,210 mg/kg/day, respectively, for 90 days (Morgan et al. 1990; NTP 1991).

## 2.6 HEMATOLOGICAL

No studies were located regarding hematological effects in humans and animals after dermal exposure to 1,2-dichloroethane.

Transient leukocytosis was reported 5 days after a single 4-hour occupational exposure in three knitting factory workers who wrung out yarn that had soaked in an open vat of 1,2-dichloroethane (Wirtschafter and Schwartz 1939). McNally and Fostvedt (1941) indicated that hematological parameters (hemoglobin concentration, erythrocyte count, leukocyte count, and differential counts) in packing plant workers were not adversely affected following repeated occupational exposures to unreported (but potentially occasionally high) air concentrations of 1,2-dichloroethane over 2- or 5-month periods. Chen et al. (2015) noted increased white blood cell counts in the cerebrospinal fluid of factory workers occupationally exposed to unknown concentrations of 1,2-dichloroethane for at least 10 months.

Adverse hematological effects, such as increased prothrombin time and reduction in blood clotting factors, were observed in 18- and 57-year-old men who had ingested approximately 40 mL (~570 mg/kg) of 1,2-dichloroethane (Martin et al. 1969; Schönborn et al. 1970) and in a 14-year-old boy who had ingested approximately 15 mL (~360 mg/kg, using an approximate body weight of 51.3 kg) of 1,2-dichloroethane (Yodaiken and Babcock 1973). The alterations in coagulation parameters described above may have been associated to some degree with liver dysfunction as the liver is the site of production of most of the plasma coagulant factors (such as fibrinogen, prothrombin, and factors V, VII, IX, and X). Hepatic disorders may result in abnormalities in coagulation tests; Martin et al. (1969) and Yodaiken and Babcock (1973) both observed hepatic damage, including atrophy, damaged hepatocytes, and necrosis.

Few studies provided any indication of hematological effects in animals exposed by inhalation. Increased plasma prothrombin clotting time was reported in two monkeys exposed to 400 ppm 1,2-dichloroethane 7 hours/day for 8–12 days (Spencer et al. 1951). This study was limited because only two monkeys were examined, and one moribund monkey was necropsied after eight exposures. Intermediate-duration studies of 1,2-dichloroethane found no hematological changes in rats, guinea pigs, rabbits, or dogs following exposures to 200–400 ppm for 7 hours/day, 5 days/week for 32–35 weeks (Heppel et al. 1946; Spencer et al. 1951). Chronic-duration exposure to 50 ppm for 2 years did not produce indications of blood cell changes in rats as detectable by histological examination of the spleen and bone marrow (Cheever et al. 1990); blood parameters were not monitored, limiting the usefulness of the study for assessing hematological effects. No exposure-related hematological changes were found in mice or rats exposed to concentrations as high as 90 or 160 ppm, respectively of 1,2-dichloroethane for 2 years (Nagano et al. 2006). No further information on examined hematological parameters was given.

Similar hematological effects have not been reported in animals following oral exposure. However, a 30% decrease in leukocytes was reported in mice given daily gavage doses of 49 mg/kg of 1,2-dichloroethane for 2 weeks (Munson et al. 1982). This effect may have had some relation to immunosuppressive effects reported in the same study. In rats, hematological parameters were unaffected by exposure to 100 mg/kg/day by gavage for 10 or 14 days (Daniel et al. 1994; van Esch et al. 1977) or to 480 mg/kg/day by gavage for 90 days (Daniel et al. 1994; Morgan et al. 1990; NTP 1991; van Esch et al. 1977). Mice that were administered up to 189 mg/kg/day in the drinking water for 90 days did not exhibit any differences from control animals with regard to hemoglobin, hematocrit, red or white blood cell counts, or platelets (Munson et al. 1982). Similarly, there were no hematological changes in mice exposed to 4,210 mg/kg/day in the drinking water for up to 13 weeks (Morgan et al. 1990; NTP 1991). To explain

the apparent contradiction in their results, Munson et al. (1982) suggested that more 1,2-dichloroethane may enter systemic circulation when the animals are given a concentrated solution in bolus form, than when they are allowed to drink water containing lower concentrations of 1,2-dichloroethane. They also suggested that, during the longer exposure time, 1,2-dichloroethane might induce its own metabolism and therefore be removed from the blood and other organs more rapidly. No hematological changes were seen in rats exposed to 492 mg/kg/day in drinking water for 90 days (Morgan et al. 1990; NTP 1991).

## 2.7 MUSCULOSKELETAL

No studies were located regarding musculoskeletal effects in humans after oral or dermal exposure to 1,2-dichloroethane. No studies were located regarding musculoskeletal effects in animals after dermal exposure to 1,2-dichloroethane.

Limb weakness was one of several reported symptoms in a woman occupationally exposed by inhalation to an unknown concentration of 1,2-dichloroethane for 3 months (Dang et al. 2019). The symptom resolved following treatment with steroids and/or mannitol and a 6-month follow-up. No further information was found to elucidate the musculoskeletal effects of 1,2-dichloroethane on humans.

There is no indication that ingested 1,2-dichloroethane produces musculoskeletal effects in animals. Histological examination of skeletal muscle showed no effects in rats that were exposed to 50 ppm of 1,2-dichloroethane for 7 hours/day, 5 days/week for 2 years (Cheever et al. 1990).

Histological changes in muscle and bone were not observed in rats administered 100 mg/kg/day by gavage for 10 days (Daniel et al. 1994), in rats administered 480 mg/kg/day by gavage for 90 days (Daniel et al. 1994; Morgan et al. 1990; NTP 1991; van Esch et al. 1977), or in rats and mice exposed at 492 and 4,210 mg/kg/day, respectively, in drinking water for 90 days (Morgan et al. 1990; NTP 1991).

## 2.8 HEPATIC

No studies were located regarding hepatic effects in humans or animals after dermal exposure to 1,2-dichloroethane.

The liver may be a target of 1,2-dichloroethane toxicity following inhalation exposure in humans. In a case report, Nouchi et al. (1984) found an enlarged liver, high serum levels of lactate and ammonia, and

increased serum levels of AST and ALT in a man exposed to concentrated 1,2-dichloroethane vapors for 30 minutes. The man died 5 days after exposure and postmortem histopathological examination of the liver revealed extensive centrilobular necrosis and the presence of very few vacuolated cells, although it is not known whether this condition was preexisting. Workplace exposure to mixed 1,2-dichloroethane and vinyl chloride (area sampling levels up to 5.3 and 23.5 ppm, respectively, and personal sampling levels up to 334 and 6.2 ppm, respectively) in a group of 251 male workers at a vinyl chloride manufacturing facility was associated with an exposure-related increase in the prevalence of abnormal levels of ALT (Cheng et al. 1999). The contribution of 1,2-dichloroethane to the observed effect is uncertain, especially given vinyl chloride's well-established hepatotoxicity. Increased serum levels of ALT were observed in three workers occupationally exposed to unknown air concentrations of 1,2-dichloroethane when they presented for medical attention following onset of symptoms (Chen et al. 2015).

1,2-Dichloroethane has been implicated as a hepatotoxicant in humans after acute oral poisoning. A case of acute ingestion by a 25-year-old man resulted in hepatic damage (not specified) with cirrhosis and coagulopathy syndrome (Przezdziak and Bakula 1975). Following treatment with heparin, the patient was discharged after 87 days. Ingestion of 570 mg/kg/day of 1,2-dichloroethane resulted in severe hepatocellular damage and liver atrophy (Martin et al. 1969), and necrosis (Schönborn et al. 1970), although the degree to which these conditions were preexisting is unknown. No gross changes were reported in the liver of a man who died from ingesting a "small" quantity of 1,2-dichloroethane, but hepatocellular fatty vacuolation and inflammation, "engorged" hepatic vasculature, and mild lymphocytic infiltration of portal spaces were observed microscopically (Hubbs and Prusmack 1955).

In animals, acute-duration inhalation exposure to 1,2-dichloroethane leads to liver damage. Serum levels of enzyme indicators of hepatic damage (e.g., AST, ALT, sorbitol dehydrogenase [SDH]) were elevated in rats exposed to 850 ppm for 4 hours (Brondeau et al. 1983). No effect was observed at 618 ppm. No histopathology was evaluated in this study. In another 4-hour inhalation study in rats, decreased liver to body weight ratios were seen in male rats exposed to 2,029 ppm, yet increased liver weights were seen in female rats exposed to 607.8 and 2,029 ppm (Hotchkiss et al. 2010). Three males and five females exposed to 2,029 ppm had macrophage aggregation with necrotic hepatocytes in the centrilobular region. No hepatic effects were observed at concentrations <607.8 ppm. Serum chemistry was not evaluated in the study. Rats exposed to 577 ppm 1,2-dichloroethane 6 hours/day for 5 days had increased liver to body weight ratio, increased serum levels of ALT, AST, and cholesterol, and ultrastructural changes in the liver (Pang et al. 2018). Monkeys exposed to 400 ppm for 8–12 days had marked fatty degeneration of the liver (Spencer et al. 1951). Slight parenchymous degradation of the liver was found in guinea pigs

exposed to 400 ppm for up to 14 days but a limited number of animals were tested (Spencer et al. 1951). No adverse effect was seen on serum levels of AST or ALT in mice exposed to up to 222 ppm 1,2-dichloroethane for 3.5 hours/day for 10 days (Sun et al. 2016).

In an intermediate-duration study, Wang et al. (2017) observed increased serum levels of AST and ALT, increased liver to body weight ratio, and increased hepatic fatty acids and triglycerides in mice exposed to 86 and 173 ppm of 1,2-dichloroethane by inhalation for 6 hours/day for 28 days. Longer-term exposure to 1,2-dichloroethane vapor produced hepatic effects in guinea pigs, dogs, and monkeys. Guinea pigs exposed to 100 ppm of 1,2-dichloroethane for 7 hours/day, 5 days/week for 246 days exhibited increased liver weight and hepatic fatty infiltration (Spencer et al. 1951). Monkeys exposed to 200 ppm for 25 weeks and dogs exposed to 400 ppm for 8 months also exhibited fatty degeneration of the liver (Heppel et al. 1946). However, no hepatic effects were observed upon gross and microscopic examination in mice, rats, or rabbits exposed to concentrations of 100–400 ppm for 7 hours/day, 5 days/week for 4–30 weeks (Heppel et al. 1946; Spencer et al. 1951). There were several deficiencies in the studies by Heppel et al. (1946) and Spencer et al. (1951); many of the tests used a limited number of animals, and no control monkeys were examined by Heppel et al. (1946). No liver effects were seen in parental rats exposed to concentrations up to 150 ppm in a one-generation reproductive toxicity study (Rao et al. 1980).

In one chronic-duration inhalation study of 1,2-dichloroethane, no histological changes were found in the liver, bile duct, or any other tissues of rats exposed to 50 ppm for 7 hours/day, 5 days/week for 2 years (Cheever et al. 1990). Nagano et al. (2006) found no changes in liver weights and no nonneoplastic hepatic lesions in rats exposed to up to 160 ppm or in mice exposed to up to 10 ppm; however, liver tumors were observed in mice at 30 ppm.

Studies in orally exposed animals have not found serious liver effects. Rats administered single gavage doses (80 mg/kg) of 1,2-dichloroethane showed no effects on liver triglyceride, SDH, or ALT levels (Aragno et al. 1992; Danni et al. 1992). In another acute-duration study in rats, a single gavage dose of 628 mg/kg 1,2-dichloroethane induced liver toxicity characterized by increased serum levels of ALT, AST, and lactate dehydrogenase (LDH) (<2-fold) and moderate hepatic steatosis observed microscopically (Cottalasso et al. 2002). Daniel et al. (1994) found no significant hepatic effects in rats administered 100 mg/kg/day by gavage for 10 days. No changes in liver weights were observed in mice exposed to 49 mg/kg/day by gavage for 14 days (Munson et al. 1982); histology was not evaluated. Van Esch et al. (1977) reported fatty degeneration in the livers of rats given 300 mg/kg/day 1,2-dichloroethane

by gavage in a 14-day study; however, all animals receiving this dose died prematurely. Hepatic biochemical changes consisting of a 15% increase in fat accumulation and increases in total triglycerides (indicative of liver damage) were observed in rats fed 80 mg/kg/day of 1,2-dichloroethane in the diet for 5–7 weeks (Alumot et al. 1976). Liver weights were unchanged and histological examinations were not performed. No liver biochemistry changes occurred at 30 mg/kg/day. This study had several significant limitations, including unknown purity of the compound, unclear concentrations of 1,2-dichloroethane in the mash diet and dose consumed, and absence of gross or histological examination of organs or tissues. No liver biochemistry changes occurred at 30 mg/kg/day. Increased liver weight with no hepatic histological alterations occurred in intermediate-duration studies conducted by NTP (1991) in rats and mice. Following a 13-week gavage exposure in rats, both liver weight and liver-to-body-weight ratio were elevated in a dose-related fashion with significance at doses ≥18 mg/kg/day in females and at 120 mg/kg/day in males (liver weight was not measured in higher-dose animals because of mortality). Following a 13-week drinking water exposure, liver-to-body-weight ratio was significantly elevated at doses ranging from 60 to 518 mg/kg/day in Sprague-Dawley males without corresponding decreases in body weight; in mice, liver-to-body-weight ratio was significantly elevated at 249–4,210 mg/kg/day in males and 448–4926 mg/kg/day in females without corresponding decreases in body weight. Similarly, relative liver weights were increased with no accompanying histopathological changes in rats administered 150 mg/kg/day by gavage for 90 days (Daniel et al. 1994; van Esch et al. 1977). In the absence of histopathological or biochemical changes in the liver, the changes in liver weight that are observed in the NTP (1991), Daniel et al. (1994), and van Esch et al. (1977) studies are not considered to be adverse effects. No changes in liver weights were observed in mice exposed to 189 mg/kg/day in drinking water for 90 days (Munson et al. 1982); histology was not evaluated.

No histological changes were observed in the liver of rats and mice that were administered 95 and 299 mg/kg/day, respectively, by gavage for 78 weeks (NCI 1978). Chronic-duration exposure of rats to 25 mg/kg/day in food for 2 years did not result in abnormalities in liver function, as measured by transaminases and cholesterol values (Alumot et al. 1976); however, the animals were not evaluated grossly or microscopically for liver lesions. In the Alumot et al. (1976) study, there also were reported losses of 1,2-dichloroethane due to volatilization from the food; consequently, actual exposures would probably have been less than nominal exposures.

***Mechanisms.*** In the liver, 1,2-dichloroethane may induce its own metabolism. As discussed further in Section 3.1.3, 1,2-dichloroethane is metabolized primarily by microsomal cytochrome P450 (CYP) 2E1 to the reactive 2-chloroacetaldehyde intermediate. Mice exposed to ~111 and ~222 ppm of

1,2-dichloroethane by inhalation for 3.5 hours/day for 10 days had significantly increased microsomal CYP2E1 protein expression and activity as well as changes in hepatic markers of oxidative stress; malondialdehyde (MDA) levels were increased, and superoxide dismutase (SOD) activities and nonprotein sulfhydryl levels were decreased (Sun et al. 2016). Increased hepatic CYP2E1 messenger ribonucleic acid (mRNA) and protein expression were also observed in mice exposed to ~86 and ~173 ppm for 6 hours/day for 28 days (Wang et al. 2017). Given these findings, it is possible that an initial exposure may appear more toxic than longer-term exposures at the same level when microsomal CYP enzymes are induced (due to increased formation of reactive metabolites). In addition, since glutathione conjugation is a primary metabolic pathway for 1,2-dichloroethane, depletion of glutathione may also contribute to hepatic toxicity (Jean et al. 1992).

## 2.9 RENAL

No studies were located regarding renal effects in humans after dermal exposure to 1,2-dichloroethane.

1,2-Dichloroethane is acutely nephrotoxic in humans following inhalation exposure. In the case report reported by Nouchi et al. (1984), a man who inhaled 1,2-dichloroethane fumes for 30 minutes eventually exhibited kidney failure, as part of general organ failure, followed by cardiac arrest and death. Microscopic examination revealed acute tubular necrosis.

Acute renal damage resulting from ingestion of 1,2-dichloroethane has been observed in humans. Ingestion of 1,2-dichloroethane resulted in renal bleeding and hyperemia in an 18-year-old man who consumed a single dose of 714 mg/kg (Schönborn et al. 1970), and in a male hospital patient who died after accidentally ingesting a “small” quantity (Hubbs and Prusmack 1955). Microscopic examination of the kidney at autopsy in the latter case showed swelling, vacuolation, degeneration of the renal tubule epithelial cells, sloughing of the glomerular capsular epithelium, and nearly complete loss of the bladder epithelium (Hubbs and Prusmack 1955). In one case report, renal damage that resulted from an unknown oral dose of 1,2-dichloroethane ingested by a 25-year-old man was not considered severe or permanent, and the patient fully recovered (Przezdziak and Bakula 1975). However, individuals who died following ingestion of an estimated 15–30 mL of 1,2-dichloroethane had severe kidney damage, primarily in the form of diffuse renal necrosis (Hueper and Smith 1935; Lochhead and Close 1951; Yodaiken and Babcock 1973).

Acute-duration inhalation exposure to 1,2-dichloroethane produced renal effects in animals. An increase in mean absolute kidney weight was observed in rats exposed to 2,029 ppm of 1,2-dichloroethane vapor for 4 hours (Hotchkiss et al. 2010). Mice of both sexes had slightly increased basophilia of the renal tubular epithelium; female mice also showed degeneration with individual cell necrosis of the outer zone (outer stripe) of the medulla of the kidney. No renal effects were observed in rats from inhalation of 1,2-dichloroethane vapor at concentrations of 607.8 for 4 hours or 155.8 ppm for 8 hours (Hotchkiss et al. 2010). Cloudy swelling of the renal tubular epithelium and increased kidney weight were reported in guinea pigs, and degeneration of the tubular epithelium was reported in monkeys following exposure to 400 ppm for 7 hours/day for 8–12 days (Spencer et al. 1951); no renal effects were noted at 100 ppm.

Kidney lesions have also been reported following longer-term inhalation exposure of animals to 1,2-dichloroethane. Dogs exposed to 400 ppm for 7 hours/day, 5 days/week for 8 months exhibited fatty changes in the kidney (Heppel et al. 1946). In guinea pigs, degeneration of the kidney was observed, but only at lethal concentrations (Heppel et al. 1946). Renal effects were not detected in rats, mice, guinea pigs, or rabbits exposed to 100–400 ppm of 1,2-dichloroethane for 4–30 weeks (Heppel et al. 1946; Rao et al. 1980; Spencer et al. 1951). These studies had limited numbers of animals and histopathology evaluations. In a chronic-duration study, no histopathological changes developed in the kidneys of rats exposed to 50 ppm of 1,2-dichloroethane for 7 hours/day, 5 days/week for 2 years (Cheever et al. 1990). No nonneoplastic renal changes were observed in rats exposed to 160 ppm or in mice exposed to 90 ppm (Nagano et al. 2006).

Acute-duration (10–14 days) gavage administration of up to 100 mg/kg/day did not result in treatment-related changes in kidney weight or in the incidence of gross or histopathological changes in the kidney in rats (Daniel et al. 1994; van Esch et al. 1977). There were no changes in kidney weight in mice after administration of 49 mg/kg/day by gavage for 14 days (Munson et al. 1982).

Renal effects reported in animals following oral administration include increases in kidney weight and minimal-to-moderate histopathological changes after longer-term exposures. Relative kidney weights were increased without altered histology in rats that were treated with 75–90 mg/kg/day by gavage for 90 days (Daniel et al. 1994; van Esch et al. 1977). In a 13-week gavage study in F344 rats, NTP (1991) found dose-related increases in kidney weight and kidney-to-body-weight ratio at 30–120 mg/kg/day in males (high mortality at 150 mg/kg/day precluded kidney weight measurements) and 75–150 mg/kg/day in females. No effects on the kidneys were observed in Sprague-Dawley or Osborne-Mendel rats in the same study. Consumption of 1,2-dichloroethane in the drinking water for 13 weeks caused significant

dose-related increases in kidney weight and kidney-to-body-weight ratio as well as renal tubule regeneration in female rats at 102 mg/kg/day (Morgan et al. 1990; NTP 1991). Increased incidences of tubular regeneration were observed in male mice at 2710 mg/kg/day, indicative of previous tubular injury with subsequent repair. More severe renal effects including karyomegaly, dilation, protein casts, and mineralization occurred in male mice at 4,210 mg/kg/day. In another study in which male mice were administered 189 mg/kg/day in drinking water for 90 days, no changes in kidney weight were observed but histopathology analysis was not performed (Munson et al. 1982).

Chronic-duration oral studies in animals failed to find evidence of kidney damage produced by 1,2-dichloroethane. No histological changes were observed in the kidneys of rats and mice that were administered 95 and 299 mg/kg/day, respectively, by gavage for 78 weeks (NCI 1978). The discrepancy between the negative results of this bioassay and the finding of kidney effects in the NTP (1991) 13-week study may be related to animal strain: NTP (1991) found renal changes in F344/N rats, whereas NCI (1978) tested Osborne-Mendel rats; tests of Osborne-Mendel and Sprague-Dawley rats by NTP (1991) were also negative. While kidney histology was not evaluated, kidney function, as measured by changes in serum levels of urea and uric acid, was unchanged in rats exposed to 25 mg/kg/day in food for 2 years (Alumot et al. 1976).

A single intermediate-duration study (a short-term carcinogenicity study using RasH2 transgenic mice reported renal effects after dermal exposure to 1,2-dichloroethane. Following application of 126 mg of 1,2-dichloroethane (dissolved in 200 µL acetone) to dorsal skin for 26 weeks, mice of both sexes had mild distal tubular karyomegaly, and female mice also showed tubular degeneration (Suguro et al. 2017).

## 2.10 DERMAL

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

The skin does not appear to be a target of 1,2-dichloroethane exposure by inhalation or oral routes. Histological examinations showed no changes in the skin of rats exposed by inhalation to 50 ppm of 1,2-dichloroethane for 2 years (Cheever et al. 1990). No microscopic changes were seen in the skin of rats administered 100 mg/kg/day by gavage for 14 days (Daniel et al. 1994), in rats administered 480 mg/kg/day by gavage for 90 days (Daniel et al. 1994; Morgan et al. 1990; NTP 1991; van Esch et al.

1977), or in rats and mice exposed to 492 and 4,210 mg/kg/day, respectively, in drinking water for 90 days (Morgan et al. 1990; NTP 1991).

In guinea pigs, dermal application of unspecified amounts of liquid 1,2-dichloroethane under a cover slip for 4 hours resulted in skin changes including karyopyknosis (shrinkage of cell nuclei), perinuclear edema, spongiosis, and junctional separation (Kronevi et al. 1981); however, only one dose was tested, and no control data were presented.

## 2.11 OCULAR

No studies were located regarding ocular effects in humans after oral or dermal exposure to 1,2-dichloroethane.

One man exposed in the workplace by inhalation to an unknown concentration of 1,2-dichloroethane for 1 year reported symptoms of blurred vision along with neurological symptoms (Dang et al. 2019). Treatment with steroids and/or mannitol and 1-year follow-up resolved all symptoms. The patient's blurred vision was thought to be related to encephalopathy brought on by acute-duration 1,2-dichloroethane exposure. No further information was found regarding ocular effects of 1,2-dichloroethane on humans.

Studies in animals reported direct-contact ocular effects following exposure to 1,2-dichloroethane as a vapor in the air. Dogs exposed to 1,500 ppm 1,2-dichloroethane as a vapor for 7 hours/day for 6 days developed corneal opacity (Heppel et al. 1945). Corneal opacity was not reported in other similarly exposed species studied by Heppel et al. (1945, 1946); however, lacrimation was reported in guinea pigs exposed to 1,500 ppm of 1,2-dichloroethane vapor for 4 days (Heppel et al. 1945). In a chronic-duration study, rats that were exposed to 50 ppm of 1,2-dichloroethane for 7 hours/day, 5 days/week for 2 years had no histological changes in the eyes (Cheever et al. 1990).

In rats that were treated with up to150 mg/kg/day of 1,2-dichloroethane by gavage in a 90-day study, ophthalmoscopic examinations, performed prior to treatment and during the last week of the study, showed no effects (Daniel et al. 1994). Other 90-day gavage studies similarly found no gross ocular changes in the eyes of rats treated with 480 mg/kg/day by gavage, or in rats and mice exposed to 492 and 4,210 mg/kg/day, respectively, in drinking water (Morgan et al. 1990; NTP 1991).

## 2.12 GASTROINTESTINAL

No studies were located regarding effects on the gastrointestinal system in humans or animals after dermal exposure to 1,2-dichloroethane.

Vomiting has been reported following occupational exposures to 1,2-dichloroethane (Liu et al. 2010; McNally and Fostvedt 1941; Nouchi et al. 1984; Wirtschafter and Schwartz 1939; Zhan et al. 2011; Zhou et al. 2015). A 51-year-old man who inhaled a thick vapor of 1,2-dichloroethane for 30 minutes vomited periodically following exposure and died 5 days later (Nouchi et al. 1984). Nausea and vomiting were reported following a single 4-hour occupational exposure in three knitting factory workers who wrung out yarn that had soaked in an open vat of 1,2-dichloroethane (Wirtschafter and Schwartz 1939). Two packing plant employees who were repeatedly exposed to unreported air concentrations of 1,2-dichloroethane on the job for 2–5 months experienced periods of epigastric pain, nausea, and vomiting (McNally and Fostvedt 1941). Nausea and vomiting were reported by factory workers (aged 20–43 years) occupationally exposed to unknown concentrations of 1,2-dichloroethane for durations ranging from 2 months to 1 year who sought medical attention following the onset of symptoms; one female worker reported repeated vomiting and nausea for 2 weeks prior to seeking medical attention (Liu et al. 2010; Zhan et al. 2011; Zhou et al. 2015).

Gastrointestinal symptoms have been observed in humans prior to death following oral exposure to 570 or 714 mg/kg/day of 1,2-dichloroethane. These symptoms included nausea, vomiting, and diarrhea (Hueper and Smith 1935; Lochhead and Close 1951; Martin et al. 1969; Schönborn et al. 1970; Yodaiken and Babcock 1973). Hemorrhagic colitis, hemorrhagic gastritis, and focal hemorrhages of the gastrointestinal tract have also been reported upon autopsy (Garrison and Leadingham 1954; Hubbs and Prusmack 1955; Hueper and Smith 1935; Lochhead and Close 1951; Martin et al. 1969; Schönborn et al. 1970).

In animal studies, gastrointestinal effects, including emesis and passing of red watery stools, preceded death in dogs exposed to 1,500 ppm of 1,2-dichloroethane for 7 hours/day for 6 days (Heppel et al. 1945). Congestion of the gastrointestinal tract was noted in these animals at necropsy. Gastrointestinal lesions were not found in rats exposed to 50 ppm of 1,2-dichloroethane for 2 years (Cheever et al. 1990).

Gastrointestinal lesions have also been found in animals given bolus doses of 1,2-dichloroethane. Forestomach lesions consisting of minimal mucosal and submucosal inflammation developed in rats given gavage doses of 100 mg/kg/day for 10 days (Daniel et al. 1994). Mild hyperplasia and

inflammation of the forestomach were noted in rats administered 240 mg/kg/day for 13 weeks (Morgan et al. 1990; NTP 1991). Similar lesions were not found in rats exposed to corresponding doses (492 mg/kg/day) in the drinking water for 13 weeks or mice exposed to much higher doses (4,210 mg/kg/day) in the drinking water for 13 weeks (Morgan et al. 1990; NTP 1991). No changes in histopathology in the stomach or intestines were observed in rats after intermittent gavage doses of up to 90 mg/kg/day over a 90-day period (van Esch et al. 1977). In rats given 47 mg/kg/day via gavage for 78 weeks, acanthosis and hyperkeratosis of the forestomach occurred (NCI 1978). There were no increased incidences of non-neoplastic lesions of the stomach, large intestine, and colon in mice administered up to 299 mg/kg/day by gavage for 78 weeks (NCI 1978). The gastrointestinal lesions observed in humans and animals ingesting bolus doses are probably produced by direct contact with concentrated 1,2-dichloroethane; the concentration in drinking water (8,000 mg/L) tested by NTP (1991), although close to the solubility limit for this chemical (9,000 mg/L), was apparently too low to have this effect.

## 2.13 ENDOCRINE

No studies were located regarding endocrine effects in humans after inhalation, oral, or dermal exposure to 1,2-dichloroethane. No studies were located regarding endocrine effects in animals after dermal exposure to 1,2-dichloroethane. Endocrine function has not been evaluated in toxicity studies in animals. Histological examinations of endocrine system tissues were performed in several studies with essentially negative results, but lack of histopathology does not necessarily indicate that there were no functional endocrinologic changes.

Acute-duration exposure to 1,2-dichloroethane caused congestion of the adrenal cortex in guinea pigs exposed to 1,500 ppm for 7 hours/day for 4 days (Heppel et al. 1945, 1946), but this exposure was lethal in most animals. An intermediate-duration study noted calcification of the adrenal medulla in one of two monkeys exposed to 200 ppm for 7 hours/day, 5 days/week for 25 weeks (Heppel et al. 1946), but the evidence for this effect is inconclusive because only two monkeys were studied, no control animals were examined, and adrenal effects have not been reported in other long-term inhalation studies by Heppel et al. (1946) or other investigators. Histopathological examinations failed to detect changes in endocrine tissues following exposures to 100 ppm for 7 hours/day, 5 days/week for 4 or 15 weeks in rats and mice (Heppel et al. 1946), 200 ppm for 25–35 weeks in rats, guinea pigs, and rabbits (Heppel et al. 1946; Spencer et al. 1951), 200 or 400 ppm for 32–35 weeks in rabbits (Heppel et al. 1946; Spencer et al. 1951),

or 400 ppm for 8 months in dogs (Heppel et al. 1946). The histological examinations in these studies were limited to the adrenal gland and/or pancreas.

A chronic-duration inhalation study of 1,2-dichloroethane found that exposure to 50 ppm for 7 hours/day, 5 days/week for 2 years induced a slight increase in the incidence of unspecified basophilic focal changes in the pancreas in female rats, but no histological alterations in the adrenal, thyroid, parathyroid, or pituitary glands (Cheever et al. 1990). The toxicological significance of the pancreatic changes is unclear because the incidence was not reported and the effect was induced in only one sex (females).

Histopathological examinations failed to detect changes in endocrine tissues in rats administered 100 mg/kg/day by gavage for 10 or 14 days (Daniel et al. 1994; van Esch et al. 1977), rats administered 480 mg/kg/day by gavage for 90 days (Daniel et al. 1994; Morgan et al. 1990; NTP 1991; van Esch et al. 1977), rats and mice exposed to 492 and 4,210 mg/kg/day, respectively, in drinking water for 90 days (Morgan et al. 1990; NTP 1991), or rats and mice exposed to 95 and 299 mg/kg/day, respectively, by gavage for 78 weeks (NCI 1978). The examinations in the NCI (1978) and NTP (1991; Morgan et al. 1990) studies were the most extensive and included tissues from the adrenal, pancreas, pituitary, thyroid, and parathyroid glands.

## 2.14 IMMUNOLOGICAL

No studies were located regarding immunological effects in humans after inhalation or dermal exposure or in animals after dermal exposure to 1,2-dichloroethane.

Limited information was located regarding immunological effects in humans after oral exposure to 1,2-dichloroethane. At autopsy of a male patient who ingested a “small” quantity of 1,2-dichloroethane, gross findings included a dark appearance of the spleen; hemorrhaging and congestion of the red pulp were observed microscopically (Hubbs and Prusmack 1955).

Acute-duration exposure to 1,2-dichloroethane caused chronic splenitis in rats exposed to 1,000 ppm for 7 hours/day, 5 days/week for 14 days (Heppel et al. 1946), but this exposure was lethal in most of the animals tested.

There is evidence that acute-duration exposure to 1,2-dichloroethane may affect the ability to fight infection arising from inhaled microbial pathogens in female mice, but not male rats (Sherwood et al.

1987). Male mice and female rats were not evaluated in this study. Female mice (4–5 weeks old) exposed to 5.4–10.8 ppm of 1,2-dichloroethane for 3 hours exhibited increased susceptibility to *Streptococcus zooepidemicus* (i.e., increased mortality following infection), suggesting reduced pulmonary defenses. No effect was observed at 2.3 ppm. In the same study, female mice that were similarly exposed to 10.8 ppm had reduced bactericidal activity in the lungs 3 hours after exposure to *Klebsiella pneumoniae*. Male rats exposed to 100 ppm for 5 hours/day for 12 days, or to a single 5-hour exposure to 200 ppm, did not exhibit reduced bactericidal activity after *K. pneumoniae* challenge; mortality following *S. zooepidemicus* challenge was not evaluated in rats (Sherwood et al. 1987). In addition, no effects on lymphocyte function (as indicated by blastogenesis to T- and B-cell mitogens) were seen in male rats exposed to 100 ppm 5 hours/day for 12 days; mice were not evaluated. Results reported in Sherwood et al. (1987) suggest that rats may be less susceptible to the immunological effects of 1,2-dichloroethane than mice, and/or that male rodents are less susceptible than females.

Immune function has not been evaluated in intermediate- or chronic-duration inhalation studies of 1,2-dichloroethane, although histopathological examinations failed to detect lesions in immune system tissues following intermittent exposure to 200 ppm for 212–246 days in rats and guinea pigs (Spencer et al. 1951), 400 ppm for 232–248 days in rabbits (Spencer et al. 1951), or 50 ppm for 2 years in rats (Cheever et al. 1990).

No increase in the incidences of gross or histopathological changes were observed in the spleen, lymph nodes, or thymus in rats administered up to 100 mg/kg/day by gavage for 10 days (Daniel et al. 1994). Munson et al. (1982) investigated humoral and cellular immune responses in 5-week-old mice exposed to 4.9 and 49 mg/kg/day 1,2-dichloroethane by gavage for 14 days. Immunoglobulin M (IgM) antibody response to sheep red blood cells (SRBCs) was significantly reduced at 4.9 mg/kg/day. Cell-mediated immunity response, measured by delayed-type hypersensitivity response to sheep erythrocytes, was significantly (but not in a dose-related manner), reduced at 4.9 mg/kg/day and at 49 mg/kg/day; these effects were accompanied by a 30% decrease in total leukocyte number (Munson et al. 1982). Mice given drinking water containing up to 189 mg/kg/day of 1,2-dichloroethane for 90 days displayed no treatment-related effects on either the antibody-forming cell response or the delayed-type hypersensitivity response after immunization with sheep erythrocyte antigens (Munson et al. 1982).

Immune function tests were not included in intermediate- and chronic-duration oral studies. However, immune system tissues were examined for histopathological lesions in some of these studies. Thymic necrosis was observed in moribund rats given 240 mg/kg/day of 1,2-dichloroethane by gavage for

13 weeks (Morgan et al. 1990; NTP 1991). However, 1,2-dichloroethane did not produce lesions in immune system tissues in rats and mice exposed to 492 and 4,210 mg/kg/day, respectively, in drinking water for 13 weeks (Morgan et al. 1990; NTP 1991), rats exposed by gavage to 150 mg/kg/day for 90 days (Daniel et al. 1994), or rats and mice exposed to 95 and 299 mg/kg/day, respectively, by gavage for 78 weeks (NCI 1978).

## 2.15 NEUROLOGICAL

No studies were located regarding neurological effects in humans or animals after dermal exposure to 1,2-dichloroethane.

Inhalation of high concentrations of 1,2-dichloroethane can affect the nervous system of humans. A 51-year-old man exposed to a concentrated vapor of 1,2-dichloroethane for 30 minutes suffered central nervous system effects (Nouchi et al. 1984). Immediately following exposure, he experienced irritability. Twenty hours later, symptoms included drowsiness, delirium, and tremors. After 24 hours, he was in a coma with a generalized, continuous, clonic jerk, and an abnormal slow wave in the electroencephalogram; he died 5 days after exposure. Upon autopsy, the Purkinje cell layer of his cerebellum showed a shrunken appearance with pyknotic nuclei. Toxic encephalopathy, primarily characterized by cerebral edema, has been observed in 1,2-dichloroethane-exposed workers. Following a single 4-hour exposure in a knitting factory, weakness, dizziness, and trembling were reported by three workers who had wrung out yarn that had soaked in an open vat of 1,2-dichloroethane (Wirtschafter and Schwartz 1939). Related symptoms reported in workers exposed to 1,2-dichloroethane by inhalation included headaches, dizziness, seizures (including generalized tonic-clonic), recent amnesia, and a slow response to verbal commands (Chen et al. 2015, Dang et al. 2019; Liu et al. 2010; Zhan et al. 2011). Dang et al. (2019) observed toxic encephalopathy in four cases of workers exposed to unknown concentrations of 1,2-dichloroethane for 3 months to 1 year. Imaging showed evidence of brain edema and intracranial hypertension with severe mixed edema in white matter, dentate nucleus, globus pallidus, and bilateral cortex. Brain biopsies of two patients revealed extensive and severe neural edema, glial cell necrosis, and edema in glial cytoplasm and neurites. Similarly, neuroimaging findings in five female workers exposed to unknown concentrations showed extensive edema in subcortical white matter, bilateral globus pallidus, and/or dentate nucleus (Liu et al. 2010). In addition, one female had a modified Rankin scale test value of 2 (unable to perform all activities prior as before but does not need daily assistance) 6 weeks after exposure (Liu et al. 2010). In both studies, all patients recovered from neurological symptoms. Chen et al. (2015) reported on five cases of 1,2-dichloroethane-induced toxic

encephalopathy in factory workers who were exposed to 1,2-dichloroethane in air over periods ranging from 2 months to 6 years. Imaging showed signs of edema including abnormal signal intensities in the cerebellar dentate nucleus, basal ganglia, and white matter in the bilateral cerebral hemispheres. Additionally, increased white blood cell count was seen in cerebrospinal fluid of all workers, suggesting nonspecific inflammation in the central nervous system (Chen et al. 2015).

Neuronal necrosis and white matter demyelination were reported in another case report of a male worker exposed to 1,2-dichloroethane for 6 months (Zhan et al. 2011). Toxic leukoencephalopathy, a type of encephalopathy primarily affecting white matter, was suspected in a 20-year-old female occupationally exposed to unknown concentrations of 1,2-dichloroethane (Zhou et al. 2015). MRI showed obvious lesions with diffuse brain edema in white matter and high intracranial pressure, and an abnormally high concentration of 1,2-dichloroethane was measured in working brain cells (Zhou et al. 2015).

Neuropsychological impairment was reported in a group of 221 workers who cleaned up over 69 million pounds of 1,2-dichloroethane spilled in water and soil (Bowler et al. 2003). Clean-up workers were exposed to 1,2-dichloroethane in air and dermally. Significant impairment was demonstrated on tests of attention, non-verbal processing speed, verbal memory and learning, and motor strength and speed. Motor (motor coordination and speed) and neuropsychological (processing speed, attention, cognitive flexibility, verbal memory, verbal fluency, and visio-spatial ability) impairments showed associations with 1,2-dichloroethane exposure (Bowler et al. 2003).

Neurological effects, such as central nervous system depression, have been reported in humans following acute oral intoxication with 1,2-dichloroethane (Hubbs and Prusmack 1955; Lochhead and Close 1951; Yodaiken and Babcock 1973). Patients who died of acute oral poisoning by 1,2-dichloroethane had morphological alterations in the nervous system including vascular disorders, diffuse changes in cerebellar cells, parenchymatous changes in brain and spinal cord, myelin degeneration, and hyperemia, swelling, edema, and hemorrhage of the brain (Hubbs and Prusmack 1955; Hueper and Smith 1935; Lochhead and Close 1951).

Acute-duration exposure to concentrated 1,2-dichloroethane produces neurological effects in animals. Spencer et al. (1951) found that rats exposed to ≥12,000 ppm for 30 minutes exhibited central nervous depression, and exposure to 20,000 ppm for 15 minutes was severe enough to cause death. Clinical signs observed at 3,000 ppm included inactivity, stupor, and “slowness of response to handling” but no histological evaluation of the central nervous system was performed. Uncertain gait, narcosis,

prostration, and unconsciousness were seen in rats, guinea pigs, and/or rabbits exposed once to 3,000 ppm for 7 hours but were not observed at 1,500 ppm; however, 7-hour exposures to 1,500 ppm on 5 consecutive days induced transitory tremors, convulsions, and/or coma in rats and dogs (Heppel et al. 1945). Forelimb flexion and body tremors, which can result from cerebral injury, were observed in mice exposed to 1,2-dichloroethane in air at 253 ppm 3.5 hours/day for 3 days (Jin et al. 2018a). No exposure-related histopathologic observations were reported in the central or peripheral nervous systems of rats exposed to ≤2,029 ppm for 4 hours (Hotchkiss et al. 2010).

Numerous acute-duration studies of animals exposed to 1,2-dichloroethane by inhalation have reported brain edema and related histological changes such as increased brain water content, enlarged perinuclear spaces, widened lacunar places, and swelling (Jin et al. 2018a, 2018b, 2019; Wang et al. 2014, 2018; Yang et al. 2021; Zhang et al. 2011; Zhou et al. 2016). Mice exposed to concentrations as low as ~246 ppm of 1,2-dichloroethane 3.5 hours/day for 3 days developed brain edema, indicated by significantly increased brain water content and morphological changes (Jin et al. 2018a, 2019; Wang et al. 2014; Yang et al. 2021). Histopathological changes included enlarged perinuclear spaces, widened lacunar spaces surrounding vessels, lightly stained intercellular matrix and cytoplasm, and swelling cell bodies in the cerebral tissues. In other studies using the same species, exposure regimen, and comparable exposure concentrations, no edema or brain histological changes were observed (Wang et al. 2014; Zhang and Jin 2019). Edema and hydrocephalus, characterized by loose tissues and enlarged spaces surrounding the cells, were apparent in rats exposed to 1,235 ppm of 1,2-dichloroethane by inhalation for 6 hours (Zhang et al. 2011). Edema severity increased with longer exposure duration (from 6 to 12 hours) when animals were tested at the same concentration (Zhang et al. 2011). Edema in the white matter in both hemispheres of the brain was seen in rats exposed to 988 ppm of 1,2-dichloroethane for 4 hours by inhalation (Zhou et al. 2016). Brain edema, characterized by increased water weight and histopathology was observed in male rats exposed to 420 ppm and female rats exposed to 137 ppm for 8 hours/day for 7 days; males also had increased relative brain weights (Zhong et al. 2020).

Acute-duration inhalation exposure to 1,2-dichloroethane also produced neurobehavioral effects in animals in multiple studies (Hotchkiss et al. 2010; Wang et al. 2013). Central nervous system depression as indicated by changes in functional operational battery was observed in mice on day 1 after a single 4-hour exposure to 607.8 ppm but was no longer evident 8 days post-exposure (Hotchkiss et al. 2010). In female rats, motor activity significantly decreased following exposure to 2,029 ppm 1,2-dichloroethane for 4 hours; this effect was not seen in male rats (Hotchkiss et al. 2010). Mice exhibited reduced

ambulation in an open field when evaluated 2 hours after the last exposure to 156 and 222 ppm of 1,2-dichloroethane for 3.5 hours/day for 10 days (Wang et al. 2013).

Mice exposed to 179.87 ppm 1,2-dichloroethane on 6 hours each day, 5 days each week for 28 days exhibited reduced activity in open field tests and microscopic damage to cerebellar granular cells including pyknosis and apoptosis (Huang et al. 2020). No neurological effects were noted at 90.96 ppm. Zhong et al. (2022) determined that mice exposed to 86 ppm 1,2-dichloroethane for 6 hours/day on 28 consecutive days had altered behavior in open field consisting of reduced distance and time in the central area. However, histopathology examination of the brain showed vacuolation in the cerebral cortex at exposure concentrations ranging from 86 to 173 ppm (Liang et al. 2021; Zhong et al. 2020, 2022). Brain edema was observed in mice exposed to 173 ppm 1,2-dichloroethane for 6 hours/day for 28 days (Zhong et al. 2020). No clinical signs of neurotoxicity were observed in dogs exposed to 400 ppm for 7 hours/day, 5 days/week for 8 months (Heppel et al. 1946). In addition, histopathological examination of the brain from rats exposed to 50 ppm for 2 years showed no treatment-related changes (Cheever et al. 1990).

In rats exposed to 1,2-dichloroethane orally, fewer neurological effects were seen, and none of the available studies reported clear evidence of brain edema. A single gavage exposure to 170 mg/kg in rats did not significantly alter neurotransmitter levels in various parts of the brain (Kanada et al. 1994), and a 10-day gavage exposure to up to 100 mg/kg/day did not affect brain weight or the incidences of gross or microscopic lesions in nervous system tissues of rats (Daniel et al. 1994).

Neurological effects have been observed in animals exposed to 1,2-dichloroethane by ingestion for intermediate durations. Clinical signs in rats exposed to 240 mg/kg/day by gavage for 13 weeks included tremors, salivation, emaciation, abnormal posture, ruffled fur, and dyspnea (Morgan et al. 1990; NTP 1991). Upon microscopic examination, mild necrotic lesions were observed in the cerebellum of rats dosed with 240 or 300 mg/kg/day. These lesions were not found in rats dosed with 480 mg/kg/day, but these rats all died after only 3 days of treatment and may not have had time to develop the lesion. Gavage exposure to 90 mg/kg/day, 5 days/week for 90 days resulted in an 8% increase in relative brain weight in female, but not male rats (van Esch et al. 1977). Absolute organ weights were not reported; however, body weights were not decreased in the female rats. No clinical signs or treatment-related histological changes in the brain or spinal cord were observed in either sex at any dose (van Esch et al. 1977). Gavage administration of 75 and 150 mg/kg/day for 90 days in male rats induced significant increases (8 and 22%, respectively, compared to controls) in relative brain weight in the absence of treatment-related

neurological clinical signs or lesions of the brain or sciatic nerve (Daniel et al. 1994). Absolute organ weights were not reported, and the increase in relative brain weight may have been due to an observed dose-related decrease in body weight (and concomitant decrease in food consumption) in the male rats. No neurological effects of any kind were reported in females or in either sex at lower exposure levels. NTP (1991) found 1,2-dichloroethane administered in the drinking water for 13 weeks did not produce increased brain weights, abnormal clinical signs, or lesions in nervous system tissues in rats at 492 mg/kg/day or in mice at 4,210 mg/kg/day. The absence of effects after drinking water exposure at higher doses than those inducing effects after gavage exposure may be attributable to higher systemic exposure resulting from bolus dosing and/or saturation of metabolism.

***Mechanisms of Neurotoxicity.*** The pathogenesis underlying the brain edema induced by inhalation exposure to 1,2-dichloroethane has not been fully elucidated. Metabolism via CYP2E1 appears to play a role, as mice exposed to 1,2-dichloroethane in combination with diallyl sulfide (a CYP2E1 inhibitor) showed marked improvement of edema-related pathological changes compared with those exposed to 1,2-dichloroethane alone (Jin et al. 2018a). In the same study, increases in brain markers of oxidative stress (malondialdehyde and antioxidant enzyme activities) induced by 1,2-dichloroethane were also mitigated by cotreatment with diallyl sulfide, suggesting that oxidative stress may play a role in the brain pathology. Jin et al. (2018a) also reported upregulation of transcription factors involved in expression of antioxidant enzyme genes (Nrf2 and downstream HO-1) in mice exposed to 1,2-dichloroethane.

Several studies have provided evidence that 1,2-dichloroethane may increase the permeability of the blood-brain barrier via effects on tight junction proteins. Tight junction proteins such as occludin, claudins, and ZO-1 are structural components of the blood-brain barrier. Following inhalation exposure to 1,2-dichloroethane, blood brain barrier permeability was increased (Jin et al. 2018b) and expression of tight junction mRNA and protein levels were reduced in the brains of mice (Jin et al. 2018b; Wang et al. 2018).

Wang et al. (2018) also observed that 1,2-dichloroethane increased intracellular free $Ca^{2+}$ and suppressed $Ca^{2+}$ ATPase activity in brain cells from mice exposed by inhalation. The study authors proposed that perturbation of calcium homeostasis in brain cells could play an important role in the early phase of brain edema formation.

It is likely that several mechanisms are involved in the neurotoxicity of 1,2-dichloroethane; however, pathogenesis underlying the brain edema is not fully understood.

Behavioral changes in mice exposed by inhalation to 1,2-dichloroethane correlated with neurotransmitter levels (Wang et al. 2013). Decreased activity occurred at the same exposure concentrations at which increased brain levels of GABA (an inhibitory neurotransmitter) were seen, while increased activity occurred at exposure concentrations associated with decreased GABA levels (Wang et al. 2013).

## 2.16 REPRODUCTIVE

No studies were located regarding reproductive effects in humans after oral or dermal exposure or in animals after dermal exposure to 1,2-dichloroethane.

Studies regarding reproductive effects in humans after inhalation exposure to 1,2-dichloroethane are limited to a single account of increased rates of premature births in 54 female workers and wives of 44 male workers exposed in a Chinese synthetic fiber factory (Zhao et al. 1989). Concentrations of 1,2-dichloroethane ranged from 0.4 to 384 ppm measured at two locations. Female subjects were exposed throughout pregnancy, and male workers were exposed for at least 1 year before their wives, who were not occupationally exposed, became pregnant. Study limitations include a small number of subjects, co-exposure to other chemicals, and deficient reporting and design including not accounting for possible confounding environmental and behavioral factors.

Effects on reproduction have been observed in animals exposed to 1,2-dichloroethane by inhalation. Swiss mice exposed to up to 173 ppm 1,2-dichlorethane for 6 hours/day for 1 week had pathological changes including vacuolar degeneration of germ cells in seminiferous tubules and sloughing of spermatogenic cells into the lumen, as well as reduced sperm concentration, motility, and progressive motility; and increased abnormalities of the sperm head, body, and tail (Zhang et al. 2017). In mice similarly exposed for 4 weeks, severe degenerative pathological changes and effects on sperm parameters were present in testes of mice exposed to 86 and 173 ppm of 1,2-dichloroethane. A dose-dependent increase in the percentage of abnormal sperm was observed in all 1,2-dichloroethane exposure groups. At 25 ppm, the percentage of abnormal sperm was 8.8% relative to 4.0% in controls; however, the toxicological significance of this small increase is uncertain. No gross or histopathological lesions were observed in reproductive organs of rats exposed to 50 ppm intermittently for 2 years (Cheever et al. 1990).

Some intermediate-duration studies in rodents found that inhalation exposure to 1,2-dichloroethane during gestation with or without a premating exposure resulted in pre-implantation loss and embryo lethality, although the studies were of questionable reliability due to deficiencies in reporting information on study design and results. Pre-implantation loss was increased approximately 3-fold (31.0% compared to 10.2% in controls) in unspecified rodents that were exposed to 51.9 ppm "during the entire pregnancy period" (Zhao et al. 1989). A significant increase in embryo mortality and preimplantation loss (5-fold) was observed in rats following 4 months of exposure of unknown frequency prior to mating, and throughout pregnancy to 4.7 ppm 1,2-dichloroethane (Vozovaya 1977). Fertility was decreased, and stillbirths and perinatal mortality were increased in the first generation of a two-generation reproduction study in rats that were exposed to 14 ppm of 1,2-dichloroethane over a period of 6 months (Vozovaya 1974). A well-designed study by Rao et al. (1980) showed no adverse effects on the fertility, gestation, or survival in pups of male and female rats exposed to 150 ppm for 6 hours/day, 5 days/week for 60 days pre-mating, then 7 days/week throughout mating, gestation, and lactation (excluding gestation day [GD] 21 through postpartum day 4).

In oral studies of systemic toxicity, no histological changes were observed in male or female reproductive tissues in rats administered 100 mg/kg/day by gavage for 10 days (Daniel et al. 1994), in rats administered 480 mg/kg/day by gavage for 90 days (Daniel et al. 1994; Morgan et al. 1990; NTP 1991; van Esch et al. 1977), in rats and mice exposed to 492 and 4,210 mg/kg/day, respectively, in drinking water for 13 weeks (Morgan et al. 1990; NTP 1991); or in rats and mice exposed to 95 and 299 mg/kg/day, respectively, by gavage for 78 weeks (NCI 1978).

Studies of reproductive function suggest that effects after oral exposure may occur only at doses that are also maternally toxic; however, there are few available studies. Dams that were treated with up to 198 mg/kg/day 1,2-dichloroethane by gavage for 14 days during gestation (GDs 6–20) showed 30% reduced body weight gain and dose-related increased percentages of non-surviving implants per litter (resorptions plus dead fetuses) and resorption sites per litter (Payan et al. 1995). These effects did not occur at 158 mg/kg/day, and no changes in mean numbers of implantation sites or live fetuses per litter were observed. One- and two-generation reproduction studies showed no dose-dependent effects on fertility, gestation, viability, or lactation indices in mice exposed to doses of 5–50 mg/kg/day in drinking water for 24–49 weeks (Lane et al. 1982). There were no effects on fertility indices (e.g., percentage pregnant, percent bearing litters, and litter size) in five pregnancies throughout a 2-year study, during which rats ingested dietary doses of 21.3 or 42.5 mg/kg/day (Alumot et al. 1976).

***Mechanisms of Reproductive Toxicity.*** Little information is available on the mechanisms by which 1,2-dichloroethane might induce reproductive effects. Zhang et al. (2017) observed the induction of apoptosis (measured by TUNEL assay) in the germ cells of mice exposed to 1,2-dichloroethane by inhalation and suggested that this was a potential mechanism for its effects on sperm. No supporting evidence for this mechanism was located in the available literature.

## 2.17 DEVELOPMENTAL

No studies were located regarding developmental effects in humans or animals after dermal exposure to 1,2-dichloroethane.

Only one study examined developmental effects in humans exposed to 1,2-dichloroethane by inhalation. In a population-based case-control study with 60,613 cases and 244,947 controls, Brender et al. (2014) suggests maternal environmental exposure to 1,2-dichloroethane in air, was positively associated with birth defects in offspring after adjustment for year of delivery, maternal age, education, race/ethnicity, and region. Maternal residential proximity to industrial air emissions of 1,2-dichloroethane was positively associated with neural tube defects and spina bifida in offspring. When the data were stratified by maternal age, the association with neural tube defects and spina bifida were more pronounced in mothers <35 years old. Among mothers >35 years, positive associations were observed with cleft palate and any cleft defect. There was an exposure intensity-related trend between residential location and septal heart defects and spina bifida. Although there was a large sample size, factors that could not be properly adjusted for include number of maternal offspring and smoking, which was suspected to be underreported (Brender et al. 2014). In addition, reliance on residential location and industry emission estimates as a surrogate for exposure may have resulted in exposure misclassification.

No studies were located regarding developmental effects in humans exposed solely to 1,2-dichloroethane by ingestion. A cross-sectional epidemiologic study investigated whether elevated levels of routinely sampled organic contaminants in New Jersey public water systems, including 1,2-dichloroethane, were associated with increased prevalence of adverse birth outcomes (Bove 1996; Bove et al. 1995). The study population consisted of all live births and fetal deaths that occurred during 1985–1988 to residents of 75 towns in a four-county area where some municipal water supplies were contaminated. A total of 80,938 live births and 594 fetal deaths, excluding plural births, fetal deaths due to therapeutic abortions, and chromosomal anomalies, were studied. The comparison group comprised 52,334 (all) live births from the study population that had no birth defects and were not low birth weight, small for gestational

age, or pre-term. A number of associations between various chemicals and birth outcomes were found, including a positive association between 1,2-dichloroethane and major cardiac defects for exposure levels >1 ppb compared to ≤1 ppb (OR 2.11). The OR increased to 2.81 when exposure was recategorized as detected versus not detected. Croen et al. (1997) reported an increased crude OR (2.8; 95% confidence interval [CI] 1.0–7.2; 14 exposed cases) for neural tube defects in offspring of residents within the census tract of NPL sites contaminated with 1,2-dichloroethane. The OR for residence within 1 mile of the NPL site was elevated but was not significant (OR 1.7; 95% CI 0.8–3.6; 18 exposed cases). Although an association between 1,2-dichloroethane in drinking water and major birth defects was found in these epidemiological studies, because of concurrent mixed chemical exposures in addition to the lack of individual exposure estimates, these studies should be interpreted with caution. Routes of exposure in these epidemiological studies may have been both oral and inhalation (including inhalation of 1,2-dichloroethane volatilized from household water).

The overall evidence from inhalation studies in rats and rabbits indicates that 1,2-dichloroethane is not a developmental toxicant. Exposure of rats to 300 ppm 1,2-dichloroethane for 7 hours/day on GDs 6–15 produced high maternal mortality (10/16 maternal deaths); resorptions were 100%, with no live fetuses (Schlacter et al. 1979). No mortality or fetolethality were observed in rats that were similarly exposed to 100 ppm. Payan et al. (1995) similarly found that exposure to 1,2-dichloroethane for 6 hours/day during GDs 6–20 was not fetotoxic or teratogenic to rats at concentrations as high as those producing maternal toxicity (329 ppm). There were no exposure-related changes in numbers of implantations, resorptions, and live fetuses, fetal sex ratio or body weights, or external, visceral, or skeletal development. Maternal body weight gain from GD 6 to 21was reduced 24% at 329 ppm; no maternal effects occurred at lower concentrations (150–254 ppm) (Payan et al. 1995). Zhao et al. (1984) reported no developmental changes in F1 and F2 generations of mice after the parental dams were exposed to up to 62.5 ppm on GDs 6–15, or to 250 ppm on GDs 9 and 10 for 4 hours/day. Rabbits that were exposed to 100 or 300 ppm of 1,2-dichloroethane for 7 hours/day on GDs 6–18 experienced some maternal deaths, but there were no exposure-related developmental effects as indicated by pregnancy and resorption incidences, litter size, fetal body measurements, and soft-tissue and skeletal examinations (Rao et al. 1980).

Developmental toxicity was reported in one study in rats, but the reliability of the data is uncertain. Exposure to 4.7 ppm of 1,2-dichloroethane for 4 months before mating followed by exposure during pregnancy resulted in increased litters with hematomas in the head and neck region and anterior extremities of the fetuses (Vozovaya 1977). The reliability of the Vozovaya (1977) data cannot be assessed due to lack of statistical analysis and uncertainties in the reported results.

Developmental toxicity studies in animals have not shown 1,2-dichloroethane to be fetotoxic or teratogenic following oral exposure, although indications of embryo lethality at maternally toxic doses have been reported. Drinking water studies in mice found no increased incidences of fetal visceral and skeletal abnormalities following exposure to 50 mg/kg/day on GDs 0–18 (Lane et al. 1982) or 510 mg/kg/day on GDs 7–14 (Kavlock et al. 1979). Rats that were treated with 198 mg/kg/day by gavage on GDs 6–20 showed 30% reduced body weight gain and increased embryo-lethal effects such as increased nonsurviving implants and resorption sites per litter, but no fetotoxicity or teratogenicity as indicated by fetal sex ratio, fetal body weight, or incidences of visceral and skeletal variations and malformations (Payan et al. 1995). No developmental effects were observed in rats administered 25 mg/kg/day in the diet for 2 years (Alumot et al. 1976).

## 2.18 OTHER NONCANCER

No studies were located regarding other noncancer health effects in humans from inhalation, oral, or dermal exposure or in animals after dermal or oral exposure to 1,2-dichloroethane.

Blood glucose levels were reduced in mice exposed to 173 ppm for 6 hours/day for 28 days (Wang et al. 2017). Intermediate-duration exposure of 28 days to 1,2-dichloroethane can significantly disrupt hepatic glucose and lipid homeostasis in mice (Wang et al. 2017; Zeng et al. 2018). All mice exposed to 1,2-dichloroethane had significant increases in liver free fatty acid and triglycerides, and a significant decrease in blood glucose levels, compared to control groups (Wang et al. 2017; Zeng et al. 2018). Impaired hepatic glucose and lipid homeostasis may result from the down regulation of mRNA and protein expression of glucose-6-phosphatase catalytic subunit (G6PC) and liver glycogen phosphorylase (PYGL); rate limiting enzymes in glycogenolysis associated with hepatic glucose metabolism (Wang et al. 2017; Zeng et al. 2018), although this may be primarily mediated by a 1,2-dichloroethane metabolite rather than 1,2-dichloroethane. No other noncancer effects were observed in animals following inhalation exposure.

## 2.19 CANCER

U.S. Federal agencies and international scientific organizations have reviewed the literature on 1,2-dichloroethane's carcinogenicity. The HHS has determined that 1,2-dichloroethane is reasonably anticipated to be a human carcinogen (NTP 2021). IARC has placed 1,2-dichloroethane in Group 2B

(possibly carcinogenic to humans) (IARC 2016). Using a weight-of-evidence approach, EPA (IRIS 1987) has classified 1,2-dichloroethane as a probable human carcinogen (Group B2) based on sufficient evidence in animals. EPA (IRIS 1987) derived an oral slope factor of 0.091 $(mg/kg/day)^{-1}$ and inhalation unit risk of $2.6x10^{-5}$ $(\mu g/m^3)^{-1}$. Both are based on the incidence of hemangiosarcomas in rats after oral exposure in the chronic-duration study by NCI (1978).

No studies were located regarding cancer in humans after dermal exposure to 1,2-dichloroethane.

Several epidemiological studies have been conducted on workers in the chemical industry to investigate the high incidence of brain tumors observed among workers employed in petrochemical plants (Austin and Schnatter 1983a, 1983b; Reeve et al. 1983; Teta et al. 1989; Waxweiler et al. 1983), the incidence of stomach cancer and leukemia at a plant that used 1,2-dichloroethane in the production of ethylene oxide (Hogstedt et al. 1979), and mortalities due to pancreatic cancer and lymphatic and hematopoietic cancers in a cohort of workers in chlorohydrin production plants where 1,2-dichloroethane was a byproduct (Benson and Teta 1993). Danish men who were occupationally exposed to gasoline and combustion products containing 1,2-dichloroethane had increased odds of primary breast cancer compared to workers who were not exposed (according to job type and trade code) (Hansen 2000). Male residents in areas near a municipal solid waste site in Montreal, Quebec, which emitted airborne 1,2-dichloroethane (among a number of other volatile substances) showed slightly elevated odds of stomach cancers and cancers of the trachea, bronchus, and lung, while female residents showed slightly elevated odds of stomach cancer (Goldberg et al. 1995). None of these epidemiology studies included measurements of 1,2-dichloroethane exposure levels in air or biomarkers of exposure to this chemical, nor did they evaluate risks associated specifically with 1,2-dichloroethane. In addition, concurrent exposure to other chemicals or solvents may have confounded the results.

One study examined the development of cancer in humans following ingestion of 1,2-dichloroethane. Isacson et al. (1985) used indices of drinking water contamination to examine the relationship between cancer incidence and exposure to environmental pollutants in groundwater and surface water samples. Statistically significant associations were observed between the presence of 1,2-dichloroethane in drinking water and increased incidences of colon ($p=0.009$) and rectal ($p=0.02$) cancer in men aged ≥55 years. However, the study population was likely concomitantly exposed to other chemicals.

The carcinogenicity of inhaled 1,2-dichloroethane has been evaluated in chronic-duration studies in both rats and mice. Nagano et al. (2006) exposed F344 rats and BDF1 mice to 1,2-dichloroethane

concentrations of 0, 10, 40, or 160 ppm and 0, 10, 30, or 90 ppm, respectively, for 6 hours/day, 5 days/week, for 2 years. In rats, dose-related increases in the following tumor incidences were observed in both sexes at 160 ppm: subcutis fibroma; and adenoma and fibroadenoma of the mammary gland. Increased incidences of liver hemangiosarcoma were observed at 30 and 90 ppm in male mice. Previous studies on mice and rats did not show increased tumor incidences following chronic-duration exposure to 1,2-dichloroethane (Cheever et al. 1990; Maltoni et al. 1980). Maltoni et al. (1980) exposed Sprague-Dawley rats and Swiss mice to 1,2-dichloroethane via inhalation at concentrations of 5, 10, 50, or 150–250 ppm 7 hours/day, 5 days/week, for 78 weeks and found no treatment-related increase in tumors. This study has limitations such as the short exposure duration and low survival in mice exposed to the highest dose tested; therefore, only a small number of surviving animals were at risk for late-developing tumors. Cheever et al. (1990) exposed rats to 50 ppm of 1,2-dichloroethane (7 hours/day, 5 days/week) for 2 years and observed no exposure-related increases in tumor incidence; this study was limited by its use of a single exposure level, which may have been too low to demonstrate tumor induction, based on the findings of Nagano et al. (2006).

1,2-Dichloroethane was found to be carcinogenic in rats and mice that were exposed by gavage for up to 78 weeks (NCI 1978). Increased incidences of fibromas of the subcutaneous tissue and hemangiosarcomas of the spleen, liver, pancreas, and adrenal gland (as well as other organs and tissues) occurred in male rats at 47 and 95 mg/kg/day. In the 95 mg/kg/day group, male rats had increased squamous cell carcinomas of the forestomach, and female rats had increased frequencies of adenocarcinomas and fibroadenomas of the mammary gland. In mice, the incidences of hepatocellular carcinomas and alveolar/bronchiolar adenomas were increased in males given 195 mg/kg/day. In female mice from both the 149- and 299-mg/kg/day exposure groups, there were increased incidences of alveolar/bronchiolar adenomas, adenocarcinomas of the mammary gland, and endometrial stromal polyps and stromal sarcomas. The NCI (1978) study has a number of limitations including dosage adjustments throughout the course of the bioassay (because of the toxicity of 1,2-dichloroethane), testing of other volatile organic chemicals in the same room, small numbers of concurrent controls, poor survival of treated animals, imprecise reporting of 1,2-dichloroethane purity, and use of a corn oil vehicle, which can alter the disposition of lipophilic compounds and the incidence of some spontaneous tumors.

In studies of tumor promotion, 1,2-dichloroethane was not a promoter. In an initiation/promotion study, B6C3F1 mice were separated into groups that were either untreated during initiation or initiated with diethyl nitrosamine (DEN) for 4 weeks (Klaunig et al. 1986). Following the initiation period, mice were subsequently treated with 159 or 475 mg/kg/day 1,2-dichloroethane in the drinking water for 52 weeks.

1,2-dichloroethane did not induce increased incidences of lung or liver tumors either alone or as a tumor promoter. However, severe study limitations including short duration, high liver tumor incidence in untreated controls [20%] and in DEN-initiated [100%] mice after 52 weeks, lack of positive controls, and failure to specify the compound purity limit the validity of the study. A shorter-term initiation/promotion study in rats using enzyme-altered liver foci as a marker for preneoplastic changes showed no increase in the number of foci among animals exposed to 1,2-dichloroethane by gavage (Milman et al. 1988), but was limited by use of a single dose level (100 mg/kg) and short exposure duration (single dose in initiation study and 7 weeks in promotion study).

The carcinogenicity of 1,2-dichloroethane following dermal exposure has been evaluated in mice (Suguro et al. 2017; Van Duuren et al. 1979). A statistically significant increase in lung tumors was observed in mice treated with 126 mg of 1,2-dichloroethane 3 times/week for 428–576 days (van Duuren et al. 1979). These results indicate a significant increase in benign tumors remote from the site of application and suggest that 1,2-dichloroethane can penetrate through the skin into the circulatory system. In a 26-week (shortened) carcinogenicity study using transgenic (rasH2) mice (mice hemizygous carrying the c-Ha-ras oncogene for enhanced susceptibility to cancer earlier allowing for a shorter exposure period), dermal exposure to 80 mg/mL 1,2-dichloroethane 3 times/week resulted in increased incidence and multiplicity of bronchioloalveolar adenomas and adenocarcinomas in mice of both sexes and increased incidence of bronchiolar-alveolar hyperplasia in female mice (Suguro et al. 2017).

## 2.20 GENOTOXICITY

No studies were located regarding genotoxicity in humans after oral or dermal exposure to 1,2-dichloroethane. No studies were located regarding genotoxic effects in animals after dermal exposure to 1,2-dichloroethane.

A study on 71 male workers from two vinyl chloride monomer manufacturing (VCM) plants, showed exposure to 1,2-dichloroethane in air at around 1 ppm was associated with increased sister chromatid exchange (SCE) frequency in peripheral lymphocytes (Cheng et al. 2000). Mean duration of employment for all employees ranged from 7.1 to 9.7 years, and workers were stratified into a control, non-exposed group and three exposure groups: low VCM-low 1,2-dichloroethane, low VCM-moderate 1,2-dichloroethane, and moderate VCM-moderate 1,2-dichloroethane exposure. Statistically significant increases in SCE frequency were observed in both groups exposed to moderate 1,2-dichloroethane: low VCM-moderate 1,2-dichloroethane (0.69–1.31 ppm) and moderate VCM-moderate 1,2-dichloroethane

(0.77 ppm) compared to the control group. Increased SCE frequency was also associated with smoking, but not age. Limitations of this study include the small age range of workers in the study and lack of accounting for other lifestyle factors.

Numerous studies have been published evaluating 1,2-dichloroethane's genotoxic potential *in vitro* (summarized in Table 2-3) and *in vivo* using experimental animals (summarized in Table 2-4). The available evidence indicates that 1,2-dichloroethane is likely mutagenic, may induce chromosomal aberrations, and does induce deoxyribonucleic acid (DNA) damage by DNA binding.

**Table 2-3. Genotoxicity of 1,2-Dichloroethane *In Vitro***

| Species (test system) | Endpoint | Results | | Reference |
|---|---|---|---|---|
| | | With activation | Without activation | |
| Prokaryotic organisms | | | | |
| *Salmonella typhimurium* | Gene mutation | + | + | Barber et al. 1981; Kanada and Uyeta 1978; Milman et al. 1988; Nestmann et al. 1980; Rannug et al. 1978; van Bladeren et al. 1981 |
| *S. typhimurium* | Gene mutation | + | No data | Rannug and Beije 1979 |
| *S. typhimurium* | Gene mutation | + | – | Cheh et al. 1980; Moriya et al. 1983 |
| *S. typhimurium* | Gene mutation | – | – | King et al. 1979 |
| *S. typhimurium* | Gene mutation | No data | + | Simula et al. 1993; Thier et al. 1993 |
| *S. typhimurium*/spot test | Gene mutation | No data | (+) | Brem et al. 1974 |
| *S. typhimurium*/spot test | Gene mutation | No data | – | Buijs et al. 1984 |
| *S. typhimurium*/Ara test (standard) | Gene mutation | + | – | Roldan-Arjona et al. 1991 |
| *S. typhimurium*/Ara test (liquid) | Gene mutation | (+) | (+) | Roldan-Arjona et al. 1991 |
| *Escherichia coli* K12/343/113 | Gene mutation | – | – | King et al. 1979 |
| *E. coli* WP2 | Gene mutation | No data | (+) | Hemminki et al. 1980 |
| *E. coli* WP2 | Gene mutation | – | – | Moriya et al. 1983 |
| *E. coli* Pol A | DNA damage | No data | (+) | Brem et al. 1974 |
| *Bacillus subtilis*/rec-assay | DNA damage | – | – | Kanada and Uyeta 1978 |
| Eukaryotic organisms | | | | |
| Fungi: | | | | |
| *A. nidulans* | Mitotic segregation aberrations | No data | + | Crebelli et al. 1984 |
| *A. nidulans* | Aneuploidy induction | No data | + | Crebelli et al. 1988 |

**Table 2-3. Genotoxicity of 1,2-Dichloroethane *In Vitro***

| Species (test system) | Endpoint | Results | | Reference |
|---|---|---|---|---|
| | | With activation | Without activation | |
| Animal cells | | | | |
| Hamster CHO/HGPRT | Gene mutation | + | (+) | Tan and Hsie 1981 |
| Hamster Chinese SP5 | Intrachromosomal recombination | – | No data | Zhang and Jenssen 1994 |
| Rat hepatocytes | Unscheduled DNA synthesis | No data | + | Williams et al. 1989 |
| Mouse hepatocytes | Unscheduled DNA synthesis | No data | + | Milman et al. 1988 |
| Mouse liver DNA | DNA binding | + | No data | Banerjee 1988 |
| Calf thymus DNA | DNA binding | + | No data | Prodi et al. 1986 |
| Salmon sperm DNA | DNA binding | + | – | Banerjee and Van Duuren 1979; Banerjee et al. 1980 |
| Mouse BALB/c-3T3 | Cell transformation | No data | – | Milman et al. 1988 |
| Human cells | | | | |
| Human lymphoblasts AHH-1 | Gene mutation | No data | + | Crespi et al. 1985 |
| Human lymphoblasts TK6 | Gene mutation | No data | + | Crespi et al. 1985 |
| Human lymphoblasts AHH-1 | Micronuclei | No data | + | Doherty et al. 1996 |
| Human lymphoblasts MCL-5 | Micronuclei | No data | + | Doherty et al. 1996 |
| Human lymphoblasts h2E1 | Micronuclei | No data | + | Doherty et al. 1996 |
| Human embryo epithelial-like EUE cells | Gene mutation | No data | + | Ferreri et al. 1983 |
| Human peripheral lymphocytes | Unscheduled DNA synthesis | + | – | Perocco and Prodi 1981 |
| Human peripheral lymphocytes | Micronuclei | – | + | Tafazoli et al. 1998 |
| Human peripheral lymphocytes | DNA damage | – | + | Tafazoli et al. 1998 |

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

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

| Species (test system) | Endpoint | Results | Reference |
|---|---|---|---|
| Mammalian assays | | | |
| Mouse liver and testis | Gene mutation | – | Hachiya and Motohashi 2000 |
| Mouse/spot test | Gene mutation | (+) | Gocke et al. 1983 |
| Human blood | Sister chromatid exchange | + | Cheng et al. 2000 |
| Mouse bone marrow | Sister chromatid exchange | + | Giri and Que Hee 1988 |

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

| Species (test system) | Endpoint | Results | Reference |
|---|---|---|---|
| Rat bone marrow cells | Chromosomal aberration | + | Lone et al. 2016 |
| Mouse peripheral blood | Micronuclei | – | Witt et al. 2000 |
| Mouse | Micronuclei | – | Jenssen and Ramel 1980; King et al. 1979 |
| Mouse, Eμ-PIM-1 | Micronuclei | – | Armstrong and Galloway 1993 |
| Rat bone marrow | Micronuclei | + | Lone et al. 2016 |
| Mouse liver, kidney, lung, and stomach | DNA binding | + | Prodi et al. 1986 |
| Mouse forestomach and kidney | DNA binding | + | Hellman and Brandt 1986 |
| Mouse liver | DNA binding | + | Banerjee 1988 |
| Mouse liver and kidney | DNA binding | + | Watanabe et al. 2007 |
| Rat liver, kidney, lung, and stomach | DNA binding | + | Prodi et al. 1986 |
| Rat liver and kidney | DNA binding | + | Inskeep et al. 1986, Watanabe et al. 2007 |
| Rat liver and lung | DNA binding | + | Baertsch et al. 1991 |
| Rat liver | DNA binding | + | Banerjee 1988, Cheever et al. 1990 |
| Mouse liver | DNA damage | + | Storer and Conolly 1983, 1985; Storer et al. 1984, Taningher et al. 1991 |
| Mouse liver and kidney | DNA damage | – | Watanabe et al. 2007 |
| Mouse liver, kidney, bladder, lung, brain, bone marrow | DNA damage | + | Sasaki et al. 1998 |
| Rat blood | DNA damage | + | Lone et al. 2016 |
| Rat liver and kidney | DNA damage | – | Watanabe et al. 2007 |
| Rat mammary tissue | DNA damage | – | Boverhof et al. 2018 |
| Insect assays | | | |
| *Drosophila melanogaster*/somatic mutation | Gene mutation | + | Ballering et al. 1994; Chroust et al. 2001, 2007; Kramers et al. 1991; Nylander et al. 1978; Romert et al. 1990; Vogel and Nivard 1993 |
| *D. melanogaster*/sex-linked recessive | Gene mutation | + | King et al. 1979; Kramers et al. 1991 |
| *D. melanogaster*/recessive lethal | Gene mutation | + | Ballering et al. 1993 |
| *D. melanogaster* | Chromosomal recombination | (+) | Rodriguez-Arnaiz 1998 |
| *D. melanogaster*/chromosome loss | Chromosomal aberration | + | Ballering et al. 1993 |
| *D. melanogaster* | DNA binding | + | Fossett et al. 1995 |

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

| Species (test system) | Endpoint | Results | Reference |
|---|---|---|---|
| Host-mediated assays | | | |
| *Escherichia coli* K12/343/113 mouse host mediated assay | Gene mutation | – | King et al. 1979 |

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

***Bacterial Mutagenicity.*** In all *Salmonella typhimurium* strains, 1,2-dichloroethane was positive for mutagenicity with activation and yielded mixed results without activation (Barber et al. 1981; Brem et al. 1974; Buijs et al. 1984; Cheh et al. 1980; Kanada and Uyeta 1978; King et al. 1979; Milman et al. 1988; Moriya et al. 1983; Nestmann et al. 1980; Rannug and Beije 1979; Rannug et al. 1978; Roldan-Arjona et al. 1991; Simula et al. 1993; Thier et al. 1993; van Bladeren et al. 1981). The presence of an exogenous mammalian metabolic system was not required, but increased mutagenic activity was observed in tests with a metabolic activation system supplemented with glutathione. The results in bacterial mutagenicity assays suggest that 1,2-dichloroethane is a very weak, direct-acting mutagen that can be activated to a more effective species by glutathione and glutathione S-transferases (DeMarini and Brooks 1992). Mutagenicity was increased in *S. typhimurium* TA100 strain expressing the alpha class of human glutathione S-transferase via regulatable tac promoter expression, but not in bacteria expressing the pi class of human glutathione S-transferase (Simula et al. 1993). S-(Chloroethyl)-cysteine itself, an analog of the proposed intermediate product of the conjugation of 1,2-dichloroethane with glutathione, was found to be a potent mutagen in *S. typhimurium* (Humphreys et al. 1990; Vamvakas et al. 1988, 1989). Mutation studies in *Escherichia coli* were primarily negative (Hemminki et al. 1980; King et al. 1979; Moriya et al. 1983).

***Clastogenicity and Aneugenicity.*** Results were positive in *in vitro* assays for mitotic segregation aberrations leading to aneuploidy in fungi exposed to 1,2-dichloroethane (Crebelli et al. 1984, 1988). Micronuclei were induced following 1,2-dichloroethane exposure in human lymphoblast cells without activation (Doherty et al. 1996) and in human peripheral lymphocytes (Tafazoli et al. 1998). S-(Chloroethyl)-cysteine, an analog of the proposed intermediate product of the conjugation of 1,2-dichloroethane with glutathione, induced micronucleus formation in mammalian cells *in vitro* (Vamvakas et al. 1988, 1989). Genotoxicity assays for clastogenic effects *in vivo* showed mixed results, with a positive effect on SCE (believed to be caused by strand breakage) in bone marrow cells of mice administered a single intraperitoneal injection of up to 16 mg/kg, but no effect on micronucleus formation in mice after a single intraperitoneal injection of between 45 and 400 mg/kg (Jenssen and Ramel 1980;

King et al. 1979). Mice administered 1,2-dichloroethane in drinking water for 90 days exhibited no increase in micronuclei in peripheral blood smears (Witt et al. 2000).

***DNA Damage, Synthesis, and Adducts.*** The evidence from available studies indicates that 1,2-dichloroethane is capable of interacting with DNA to produce genotoxic effects *in vitro*. Results were positive in *in vitro* assays for unscheduled DNA synthesis (i.e., DNA repair activity) in human and animal cells (Perocco and Prodi 1981; Milman et al. 1988; Williams et al. 1989) and DNA adducts in animal cells (Banerjee 1988; Banerjee and Van Duuren 1979; Banerjee et al. 1980; Prodi et al. 1986). Glutathione conjugation produces S-chloro ethyl conjugates (cysteine, glutathione, methyl ester, and N-acetyl derivatives). Humphreys et al. (1990) compared these derivatives and found DNA guanyl adduct alkylation with S-(2-chloroethyl)-glutathione and -cysteine yielding intermediate levels of alkylation *in vitro* (Humphreys et al. 1990).

The results of *in vivo* genotoxicity studies by all routes of exposure are summarized in Table 2-4. Inhalation exposure to 1,000 ppm 1,2-dichloroethane for 4 hours produced DNA damage in mice as evidenced by single-stranded breaks in hepatocytes, although this genetic damage was seen at a concentration that produced mortality in 80–100% of treated mice within 24 hours (Storer et al. 1984). A study of Fischer-344 rats exposed to 200 ppm of 1,2-dichloroethane by inhalation for 6 hours/day, 7 days/week for 28 days, did not find increased DNA damage in mammary epithelial cells (Boverhof et al. 2018). No effect on cell proliferation was seen in mammary epithelial cells, and DNA adduct levels, including the N7-guanylethyl glutathione crosslinks, were not considerably high compared to levels in the liver. A single oral dose of 100 mg/kg of 1,2-dichloroethane produced single-stranded breaks in hepatocytes (Storer et al. 1984). Hepatocytic DNA damage was also induced in female rats receiving two gavage doses of 1,2-dichloroethane (in corn oil) at 134 mg/kg each, but not in rats receiving two doses of 13.4 mg/kg (Kitchin and Brown 1994).

The ability of 1,2-dichloroethane to covalently bind DNA in rodents *in vivo* has been well established in the liver as well as in other organs such as the kidney and lung. DNA binding has been observed after inhalation, oral, and intraperitoneal exposures in rats and mice (Banerjee 1988; Prodi et al. 1986; Watanabe et al. 2007). DNA covalent binding indices in liver and lung were elevated in female Fischer-344 rats exposed either to 80 ppm of 1,2-dichloroethane for 4 hours (“constant-low” exposure) or 4,400 ppm for a few minutes (“peak” exposure) (Baertsch et al. 1991). However, in both the liver and the lung, the effect was much greater (approximately 35 times greater) after peak exposure, suggesting that acute-duration exposure to highly concentrated 1,2-dichloroethane may pose a greater genotoxic hazard

than protracted low-level exposure. A single oral dose of 150 mg/kg produced high levels of DNA binding in the liver of rats (Cheever et al. 1990). Structural damage to DNA, in the form of single-stranded breaks and unwinding of the DNA molecule, has also been demonstrated in mice after single intraperitoneal injections of 45–360 mg/kg (Sasaki et al. 1998; Storer and Conolly 1983, 1985; Storer et al. 1984; Taningher et al. 1991). There were no increased DNA adducts in the kidney and liver following a single intraperitoneal injection of 5 mg/kg body weight in male rats and male and female mice (Watanabe et al. 2007). Banerjee (1988) found that DNA binding was associated with decreased rates of DNA synthesis and transcription; however, the results of this study are questionable.

***Other.*** There is abundant evidence that 1,2-dichloroethane produces both somatic and sex-linked recessive lethal mutations in *D. melanogaster in vivo* (Ballering et al. 1993, 1994; Chroust et al. 2001, 2007; King et al. 1979; Kramers et al. 1991; Nylander et al. 1978; Romert et al. 1990; Vogel and Nivard 1993).

A brief account of a mouse dominant lethal assay reported reduced impregnation rate, increased preimplantation loss, and increased ratio of total embryonic loss to number of corpora lutea compared to controls in female mice mated to males that had been exposed by inhalation to 200 ppm 1,2-dichloro-ethane for 4 hours/day for 2 weeks (Zhao et al. 1989). No effects were observed after exposure to 6.3 ppm for 2 weeks, nor at any concentration after exposure durations of 1, 3, or 4 weeks. The reliability of the results is uncertain because of reporting deficiencies in the study design (Zhao et al. 1989).

No significant increase in lactose operon (lacZ) mutation frequency was seen in the liver or testes of male Muta™ mice 7, 14, or 28 days after receiving single gavage doses of 75 or 150 mg/kg 1,2-dichloroethane or successive intraperitoneal injections totaling 200 mg/kg (five doses of 40 mg/kg) or 280 mg/kg (six doses of 20 mg/kg plus four doses of 40 mg/kg) (Hachiya and Motohashi 2000). This study was limited by the large data variability observed in mutation frequency that could not be properly accounted for in statistical analysis.

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

## 3.1 TOXICOKINETICS

Information on the toxicokinetics of 1,2-dichloroethane is available from a limited number of human studies and several animal studies:

- 1,2-Dichloroethane is well absorbed after inhalation exposure through the lungs, through the gastrointestinal tract after oral exposure, and through the skin after dermal exposure in humans. In animal studies, equilibrium blood concentrations of 1,2-dichloroethane were obtained 2–3 hours after inhalation exposure, 15–60 minutes after oral exposure, and 1–2 hours after aqueous dermal exposure. Absorption probably occurs by passive diffusion for all three routes of exposure.

- Upon absorption, 1,2-dichloroethane is widely distributed within the body. Experiments in animals exposed orally or by inhalation showed that the highest concentrations of 1,2-dichloroethane (7–17 times that of the blood) were found in adipose tissue. The liver and lung were shown to have lower equilibrium levels of 1,2-dichloroethane than the blood.

- 1,2-Dichloroethane is readily metabolized in the body. The primary metabolic pathways for this chemical are oxidation by CYP and glutathione conjugation. Oxidative metabolites include 2-chloroacetaldehyde, 2-chloroethanol, and 2-chloroacetic acid. CYP metabolism of 1,2-dichloroethane appears to be saturable at oral gavage doses ~25 mg/kg and inhalation concentrations of ~150 ppm, both of which correspond to blood levels of 5–10 µg/mL. Glutathione conjugation becomes relatively more important at higher doses, and increased metabolism by this pathway may be responsible for the toxic effects noted at these high doses.

- Excretion of 1,2-dichloroethane and its metabolites is rapid; in animal studies, excretion was essentially complete 48 hours after acute-duration exposure. Following inhalation exposure to 1,2-dichloroethane, excretion of 1,2-dichloroethane was primarily in the form of metabolites (thiodiglycolic acid and thiodiglycolic acid sulfoxide) in the urine (84%), and as carbon dioxide ($CO_2$) in the exhaled air (7%). Following oral exposure to 1,2-dichloroethane, the largest percentage of the administered dose (29%) was excreted as unchanged 1,2-dichloroethane in the exhaled air, which may reflect metabolic saturation.

### 3.1.1 Absorption

1,2-Dichloroethane is readily absorbed through the lungs following inhalation exposure in both humans and experimental animals. This is expected, based on 1,2-dichloroethane's high vapor pressure of 78.9 mmHg at 20°C and high serum/air partition coefficient of 19.5 (Gargas et al. 1989). Thus, absorption occurs most likely via passive diffusion across alveolar membranes. Gargas et al. (1989) estimated a blood:air partition coefficient of 19.5±0.7 for humans, and a blood:air partition coefficient of 30.4±1.2 for F-344 rats. Nursing women exposed to 15.6 ppm of 1,2-dichloroethane in the workplace air

(with concurrent dermal exposure) accumulated the chemical in breast milk (Urusova 1953). The concentration of the chemical in milk gradually increased, reaching the maximum level 1 hour after work ended, although the validity of the results could not be assessed because of a lack of sufficient detail in reported methods and because the sample size was not provided. EPA (1980) also found 1,2-dichloroethane in the milk of lactating women. These results indicate that 1,2-dichloroethane is absorbed through the lungs by humans and accumulates (because of its high lipid-water partition coefficient) in the breast milk of nursing women. Concurrent levels of 1,2-dichloroethane in blood were not measured (EPA 1980; Urusova 1953).

Nouchi et al. (1984) reported a fatal case of 1,2-dichloroethane poisoning in a man exposed to 1,2-dichloroethane vapors for approximately 30 minutes in an enclosed space (concentration in air not specified), providing indirect evidence that this chemical undergoes absorption from inhalation exposure in humans. However, adverse effects were seen at 20 hours post-exposure, prompting the study authors to suggest that the formation of reactive metabolites is a necessary first step in the expression of 1,2-dichloroethane-induced toxicity. An alternative explanation is that the 1,2-dichloroethane is, in part, slowly released from adipose tissue or other compartments (see Section 3.1.3).

The rapid absorption of 1,2-dichloroethane following inhalation exposure has also been demonstrated in experimental animals. Reitz et al. (1980, 1982) found that peak blood levels reached a near-steady state concentration of 8 µg/mL 1–2 hours after the onset of a 6-hour inhalation exposure to 150 ppm of 1,2-dichloroethane in rats. Similar results were obtained by Spreafico et al. (1980) at inhalation exposures of 50 ppm of 1,2-dichloroethane. However, at 250 ppm of 1,2-dichloroethane, equilibrium was not achieved until 3 hours from the start of exposure. It is likely that as the concentration of inspired 1,2-dichloroethane increases, the time required to reach an equilibrium concentration of 1,2-dichloroethane in the blood also increases. Repeated exposure of rats to 200 ppm 1,2-dichloroethane for 6 hours/day for 5 days (nose-only) showed similar steady-state blood concentrations within an hour of exposure and no accumulation in the blood of rats sacrificed after multiple exposures (Saghir et al. 2006). In rats that had been exposed to 1,2-dichloroethane vapor (50 ppm) intermittently for 2 years, blood levels of 1,2-dichloroethane 15 minutes after the end of a 7-hour exposure to 50 ppm were 0.26–0.28 µg/mL (Cheever et al. 1990). Blood levels were not increased, but rather only slightly reduced after an additional 2 hours, which suggests that equilibrium had been reached during the exposure period. In mice exposed to 25, 87, or 185 ppm 1,2-dichloroethane for 6 hours, maximal blood concentrations were achieved within 2 hours and remained constant until the end of the exposure period ($C_{max}$ values of 208.06±34.79, 551.86±61.76, and 1,334.41±201.72 µg/L, respectively) (Zhong et al. 2022). 1,2-Dichloroethane was

rapidly eliminated from mouse blood with elimination half-life ($t_{1/2}$) values of 0.48±0.18, 0.43±0.012, and 0.37±0.11 hours, respectively (Zhong et al. 2022).

No studies were located regarding absorption in humans following oral exposure to 1,2-dichloroethane. However, it can be inferred from case studies, which described toxic effects (including death) after accidental (Hueper and Smith 1935) or intentional (Lochhead and Close 1951; Yodaiken and Babcock 1973) ingestion of 1,2-dichloroethane by humans. It is likely that 1,2-dichloroethane is rapidly absorbed into the systemic circulation following exposure by the oral route. 1,2-Dichloroethane is lipophilic, with a log $K_{ow}$ of 1.48, and is expected to be absorbed largely via passive diffusion across the mucosal membranes of the gastrointestinal tract.

Studies in experimental animals indicate that the oral absorption of 1,2-dichloroethane is rapid, complete, and essentially linear (Reitz et al. 1980, 1982; Spreafico et al. 1980). Reitz et al. (1982) reported that peak blood levels of 1,2-dichloroethane were reached within 15 minutes after oral administration of 150 mg/kg by gavage in corn oil to male Osborne-Mendel rats, attesting to the rapid nature of oral absorption. These investigators reported complete recovery of orally administered radioactivity (from [$^{14}$C]-1,2-dichloroethane) in exhaled air, urine, and carcass, thereby demonstrating that absorption of 1,2-dichloroethane from the gastrointestinal tract of rats is virtually complete (Reitz et al. 1980). The percentage of radioactivity recovered in the feces following inhalation or oral exposure to [$^{14}$C]-1,2-dichloroethane was 1.7–2.1%; 7.0–7.7% of the administered dose was recovered in the expired air following exposure by either route (Reitz et al. 1980). This implies that at least 90% of the inhaled or orally administered 1,2-dichloroethane was absorbed at 150 ppm and 150 mg/kg, respectively.

Data reported by Spreafico et al. (1980) supported the observation that absorption of 1,2-dichloroethane is rapid and complete. In Sprague-Dawley rats, peak blood levels were achieved within 30–60 minutes of oral administration at doses of 25, 50, and 150 mg/kg in corn oil. One-half of the low dose was absorbed within 3.3 minutes, and one-half of the high dose was absorbed within 6.4 minutes (Spreafico et al. 1980). Peak blood levels achieved were proportional to the dose administered, thus providing evidence that 1,2-dichloroethane is absorbed by passive transport across the gastrointestinal tract. Furthermore, comparison of blood levels attained after intravenous (i.e., reflective of 100% absorption) and oral administration of 1,2-dichloroethane in rats indicates that oral absorption is 100%, if first-pass effects through the liver and lung are taken into consideration (Spreafico et al. 1980).

The vehicle used in oral administration studies appears to play a role in the time course of absorption. Withey et al. (1983) found that 1,2-dichloroethane is absorbed more readily by the gastrointestinal tract when administered in water than in corn oil. Peak blood concentrations ($C_{max}$) of 1,2-dichloroethane were about 4 times higher following oral administration in water than when given in corn oil. Furthermore, the time taken to reach peak levels was approximately 3 times longer when administered in corn oil, compared to water. Similar findings were reported in rats given gavage doses of 150 mg/kg/day in corn oil ($C_{max}$ at 30 minutes) or 43 mg/kg/day in water ($C_{max}$ at 15 minutes) (Saghir et al. 2006). Repeated gavage exposure for 5 days did not result in accumulation in the blood for either vehicle; however, elimination from blood was faster in rats given water (within 2 hours) compared to rats given corn oil (by 8–16 hours after exposure) (Saghir et al. 2006). This may have important implications with regard to human exposure to 1,2-dichloroethane. Since animal data and the available information in humans indicate that oral absorption of 1,2-dichloroethane in aqueous solutions is rapid and complete, ingestion of water contaminated with high levels of 1,2-dichloroethane is of particular concern and could result in adverse health effects in humans. However, no unequivocal information was available concerning health effects in humans after long-term exposure to low levels of 1,2-dichloroethane in drinking water.

Urusova (1953) reported a gradual increase in the concentration of 1,2-dichloroethane in the breast milk of nursing women following both dermal and inhalation exposure to 1,2-dichloroethane at the workplace. Maximum levels were reached within 1 hour (2.8 mg/100 mL of milk) after skin contact and decreased over time. Eighteen hours later, the concentration of 1,2-dichloroethane in milk ranged between 0.195 and 0.63 mg/100 mL of milk. The findings of Urusova (1953) indicate that percutaneous absorption via contact with contaminated water or the chemical itself may be a potential route of exposure to 1,2-dichloroethane in humans. However, no details of analytical methodology were reported, and the sample size was not provided; thus, the reliability of these results cannot be assessed. A more recent study conducted by Gajjar and Kasting (2014) found that the majority of all applied doses of 1,2-dichloroethane to *in vitro* human skin evaporated from the skin's surface. Specifically, 0.21% of the lowest administered dose of 7.9 mg/cm$^2$ 1,2-dichloroethane was absorbed by the skin, while 0.13% of the highest administered dose of 63.1 mg/cm$^2$ was absorbed, over the course of a 24-hour period.

Studies in animals have shown that 1,2-dichloroethane is well absorbed through the skin following dermal exposure. Male rats exposed to 2 mL of 1,2-dichloroethane under cover on a shaved area of the back had blood 1,2-dichloroethane levels of 25 µg/mL after 30 minutes (Morgan et al. 1991). After 24 hours, blood levels were 135 µg/mL, and a total of 1.08 mL had been absorbed. The continued build-up of blood levels throughout the 24-hour exposure period shows that the rate of absorption exceeded that of

distribution and elimination throughout this entire period. When the experiment was repeated using solutions of 1,2-dichloroethane in water, blood levels peaked after 1–2 hours (at concentrations of 0.35–1.4 µg/mL, depending on degree of saturation of the applied solution) and then declined to control levels within 24 hours. Analysis of the aqueous solutions remaining in the exposure chamber after 24 hours showed that they contained <1% of the initial 1,2-dichloroethane concentration. This result suggests that 1,2-dichloroethane in water was rapidly and completely absorbed from solution, thus allowing elimination processes to reduce blood concentration to control levels within the 24-hour exposure period. 1,2-Dichloroethane was among the best absorbed of the 14 volatile organic compounds (VOCs) tested in this experiment. It should be noted that some degree of uncertainty exists with results from Morgan et al. (1991), as the shaving of the animals' backs abrades the stratum corneum (Hamza et al. 2015), which in turn removes a main barrier to the percutaneous absorption of VOCs like 1,2-dichloroethane. Thus, this shaving could have affected the levels of dermal absorption of 1,2-dichloroethane in the study in a way that would not be applicable in a naturally occurring setting.

Supporting data for the time course of absorption following neat exposure were obtained by Jakobson et al. (1982), who studied the dermal absorption of 1,2-dichloroethane in anesthetized guinea pigs. Blood concentrations rose rapidly during the first half-hour after application, followed by steadily increasing blood levels throughout the 12-hour exposure period. Tsuruta (1975) estimated the rate of percutaneous absorption of 1,2-dichloroethane. After a 15-minute exposure, the absorption rate through the abdominal skin of mice was 480 nmol/minute/$cm^2$. In contrast to the results of Morgan et al. (1991), comparisons of this absorption rate with those of other chlorinated hydrocarbons tested in the same study did not support the conclusion that 1,2-dichloroethane is among the more rapidly absorbed of these chemicals.

In an *in vitro* study of dermal absorption and lag time using hairless guinea pig skin carried out by two separate laboratories, Frasch et al. (2007) estimated mean steady-state fluxes ($J_{ss}$) of neat 1,2-dichloroethane of 6,280 and 3,842 µg/$cm^2$-hour by each laboratory, respectively. Compared with neat fluxes measured in the same laboratory, flux from saturated aqueous solution was slightly lower. An *in vitro* study using static diffusion cells and pig skin reported a $J_{ss}$ value of 1,360 µg/$cm^2$-hour and an apparent partition coefficient ($K_p$) of $1.9 \times 10^{-3}$ cm/hour (Schenk et al. 2018).

### 3.1.2 Distribution

1,2-Dichloroethane was detected in the breath (14.3 ppm) and breast milk (0.54–0.64 mg % [per 100 mL]) of nursing mothers 1 hour after leaving factory premises containing 15.6 ppm 1,2-dichloroethane in the air (Urusova 1953). This observation suggests a possible rapid distribution of 1,2-dichloroethane in humans following inhalation exposure, although these workers could have been exposed to the chemical over a number of days prior to and up to this observation.

The distribution of 1,2-dichloroethane in rats following a 6-hour inhalation exposure to 50 or 250 ppm occurred readily throughout body tissues; levels achieved in tissues were dose-dependent (Spreafico et al. 1980). The investigators measured 1,2-dichloroethane in blood, liver, lung, and fat, and found that blood and tissue levels reached equilibrium by 2 hours after exposure to 50 ppm and 3 hours after exposure to 250 ppm. Concentrations of 1,2-dichloroethane in liver and lung were lower than those in blood. The highest concentration of 1,2-dichloroethane was found in fat (8–9 times that seen in blood). A similar study exposed male rats to 160 ppm of 1,2-dichloroethane vapor for 6 hours and also found that the highest concentration of the chemical was distributed in abdominal fat (Take et al. 2013). 1,2-Dichloroethane was found in maternal blood (83.6±20.2 mg %), placental tissue (43.0±9.6 mg %), amniotic fluid (55.5±11.1 mg %), and fetal tissue (50.6±11.5 mg %) after inhalation exposure of female rats to 247±10 ppm 1,2-dichloroethane during pregnancy (Vozovaya 1977), but the reliability of the data is unclear. The geometric mean concentration of 1,2-dichloroethane in maternal blood and in fetuses of rats that inhaled 150–2,000 ppm for 5 hours increased linearly with increasing exposure level (Withey and Karpinski 1985), indicating transplacental distribution of 1,2-dichloroethane. The slope and intercept of the relation between fetal concentration of 1,2-dichloroethane (µg/g) and exposure level were 0.035 and -3.95, respectively, and for concentration in maternal blood (µg/g), they were 0.092 and -10.4, respectively. However, details of the methods used to detect 1,2-dichloroethane and quantify its concentration in tissues were not provided in Withey and Karpinski (1985), so the validity of the results cannot be confirmed.

No studies were located regarding distribution in humans after oral exposure to 1,2-dichloroethane. However, the wide variety of effects noted in humans following oral exposure suggest a wide distribution.

1,2-Dichloroethane was distributed readily throughout the body following oral administration of single doses to rats (Spreafico et al. 1980). As was seen following inhalation exposure, peak tissue levels were dose dependent. Spreafico et al. (1980) reported that 1,2-dichloroethane absorbed through the

gastrointestinal tract reached peak concentrations in the liver within 10 minutes. Again, equilibrium levels in liver and lung (achieved by 2 hours post-exposure) were lower than in blood, while levels in fat were 7–17 times greater than in blood. This difference in tissue levels decreased with increasing dose. Thus, there appears to be little difference between oral and inhalation exposure with regard to tissue distribution in animals, and specific target organ toxicity cannot be explained by differential distribution of 1,2-dichloroethane.

Payan et al. (1995) evaluated [$^{14}$C]-1,2-dichloroethane distribution in maternal rats following a single bolus oral dose of approximately 160 mg/kg on GD 12. At 1 hour after exposure, 50% of the orally administered dose was in gastrointestinal tract tissues, falling to 0.2% of the administered dose by 48 hours after exposure, while <1% was accounted for in the feces. Aside from the absorptive tissues, the liver and kidney accounted for most of the distributed radioactivity throughout the 48-hour post-exposure observation period, although adipose tissue and brain and spinal cord tissues, possible sites of accumulation, were not included in the evaluation. The highest tissue concentrations were found in the liver, ovary, and kidney. Transplacental distribution of radiocarbon was demonstrated by the presence of radioactivity in the developing conceptus at 1-hour post-exposure, with the highest amount in the conceptus (0.057% of administered dose) occurring at approximately 4 hours post-exposure. At 48 hours post-exposure, most of the residual radioactivity was located in the liver (0.215% of administered dose). When 160 mg/kg was administered on GD 18, the pattern of distribution was similar, except that greater accumulation occurred in the developing fetus and placenta. At 48 hours post-exposure (the 20$^{th}$ day of gestation), most of the residual radioactivity burden was located in the fetus (0.167% of administered dose) and the liver (0.156% of administered dose).

Spreafico et al. (1980) studied the distribution of 1,2-dichloroethane in rats following repeated oral administration (11 daily doses). They demonstrated that there was no difference between blood or tissue levels following either single or repeated exposure. This finding suggests that bioaccumulation of 1,2-dichloroethane does not occur with repeated oral exposure.

1,2-Dichloroethane was detected in the breast milk of nursing mothers following dermal exposure (with probable concurrent inhalation exposure) to liquid 1,2-dichloroethane at the workplace (Urusova 1953). The concentration in milk gradually increased, with the maximum level (2.8 mg %) reached 1 hour after work ended. Eighteen hours later, the levels in milk ranged from 0.195 to 0.63 mg %. This study did not report the dermal exposure concentration of 1,2-dichloroethane. Because of the lack of details on methodology, the validity of these findings cannot be assessed.

No studies regarding distribution in animals following dermal exposure to 1,2-dichloroethane were located. Since the tissue distribution of this chemical did not appear to be route-dependent after either inhalation or oral exposure, and since it is well absorbed through the skin, the distribution pattern of 1,2-dichloroethane following percutaneous application may possibly resemble that observed following exposure via other routes.

No studies were located regarding distribution in humans after parenteral exposure to 1,2-dichloroethane.

Mice exposed to radiolabeled 1,2-dichloroethane by a single intravenous injection had high levels of tightly bound radioactivity in the nasal mucosa and tracheobronchial epithelium within 1 minute of exposure; these levels persisted throughout the 4-day observation period (Brittebo et al. 1989). Lower levels of radioactivity were bound to epithelia of the upper alimentary tract, eyelid, and vagina, as well as the liver, kidney, adrenal cortex, and submaxillary gland. The bound radioactivity was considered to represent nonvolatile reactive metabolites formed in the tissues where it was found. A study of tissue kinetics of 1,2-dichloroethane in rats after a single intravenous dose of 15 mg/kg reported preferential initial distribution to fat (Withey and Collins 1980) and first-order elimination from each tissue studied (except blood). The estimated initial concentration in fat was 36.9 µg/g, while for other soft tissues (including heart, lung, liver, spleen, kidney, and brain), the initial concentrations were relatively uniform, with estimates ranging from 4.2 to 9.2 µg/g. The study also showed that distributed 1,2-dichloroethane remained in fat longer than in other soft tissues, as indicated by a lower estimated elimination coefficient in fat (0.0088 $minute^{-1}$) relative to other tissues (ranged from 0.0226 to 0.0514 $minute^{-1}$).

*In vitro* tissue:air partition coefficients were measured using rat tissue homogenates and the vial equilibration method (Saghir et al. 2006). Mean tissue:air partition coefficients in the brain, kidney, testis, and ovary were 39.50±2.89, 44.89±6.77, 31.14±7.98, and 74.59±9.82, respectively.

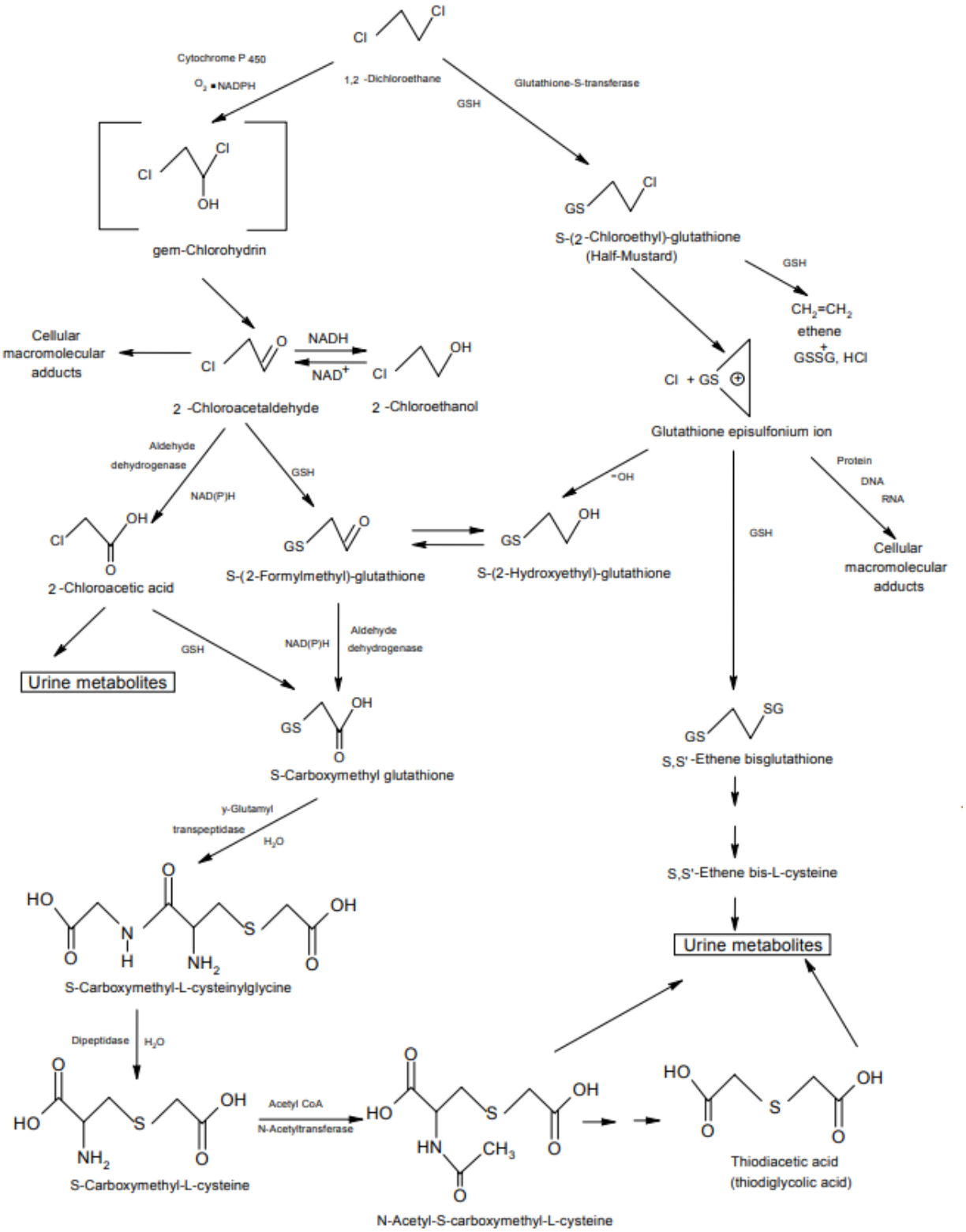
### 3.1.3 Metabolism

No studies regarding metabolism in humans following inhalation, oral, or dermal exposure to 1,2-dichloroethane were located. The biotransformation of 1,2-dichloroethane has been studied extensively in rats and mice both *in vivo* and *in vitro*. Proposed metabolic pathways for 1,2-dichloroethane are shown in Figure 3-1. The results of the *in vivo* studies indicate that 1,2-dichloroethane is readily metabolized in the body, the primary route of biotransformation involves conjugation with glutathione to yield nonvolatile urinary metabolites, and the enzymes involved in the biotransformation of 1,2-dichloroethane are saturable at approximately 25 mg/kg/day (gavage) and 150 ppm (inhalation) in rats (D'Souza et al. 1988; Reitz et al. 1982; Spreafico et al. 1980). Metabolic saturation appears to occur at lower concentrations after gavage administration than after inhalation exposure. A physiological pharmacokinetic model explains the route-of-exposure difference in quantifying the amount of 1,2-dichloroethane-glutathione conjugate produced in target organs after oral and inhalation exposures (D'Souza et al. 1987, 1988).

Zeng et al. (2019) attributed hepatic apoptosis to down-regulation of an anti-apoptosis insulin growth factor *in vitro*. The researchers hypothesized this was due to 2-chloroacetaldehyde, an oxidative metabolite of 1,2-dichloroethane. 2-Chloroacetaldehyde is a very potent mutagen *in vitro* (McCann et al. 1975). Several researchers have also presented *in vitro* evidence that 1,2-dichloroethane is activated to a mutagen by glutathione conjugation (Rannug et al. 1978; van Bladeren et al. 1979). Electrophilic episulfonium ions formed via the glutathione pathway are believed to bind to DNA and cause genetic damage (Guengerich et al. 1987). Kramer et al. (1987) described the role of glutathione-generated episulfonium ions in 1,2-dichloroethane-induced nephrotoxicity in rats. Results of relatively recent research indicate that oxidative metabolites of 1,2-dichloroethane are also responsible for kidney injury.

Reitz et al. (1982) studied the metabolism of 1,2-dichloroethane in male rats following a 6-hour exposure to 150 ppm of [$^{14}$C]-1,2-dichloroethane. The exact metabolic pathways were not determined, but an observed depression of hepatic nonprotein sulfhydryl groups may indicate that glutathione plays a major role in the metabolism of 1,2-dichloroethane following inhalation exposure. Saturation of biotransformation enzymes was not apparent at this dose since 84% of the administered $^{14}$C was recovered as urinary metabolites and only 2% of the administered $^{14}$C was recovered as parent compound in the expired air. However, the data of Spreafico et al. (1980) suggest that saturation does occur after inhalation exposure in rats, since peak blood levels of 1,2-dichloroethane rose 22-fold when the exposure concentration was increased from 50 to 250 ppm. Based on the data of these two groups of investigators,

## Figure 3-1. Proposed Pathways for 1,2-Dichloroethane Metabolism




Source: NTP (1991)

it appears that saturation of 1,2-dichloroethane metabolism occurs when blood levels reach 5–10 µg/mL blood or after exposure to 150–250 ppm 1,2-dichloroethane. When blood concentrations of 1,2-dichloroethane exceed these levels (i.e., at exposure concentrations >150 ppm), manifestations of toxicity became more apparent. For example, Maltoni et al. (1980) reported that most of the toxicity associated with inhalation exposure to 250 ppm 1,2-dichloroethane in rats and mice was alleviated when exposure levels were reduced to 150 ppm, and no treatment-related effects were noted at 50 ppm. These findings suggest that 1,2-dichloroethane-induced toxicity occurs once a threshold blood level has been exceeded.

Reitz et al. (1982) also studied the metabolism of 1,2-dichloroethane following the administration of single oral doses of 150 mg/kg [$^{14}$C]-1,2-dichloroethane. Again, the exact metabolic pathways were not determined, but the observation that hepatic nonprotein sulfhydryl groups were depressed indicated that glutathione may also play a major role in the metabolism of 1,2-dichloroethane following oral exposure. Saturation of biotransformation enzymes was apparent at this dose since only 60% of the administered radiolabel was recovered as urinary metabolites, and 29% of the administered radiolabel was associated with unchanged parent compound in the expired air. As with inhalation, it appeared that saturation of 1,2-dichloroethane metabolism occurred when blood levels reached 5–10 µg/mL blood or after administration of ~25 mg/kg 1,2-dichloroethane (D'Souza et al.1988; Reitz et al. 1982; Spreafico et al. 1980). This blood threshold level again correlated with observed toxicity in animal studies (NCI 1978), as discussed above.

Although the saturable pathways appear to be the same for both oral and inhalation exposure, oral administration of 1,2-dichloroethane by gavage results in saturation at lower administered doses than inhalation exposure. Reitz et al. (1982) demonstrated that administration of 150 mg/kg 1,2-dichloroethane by gavage resulted in a 1.3-fold higher absolute dose to the animals than 150 ppm via inhalation (which is approximately equal to 502 mg/kg). Gavage administration produced approximately twice as much total metabolite as inhalation, and peak levels of 1,2-dichloroethane in blood were almost 5 times higher following gavage versus inhalation. Gavage administration does not represent typical oral exposure in humans. Gavage administration results in large bolus doses absorbed at one time thereby leading to spikes in blood levels and a more pronounced expression of toxicity. Oral exposure to 1,2-dichloroethane by humans will most likely occur via ingestion of contaminated drinking water in small doses spread out over the course of a day. In such instances, biotransformation processes will probably not become saturated; thus, the risk for adverse effects is not as high as would be predicted from gavage administration of equivalent doses.

In female albino mice given 1,2-dichloroethane intraperitoneally, the metabolism of 1,2-dichloroethane appeared to be initiated by hydrolytic dehalogenation followed by reduction to yield 2-chloroethanol (Yllner 1971). This was then converted to 2-chloroacetic acid by microsomal oxidation. Final metabolites identified in the urine of these animals in percent radioactivity recovered included *S*-carboxymethyl-L-cysteine (44–46% free; 0.5–5% conjugated), thiodiacetic acid (33–34%), *S,S'*-ethylene-*bis*-cysteine (1.0%), which are indicative of glutathione conjugation, in addition to chloroacetic acid (6–23%) and 2-chloroethanol (0–0.8%) (see Figure 3-1).

The pathways of 1,2-dichloroethane metabolism have been elucidated primarily by *in vitro* studies in isolated rat hepatic microsomes.

In one *in vitro* study, 1,2-dichloroethane was metabolized mainly to 2-chloroacetaldehyde by hepatic nuclear CYP (Casciola and Ivanetich 1984). Guengerich et al. (1980) proposed a pathway involving microsomal CYP (in the presence of oxygen and NADPH) and mixed function oxidase (MFO) to explain the production of 2-chloroacetaldehyde. 1,2-Dichloroethane undergoes oxygen insertion to yield an unstable chlorohydrin, which spontaneously dechlorinates to form 2-chloroacetaldehyde that can react with macromolecules. 2-Chloroacetaldehyde can also be reduced to chloroethanol or be further oxidized to chloroacetic acid. Guengerich et al. (1991) demonstrated that CYP2E1 is the primary oxidation catalyst of 1,2-dichloroethane in humans.

Conjugation of 1,2-dichloroethane with glutathione is proposed to be a major metabolic pathway *in vivo* (Yllner 1971); this has been confirmed by the *in vitro* studies of Livesey and Anders (1979), Anders and Livesey (1980), and Jean and Reed (1989). This pathway is outlined on the right side of Figure 3-1. The depletion of hepatic glutathione by 1,2-dichloroethane has been demonstrated *in vitro* (Albano et al. 1984) and *in vivo* in rats exposed by inhalation or gavage (Saghir et al. 2006). Johnson (1967) demonstrated that, *in vitro*, conjugation of 2-chloroacetic acid with glutathione also proceeded by a nonenzymatic process, yielding S-carboxymethylglutathione. This compound subsequently degraded to yield glycine, glutamic acid, and S-carboxymethylcysteine. S-Carboxymethylcysteine may then be further oxidized to thiodiglycolic acid. Both S-carboxymethylcysteine and thiodiglycolic acid were found as urinary metabolites in rats and mice given 1,2-dichloroethane *in vivo* (Spreafico et al. 1980; Yllner 1971). This scheme is also supported by studies with 1,2-dibromoethane (Nachtomi et al. 1966; van Bladeren 1983).

### 3.1.4 Excretion

Women inhaling approximately 15.6 ppm 1,2-dichloroethane present in the workplace air eliminated the compound unchanged in the expired air. Similar observations were also reported in women exposed via dermal contact to liquid 1,2-dichloroethane. In both cases, the amount of 1,2-dichloroethane in the expired air was greater immediately following exposure and decreased gradually with time (Urusova 1953).

Elimination of 1,2-dichloroethane following inhalation exposure in rats occurred primarily via the excretion of soluble metabolites and unchanged parent compound in the urine and carbon dioxide in the expired air (Reitz et al. 1982; Spreafico et al. 1980). Urinary metabolites accounted for 84% of the absorbed dose, unchanged fecal 1,2-dichloroethane accounted for 2%, and carbon dioxide accounted for 7% of the absorbed dose following the inhalation of 150 ppm by rats (Reitz et al. 1982). The primary urinary metabolites identified in rats following inhalation exposure were thiodiacetic acid (70%) and thiodiacetic acid sulfoxide (26–28%). The rapidity of elimination is demonstrated by the fact that a few hours after exposure, 1,2-dichloroethane was not detected in blood and was detected only to a small extent 48 hours after exposure in various tissues (liver, kidney, lung, spleen, forestomach, stomach, carcass) (Reitz et al. 1982). Rapid elimination was also observed in mice exposed to 25, 87, or 185 ppm 1,2-dichloroethane for 6 hours, with clearance from the blood being near complete within an hour after exposure (Liang et al. 2021; Zhong et al. 2022). A concentration-dependent increase in urinary 2-chloroacetic acid levels was observed in mice following 28 days of exposure to 25, 87, or 185 ppm 1,2-dichloroethane for 6 hours/day, 5 days/week (approximately 300, 1,000, and 1,300 µg/L, respectively) (Liang et al. 2021).

Spreafico et al. (1980) studied the kinetics of 1,2-dichloroethane excretion in rats following inhalation exposure of 50 or 250 ppm 1,2-dichloroethane for 5 hours. They determined that elimination was monophasic with the half-times of 12.7 and 22 minutes at 50 and 250 ppm exposure, respectively. The disappearance of 1,2-dichloroethane was dose-dependent since the percentage of parent compound recovered in the expired air increased exponentially with dose. This was presumably a reflection of the saturable metabolic processes. Spreafico et al. (1980) also determined that elimination of 1,2-dichloroethane from adipose tissue was slower than elimination of 1,2-dichloroethane from the blood, liver, and lung.

No studies were located regarding excretion in humans after oral exposure to 1,2-dichloroethane.

Elimination of 1,2-dichloroethane following oral administration in rats was also rapid and occurred primarily via excretion of soluble metabolites in the urine, and unchanged parent compound and carbon dioxide in the expired air (Mitoma et al. 1985; Payan et al. 1993; Reitz et al. 1982; Spreafico et al. 1980). Reitz et al. (1982) conducted a complete $^{14}C$-balance study in male Osborne-Mendel rats and found that urinary metabolites accounted for 60% of the radioactivity administered as a single oral dose of 150 mg $^{14}C$-1,2-dichloroethane/kg body weight. Unchanged 1,2-dichloroethane in the breath accounted for 29% and carbon dioxide in the breath accounted for 5% of the administered radioactivity. The remaining 6% of the administered radioactivity was recovered in the carcass, feces, and cage washes. The primary urinary metabolites identified were the same as those seen following inhalation exposure: thiodiacetic acid (70%) and thiodiacetic acid sulfoxide (26–28%). Elimination of 1,2-dichloroethane was 96% complete within 48 hours. The results were similar in rats given a single gavage dose of 150 mg/kg following 2 years of intermittent inhalation exposure to 50 ppm of 1,2-dichloroethane (Cheever et al. 1990).

Mitoma et al. (1985) studied the elimination of single gavage doses of $^{14}C$-labeled 1,2-dichloroethane from rats and mice (doses of 100 and 150 mg/kg, respectively, in corn oil) after pretreatment with unlabeled compound 5 days/week for 4 weeks. At 48 hours after administration of the radiolabeled compound, expired volatile metabolites, $CO_2$, excreta (feces and urine), and the carcass accounted for approximately 11.5, 8.2, 69.5, and 7% of administered radioactivity in rats, respectively, and 7.7, 18.2, 81.9, and 2.4% of the administered dose in mice, respectively.

Spreafico et al. (1980) studied the kinetics of 1,2-dichloroethane excretion in rats following the oral administration of 50 mg/kg 1,2-dichloroethane (in corn oil) and found that kinetics were best described by a two-compartment model. Withey et al. (1983) reported that administration in water resulted in a shorter elimination half-time than administration in vegetable oil. Reitz et al. (1982) also reported a two-compartment model of elimination following the gavage administration of 150 mg/kg 1,2-dichloroethane. The initial elimination phase had a half-life of 90 minutes, but elimination became more rapid when blood levels fell to 5–10 µg/mL, characterized by a half-life of approximately 20–30 minutes. This is in contrast, however, to what was observed following inhalation exposure. Spreafico et al. (1980) suggested that the oral profile represented both an absorption-distribution phase and an elimination phase, whereas the inhalation profile reflected only elimination. This elimination of 1,2-dichloroethane was also dose-dependent following oral administration in rats, as the percentage of parent compound recovered in the expired air increased exponentially with dose. Again, this is a

reflection of saturable metabolic processes. The rate of elimination from adipose tissue was similar to that from blood and other tissues, in contrast to the results for inhalation exposure.

These results indicate that 1,2-dichloroethane will most likely not accumulate in nonlipid components of the human body following repeated exposure by any route, as elimination of the compound is rapid and complete. Available data also suggest that 1,2-dichloroethane is not particularly persistent in adipose tissue following oral exposure (Spreafico et al. 1980), but it may accumulate to some extent in adipose tissue after inhalation exposure (Spreafico et al. 1980). In the past, 1,2-dichloroethane was detected in human milk of nursing women (Urusova 1953), but more recent data showing 1,2-dichloroethane in breast milk were not located. Historic data likely reflect exposures from former use patterns that are no longer relevant today.

1,2-Dichloroethane was eliminated unchanged in the expired air following dermal exposure of nursing mothers to liquid 1,2-dichloroethane in the workplace (Urusova 1953). The amount of 1,2-dichloroethane in the expired air was greatest immediately after skin contact and gradually decreased with time.

No studies were located regarding excretion in animals after dermal exposure to 1,2-dichloroethane.

Studies conducted in animals in which 1,2-dichloroethane was administered via other routes (e.g., intraperitoneal or intravenous) support the findings of the studies discussed above; excretion of 1,2-dichloroethane via urine and expired air was rapid and complete, and the route of excretion as well as the form of the chemical excreted were dose-dependent (Spreafico et al. 1980; Yllner 1971).

Estimates of an elimination constant (ke) for 1,2-dichloroethane were similar between two- and three-compartment pharmacokinetic models fitted to a time-series of blood concentration data that were obtained from rats given single intravenous doses (Withey and Collins 1980). The ke values for elimination from blood were roughly inversely related to dose; mean values of 0.143, 0.122, 0.091, 0.096, or 0.097 were obtained at dose levels of 3, 6, 9, 12, or 15 mg/kg, respectively.

### 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.

Two PBPK models have been developed to describe the amount of 1,2-dichloroethane and its metabolites that reach the blood and target tissues following different exposure routes in rats (D'Souza et al. 1987, 1988; Sweeney et al. 2008). The Sweeney et al. (2008) PBPK model was developed as an extension and refinement of the previously developed D'Souza et al. (1987, 1988) model.

The D'Souza et al. (1987, 1988) model simulates the metabolism and distribution of 1,2-dichloroethane in rats using five compartments: lung, liver, richly perfused tissues (such as kidney and spleen), slowly perfused tissues (such as muscle and skin), and fat. The model assumes that metabolism of 1,2-dichloroethane in the body only occurs in the lung and the liver and is designed to account for exposure by the inhalation and ingestion routes. 1,2-dichloroethane is metabolized by both a saturable oxidation pathway and direct conjugation with glutathione. The model predicts that inhalation exposures to 1,2-dichloroethane produce less glutathione-conjugate metabolites in the liver and lung of rats than equivalent oral exposures. The model was validated experimentally for both rats and mice.

Sweeney et al. (2008) used the D'Souza et al. (1987, 1988) model as the basis for developing an updated PBPK model that reflected advances in knowledge of 1,2-dichloroethane metabolism since the first model was developed. This updated model had a revised oral absorption rate, a revised constant for the time delay for resynthesis of glutathione following depletion and included a revision to the levels of glutathione in the lungs versus the liver. The updated model also included two new gastrointestinal compartments, as well as a separate compartment for the kidney, which was previously grouped with the richly perfused tissues. The model also added an additional metabolism pathway through unspecified extrahepatic enzymes. The predictions from this updated model were then compared with 1,2-dichloroethane kinetics study results from a multitude of studies with varying routes of exposure: intravenous dosing, closed chamber inhalation, open chamber inhalation, gavage in water, and gavage in oil. The model performed well for single or repeated exposure to the chemical for each of these routes of exposure in four strains of rats. The Sweeney et al. (2008) model was used in Sweeney and Gargas (2016) to extrapolate the oral NOAEL and LOAEL of existing health effect studies in rats to the

inhalation route. However, it is unclear how well the Sweeney et al. (2008) model would perform in extrapolating doses between species, such as between rats and humans.

### 3.1.6 Animal-to-Human Extrapolations

The metabolism of 1,2-dichloroethane has not been studied in humans. The lack of this information precludes a non-speculative attempt to discuss potential interspecies differences or similarities in the toxicity of 1,2-dichloroethane, as well as a determination of which animal species is the most appropriate model for humans. Extrapolations of 1,2-dichloroethane oral toxicity data from animals to humans should consider the type of exposure because some of the differences in toxic and carcinogenic responses in animal studies can be explained on the basis of saturation of the detoxification/excretion mechanism due to bolus (gavage) administration. Frasch et al. (2007), however, did provide evidence that the use of hairless guinea pig skin was a strong model for 1,2-dichloroethane dermal permeability in humans, as no significant differences were found between human and hairless guinea pig skin in permeability coefficients or lag times.

## 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-dichloroethane are discussed in Section 5.7, Populations with Potentially High Exposures.

### 3.2.1 Children's Susceptibility

Data on the health effects of 1,2-dichloroethane exposure in children are limited to a single case report of a 14-year-old boy who swallowed 15 mL of the compound (Yodaiken and Babcock 1973). The most immediate signs of toxicity were headache and staggering gait within 2 hours of exposure, followed soon after by lethargy and vomiting. During the next few days, the boy developed symptoms of toxicity, increasing in variety and severity, that involved several organ systems, including adverse hematological effects, pulmonary edema, cardiac arrest (he was resuscitated), and eventual death on the 5$^{th}$ day after exposure from massive hepatic necrosis and renal tubular necrosis. Data from this case report and from reports of adult humans who died following acute-duration exposure to high levels by inhalation or ingestion are consistent with animal studies indicating that the main targets of acute toxicity include the central nervous system, respiratory tract, stomach, liver, and kidneys. Considering the consistency of effects in acutely exposed humans and animals, and data showing that the liver, kidney, and immune system are sensitive targets of lower-dose and longer-term inhalation and oral exposures in animals, it is reasonable to assume that effects in these tissues would also be seen in similarly exposed adults and children.

No studies that provide reliable information on adverse developmental effects in humans exposed to 1,2-dichloroethane are available. A cross-sectional epidemiologic study that investigated whether elevated levels of routinely sampled organic contaminants in New Jersey public water systems, including 1,2-dichloroethane, were associated with increased prevalence of adverse birth outcomes (Bove 1996; Bove et al. 1995) was located. A number of associations between various chemicals and birth outcomes were found, including a positive association between ingestion of 1,2-dichloroethane in drinking water and major cardiac birth defects; however, the mixed chemical exposures indicate that the results are only suggestive, do not establish a cause-and-effect relationship, and should be interpreted with caution.

Studies in rats, mice, and rabbits indicate that 1,2-dichloroethane is not developmentally toxic following inhalation or oral gestational exposure, although indications of embryo lethality at maternally toxic doses have been reported (Kavlock et al. 1979; Lane et al. 1982; Payan et al. 1995; Rao et al. 1980). While Kavlock et al. 1979 reported no developmental effects, limitations of the study include treatment using municipal water sources and a mixture of volatile components, so the concentration and relative contribution of 1,2-dichloroethane is unclear.

Evidence from mouse studies suggests that the specific nature of oral exposure may play a role in the degree of immunotoxicity expressed in young animals. Bolus doses of 1,2-dichloroethane appear to be more effective in eliciting an immunotoxic response than drinking-water exposures in 5-week-old mice. There was a significant, dose-related reduction in IgM response to sheep erythrocytes, and a significant, but not dose-related, reduction in delayed-type hypersensitivity response to sheep erythrocytes in 5-week-old CD-1 mice exposed for 14 days by gavage to 4.9 and 49 mg/kg/day (Munson et al. 1982). In mice provided 49 mg/kg/day, these effects were accompanied by a 30% decrease in total leukocyte number. In contrast, mice given drinking water containing 189 mg/kg/day of 1,2-dichloroethane for 90 days beginning at 5 weeks of age displayed no treatment-related effects on either the antibody-forming cell response or the delayed-type hypersensitivity response after immunization with sheep erythrocyte antigens (Munson et al. 1982). The fact that the animal evidence for oral immunotoxicity of 1,2-dichloroethane includes decreased immune responses in 5-week-old mice provides a limited indication of the potential susceptibility of children to immunotoxic effects, particularly after bolus ingestion by children, that could occur, for example, with accidental ingestion of older household products that contain 1,2-dichloroethane.

Young mice were also susceptible to reduced immune function after brief inhalation exposure to 1,2-dichloroethane. A single 3-hour exposure to 5–11 ppm of 1,2-dichloroethane induced increased susceptibility to *S. zooepidemicus* (i.e., increased mortality following infection) in 4–5-week-old female mice, suggesting reduced pulmonary immunological defenses in the exposed mice (Sherwood et al. 1987). No immunological effects were observed at 2.3 ppm. Young female mice exposed to 11 ppm also had reduced bactericidal activity in the lungs 3 hours after inhalation challenge with *K. pneumoniae*. In contrast, young male rats (ages ranging from 4 to 5 weeks) that were exposed once to 200 ppm for 5 hours or 100 ppm 5 hours/day for 12 days did not exhibit any increased susceptibility to infection from these microbes, suggesting that rats may be less susceptible to the detrimental immunological effects of 1,2-dichloroethane than mice and/or that male rodents are less susceptible than females (Sherwood et al. 1987). The relevance of the young mouse inhalation data to child susceptibility is unknown, particularly in the light of the observed interspecies differences. However, the data do suggest that it would be prudent to prevent 1,2-dichloroethane inhalation exposures in children.

No studies that evaluated for the distribution of 1,2-dichloroethane or its metabolites across the placenta in humans were located. However, there is some evidence that 1,2-dichloroethane and/or its metabolites cross the placenta after inhalation and oral exposures in animals. 1,2-Dichloroethane was found in maternal blood (83.6±20.2 mg %) [per 100 mL], placental tissue (43.0±9.6 mg % [per 100 mg]), amniotic

fluid (55.5±11.1 mg % [per 100 mL]), and fetal tissue (50.6±11.5 mg % [per 100 mg]) after inhalation exposure of female rats to 247±10 ppm 1,2-dichloroethane during pregnancy (Vozovaya 1977). Additional evidence of transplacental distribution of 1,2-dichloroethane after inhalation exposure is provided by Withey and Karpinski (1985), who found that the geometric mean concentration of 1,2-dichloroethane in the fetuses of rats that inhaled 150–2,000 ppm for 5 hours increased linearly with increasing exposure level. However, the reliability of the Vozovaya (1977) data is unclear, and the methods for evaluating 1,2-dichloroethane tissue concentrations were not reported in Withey and Karpinski (1985).

There is clearer evidence for transplacental distribution of 1,2-dichloroethane and/or its metabolites after maternal oral exposure. Payan et al. (1995) evaluated [$^{14}$C]-1,2-dichloroethane distribution in maternal rats following a single oral bolus dose of approximately 160 mg/kg on GD 12 or 18. In both cases, transplacental distribution of radiocarbon was demonstrated by the presence of radioactivity in the developing conceptus. A greater accumulation occurred in the developing fetus and placenta 48 hours after the GD 18 administration than after the GD 12 administration. At 48 hours after the GD 18 dosing, the majority of residual radioactivity burden was located in the fetus (0.167% of administered dose) and the liver (0.156% of administered dose).

No studies regarding 1,2-dichloroethane metabolism in children were located. The metabolism of 1,2-dichloroethane is well described (see Figure 3-1), and it is reasonable to assume that the metabolic pathways are, for the most part, the same between adults and children. However, the expression of certain enzymes is known to be developmentally regulated, and one of these enzymes may be involved in 1,2-dichloroethane metabolism. NAT is involved in 1,2-dichloroethane metabolism at a step subsequent to glutathione conjugation (see Figure 3-1). NAT performs the N-acetylation of S-carboxymethyl-L-cysteine to N-acetyl-S-carboxymethyl-L-cysteine, a major urinary metabolite. There are, however, two NATs (NAT1 and NAT2) that are expressed in humans with separate but overlapping substrate specificities (Parkinson 1996). NAT2 is apparently expressed only in the liver and the gut (Parkinson 1996) and is known to be developmentally regulated (Leeder and Kearns 1997). Some NAT2 activity is present in the fetus at 16 weeks, but NAT2 activity is low in virtually 100% of infants, not reaching adult activity levels until 1–3 years of age (Leeder and Kearns 1997). It is not clear in NTP (1991) whether the NAT involved in 1,2-dichloroethane metabolism is NAT1 or NAT2, although both enzymes N-acetylate some xenobiotics equally well (Parkinson 1996). Additionally, CYP2E1 levels in human infants steadily increase from infancy to adulthood, where fetal samples were found to have undetectable levels of CYP2E1, infants 1–3 months of age exhibited mean levels of the enzyme of about 10% of adult values,

infants 3–12 months of age exhibited mean values of about 30% of adult values, and children between 1 and 10 years of age exhibited mean values no different than adults, suggesting an age-dependent increase in CYP2E1 levels (Hines 2008; Vieira et al. 1998). There is less of a consensus about the general ontogeny of glutathione in humans (Hines 2008).

In the past, 1,2-dichloroethane has been detected in human milk (EPA 1980; Urusova 1953), indicating that developing children could possibly be exposed to 1,2-dichloroethane from breast-feeding mothers. However, historic data likely reflect exposures from former use patterns that are no longer relevant today. Thus, the importance of this route of developmental exposure is unclear because current data on the concentration of 1,2-dichloroethane in breast milk are not available. 1,2-Dichloroethane also accumulated in the adipose tissue of rats after inhalation exposure and was eliminated from fat more slowly than from blood, liver, and lung (Spreafico et al. 1980), suggesting the possibility that the maternal body burden of 1,2-dichloroethane in fat could be available for exposure to the fetus or nursing infant for a somewhat extended period after maternal exposure. Supporting data for relatively slow elimination of 1,2-dichloroethane from fat are provided in an intravenous exposure study in rats (Withey and Collins 1980).

### 3.2.2 Other Populations that are Unusually Susceptible

Populations that drink alcohol may be likely to experience increased liver toxicity when exposed to 1,2-dichloroethane. 1,2-Dichloroethane is a known substrate for human CYP2E1 (Gonzalez and Gelboin 1994). CYP 2E1 is induced in people who frequently drink alcohol, as well as people with medical conditions such as diabetes. It is likely that the induction of this enzyme increases the amount of 1,2-dichloroethane that is metabolized via this pathway rather than by glutathione conjugation, allowing for binding of the increased quantities of oxidative metabolites to the target organ. Mice with increased CYP2E1 expression exhibited enhanced metabolism of 1,2-dichloroethane to reactive intermediates, increased oxidative stress, resulting in enhanced susceptibility to hepatotoxic effects (Sun et al. 2016). Cottalasso et al. (2002) found that 1,2-dichloroethane increased liver toxicity in rats following chronic ethanol consumption. In *in vitro* experiments conducted on isolated hepatocytes from rats chronically exposed to ethanol (which induces CYP2E1) and 25 µL of 1,2-dichloroethane added to the closed system, it was found that 1,2-dichloroethane hepatotoxicity was enhanced by further increasing levels of ALT, AST, and LDH (Cottalasso et al. 2002).

Inactivation of plasma alpha-1-proteinase inhibitor has been proposed to be an important factor in the development of lung emphysema. The occurrence of a synergistic inactivation of plasma alpha-1 proteinase inhibitor by 1,2-dichloroethane and cigarette smoke components (acrolein and pyruvic aldehyde) *in vitro* suggests that smokers as well as those exposed to passive smoke may be more susceptible to lung emphysema following repeated exposure to 1,2-dichloroethane (Ansari et al. 1988). Further, those with genetically reduced plasma alpha-1-proteinase inhibitor, who are predisposed to emphysema, may be at increased risk.

## 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-dichloroethane 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-dichloroethane 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-dichloroethane 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

Levels of 1,2-dichloroethane in breath, blood, and urine may be used to indicate exposure to this chemical. However, 1,2-dichloroethane is rapidly eliminated from the body (see Section 3.1.4); thus, if measurements are not made close to the time of exposure, 1,2-dichloroethane may not be detected. Therefore, the rapid elimination would limit the time when sampling may result in detection of 1,2-dichloroethane. A number of studies have investigated the relationship between tissue and environmental levels of 1,2-dichloroethane. In general, small amounts of 1,2-dichloroethane detected in the breath and urine (trace–0.2 ppb and 50–140 ng/L, respectively) were associated with exposure to 1,2-dichloroethane in air and water (trace–100 ng/$m^3$ and 50 mg/L, respectively) (Barkley et al. 1980; Conkle et al. 1975). In two studies conducted by Wallace et al. (1984, 1986), levels of 1,2-dichloroethane in breath samples from 350 residents of New Jersey were consistently below the detection limit; therefore, no conclusions could be drawn from these studies. 1,2-Dichloroethane was also detected in the breath (14.3 ppm) and breast milk (0.54–0.64 mg %) of nursing women working in factory premises containing 15.6 ppm 1,2-dichloroethane in air (Urusova 1953). These data are insufficient to quantify the relationship between environmental exposure to 1,2-dichloroethane and resultant tissue and fluid levels.

Urinary excretion of thioethers is another biomarker of exposure to 1,2-dichloroethane. Payan et al. (1993) showed in male Sprague-Dawley rats during a 24-hour post-administration period that total excreted urinary thioethers increased linearly with increasing oral dose (for doses between 0.25 and 4.04 mmol/kg [11.9 mg/kg/d and 400 mg/kg/d, respectively]), at a rate of 0.028 mmol thiol group eliminated per millimole of 1,2-dichloroethane administered. This occurred in spite of the fact that the total percentage of orally administered radioactivity excreted in the urine decreased with increasing dose (possibly due to saturation of certain metabolic pathways leading to urinary metabolites). Thioethers are commonly produced by conjugation reactions involving glutathione and comprise the primary urinary metabolites of 1,2-dichloroethane (see Sections 3.1.3 and 3.1.4). Increased urinary excretion of thioethers following exposure to 1,2-dichloroethane has been demonstrated in rats (Igwe et al. 1988; Payan et al. 1993), showing that this endpoint is sensitive to 1,2-dichloroethane exposure. Payan et al. (1993),

however, found that urinary thiodiglycolic acid (measured by gas chromatography), a thioether compound that is not extractable by alkaline hydrolysis, is a more sensitive marker of 1,2-dichloroethane exposure than total thioethers. As discussed above for the parent compound, rapid excretion of 1,2-dichloroethane and metabolites (essentially complete after 48 hours in animal studies) means that measurements would have to be made at a known time since exposure to be of any quantitative value. There is an additional problem with use of increased urinary thioether excretion as a biomarker for 1,2-dichloroethane exposure. Since many xenobiotics form conjugates with glutathione, exposure to any number of compounds may increase urinary excretion of total thioethers (Monster 1986). Therefore, its use as a biomarker of 1,2-dichloroethane exposure is limited unless exposure to other compounds can be ruled out.

Kim and Guengerich (1989) found that urinary mercapturic acid was linearly dose-related to intraperitoneally injected 1,2-dibromoethane in rats, and the urinary excretion of mercapturic acid was correlated with formation of hepatic and renal DNA adducts. It is possible that a similar relationship exists for relevant 1,2-dichloroethane exposures, although the methods proposed by Kim and Guengerich (1989) would not discriminate between other halogenated ethane compounds (e.g., 1,2-dibromoethane).

Erve et al. (1996) investigated whether human hemoglobin, alkylated with the episulfonium ion of S-(2-chloroethyl) glutathione (a 1,2-dichloroethane metabolite via the glutathione-conjugation metabolic pathway), could be a useful biomarker for human exposure to 1,2-dichloroethane. They found that the method was not a very sensitive indicator for exposure, since an approximately 100-fold molar excess of S-(2-chloroethyl)glutathione over the hemoglobin concentration was required before alkylation was detectable *in vitro*.

Jin et al. (2018a) used urinary levels of chloroacetic acid, the final metabolite of 1,2-dichloroethane in mice, as a measure of a particular metabolism pathway of 1,2-dichloroethane that is mediated by CYP2E1. The urinary levels of chloroacetic acid increased significantly in the group of mice exposed to 1,2-dichloroethane through inhalation for up to 3 days, while the intervention group that was also exposed to 1,2-dichloroethane but was fed a substance that inhibits CYP2E1 had no significant changes in their urinary levels of chloroacetic acid.

The National Health and Nutrition Examination Survey (NHANES) also measures levels of 1,2-dichloroethane in the human blood and has done so since the 2003–2004 data collection cycle of the survey to the 2015–2016 cycle. The NHANES used an analytical method that quantifies trace levels of 1,2-dichloroethane in the blood using solid-phase microextraction, capillary gas chromatography, and

quadrupole mass spectrometry together (Blount et al. 2006). Blood levels of 1,2-dichloroethane from recent NHANES data are presented in Chapter 5 and show that most of the values collected are below the limit of detection.

### 3.3.2 Biomarkers of Effect

The health effects observed in humans exposed to 1,2-dichloroethane are all nonspecific effects and may be produced from any number of causes, including other causes that do not involve environmental exposure to xenobiotics such as 1,2-dichloroethane. Therefore, these effects would not be useful as specific indicators of effect from exposure to 1,2-dichloroethane. Even if other causes could be ruled out, the specific levels that produce the various effects in humans are not known, so it would not be possible to quantify exposure based on the observed effects. The effects discussed below are not unique effects of exposure to 1,2-dichloroethane, but are the most sensitive effects than may occur.

The primary probable targets of 1,2-dichloroethane identified in humans are the central nervous system, liver, and kidney (for a detailed description of the health effects of 1,2-dichloroethane, see Chapter 2). Another likely target is the immune system, for which very limited information was available in humans but was a sensitive target of 1,2-dichloroethane in animals. The effect on the immune system is immunosuppression (Munson et al. 1982; Sherwood et al. 1987). The observed biomarkers for this effect are reduced ability to fight induced bacterial infection, reduced immunoglobulin response to sheep erythrocytes, and reduced delayed-type hypersensitivity response to sheep erythrocytes, all of which show reduced immune system response to a challenge. The neurological effects observed included a variety of symptoms such as headache, irritability, drowsiness, tremors, partial paralysis, and coma (Chen et al. 2015; Dang et al. 2019; Garrison and Leadingham 1954; Liu et al. 2010; Nouchi et al. 1984; Wirtschafter and Schwartz 1939; Zhan et al. 2011). These effects were accompanied by histopathological changes in the brain in both humans and animals (Chen et al. 2015; Dang et al. 2019; Jin et al. 2018a, 2018b; Liu et al. 2010; Wang et al. 2014, 2018; Zhan et al. 2011; Zhang et al. 2011; Zhou et al. 2015, 2016). The symptoms that occur at the lowest levels (such as headache, irritability, drowsiness, and tremors) may be considered biomarkers for the neurological effects of 1,2-dichloroethane. However, these suggested biomarkers of effects are not specific to 1,2-dichloroethane-induced toxicity.

Liver damage is a prominent feature of 1,2-dichloroethane exposure. Biomarkers for hepatotoxicity observed in humans and animals were alkylation of hepatocellular macromolecules, increased liver weight, and elevated levels of serum enzymes (ALT, AST, SDH) (Alumot et al. 1976; Chen et al. 2015;

Cheng et al. 1999; Daniel et al. 1994; Heppel et al. 1946; Morgan et al. 1990; Nouchi et al. 1984; NTP 1991; Spencer et al. 1951; Sun et al. 2016; van Esch et al. 1977; Wang et al. 2017). Kidney damage is another major effect of 1,2-dichloroethane; kidney failure has been reported in humans following high-level exposure (Hueper and Smith 1935; Lochhead and Close 1951; Nouchi et al. 1984; Schönborn et al. 1970; Yodaiken and Babcock 1973). Biomarkers of renal effects in humans and animals included binding of macromolecules in renal cells and increased kidney weight (Daniel at al. 1994; Hubbs and Prusmack 1955; Morgan et al. 1990; NTP 1991; van Esch et al. 1977). Glomerular involvement may be indicated by urinary excretion of the glomerular structural protein fibronectin (Bundschuh et al. 1993). Research also shows that reproductive effects are characteristic of exposure to 1,2-dichloroethane. A study in humans showed increased rates of premature births in female workers and wives of workers exposed to 1,2-dichlorethane (Zhao et al. 1989). Animal studies have shown reproductive toxicity in males, including pathological changes in reproductive organs, and morphological changes in sperm (Zhang et al. 2017). Although embryo lethality, decreased fertility, and stillbirths have been observed in gestational studies of 1,2-dichloroethane exposure (Vozovaya 1974, 1977; Zhao et al. 1989), the literature supporting this evidence is mixed.

## 3.4 INTERACTIONS WITH OTHER CHEMICALS

No studies regarding interactions of 1,2-dichloroethane with other chemicals in humans were located. Based on metabolic data resulting from animal studies, various interactions can be expected to occur. Inducers and inhibitors of CYP enzymes, glutathione precursors and depleting agents, and dietary/nutritional status can all influence the rate of formation and excretion of the various toxic intermediates resulting from exposure to 1,2-dichloroethane.

Induction of hepatic CYP enzymes by phenobarbital and/or Aroclor 1254 increases the rate metabolism of 1,2-dichloroethane by CYP mixed function oxidases (MFO) *in vitro* (Hayes et al. 1973; Sipes and Gandolfi 1980). Alterations in metabolism could potentially produce profound effects on toxicity. Enhanced enzymatic metabolism of 1,2-dichloroethane also occurs after treatment with ethanol *in vitro* (Sato et al. 1981). Ethanol is an inducer of CYP2E1, the major MFO enzyme involved in 1,2-dichloroethane metabolism (Guengerich et al. 1991). Since ethanol and 1,2-dichloroethane are both CYP2E1 substrates, they act as competitive metabolic inhibitors when administered together. However, the effect of the consumption of ethanol before *in vitro* exposure to 1,2-dichloroethane varies greatly depending on the actual tissue concentration of ethanol reached during the metabolism of 1,2-dichloro-ethane (Sato et al. 1981). At low tissue ethanol concentration, CYP activity is stimulated. At high tissue

ethanol concentrations, especially just before exposure to 1,2-dichloroethane, suppression of 1,2-dichloroethane metabolism occurs (Sato et al. 1981). Metabolism of 1,2-dichloroethane (50 ppm in air) was unaffected by chronic co-exposure to ethanol (5% in drinking water) in a 2-year study in rats (Cheever et al. 1990). Toxicity was also unaffected in this study.

Concurrent administration of 0.15% disulfiram (also known as tetraethylthiuram disulfide, Antabuse, and DSF; disulfiram is common in the rubber industry and as a treatment for alcohol use disorder) in the diet and inhaled 1,2-dichloroethane (10, 153–304, 455 ppm) in animals markedly increased hepatotoxicity much more than would occur with exposure to 1,2-dichloroethane alone (Igwe et al. 1986a, 1988). Similarly, after chronic co-treatment with 50 ppm of 1,2-dichloroethane by inhalation and 0.05% disulfiram in the diet for 2 years, a series of neoplastic lesions were produced in rats that were not produced by 1,2-dichloroethane (or disulfiram) alone (Cheever et al. 1990). The lesions included intrahepatic bile duct cholangiomas, subcutaneous fibromas, hepatic neoplastic nodules, interstitial cell tumors in the testes, and mammary adenocarcinomas.

Metabolism studies on rats co-exposed to 1,2-dichloroethane and disulfiram for 2 years showed that following a 7-hour exposure, blood levels of 1,2-dichloroethane were elevated 5-fold by co-treatment with disulfiram (Cheever et al. 1990). In addition, the amount of $^{14}C$ eliminated as unchanged 1,2-dichloroethane in the breath was elevated by disulfiram co-treatment, with a corresponding decrease in the amount of radioactivity excreted as metabolites in the urine. These results support the suggestion that disulfiram reduces the MFO metabolism of 1,2-dichloroethane, leading to accumulation of 1,2-dichloroethane in the blood and toxic effects. Diethyldithiocarbamate, the reduced form of disulfiram, is a relatively selective inhibitor of CYP2E1, the primary MFO enzyme involved in 1,2-dichloroethane metabolism (Guengerich et al. 1991).

Conjugation with glutathione is an important metabolic pathway for 1,2-dichloroethane. However, glutathione conjugation with 1,2-dichloroethane has also been hypothesized to produce reactive sulfur half-mustard metabolites, such as S-(2-chloroethyl) glutathione (D'Souza et al. 1987; Igwe et al. 1986b; Jean and Reed 1989; Lock 1989; Reitz et al. 1982). There is considerable evidence supporting the hypothesis that reactive intermediates formed by glutathione conjugation are responsible for 1,2-dichloroethane toxicity. However, studies also show a protective effect of glutathione. The administration of glutathione, precursors of glutathione, or amino acids capable of donating a sulfhydryl group for the biosynthesis of glutathione all decrease the toxic effects and mortality in rats given 1,2-dichloroethane orally (Heppel et al. 1947). This protective action of glutathione and precursors also occurs in young rats

exposed to 1,2-dichloroethane by inhalation (Johnson 1967). It is not clear how the protective effect of glutathione reported in these studies may be reconciled with the hypothesis that reactive intermediates formed by glutathione conjugation are responsible for 1,2-dichloroethane-induced toxicity. By analogy to 1,2-dibromoethane, however, the protective effect of co-administered glutathione in 1,2-dichloroethane exposures might be explained by the reaction of S-(2-chloroethyl)glutathione with glutathione, which is a nonenzymatic reaction occurring at physiological glutathione concentrations (Cmarik et al. 1990), although work with 1,2-dibromoethane indicates that levels of DNA adducts are correlated with glutathione content (Kim and Guengerich 1990). Methionine, p-aminobenzoic acid, aniline, and sulfanilamide have been shown to protect against toxicity of 1,2-dichloroethane (Heppel et al. 1945). A good correlation has been found between the urinary excretion of mercapturic acid and the formation of DNA adducts in liver and kidney DNA of 1,2-dibromoethane-treated rats (Kim and Guengerich 1989). This finding suggests that the extent of formation of adducts may be correlated with the toxic effects of 1,2-dichloroethane.

Nutritional status affects the rate of metabolic formation of toxic intermediates; liver from fasted animals showed an increased rate of 1,2-dichloroethane metabolism in vitro (Nakajima and Sato 1979) because fasting induces the formation of CYP2E1 (Johansson et al. 1988), the primary MFO enzyme involved in oxidation of 1,2-dichloroethane (Guengerich et al. 1991). Fasting also may lower hepatic levels of glutathione. According to the hypothesis that reactive intermediates formed by glutathione conjugation are responsible for 1,2-dichloroethane-induced toxicity, toxicity would be reduced under these conditions. However, the actual effect of fasting on 1,2-dichloroethane toxicity is unknown.

A few studies that investigated the toxic interactions between 1,2-dichloroethane and other xenobiotic toxicants were located. Pretreatment with orally administered 2-hexanone did not potentiate the nephrotoxicity of 1,2-dichloroethane administered by intraperitoneal injection in rats (Raisbeck et al. 1990). Co-treatment with 1,1-dichloroethylene produced only a slightly greater-than-additive effect on lipid droplet changes in rat hepatocytes (EPA 1989). A mixture of 1,2-dichloroethane (80 mg/kg) and carbon tetrachloride (200 mg/kg) administered in a single oral dose to rats produced lower liver triglyceride levels than observed with carbon tetrachloride alone. These levels were still increased above 1,2-dichloroethane-only levels (Aragno et al. 1992). Studies of *in vitro* interactions produced more positive results, though interactions observed *in vitro* do not always generalize to the intact system. tert-Butyl hydroperoxide potentiated lipid peroxidation induced by 1,2-dichloroethane in rat liver slices *in vitro* (Sano and Tappel 1990). The occurrence of lipid peroxidation is associated with physical damage to

tissues. There was a synergistic inactivation of plasma alpha-1 proteinase inhibitor when 1,2-dichloroethane was tested together with the cigarette smoke components acrolein and pyruvic aldehyde *in vitro* (Ansari et al. 1988). Inactivation of plasma alpha-1 proteinase inhibitor has been proposed as an important factor in the development of lung emphysema.

Oral administration of 1,2-dichloroethane in drinking water for 16 weeks together with three other chemical carcinogens commonly found at hazardous waste sites (arsenic, vinyl chloride, and trichloroethylene) resulted in inhibition of the promotion of preneoplastic hepatic lesions and pulmonary hyperplasia and adenomas (Pott et al. 1998). The four chemicals, including 1,2-dichloroethane, have been shown to be individually carcinogenic in laboratory animals, yet they interacted antagonistically to inhibit promotion of precancerous lesions. The study is limited, however, by a short exposure duration, small numbers of test animals, and the use of only male rats; the interactive effect of lifetime exposure to the four chemicals cannot be inferred with confidence from these results. The mechanism for this interactive effect has not been elucidated, but Pott et al. (1998) hypothesized that decreased cell proliferation, increased apoptosis, or enhanced remodeling of preneoplastic lesions may play a role. It is also possible that this effect could have been due to competitive metabolic inhibition, as vinyl chloride, trichloroethylene, and 1,2-dichloroethane are all CYP2E1 substrates (Pohl and Scinicariello 2011).

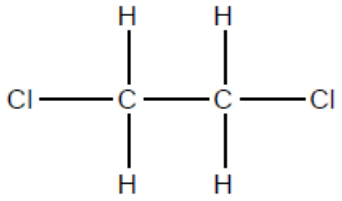
# CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

## 4.1 CHEMICAL IDENTITY

1,2-Dichloroethane is a colorless, oily liquid composed of two carbon atoms bonded together, with each carbon atom also bonded to one chlorine atom, and two hydrogen atoms. 1,2-Dichloroethane is primarily used in the production of vinyl chlorides, and as a solvent in organic synthesis. 1,2-Dichloroethane was previously used as an insect and soil fumigant, in cleaning products (especially for use on textiles), and in adhesives. 1,2-Dichloroethane is produced by chlorination of ethylene using a catalyst.

Table 4-1 lists common synonyms, trade names, and other pertinent identification information for 1,2-dichloroethane.

**Table 4-1. Chemical Identity of 1,2-Dichloroethane**

| Characteristic | Information |
|---|---|
| Chemical name | 1,2-Dichloroethane |
| Synonym(s) and Registered trade name(s) | 1,2-Dichloroethane; 1,2-Ethylene dichloride; alpha,beta-Dichloroethane; Borer sol; Brocide; Destruxol borer-sol; Di-chlor-mulsion; Dichlor-Mulsion; Dichloremulsion; Dichloroethylene; Dutch liquid; Dutch oil; EDC; Ethane dichloride; Ethylene dichloride; Ethylenechloride; Ethylene dichloride; Glycol dichloride; sym-Dichloroethane |
| Chemical formula | $C_2H_4Cl_2$ |
| Chemical structure |  |
| CAS Registry Number | 107-06-2 |

CAS = Chemical Abstracts Service

Source: NLM 2021

## 4.2 PHYSICAL AND CHEMICAL PROPERTIES

1,2-Dichloroethane is a colorless oily liquid. It is slightly soluble in water and is very soluble in a number of organic solvents. It also has a high vapor pressure and is therefore expected to volatilize in the

environment. 1,2-Dichloroethane has a very low $K_{oc}$ and is expected to be very mobile in the environment. Table 4-2 lists important physical and chemical properties of 1,2-dichloroethane.

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

| Property | Information | Reference |
|---|---|---|
| Molecular weight | 98.96 | NLM 2021 |
| Color | Clear, colorless | NLM 2021 |
| Physical state | Oily liquid; heavy liquid | NLM 2021 |
| Melting point(s) | -35.6°C | NLM 2021 |
| Boiling point(s) | 83.4°C | NLM 2021 |
| Critical temperature and pressure | 563 K and 5,360 kPa | NLM 2021 |
| Density | 1.2454 at 25°C | NLM 2021 |
| Taste | Sweet | NLM 2021 |
| Taste threshold: | No data | |
| Odor | Pleasant, chloroform-like; sweet | NLM 2021 |
| Odor threshold: | | |
| Water | 20 mg/L | Verschueren 1996 |
| Air | 12 ppm<br>50 ppm<br>100 ppm | Torkelson and Rowe 1981<br>Verschueren 1996<br>Weiss 1980 |
| Solubility: | | |
| Water | 8,600 mg/L at 25°C<br>8,690 mg/L at 20°C | NLM 2021<br>Verschueren 1996 |
| Organic solvent(s) | Miscible with alcohol, chloroform, ether; soluble in acetone, benzene, chloroform | NLM 2021 |
| Inorganic solvent(s) | No data | |
| Partition coefficients: | | |
| Log $K_{ow}$ | 1.48 | NLM 2021 |
| Log $K_{oc}$ | 1.5 | |
| Vapor pressure at 25 °C | 78.9 mmHg (10.5 kPa) | NLM 2021 |
| Henry's law constant at 25 °C | $1.18 \times 10^{-3}$ atm-$m^3$/mole | NLM 2021 |
| Degradation half-life in air via reaction with OH radicals | $2.48 \times 10^{-13}$ $cm^3$/molecule-second at 25°C | NLM 2021 |
| Dissociation constants: | No data | |
| Autoignition temperature | 413°C | NLM 2021 |
| Flash point | 13°C | NLM 2021 |
| Flammability limits in air | 6.2–16% by volume | NLM 2021 |
| Conversion factors: | 1 ppm in air = 4 $mg/m^3$<br>ppm(v/v)x4.05=$mg/m^3$<br>$mg/m^3$x0.247=ppm(v/v) | NLM 2021<br>Torkelson and Rowe 1981<br>Torkelson and Rowe 1981 |
| Explosive limits | 6.2–15.9% | NLM 2021 |

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

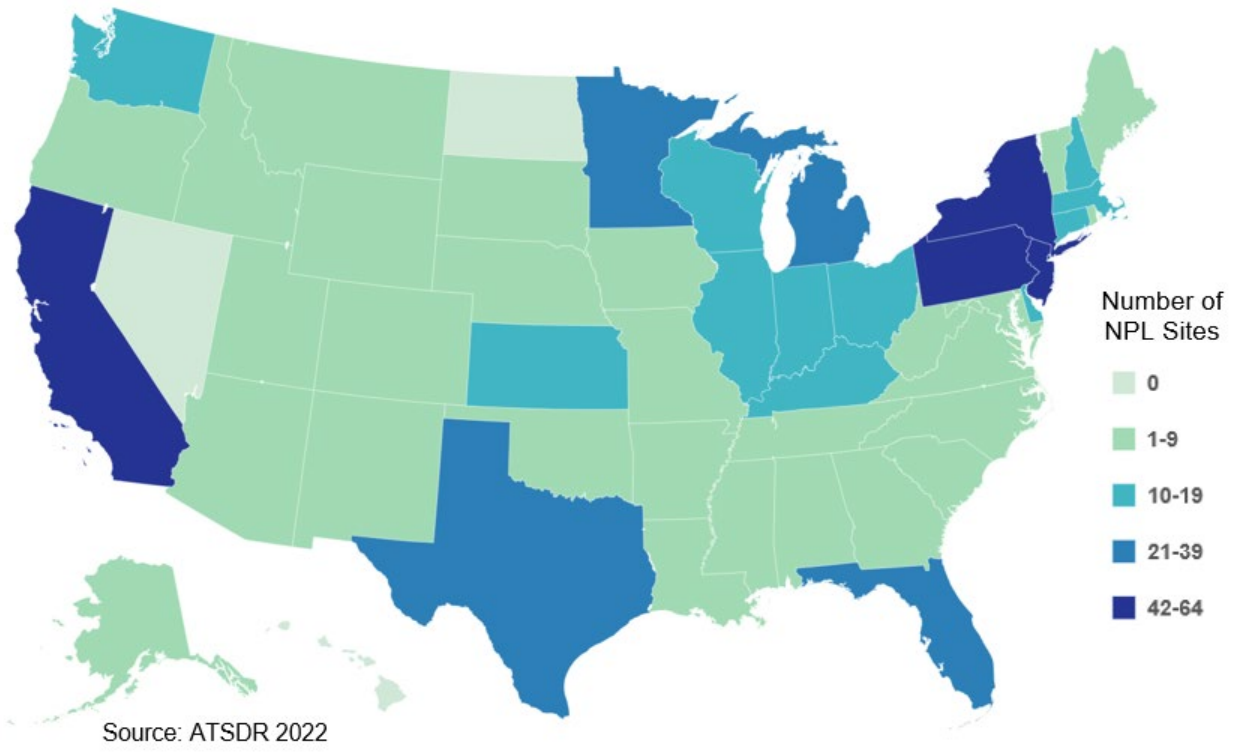
| Property | Information | Reference |
|---|---|---|
| Incompatibilities and reactivity | Incompatible with strong oxidizing agents; violent reaction with aluminum, dinitrogen tetroxide, ammonia, dimethylaminopropylamine | NLM 2021 |

# CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

## 5.1 OVERVIEW

1,2-Dichloroethane has been identified in at least 593 of the 1,868 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2022). However, the number of sites in which 1,2-dichloroethane has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 591 are located within the United States, and 2 are located in Puerto Rico (not shown).

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




- The most likely route of exposure for 1,2-dichloroethane is inhalation of ambient or workplace air.
- 1,2-Dichloroethane has been detected in ambient air, surface water, groundwater, drinking water, human breath, urine, adipose tissue, and milk samples.
- The largest releases of 1,2-dichloroethane are to air.

- 1,2-Dichloroethane is expected to volatilize rapidly in surface water in a vigorous water flow scenario, moderately in a moderate water flow scenario, and relatively slowly in quiescent water scenarios. 1,2-Dichloroethane in soil is expected to volatilize to the atmosphere or leach into groundwater. The half-life of 1,2-dichloroethane in air is 73 days, and its atmospheric lifetime is >5 months.

- The primary degradation process for 1,2-dichloroethane in soil and water is biodegradation.

1,2-Dichloroethane's production, storage, and use as a synthetic feedstock (CMR 1998; EPA 1985), and as a solvent in closed systems (Budavari et al. 2013) may result in its release to the environment. The use of 1,2-dichloroethane as a lead scavenger in gasoline has been discontinued in the United States since 2018. The largest environmental releases of 1,2-dichloroethane occur to air. 1,2-Dichloroethane released to surface water and soil is expected to volatilize rapidly to the atmosphere where it will be degraded by photochemically produced hydroxyl radicals. The half-life for this reaction in air is about 73 days, calculated from its measured rate constant (Arnts et al. 1989; Atkinson 1986), and the overall atmospheric lifetime of 1,2-dichloroethane is >5 months (EPA 1993). Hydrolysis and photolysis do not appear to be significant in determining the environmental fate of 1,2-dichloroethane. Although biodegradation occurs slowly, it is the primary degradation process for 1,2-dichloroethane in soils and waters. 1,2-Dichloroethane has been detected in ambient air, surface water, groundwater, drinking water, human breath, urine, adipose tissue, and milk samples. Concentrations in environmental media are generally greatest near source areas (e.g., industrial point sources, hazardous waste sites).

Inhalation of 1,2-dichloroethane in ambient or workplace air is generally the main route of human exposure to the compound. The 2016 Toxic Substances Control Act (TSCA) Inventory Update Reporting data details a range from <10 workers to 500–999 workers that may be occupationally exposed to 1,2-dichloroethane for each of the 17 reporting plants (EPA 2016). The estimated size of the general population potentially exposed to low levels of the compound through inhalation of polluted ambient air around industrial sites was 150,000 people (Kellam and Dusetzina 1980). Ingestion of contaminated drinking water and food may also be important routes of exposure.

## 5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

### 5.2.1 Production

1,2-Dichloroethane is an industrially produced chlorinated aliphatic hydrocarbon that is not naturally occurring (NCI 2021). It is produced by chlorination of ethylene, by direct vapor- or liquid-phase

chlorination or oxychlorination (Snedecor 2004). Direct chlorination of ethylene occurs at 40–50°C, usually using small amounts of ferric chloride as a catalyst, and less often aluminum chloride, antinomy pentachloride, and cupric chloride (Snedecor 2004). Oxychlorination of ethylene occurs at temperatures exceeding 200°C in fixed or fluidized bed reactors in the presence of oxygen and copper chloride catalyst (Al-Zahrani et al. 2001; Snedecor 2004).

The 2016 EPA Chemical Data Reporting dataset (CDR), which contains production and use information by chemical manufacturers and importers, reports that six companies domestically manufactured 1,2-dichloroethane at 11 facilities in the United States, and six facilities withheld whether they import or domestically manufacture 1,2-dichloroethane. The national aggregate production volume of 1,2-dichloroethane has been reported between 20 billion and 30 billion pounds annually from 2011 to 2015 (EPA 2016).

Table 5-1 summarizes information on facilities by state that reported manufacturing or processing of 1,2-dichloroethane to TRI in 2021. 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-Dichloroethane**

| State[a] | Number of facilities | Minimum amount on site in pounds[b] | Maximum amount on site in pounds[b] | Activities and uses[c] |
|---|---|---|---|---|
| AR | 4 | 10,000 | 999,999 | 6, 9, 10, 12 |
| CA | 1 | 0 | 99 | 1, 13 |
| IA | 1 | 1,000 | 9,999 | 1, 13, 14 |
| IL | 2 | 1,000 | 999,999 | 10, 12 |
| KS | 2 | 100 | 9,999 | 10, 12 |
| KY | 2 | 10,000 | 49,999,999 | 1, 3, 5, 6, 14 |
| LA | 10 | 10,000 | 499,999,999 | 1, 3, 4, 5, 6, 9, 10, 12, 13, 14 |
| MI | 2 | 10,000 | 999,999 | 9, 10, 12 |
| MO | 2 | 100,000 | 9,999,999 | 6, 7, 10 |
| MS | 1 | 100,000 | 999,999 | 6 |
| NC | 1 | 10,000 | 99,999 | 10 |
| NE | 1 | 10,000 | 99,999 | 9, 12 |
| NY | 1 | 0 | 99 | 12 |
| OH | 2 | 1,000 | 99,999 | 12 |
| SC | 2 | 1,000 | 9,999,999 | 1, 5, 9, 12 |
| TX | 15 | 0 | 499,999,999 | 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14 |
| UT | 1 | 10,000 | 99,999 | 9, 12 |

**Table 5-1. Facilities that Produce, Process, or Use 1.2-Dichloroethane**

| State[a] | Number of facilities | Minimum amount on site in pounds[b] | Maximum amount on site in pounds[b] | Activities and uses[c] |
|---|---|---|---|---|
| WI | 1 | 1,000 | 9,999 | 10 |
| AR | 4 | 10,000 | 999,999 | 6, 9, 10, 12 |

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

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

Source: TRI21 2022 (Data are from 2021)

### 5.2.2 Import/Export

In the period from 2014 to 2018, general imports[1] and imports for consumption[2] of 1,2-dichloroethane were equal. U.S. imports of 1,2-dichloroethane fluctuated widely in the period from 2014 to 2018, ranging from 0 kg in 2014 and 2018, to 113,482 kg in 2017 (USITC 2019).

From 2014 to 2018, domestic exports[3] and total exports[4] of 1,2-dichloroethane were equal. Exports increased from 1.143 billion kg in 2014 to 1.366 billion kg in 2017, and then decreased to 1.073 billion kg in 2018 (USITC 2019).

### 5.2.3 Use

About 95% of produced 1,2-dichloroethane is used as an intermediate in the production of vinyl chloride (OECD 2002), and less often in the production of chlorinated solvents, including 1,1,1-trichloroethane

[1]General imports are total physical arrivals of 1,2-dichloroethane to the United States from other countries that either enter consumption channels immediately or enter into bonded warehouses or Foreign Trade Zones (FTZs) (US Census 2018). A bonded warehouse is an approved private warehouse used to store imports until duties or taxes are paid (US Census 2018). FTZs are specially licensed commercial and industrial areas in or near ports of entry where goods may be brought in without paying customs duties. Imports brought to FTZs can be manipulated (i.e., sold, stored, exhibited, repacked, cleaned, manufactured, etc.) prior to re-export or entry (US Census 2018).
[2]Imports for consumption are the total amount of merchandise that has physically cleared through customs by either entering consumption channels immediately or leaving bonded warehouses or FTZs (US Census 2018).
[3]Domestic exports are goods that are grown, produced, or manufactured in the United States, or goods of foreign origin that have been changed, enhanced in value, or improved in condition in the United States (US Census 2018).
[4]Total exports are the sum of domestic exports and foreign exports, which are goods of foreign origin that are in the same condition at the time of export as they were in when imported (US Census 2018).

and tetrachloroethane (De Wildeman et al. 2001; Dreher et al. 2014). The chemical is also used in the synthesis of ethylenediamines (Dreher et al. 2014). As a solvent, 1,2-dichloroethane is used for fats, oils, waxes, gums, and resins, and in paint, varnish, and finish removers (Budavari et al. 2013). It is also reportedly used as a degreaser in engineering, textile, and petroleum industries (Larranaga et al. 2016).

Up until the ban of leaded gasoline in the 1990s, 1,2-dichloroethane was used as a lead scavenger (Henderson et al. 2009). Even after the ban of leaded gasoline, 1,2-dichloroethane was used in leaded fuel for aviation, racing cars, marine engines, and farm equipment (API 2008). This use was fully discontinued in 2018, and since 2019, 1,2-dichloroethane has seen no use in leaded gasoline. 1,2-Dichloroethane was formerly registered as a fumigant, including as an insect and soil fumigant for grains and orchards (Budavari et al. 2013; IARC 1999); however, the use of 1,2-dichloroethane as a fumigant for post-harvest grain and soil was discontinued in the late 1980s and early 1990s. The chemical was formerly registered as an ingredient in 15 pesticide products in the state of California (CDPR 2019). Other former uses include as a fumigant/cleaner for upholstery and carpet, solvent in textile cleaning and metal degreasing, spices extractant in certain food processes, and in cosmetic nail lacquers (NTP 2021).

### 5.2.4 Disposal

1,2-Dichloroethane is identified as hazardous waste by the EPA and its disposal is regulated under the Resource Conservation and Recovery Act (RCRA). Therefore, 1,2-dichloroethane falls under EPA regulations for storage, transportation, treatment, and disposal (EPA 2021c). The 2016 CDR reports that 1,2-dichloroethane was recycled at 3 facilities that domestically manufacture the chemical (EPA 2016).

Incineration is a recommended method of disposal for 1,2-dichloroethane, as it was considered a candidate for liquid injection incineration, rotary kiln incineration, and fluidized bed incineration (EPA 1981). 1,2-Dichloroethane should be burned by a licensed professional waste disposal service in a chemical incinerator with an afterburner and scrubber (Sigma-Aldrich 2020). 1,2-Dichloroethane is restricted from land disposal (EPA 2021b). 1,2-Dichloroethane is defined as a hazardous waste by EPA and generators of waste containing 1,2-dichloroethane must abide by EPA regulations to dispose of the contaminant (EPA 2021a, 2021c).

1,2-Dichloroethane can be removed from wastewater by treatment with granulated activated carbon, by aeration (air stripping), and by boiling. A drawback of granulated activated carbon is the further processing of the carbon spent by desorbing the chemical with steam or thermal carbon regeneration and concomitant incineration of the desorbed chemicals (Stucki and Thuer 1994). Boiling is an effective treatment on a short-term emergency basis when low concentrations are spilled in water. However, these processes should be used with caution, as they result in the transfer of the contaminant directly to air (EPA 1985, 1987).

## 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 2018a).

There are no known natural sources of 1,2-dichloroethane. Releases of this compound to the environment may result from the manufacture, use, storage, distribution, and disposal of 1,2-dichloroethane. Older consumer goods containing 1,2-dichloroethane that are still in use or have been discarded as waste also represent potential emission sources. 1,2-Dichloroethane may also be released to the environment from the microbial degradation of other chlorinated alkanes. For example, 1,2-dichloroethane is a known product of the anaerobic biodegradation of 1,1,2,2-tetrachloroethane (Chen et al. 1996; Lorah and Olsen 1999).

### 5.3.1 Air

Estimated releases of 410,308 pounds (~186.1 metric tons) of 1,2-dichloroethane to the atmosphere from 51 domestic manufacturing and processing facilities in 2021, accounted for about 90.2% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2022). These releases are summarized in Table 5-2.

**Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use 1,2-Dichloroethane[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 | 4 | 2,379 | 0 | 632 | 44 | 0 | 3,011 | 44 | 3,055 |
| CA | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| GA | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| IL | 2 | 5,001 | 65 | 0 | 2 | 0 | 5,001 | 67 | 5,068 |
| IA | 1 | 2,340 | 32 | 0 | 0 | 0 | 2,372 | 0 | 2,372 |
| KS | 2 | 44 | 0 | 3 | 3 | 1 | 47 | 4 | 51 |
| KY | 2 | 53,413 | 1,783 | 0 | 0 | 2,265 | 55,196 | 2,265 | 57,461 |
| LA | 10 | 232,348 | 520 | 0 | 286 | 12,692 | 232,934 | 12,912 | 245,846 |
| MI | 2 | 555 | 0 | 0 | 0 | 0 | 555 | 0 | 555 |
| MS | 1 | 271 | 0 | 0 | 0 | 0 | 271 | 0 | 271 |
| MO | 2 | 8,360 | 27 | 0 | 0 | 0 | 8,365 | 22 | 8,387 |
| NE | 1 | 144 | 0 | 0 | 23 | 0 | 144 | 23 | 167 |
| NY | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| NC | 1 | 7,870 | 0 | 0 | 0 | 52 | 7,870 | 52 | 7,922 |
| OH | 2 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| SC | 2 | 20,148 | 16 | 0 | 0 | 0 | 20,148 | 16 | 20,164 |
| TX | 14 | 77,435 | 1,682 | 24,320 | 145 | 88 | 103,440 | 230 | 103,670 |
| UT | 1 | 0 | 0 | 0 | 0 | 10 | 0 | 10 | 10 |

**Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use 1,2-Dichloroethane[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 |
| WI | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 51 | 410,308 | 4,125 | 24,955 | 503 | 15,108 | 439,355 | 15,645 | 455,000 |

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

RF = reporting facilities; UI = underground injection

Source: TRI21 2022 (Data are from 2021)

### 5.3.2 Water

Estimated releases of 4,125 pounds (~1.9 metric tons) of 1,2-dichloroethane to surface water from 51 domestic manufacturing and processing facilities in 2021, accounted for about <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2022). This estimate includes releases to wastewater treatment and publicly owned treatment works (POTWs) (TRI21 2022). These releases are summarized in Table 5-2.

In England and Wales, 1,2-dichloroethane was detected in 17% of industrial wastewater effluent samples at an average concentration of 117 µg/L, and in 9.5% of treated sewage at an average concentration of 1.39 µg/L (Stangroom et al. 1998).

### 5.3.3 Soil

Estimated releases of 503 pounds (~0.2 metric tons) of 1,2-dichloroethane to soil from 51 domestic manufacturing and processing facilities in 2021, accounted for <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2022). An additional 24,955 pounds (~11.3 metric tons), accounted for about 5.5% of the total environmental emissions, were released via underground injection (TRI21 2022). These releases are summarized in Table 5-2.

## 5.4 ENVIRONMENTAL FATE

1,2-Dichloroethane released to the environment partitions to the atmosphere. Reaction with photochemically produced hydroxyl radicals is the primary degradation mechanism of 1,2-dichloroethane in the atmosphere. 1,2-Dichloroethane released to water surfaces is expected to volatilize quickly in vigorous water flow scenarios, moderately in moderate water flow scenarios, and relatively slowly in quiescent water scenarios. 1,2-Dichloroethane released to soil surfaces is expected to volatilize to the atmosphere or leach into groundwater. Biodegradation occurs slowly in water and soil surfaces. Hydrolysis and photolysis are not expected to be important environmental fate processes for 1,2-dichloroethane.

### 5.4.1 Transport and Partitioning

**Air.** Releases of 1,2-dichloroethane to the environment as a result of industrial activity are primarily to the atmosphere (see Section 5.3). 1,2-Dichloroethane released to the atmosphere may be transported long distances before being washed out in precipitation or degraded. For example, Pearson and McConnell (1975) attributed the presence of chlorinated organic compounds, including 1,2-dichloroethane, in upland waters to long-range aerial transport and deposition in precipitation.

**Water.** Based on a Henry's law constant of 0.14 kPa-$m^3$/mol at 25°C (Haynes et al. 2015), 1,2-dichloroethane is expected to volatilize from water surfaces, with the rate of volatilization depending on water flow, depth, and temperature. An estimated volatilization half-life of 28–29 minutes was reported for 1,2-dichloroethane present at a concentration of 1 mg/L in an open water column held at 25°C and stirred at 200 revolutions/minute (Dilling 1977; Dilling et al. 1975). Removal of 90% of the compound under the same conditions occurred in 96 minutes. However, an evaporation half-life of 10 days was estimated

using the EXAMS model for a eutrophic lake. Volatilization losses were shown to be the dominant fate process following a chemical spill in the Rhine River in Germany (Brüggemann et al. 1991).

Physical properties indicate that 1,2-dichloroethane will be mobile in groundwater but will not partition out of groundwater into air and soil to a great degree (Henderson et al. 2009). Based on the solubility and gasoline-water partition constant of 1,2-dichloroethane, it can be expected in concentrations up to 3,700 µg/L in groundwater near the source area of a leaded gasoline release (Henderson et al. 2009).

**Sediment and Soil.** No information was found regarding partitioning of 1,2-dichloroethane from the water column onto sediments. However, structural analogs of the compound (i.e., dichloromethane, trichloromethane, and 1,1,1-trichloroethane) do not concentrate selectively onto sediments (Dilling et al. 1975; Pearson and McConnell 1975). Based on log $K_{oc}$ values of 1.28–1.62 (Borisover and Graber 1997; Chiou et al. 1980; Sabljić et al. 1995), 1,2-dichloroethane is not expected to adsorb to suspended solids and sediment in the water column. An experimental bioconcentration factor (BCF) of 2 indicates that 1,2-dichloroethane will not bioconcentrate in fish and aquatic organisms (Banerjee and Baughman 1991) and is not expected to bioaccumulate in the food chain (Farrington 1991). 1,2-Dichloroethane released to land surfaces is expected to volatilize to the atmosphere or leach into groundwater. Volatilization losses occur at a much slower rate for 1,2-dichloroethane present in subsurface soil. Jury et al. (1990) modeled the rate of volatilization of 1,2-dichloroethane from soil at a depth of 1 m to mimic the type of contamination that may occur from landfill leachate. When water evaporation was not considered, the yearly loss of 1,2-dichloroethane amounted to 7.1% from a sandy soil. Yearly volatilization losses increased to 30% when water evaporation was considered. Based on log $K_{oc}$ values of 1.28–1.62 (Borisover and Graber 1997; Chiou et al. 1980; Sabljić et al. 1995), 1,2-dichloroethane is expected to have very high mobility in soil surfaces and should be available for transport into groundwater. In a laboratory experiment conducted with a sandy loam, approximately 50% of an initial concentration of 0.81 mg/L of 1,2-dichloroethane applied to the soil surface was volatilized. The remainder percolated through the soil column to a depth of 140 cm, suggesting that leaching into groundwater may occur (Wilson et al. 1981). Environmental surveys conducted by EPA have detected 1,2-dichloroethane in groundwater sources in the vicinity of contaminated sites (EPA 1985). Large spills of 1,2-dichloroethane may contaminate groundwater because of the high density of this compound, which makes it sink into the aquifer in a vertical gravity-driven process (Corapcioglu and Hossain 1990).

### 5.4.2 Transformation and Degradation

**Air.** In the atmosphere, 1,2-dichloroethane is degraded by reaction with photochemically produced hydroxyl radicals. An experimental rate constant of $2.2x10^{-13}$ $cm^3$/molecule-second at 25°C (Arnts et al. 1989; Atkinson 1986) corresponds to a half-life of 73 days using an average atmospheric hydroxyl radical concentration of $5x10^5$ molecule/$cm^3$. The estimated atmospheric lifetime of 1,2-dichloroethane was reported to be >5 months with formyl chloride, chloroacetyl chloride, hydrogen chloride, and chloroethanol reported as degradation products (EPA 1993). 1,2-Dichloroethane is not expected to undergo significant atmospheric removal by oxidation with ozone or nitrate radicals, and it will not undergo removal by direct photolysis.

A recent study shows that the observed mixing ratio and the initial mixing ratio during the day of 1,2-dichloroethane are equal (0.30 ppbv), indicating that 1,2-dichloroethane is not very reactive with radicals during transport from their sources to sampling sites (Gao et al. 2018). The observed mixing ratio of 1,2-dichloroethane at night was measured to be 0.34 ppbv (Gao et al. 2018).

**Water.** Due to 1,2-dichloroethane's solubility in water, low sorption coefficient, and low Henry's law coefficient, it remains in the water phase in groundwater under average environmental conditions (De Wildeman et al. 2001); however, 1,2-dichloroethane has been found to volatilize into building structures at some contaminated sites (Kurtz et al. 2010; Ma et al. 2016). In groundwater and surface water, biodegradation is the primary degradation process for the removal of 1,2-dichloroethane. Abiotic degradation processes, such as oxidation and hydrolysis, are too slow to be environmentally significant.

1,2-Dichloroethane biodegrades under aerobic and anaerobic conditions. Under aerobic conditions, 1,2-dichloroethane is thought to biodegrade via enzymatically initiated hydrolytic dehalogenation to 2-chloroethanol or oxidation reactions to 1,2-dichloroethanol; biodegradation has been demonstrated anaerobically via a reductive dechlorination reaction to chloroethane, dihaloelimination reaction to ethane, and mineralization to $CO_2$ (Hirschorn et al. 2007). Bacteria isolated from a mixture of activated sludge from wastewater treatment plants and 1,2-dichloroethane-polluted soils have used 1,2-dichloroethane as a sole carbon source (Janssen et al. 1984; Stucki et al. 1983). Approximately 14% degradation of 5 mg/L 1,2-dichloroethane occurred after 14 days incubation in laboratory experiments using a domestic wastewater inoculum (Tabak et al. 1981). The reported loss was corrected for 27% volatilization loss in 10 days from control flasks. Reported degradation losses (corrected for volatilization) for 10 mg/L of the compound were 15% at 7 days and 30% at 14 days. Following a 24-hour incubation at 25 °C under aerobic conditions,

1,2-dichloroethane was degraded (approximately 10%) by a strain of *Pseudomonas fluorescens* bacteria isolated from soil and water contaminated with various chlorinated hydrocarbons, including 1,2-dichloroethane (Vandenbergh and Kunka 1988). 1,2-Dichloroethane was not biodegraded after 35 days under anaerobic conditions in sediment-water test systems (Jafvert and Wolfe 1987) and was not biodegraded by bacteria isolated from groundwater after 8–16 weeks of incubation (Wilson et al. 1983). The biodegradation half-life of 1,2-dichloroethane in aerobic water was reported as 100 days and the half-life in anaerobic water was reported as 400 days, but no details on the kinetic experiments used to establish these half-lives were reported (Capel and Larson 1995). The half-life represents the calculated time for loss of the first 50% of the substance, but the time required for the loss of half of that which remains may be substantially longer, and the rate of disappearance may decline further as time progresses. 1,2-Dichloroethane was 97% biodegraded in laboratory studies using aerobic groundwater microcosms obtained from a Superfund site in California over a 6-day incubation period (Cox et al. 1998). In the field, however, the biodegradation half-life of 1,2-dichloroethane in groundwater can range from <1 to 30 years depending on the conditions (Bosma et al. 1998).

A growing body of evidence indicates that the co-metabolism of 1,2-dichloroethane (the biodegradation of 1,2-dichloroethane from which the degrading organism gains no energetic benefit) occurs under aerobic conditions (see Sediment and Soil). Pure cultures of methanotrophic (methane using) bacteria obtained from both polluted and non-polluted sources degraded 1,2-dichloroethane in the presence of methane and oxygen (Oldenhuis et al. 1989). Aquifer solids obtained at an *in situ* biorestoration field study mineralized 1,2-dichloroethane to carbon dioxide in the presence of dissolved oxygen and methane (Lanzarone and McCarty 1990). Concentrated cell suspensions of methanogenic bacteria incubated at 37 or 55°C for 24–96 hours reductively dechlorinated 1,2-dichloroethane to ethene, chloroethane, and ethane (Holliger et al. 1990). One study examined the ability of upflow anaerobic sludge blanket (UASB) technology to dehalogenate 1,2-dichloroethane at high volumetric rates and demonstrates that UASB technology under optimal dechlorination conditions can be used to treat 1,2-dichloroethane contaminated waters (De Wildeman et al. 2001). De Wildeman et al. (2001) found that living methanogenic granular sludge grown in UASB reactors is able to degrade 1,2-dichloroethane.

The experimental first-order rate constants for the hydrolysis of 1,2-dichloroethane under neutral conditions were reported as $2.1 \times 10^{-8}$ and $1.8 \times 10^{-8}$ $second^{-1}$ at 25°C (Barbash and Reinhard 1989; Jeffers et al. 1989). These values correspond to half-lives of 65 and 72 years. A more recent study determined that the hydrolysis half-life of 1,2-dichloroethane was $4.9 \times 10^{4}$ years at pH 9 and 15°C (Miyamoto and Urano 1996). Barbash and Reinhard (1989) found that the presence of $5.1 \times 10^{-4}$ molar (16 ppm) solution

of hydrogen sulfide anion decreased the hydrolytic half-life to 6 years. Although still a slow process, this latter reaction may occur in hypoxic groundwater where hydrogen sulfide occurs naturally.

**Sediment and Soil.** As in surface water, direct photolysis of 1,2-dichloroethane on soil surfaces and hydrolysis in moist soil and sediment are not expected to be important environmental fate processes. The primary transformation process for 1,2-dichloroethane in sediment and soil is biodegradation. Incubation of 1,2-dichloroethane at a starting concentration of 100 ppb with an unsaturated calcareous soil resulted in 15–23% mineralization to carbon dioxide after 4 weeks, under aerobic conditions, and 3.3–3.4% mineralization under anaerobic conditions (Watwood et al. 1991). Over a 2-week incubation period, 2 μmol of 1,2-dichloroethane completely dechlorinated to ethane by anaerobic microcosms and enrichment cultures derived from river sediment (Loffler et al. 1997). A first-order biodegradation rate constant of 0.013 $day^{-1}$ was determined for 1,2-dichloroethane in an anaerobic sediment slurry (Peijnenburg et al. 1998). This rate constant corresponds to a biodegradation half-life of about 52 days. It was noted that degradation followed first-order kinetics for at least two successive half-lives in this study.

The presence of methane or increasing the proportion of methanotrophs can increase the rate of aerobic biodegradation of 1,2-dichloroethane in soil. In laboratory experiments conducted with different soil types (sand, sandy clay, silty loam, clay, and Lincoln fine sand), soils exposed to methane biodegraded 1,2-dichloroethane to carbon dioxide (Henson et al. 1988; Speitel and Closmann 1991). Based on these results, it was estimated that the bioremediation of soil contaminated with 100 ppm 1,2-dichloroethane could be complete within several months if methane is present (Speitel and Closmann 1991). Methane oxidizing cultures from soil of a California landfill readily biodegraded 1,2-dichloroethane, but toluene and phenol oxidizing cultures were not able to degrade this compound (Chang and Alvarez-Cohen 1996).

As the concentration of 1,2-dichloroethane increases in a soil surface, the degree of biodegradation that takes place may decrease due to microbial toxicity at the enhanced contaminant level. In a respirometer study of microbial toxicity to an agricultural soil, it was determined that a concentration of 0.51 mg 1,2-dichloroethane/g of soil resulted in a 50% respiratory inhibition (Regno et al. 1998).

## 5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to 1,2-dichloroethane depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens.

Concentrations of 1,2-dichloroethane 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-dichloroethane levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-3 shows the limits of detection typically achieved by analytical analysis in environmental media. Presented in Table 5-4 is a summary of the range of concentrations detected in environmental media.

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

| Media | Detection limit | Reference |
|---|---|---|
| Air | 11.2 pptv (0.00005 mg/m$^3$) | Gao et al. 2018 |
| Workplace air | 0.014 mg/m$^3$ | NIOSH 1994 |
| Drinking water | 0.03–0.07 µg/L | Kessels et al. 1992 |
| Water and wastewater | 0.002 µg/L | EPA 1994b |
| Water, wastewater, and solid waste | 5 µg/kg (soil/sediment); 0.5 µg/kg (wastes); 5 µg/L (water) | EPA 1994c |
| Fish | 10 µg/kg (wet weight) | Easley et al. 1981 |
| Table ready foods | 6 ppb (6 µg/kg) | Heikes 1987; Heikes and Hopper 1986 |
| Sediment | 20 pg/g (0.02 µg/kg) | Roose et al. 2001 |
| Breath | 0.12 µg/m$^3$ (0.00012 mg/m$^3$) | Wallace et al. 1984 |
| Human erythrocytes | No data | Ansari et al. 1987 |
| Blood/urine | No data | Barkley et al. 1980 |
| Blood | 0.010 ng/mL (0.001 µg/dL) | Blount et al. 2006 |

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

**Table 5-4. 1,2-Dichloroethane Levels in Water, Soil, and Air of National Priorities List (NPL) Sites**

| Medium | Median | Geometric mean | Geometric standard deviation[a] | Number of quantitative measures | NPL sites |
|---|---|---|---|---|---|
| Water (µg/L) | 18 | 46.4 | 26.0 | 402 | 232 |
| Soil (µg/kg) | 3,300 | 1,990 | 114 | 70 | 49 |
| Air (ppbv) | 1.95 | 2.62 | 36.3 | 46 | 35 |

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

### 5.5.1 Air

1,2-Dichloroethane has been detected in ambient air samples taken over the north Atlantic Ocean at concentrations of 0.061–0.12 µg/m$^3$ (0.015–0.030 ppb) (Class and Ballschmiter 1986) and in trace amounts in the southern Black Forest in southwestern Germany (concentration unspecified) (Jüttner 1986). The reported average surface level background concentration of the compound in ambient air at mid-latitudes is 0.168 µg/m$^3$ (Singh et al. 1982). Mean percentile distributions of 1,2-dichloroethane concentrations in ambient air in the United States available from EPA's Air Quality System database are presented in Table 5-5. Approximately 40% of sites tested had zero detections in 2021. According to the 2014 National Air Toxics Assessment, the mean 1,2-dichloroethane concentration in the United States was 0.000409 µg/m$^3$ (EPA 2018b). Concentrations ranged from undetectable in Northwest Arctic and Prince of Wales-Hyder, Alaska; Monroe, Florida; and Sanoval, New Mexico to 0.424 µg/m$^3$ in Iberville, Louisiana (EPA 2018b).

**Table 5-5. Percentile Distribution of Annual Mean 1,2-Dichloroethane Concentrations (ppbC) Measured in Ambient Air at Locations Across the United States**

| Year | Number of U.S. locations | 25$^{th}$ | 50$^{th}$ | 75$^{th}$ | 95$^{th}$ | Maximum |
|---|---|---|---|---|---|---|
| 2022 | 30 | 0 | 0 | 0 | 0 | 0.1 |
| 2021 | 142 | 0 | 0 | 0 | 0.1 | 95 |
| 2020 | 142 | 0 | 0 | 0.04 | 0.1 | 111.4 |
| 2019 | 148 | 0 | 0 | 0 | 0.10 | 31.8 |
| 2018 | 190 | 0 | 0.01 | 0.04 | 0.08 | 58 |
| 2017 | 199 | 0 | 0 | 0.03 | 0.05 | 52.6 |
| 2016 | 203 | 0 | 0.01 | 0.03 | 0.12 | 22.6 |
| 2015 | 200 | 0 | 0 | 0.03 | 0.07 | 11.9 |
| 2014 | 251 | 0 | 0.02 | 0.03 | 0.08 | 15.3 |

Source: EPA 2022

1,2-Dichloroethane has been found at higher concentrations in ambient air samples from urban areas of the United States. In a review of 950 potential papers on VOCs in air published from 1970 to 1987, a database of median daily atmospheric concentrations by site type was compiled (EPA 1988). The median daily atmospheric concentration of 1,2-dichloroethane in urban sites was 0.049 µg/m$^3$ (0.012 ppb) (1,214 samples) and 1.0 µg/m$^3$ (0.26 ppb) (182 samples) for source-dominated samples; it was not detected in 648 samples from suburban, rural, or remote sites. 1,2-Dichloroethane was detected at 83 urban locations across the United States at a median concentration of 0.04 µg/m$^3$ (0.01 ppb) (Kelly et

al. 1994). The average concentration of 1,2-dichloroethane in seven urban locations in 1980–1981 ranged from 0.405 to 6.07 μg/m$^3$ (0.100–1.50 ppb) (Singh et al. 1982). The mean concentrations of 1,2-dichloroethane in 1,412 samples of ambient air from 23 sites in 12 Canadian cities from 1988 to 1990 ranged from 0.070 to 0.28 μg/m$^3$ (0.017–0.069 ppb) with an overall mean of 0.13 μg/m$^3$ (0.032 ppb) (WHO 1995). Mean urban air concentrations of 1,2-dichloroethane measured during field experiments in March 1984 in Downey, California, Houston, Texas, and Denver, Colorado were 0.40 μg/m$^3$ (0.010 ppb), 1.82 μg/m$^3$ (0.45 ppb), and 0.089 μg/m$^3$ (0.022 ppb), respectively (Singh et al. 1992). Air samples collected in Izmir, Turkey showed that concentrations of 1,2-dichloroethane were nearly the same in summer and winter at the urban site sampled, and concentrations were higher at the urban site than at the suburban site (Elbir et al. 2007). In a 1987 survey of 35 homes in the Kanawha Valley, West Virginia, the mean concentration of 1,2-dichloroethane was 20.8 μg/m$^3$ (5.15 ppb), with a maximum concentration of 140 μg/m$^3$ (34.6 ppb) (Cohen et al. 1989). A component of the Total Exposure Assessment Methodology (TEAM) compared the outdoor concentration of toxic substances to the corresponding overnight indoor concentration. The results of this monitoring study indicated that 1,2-dichloroethane was detected in 30% of the indoor samples (median concentration: 0.025 μg/m$^3$) and 37% of the outdoor samples (median concentration: 0.025 μg/m$^3$) in Greensboro, North Carolina (fall, 1980); 89% of the indoor samples (3.6 μg/m$^3$) and 100% of the outdoor samples (2.2 μg/m$^3$) in Baton Rouge, Louisiana (winter, 1981); 18% of the indoor (0.04 μg/m$^3$) and 40% of the outdoor samples (0.045 μg/m$^3$) in Houston, Texas (summer, 1981); 64% of the indoor (0.22 μg/m$^3$) and 54% of the outdoor samples (0.21 μg/m$^3$) in Los Angeles, California (winter, 1984); 4.3% of the indoor samples (0.03 μg/m$^3$) and none of the outdoor samples in Los Angeles, California (summer, 1984); 20% of the indoor (0.12 μg/m$^3$) and none of the outdoor samples in Antioch/Pittsburgh, California (summer, 1984) (Pellizzari et al. 1986). 1,2-Dichloroethane was detected in only 1 of the 349 samples drawn from 11 cities in the 1990 Urban Air Toxics Monitoring Program (UATMP) at a concentration of 0.32 μg/m$^3$ (0.080 ppb) (EPA 1991). In a survey of homes in North Carolina, 1,2-dichloroethane was detected at a concentration of 0.40 μg/m$^3$ (0.10 ppb) in 1 out of 25 homes of smokers and was not detected in the homes of nonsmokers (Heavner et al. 1995). In a survey of New Jersey and Pennsylvania residences, 1,2-dichloroethane was detected in the homes of nonsmokers at a mean concentration of 0.03 μg/m$^3$ (0.007 ppb) and in the homes of smokers at a mean concentration of 0.32 μg/m$^3$ (0.079 ppb) (Heavner et al. 1996). The maximum concentration of 1,2-dichloroethane reported in nonsmoking households was 0.54 μg/m$^3$ (0.13 ppb), while the maximum concentration in households where at least one family member smoked was 9.72 μg/m$^3$ (2.40 ppb).

1,2-Dichloroethane has also been evaluated in samples of ambient air collected in the vicinity of hazardous waste disposal sites. 1,2-Dichloroethane was not detected in 6 air samples at Ogden Railyard in

EPA Region 8 in 2000 (WQP 2020). 1,2-Dichloroethane was detected at concentrations ranging from 0.039 to 0.049 µg/m$^3$ in 24 ambient air samples from Palermo Wellfield Superfund Site between 2013 and 2014; the concentration in 4 samples of indoor air ranged from 0.039 to 0.041 µg/m$^3$ (WQP 2020). At Superfund Intermountain Waste Oil Refinery in 2004, 1,2-dichloroethane was not detected in ambient air (WQP 2020). Trace amounts of 1,2-dichloroethane were found in samples of outdoor ambient air from two of nine residences in the Love Canal area of Niagara, New York (Barkley et al. 1980). It was also detected in indoor ambient air samples from two of the nine residences surveyed, at concentrations of 0.10 µg/m$^3$ (0.025 ppb) and 0.13 µg/m$^3$ (0.032 ppb). In addition, it has been found in ambient air samples from three of five hazardous waste sites surveyed in New Jersey at average concentrations of 0.04, 1.1, and 0.12 µg/m$^3$ (0.01, 0.28, and 0.030 ppb) (LaRegina et al. 1986). In an analysis of VOCs in five hair salons, 1,2-dichloroethane was detected in 100% of sites, with values between 63 and 99 ppb (Kaikiti, et al. 2022).

Other possible sources of indoor air pollution by 1,2-dichloroethane include volatilization from contaminated potable water in domestic shower and bath systems (Andelman 1985) and vapor intrusion from contaminated groundwater and soil gas A review of indoor air measurements from ATSDR public health assessment reports found concentrations of 1,2-dichloroethane to be below ATSDR's media-specific noncancer comparison values for indoor air and vapor intrusion (Burk and Zarus 2013). 1,2-Dichloroethane was detected in indoor air at 8 of 148 vapor intrusion sites and ranged from 0.0049 ppb (0.02 µg/m$^3$) to 6.7 ppb (27 µg/m$^3$). 1,2-Dichloroethane groundwater concentrations detected at nine of the vapor intrusion sites ranged from 0.987 to 150 µg/L. In a survey conducted by the Association of State and Territorial Solid Waste Management Officials in 2014, lead scavengers, including 1,2-dichloroethane, were a contaminant of concern in 20% of underground storage tank sites (ASTSWMO 2014).

1,2-Dichloroethane was detected at concentrations of 146 µg/m$^3$ (36 ppb) and 81 µg/m$^3$ (20 ppb) in the ambient air at municipal landfill sites in Canada (Brosseau and Heitz 1994). 1,2-Dichloroethane was detected in 11.4% of the vented air samples obtained from the Fresh Kills landfill in New York at an average concentration of 0.77 mg/m$^3$ (0.19 ppm) (EPA 1996). 1,2-Dichloroethane has been detected in samples of indoor air taken from newly renovated homes in Shanghai at a mean concentration of 33.83 µg/L (8,364 ppb), which is noticeably higher than concentrations reported in previous studies in Hong Kong, Japan, and Canada (Dai et al. 2017). In this study, 1,2-dichloroethane presented the highest median and mean cancer risks (Dai et al. 2017). Dai et al. (2017) note that renovated homes have higher

VOC concentrations, like 1,2-dichloroethane, than non-renovated homes have, and that this is due to emissions from building materials, furniture, paint, glue, floor coverings, and other materials.

A study monitoring VOC concentrations at an industrial area, traffic zone, residential zone, development zone, and background zone in Hefei city in China found that concentrations of 1,2-dichloroethane ranged from 0.68 µg/L in the industrial area to 1.51 µg/L in the background zone (Hu et al. 2018).

### 5.5.2 Water

In a survey of 14 heavily industrialized river basins in the United States, 1,2-dichloroethane was detected at a frequency of 53% in 204 surface water samples collected (EPA 1977); reported concentrations in domestic surface waters used as drinking water sources ranged from trace amounts to 4.8 µg/L (Brown et al. 1984). 1,2-Dichloroethane has also been found in samples of urban runoff from Eugene, Oregon, at a concentration of 4 µg/L (Cole et al. 1984). 1,2-Dichloroethane was detected in 26% of the river samples obtained from Osaka, Japan, at a mean concentration of 0.09 µg/L (Yamamoto et al. 1997). 1,2-Dichloroethane was detected in the Tees estuary in England in 1992 at concentrations of 0.72–4.02 µg/L, with the highest levels measured near an industrialized area where 1,2-dichloroethane and vinyl chloride monomer were produced (Dawes and Waldock 1994).

1,2-Dichloroethane is reported to be one of the predominant organohalogen pollutants in groundwater and industrial effluents, ranging from µg to g/L levels (De Wildeman et al. 2001; Hirschorn et al. 2007). Groundwater samples taken from 178 hazardous waste disposal sites contained 1,2-dichloroethane at 29.1% frequency (Plumb 1987). 1,2-Dichloroethane was detected in the groundwater of the Du Pont Necco Park Landfill in Niagara Falls, New York at concentrations of 14–4,250 µg/L (Lee et al. 1995). Reported concentrations of 1,2-dichloroethane in domestic groundwater supplies used for drinking water ranged from trace amounts to 400 µg/L (Brown et al. 1984). 1,2-Dichloroethane was detected in 10 of 943 groundwater samples across the United States at concentrations that ranged from 0.95 to 9.80 µg/L with median concentrations ranging from 0.57 to 2.9 µg/L (Westrick et al. 1984).

The disposal of organic chemicals in trenches at a waste disposal site near Ottawa, Canada resulted in 1,2-dichloroethane groundwater concentrations ranging from 3.9 to 58.0 µg/L in 30% of samples taken from a 37-well monitoring network in 1988 (Lesage et al. 1990). The concentration of 1,2-dichloroethane in the leachate samples from hazardous waste landfills in Germany ranged from 40 to 830 µg/L (Först et al. 1989). 1,2-Dichloroethane was identified, not quantified, in groundwater wells of Eau Claire,

Wisconsin (Canter and Sabatini 1994). 1,2-Dichloroethane was detected in 17% of groundwater samples obtained from 479 waste disposal sites in the United States (Barbee 1994). 1,2-Dichloroethane was detected in 27 of 82 samples of groundwater at the Darling Hill Dump, Vermont at an average concentration of 3.7 µg/L and a maximum concentration of 240 µg/L (EPA 1992a). The maximum concentration of 1,2-dichloroethane in groundwater at the Fallon Naval Air Station, Fallon, Nevada was 1,400 µg/L (Kelley et al. 1998). Groundwater from a former petro-chemical refinery in California contained 1,2-dichloroethane at concentrations ranging from 1 to 9 µg/L (EPA 1992b). 1,2-Dichloroethane was detected at concentrations of 0.8–32.8 µg/L in groundwater near the Lower Llobregat aquifer in Spain (Ventura et al. 1997). 1,2-Dichloroethane was determined to be one of two main contaminants in the groundwater at an organic chemical plant site in Chongqing, China, with concentrations ranging from 0.6 to 8,160 µg/L (Liu et al. 2016). The concentrations were much higher than the <1.45 µg/L concentration of 1,2-dichloroethane in the Yangtze River (Liu et al. 2016). In samples of shallow groundwater in new residential/commercial areas of the United States, 1,2-dichloroethane was measured at a concentration of 5 µg/L (Squillace et al. 2004).

In EPA's 3rd six-year review of drinking water contaminants (EPA 2006–2011), only 13 of 375,022 sites detected 1,2-dichlororethane above the regulated threshold of 5 µg/L (EPA 2016). 1,2-Dichloroethane was detected above the limit of detection (LOD) in 2,457 sites, with a median value of 0.89 µg/L.

### 5.5.3 Sediment and Soil

The concentration of 1,2-dichloroethane in sediment samples obtained from the Southampton Water estuary, England over an 18-month period ranged from 0.070 to 11 ppb (0.070 to 11 µg/kg) (Bianchi et al. 1991). 1,2-Dichloroethane was not detected in sediment downstream from two facilities in Canada that manufactured this compound (Oliver and Pugsley 1986). The mean concentration of 1,2-dichloroethane in soil near 20 homes in the Netherlands was 11 mg/kg, while samples in the vicinity of a garage and waste site contained <5 and 30 mg/kg, respectively (WHO 1995). 1,2-Dichloroethane was detected in soil from Claire, Michigan near seven industrial facilities at concentrations of 6–19 µg/kg (EPA 1992c). 1,2-Dichloroethane was also detected in sediments from the Scheldt Estuary in the Southern North Sea at concentrations between 0.28 and 0.58 ng/g (Roose et al. 2001). 1,2-Dichloroethane is among the 10 most prevalent chemicals found in Superfund sites in North Carolina (Tilley et al. 2017).

### 5.5.4 Other Media

Historically, 1,2-dichloroethane was used as a lead scavenger in leaded aviation gasoline, and its approximate concentration in gasoline was 0.07 g/L (Henderson et al. 2009).

In a market basket survey of over 500 samples of table-ready and prepared foods (including cereals, oils/dressings, vegetables, baked goods, nuts, dairy products, jams/candy, meats/meat dishes, fruits, infant/toddler blends, and beverages), 1,2-dichloroethane was detected in a whiskey sample at a concentration of 30 ng/g (Daft 1988, 1991). 1,2-Dichloroethane has been detected in plain granola samples at 0.31 and 12 ng/g, shredded wheat cereal samples at 8.2 ng/g (Heikes 1987), wheat grain samples at 0–180 ng/g, and bleached flour samples at 0–6.5 ng/g (Heikes and Hopper 1986). 1,2-Dichloroethane has also been qualitatively detected as a volatile component in chickpeas (Rembold et al. 1989).

1,2-Dichloroethane was formerly used as a fumigant but is not currently registered for use in agricultural products in the United States, Canada, and the United Kingdom. 1,2-Dichloroethane was not detected in 24 samples of rice analyzed in 1992 (WHO 1995) and was not detected in a U.S. Food and Drug Administration (FDA) survey of 234 table-ready foods (Heikes et al. 1995). In a survey of foods from Tokyo, Japan, 1,2-dichloroethane was not detected in bean sprouts, colas, juice, rice, lactic beverages, plain yogurt, tofu, or ice milk (Miyahara et al. 1995). It was detected at mean concentrations of 1.3 ng/g in butter, 0.2 ng/g (ppb) in cake, 0.03 ng/g in ice cream, and 0.03 ng/g in store-bought milk (Miyahara et al. 1995).

## 5.6 GENERAL POPULATION EXPOSURE

The greatest source of exposure to 1,2-dichloroethane for most of the U.S. population is inhalation of the compound in contaminated air. Vapor intrusion may also be a potential source of 1,2-dichloroethane exposure, as vapor intrusion has been observed for several VOCs with similar properties. Using a numerical model, Ma et al. (2016) concluded that exposure to 1,2-dichloroethane could occur through vapor intrusion. The model predicted that indoor air concentration of 1,2-dichloroethane can exceed EPA screening levels of 0.011 $\mu g/m^3$ if there is a sufficiently high source concentration such as those found at leaking underground storage tank sites. However, despite concerns over vapor intrusion due to groundwater contamination at two former industrial facilities in Denver, Colorado, Kurtz et al. (2010) found no evidence of vapor intrusion significantly contributing to indoor air concentrations of

1,2-dichloroethane. EPA's compilation of eight studies of background indoor air concentrations found a 1–25% detection rate for 1,2-dichloroethane in 1,661 U.S. resident samples between 1984 and 2004 (EPA 2011). The background medians ranged from less than the reporting levels (0.02–2.02 μg/m$^3$) to 0.25 μg/m$^3$, 95$^{th}$ percentiles ranged from less than the reporting levels to 1.1 μg/m$^3$, and maximum values ranged from 0.43 to 51 μg/m$^3$.

About 50% of 1,2-dichloroethane volatilizes from water while showering. Volatility from other household uses of water range from 23% (sinks, toilets) to 70% (dishwashers). Thus, the potential for inhalation exposure exists during showering, bathing, and other household water uses, such as dishwashers, clothes washers, toilets, and sinks. ATSDR's three-compartment Shower and Household Water-Use Exposure (SHOWER) model predicts air concentrations in the shower stall, bathroom, and main house throughout the day for households with up to eight members. Using these concentrations and human activity patterns, the model estimates a daily time-weighted average exposure concentration from breathing indoor air. The model also estimates dermal uptake from skin contact while bathing and washing hands.

Other potential routes of human exposure include ingestion of 1,2-dichloroethane in contaminated drinking water or food items and dermal absorption (EPA 1985; Gold 1980). Since 1,2-dichloroethane is not currently registered for use in agricultural products in the United States, the potential exposure from ingesting contaminated food sources has likely decreased. However, for populations with drinking water supplies containing >6 μg/L of the compound, oral and dermal routes are expected to be more important than inhalation (EPA 1985). The estimated daily intake of 1,2-dichloroethane in Japan attributed to food ingestion is 0.004 mg/day (Miyahara et al. 1995).

1,2-Dichloroethane is believed to be a constituent of tobacco smoke (Rodgman and Perfetti 2013). 1,2-Dichloroethane was detected at a mean concentration of 0.09 μg/m$^3$ in workplaces where smoking is not permitted and at a mean concentration of 0.03 μg/m$^3$ in workplaces where smoking is permitted (Heavner et al. 1996). These data are in contrast with the findings from the same study that showed a significantly higher concentration of 1,2-dichloroethane in the air of homes in which at least one family member smoked (see Levels Monitored in the Environment). It may be that workplaces that permit smoking have better ventilation, and thus lower ambient air contaminant levels.

Exposure of the population to 1,2-dichloroethane through releases to ambient air from a number of specific emission sources has been estimated (Kellam and Dusetzina 1980). The estimates, which are

probably too high because of the current limited use of leaded fuels, are presented in Table 5-6. The EPA TEAM studies measured personal and outdoor exposures of about 800 people to 25 VOCs, including 1,2-dichloroethane (Wallace 1991). The people were selected to represent more than one million residents in a wide variety of urban, suburban, and rural areas. The mean measured exposure to 1,2-dichloroethane, which was based on a 24-hour exposure of 750 people in 6 urban areas, was reported to be 0.5 µg/m$^3$. The outdoor air concentration based on backyard measurements in 175 homes in 6 urban areas was 7 µg/m$^3$ (Wallace 1991).

**Table 5-6. Estimated Population Exposure to 1,2-Dichloroethane Through Releases to Ambient Air from a Number of Specific Emission Sources**

| Emission source | Estimated population exposed | Ambient air concentration (ppb) |
|---|---|---|
| 1,2-Dichloroethane manufacturing plants | 12,500,000 | 0.01–10 |
| Chemical production facilities | 2,621,000 | 0.01–0.99 |
| Gasoline service stations[a] | 1,000,000 | 0.01–0.029 |
| Automobile emissions | 13,000,000 | 0.01–0.029 |
| Automobile refueling | 30,000,000 | <0.01 |

[a]Emissions from gasoline stations are in decline.

Source: Kellam and Dusetzina (1980)

In addition to industrial releases of 1,2-dichloroethane to ambient air, the general population may have been exposed to this compound in indoor air through volatilization from consumer products and from potable water (Andelman 1985). 1,2-Dichloroethane was detected in the volatile emissions of cleaning agents and pesticides, recently glued wallpaper, and recently glued carpet at concentrations of 236 µg/m$^3$ (58.2 ppb), 48±7.3 µg/m$^3$ (12±1.8 ppb), and 15±1 µg/m$^3$ (3.7±0.25 ppb), respectively (Wallace et al. 1987). Since 1,2-dichloroethane is no longer used in consumer products like cleaning agents and adhesives, this route of exposure is expected to be low today.

1,2-Dichloroethane has been detected in the expired breath and urine of humans in a number of studies, following exposure of the test subjects to the compound in ambient air and drinking water (Barkley et al. 1980; EPA 1982; Wallace et al. 1984).

1,2-Dichloroethane has been detected in child (aged 12–19 years) blood samples collected by the National Health and Nutrition Examination Survey (NHANES), although too many of the samples collected were below the LOD of 10 pg/mL to calculate selected percentiles (CDC 2018).

Inhalation of contaminated air likely represents the greatest route of potential exposure for children. 1,2-Dichloroethane has also been detected in drinking water, and therefore, ingestion of contaminated water is a possible source of exposure. 1,2-Dichloroethane was previously detected in human milk at concentrations ranging from 0.195 to 0.63 mg/100 mL of milk (EPA 1980; Urusova 1953). Current data on the concentration of 1,2-dichloroethane in breast milk are not available, and these historic data likely reflect exposures from former use patterns that are no longer relevant today. 1,2-Dichloroethane was formerly used in certain consumer household products such as cleaning agents and adhesives. The use of any household products that contained 1,2-dichloroethane to clean floors or glue carpets may result in exposure since children often crawl on floors and play on carpets. The potential for exposure is expected to diminish with time since 1,2-dichloroethane volatilizes fairly rapidly. This is expected to be a relatively minor route of exposure since most of these products have probably been used up or discarded from the majority of households. Differences from adults in susceptibility to hazardous substances are discussed in 3.2.1 Children's Susceptibility.

1,2-Dichloroethane has been detected in several food products, as discussed in Section 5.5.4, but consumption of these products should not disproportionately affect children. No data are available regarding the weight-adjusted intake of 1,2-dichloroethane. 1,2-Dichloroethane was formerly used as a fumigant but is not currently registered for use in agricultural products in the United States, Canada, or the United Kingdom. Therefore, it is expected that exposure to 1,2-dichloroethane through food sources will continue to decrease.

Children are unlikely to be exposed to 1,2-dichloroethane from parents' clothing or other objects removed from the workplace because of its volatility. It is possible that exposure may arise from the exhaled breath of parents who are occupationally exposed to 1,2-dichloroethane, but no quantitative data are available to confirm this. 1,2-Dichloroethane has been detected in humans in a number of studies, following exposure of the test subjects to the compound in ambient air and drinking water (Barkley et al. 1980; EPA 1982; Wallace et al. 1984).

There have been no documented exposures of children to 1,2-dichloroethane from pica. Children are unlikely to be exposed to 1,2-dichloroethane from pica since the majority of 1,2-dichloroethane released to the environment is emitted to the atmosphere. Furthermore, much of the 1,2-dichloroethane released to soil is expected to volatilize to air or leach into subsurface soil and groundwater.

## 5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Human exposure to 1,2-dichloroethane is expected to be highest among certain occupational groups and members of the general population living in the vicinity of industrial point emission sources (EPA 1985) and hazardous waste sites. 1,2-Dichloroethane has been detected in both ambient air and water in low concentrations (Fusillo et al. 1985; Isacson et al. 1985; Jüttner 1986; McDonald et al. 1988; Singh et al. 1982). No information was found regarding the number of people potentially exposed around hazardous waste sites. It was estimated that 150,000 people living in the vicinity of manufacturing and formulation plants were potentially exposed to concentrations ranging from 0.01 to 10 ppb 1,2-dichloroethane in ambient air in the late 1970s (Kellam and Dusetzina 1980). Hsu et al. (2018) found that concentrations of 1,2-dichloroethane were significantly high within a 5-km radius of a petrochemical complex in central Taiwan, with concentrations ranging from 0.028 to 0.432 ppb. In a study among workers in Lignite mines in India, workers were exposed to 1,2-dichloroethane at significantly high concentrations ranging from 1.52 to 2.85 ppb (Yao et al. 2021). In a study of several closed batch processes, levels of exposure to 1,2-dichloroethane were determined (Franken et al. 2020). The highest airborne concentrations were measured during rolling and handling of immersed objects, with geometric means of 437 and 324 ppm, and the lowest concentrations were measured during partially closed processes and closed processes, with geometric means of 5.3 and 10.2 ppm, respectively.

Concentrations of VOCs, including 1,2-dichloroethane, and risk levels of wastewater treatment plant employees' exposure to VOCs in Finland have been determined. The concentration of 1,2-dichloroethane was found to be elevated at one of the two plants studied, with a measured concentration of 955.8 μg/L in the trash rake (Lehtinen and Veijanen 2011). Employees at an organic chemical plant site in Chongqing, China were determined to be at elevated cancer risk due to the concentration of 1,2-dichloroethane in soil and groundwater samples (Liu et al. 2016).

Recent information on workplace exposures to 1,2-dichloroethane was not located. Information presented in this paragraph was obtained in the 1970s; thus, data are not likely to pertain to current occupational exposures. The National Occupational Hazard Survey (NOHS), conducted by NIOSH from 1972 to 1974, estimated that 1,909,530 workers in 148,165 plants were potentially exposed to 1,2-dichloroethane in the workplace in 1972–1974 (NIOSH 1976). These estimates were derived from observations of the actual use of 1,2-dichloroethane (5% of total estimate), the use of trade-name products known to contain 1,2-dichloroethane (3%), and the use of generic products suspected of containing the compound (92%).

Neither the NOHS database nor the NOES database contains information on the frequency, level, or duration of exposure of workers to any of the chemicals listed therein. They provide only estimates of workers potentially exposed to the chemicals. There was a large potential for exposure to 1,2-dichloroethane in the workplace during its previous use as a grain fumigant, solvent, and diluent in open-system operations (NIOSH 1978).

# 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-dichloroethane 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-dichloroethane.

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

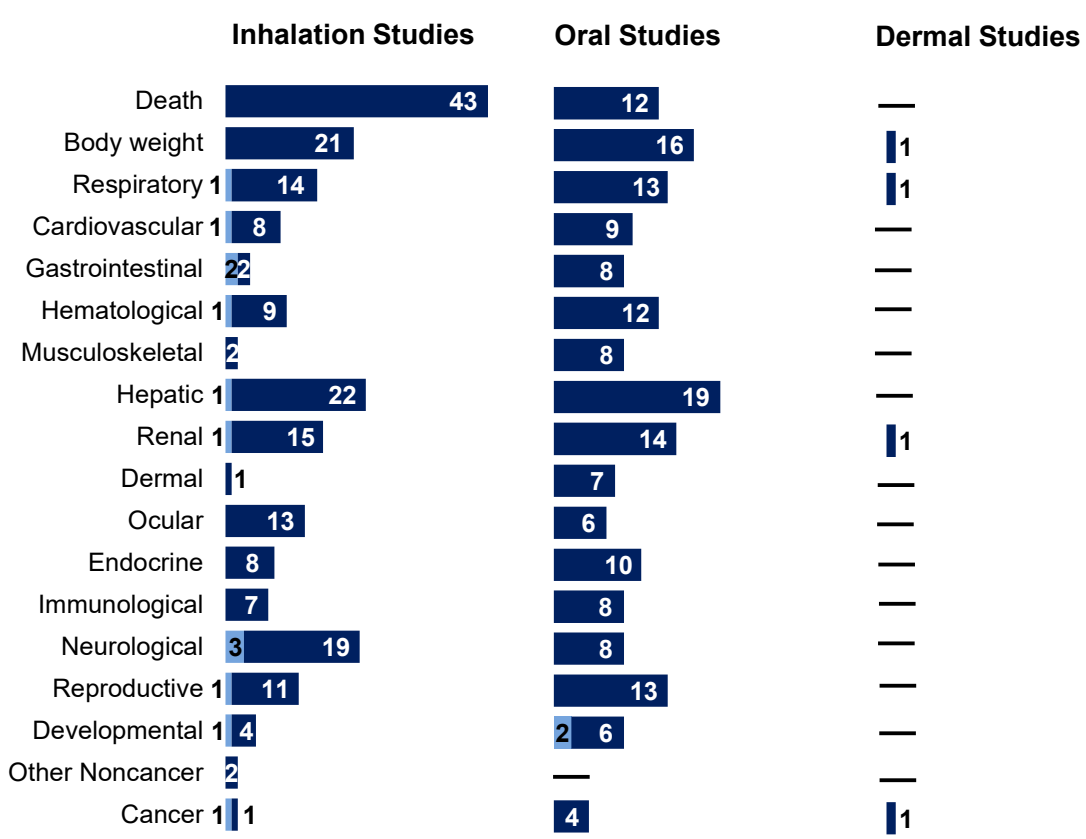
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to 1,2-dichloroethane that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of 1,2-dichloroethane. The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

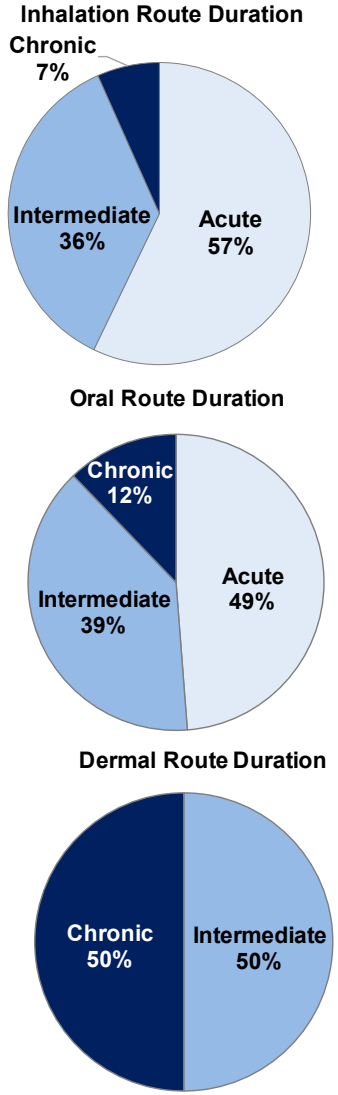
Figure 6-1 illustrates that a majority of toxicity data available for 1,2-dichloroethane comes from inhalation studies on laboratory animals. Respiratory, hepatic, neurological, and cancer endpoints were the most commonly studied endpoints. Studies on inhalation and oral exposure to humans primarily consisted of case studies. Dermal studies were limited to laboratory animals and were largely focused on cancer endpoints.

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

**Respiratory, hepatic, neurological, and cancer effects were the most studied endpoints**

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




*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. Some studies may have contributed information for more than one endpoint.

## 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 database of toxicity data on 1,2-dichloroethane was adequate to derive an acute-duration inhalation MRL. The available acute oral database was inadequate for deriving an MRL. Information on 1,2-dichloroethane toxicity in humans exposed orally is limited as it comes primarily from case reports of humans who died following acute-duration exposure to high levels of 1,2-dichloroethane by ingestion. Animal studies of acute-duration oral exposure used gavage administration, which is known to exacerbate toxicity of 1,2-dichloroethane (relative to drinking water administration), and thus is not a suitable model for human oral exposure to this chemical. The acute-duration study that identified the lowest LOAEL (Munson et al. 1982) observed immunosuppression in mice at a gavage dose of 4.9 mg/kg/day for 14 days; however, in a follow-up 90-day study reported in the same publication, no effect on immune response was seen in mice exposed to 189 mg/kg/day via drinking water. Additional studies are needed to characterize the effects of oral exposure to 1,2-dichloroethane via environmentally relevant modes of administration (e.g., drinking water or diet) to provide an appropriate basis for deriving an acute-duration oral MRL. Such data may lead to the development and use of PBPK models to extrapolate from gavage data to more environmentally relevant exposures.

**Intermediate-Duration MRLs.** The available intermediate inhalation database provided adequate data for deriving an intermediate-duration inhalation MRL. The most sensitive endpoint for deriving an intermediate-duration inhalation MRL is neurotoxicity, as demonstrated by alterations in open field tests following a 28-day exposure in mice. Additional studies evaluating neurotoxicity and male reproductive effects for longer intermediate exposure durations (e.g., >28–<365 days) may provide additional information for MRL derivation. The available intermediate oral database provided enough data to derive an intermediate-duration oral MRL for 1,2-dichloroethane.

**Chronic-Duration MRLs.** The available chronic-duration oral and inhalation databases were inadequate for deriving an MRL. The one reliable oral study on rats and mice was primarily designed to assess carcinogenicity, which is not applicable to MRL derivation. In addition, this study used gavage

administration, which is known to exacerbate toxicity of 1,2-dichloroethane (relative to drinking water administration), and thus is not a suitable model for human oral exposure to this compound. Chronic-duration oral toxicity studies are needed to identify noncancer target organs and enable derivation of a chronic-duration oral MRL. There were two chronic-duration inhalation studies of 1,2-dichloroethane. Both examined comprehensive endpoints but identified effect levels that were higher than the acute-duration inhalation point of departure (POD) (for nasal lesions) and a serious LOAEL (for sperm abnormalities) identified in an intermediate-duration inhalation study, precluding MRL derivation. One of the two chronic-duration studies (Cheever et al. 1990) identified a freestanding NOAEL for nasal lesions that was identical to the NOAEL in the acute-duration inhalation study (Hotchkiss et al. 2010) used for the acute-duration MRL. This finding suggests that 1,2-dichloroethane concentration may be a more important factor than exposure duration in the induction of nasal lesions. Studies to confirm this observation would be beneficial. Neither of the chronic-duration inhalation studies evaluated sperm parameters. The serious LOAEL for increased sperm abnormalities was identified in one 4-week inhalation study in mice (Zhang et al. 2017); no other studies have reported this effect. Additional studies are needed to provide confirmation for this effect and the exposure concentration at which it occurs.

**Health Effects.** Studies demonstrate that 1,2-dichloroethane readily absorbs dermally through human (Urusova 1953) and animal skin (Jakobson et al. 1982; Morgan et al. 1991). Dermal exposure to workers can occur in occupational settings (Bowler et al. 2003). Currently, there are no epidemiological or occupational studies examining health effects in humans exposed dermally and few studies examining animals exposed dermally. There is a need for dermal exposure studies examining a wide range of endpoints to identify possible toxicity endpoints from a variety of concentrations and exposure durations.

Toxicokinetic studies (see Section 3.1) have shown that the enzymes involved in the biotransformation of 1,2-dichloroethane are saturable at approximately 25 mg/kg/day (gavage) and 150 ppm (inhalation) in rats (D'Souza et al. 1988; Reitz et al. 1982; Spreafico et al. 1980). Support for this finding comes from the studies by NTP (1991) that showed effects (including mortality) occurring at much lower doses in animals exposed to 1,2-dichloroethane via gavage compared with those exposed by drinking water. Gavage administration does not represent typical oral exposure in humans, which is most likely to occur via ingestion of contaminated drinking water in small doses spread out over the course of a day. Under these exposure conditions, biotransformation processes will probably not become saturated; thus, the risk for adverse effects is not as high as would be predicted from gavage administration of equivalent doses.

Nearly all of the acute- and chronic-duration animal studies of oral exposure to 1,2-dichloroethane used gavage administration, and the resulting LOAEL values are likely much lower than would be seen with drinking water administration. Additional studies using drinking water exposure are needed to determine effect levels for multiple endpoints that would be relevant to human exposures.

***Respiratory.*** 1,2-Dichloroethane is readily absorbed through the lungs of humans and laboratory animals and is the most likely exposure route in humans. Two human studies (McNally and Fostvedt 1941; Nouchi et al. 1984) show adverse respiratory effects following inhalation of 1,2-dichloroethane, but the exposure concentrations were unknown in both cases. In animals, nasal olfactory degeneration/necrosis, respiratory tract irritation, and pulmonary congestion (Chan et al. 2002; Heppel et al. 1945; Hotchkiss et al. 2010) resulted from inhalation. There is an identified data need for epidemiological or occupational studies that evaluate effects on the respiratory system to humans exposed to 1,2-dichloroethane in air.

***Immunological.*** A data need to conduct additional immunotoxicity studies via inhalation and oral exposure has been identified. Immunological effects reported in humans exposed to 1,2-dichloroethane are limited to splenic lesions in a single case of accidental ingestion (Hubbs and Prusmack 1955). In mice, this chemical had immunosuppressive effects following both acute-duration inhalation exposure and acute-duration oral exposure. A single 3-hour inhalation exposure to 5 or 11 ppm increased the susceptibility of female mice to bacterial infection, and exposure to 11 ppm decreased the bactericidal activity of the lungs. No change in bactericidal activity was seen in male rats after a single 5-hour inhalation exposure to 200 ppm or 12 5-hour exposures to 100 ppm (Sherwood et al. 1987). Other immune function endpoints studied in the rats were also negative. The relevance of the endpoint (lethality due to massive streptococcal challenge) in mice to immune function is known, but its suitability as a basis for MRL derivation is uncertain. The streptococcal challenge test was used to evaluate potential immune effects of single exposures to 0, 2, 5, and 11 ppm 1,2 dichloroethane. A decreased immune response to challenge was observed at 11 ppm, with a NOAEL for immune effects of 5 ppm. However, substantial lethality was observed in both the 5- and 11-ppm exposure groups compared to controls. Therefore, the NOAEL for immunological effects cannot be used to derive an acute-duration inhalation MRL due to increased lethality. Gavage administration of 4.9 and 49 mg/kg/day of 1,2-dichloroethane to mice for 14 days reduced humoral (immunoglobulin response to sheep red blood cells) and cell-mediated (delayed-type hypersensitivity response to sheep erythrocytes) immunity. Only the humoral response was dose related. In addition, the

leukocyte number was decreased by 30% at the high dose (Munson et al. 1982). The immune system was the most sensitive target for short-term exposure to 1,2-dichloroethane by both the inhalation and gavage routes in mice, as compared with endpoints in other studies in mice and in other species. The other studies, however, had limitations including wide spacing of the exposure concentrations, such that only NOAELs and serious LOAELs were identified. In contrast to the acute-duration oral study, higher doses of 1,2-dichloroethane (189 mg/kg/day) administered to mice in their drinking water for 90 days did not affect humoral and cell-mediated immunity (Munson et al. 1982), as assessed by some of the Tier I and Tier II procedures from the immunotoxicity testing battery (Luster et al. 1988). Immune function has not been evaluated in chronic-duration studies of 1,2-dichloroethane, but histopathological examinations failed to detect immune system lesions or immune-related changes in rats and mice exposed to 1,2-dichloroethane by inhalation or oral (gavage or drinking water) routes for intermediate or chronic durations (Cheever et al. 1990; Morgan et al. 1990; NCI 1978; NTP 1991). Leukocyte counts were not affected in intermediate-duration drinking water and gavage studies in rats (Morgan et al. 1990; NTP 1991). The acute-duration data provide limited evidence that the immune system is a sensitive target of 1,2-dichloroethane in mice, but not rats. Because of the apparent interspecies differences in animal immunotoxicity, it is unclear whether the immune system could be a target of 1,2-dichloroethane in humans following acute-duration exposure by inhalation or ingestion.

Another possible explanation for the different outcomes of acute- and intermediate-duration oral exposure is that 1,2-dichloroethane may induce its own metabolism during the longer exposure period, thus reducing the dose to the immune cells. In addition to immune effects, induction of enzymes involved in 1,2-dichloroethane metabolism could also play a role across other outcomes.

The results of animal studies confirm that the central nervous system is a target of high concentrations of 1,2-dichloroethane. Clinical signs similar to those reported in humans, such as tremors, abnormal posture, uncertain gait, and narcosis, were observed after high-level, acute-duration vapor exposures (Heppel et al. 1945; Morgan et al. 1990; NTP 1991; Spencer et al. 1951). In addition, clinical signs of neurotoxicity and mild necrosis in the cerebellum were found in rats administered 240–300 mg/kg/day of 1,2-dichloroethane by gavage for 13 weeks (Morgan et al. 1990; NTP 1991). No clinical signs or neurological lesions were seen in rats exposed through their drinking water up to 492 mg/kg/day or mice exposed up to 4,210 mg/kg/day for 13 weeks (Morgan et al. 1990; NTP 1991), and no brain lesions were seen in rats intermittently

exposed to 50 ppm for 2 years (Cheever et al. 1990). No studies regarding the potential neurotoxicity of dermal exposure were located. The discrepancy in results between gavage and drinking water administration may be due to saturation of the detoxification/ excretion mechanism by the bolus gavage dosing. These data do not sufficiently characterize the potential for 1,2-dichloroethane to induce more subtle neurotoxic effects following low-level prolonged exposure by inhalation, oral, or dermal exposure. Intermediate-duration neurotoxicity studies in animals, using sensitive functional and neuropathological tests at inhalation and oral exposure levels significantly lower than those resulting in morbidity and death, would assist in the characterization of the neurotoxic potential of 1,2-dichloroethane.

***Reproductive.*** A data need to conduct additional reproductive studies via dermal exposure has been identified. A single study on reproductive effects of exposure to 1,2-dichloroethane in humans is suggestive of a decrease in duration of gestation (Zhao et al. 1989) but should be interpreted with caution since co-exposure to other chemicals occurred in most cases and the adequacy of the study design could not be evaluated because of reporting deficiencies. Results of animal studies indicate that this chemical is unlikely to cause female reproductive impairment at doses that are not maternally toxic. Although some inhalation studies found that exposure to 1,2-dichloroethane prior to mating and continuing into gestation caused pre-implantation loss and embryo lethality in rats (Vozovaya 1974, 1977; Zhao et al. 1989), the methods used by these investigators were not well reported and the reliability of the data is uncertain. In contrast to these findings, a well-designed and reported study of reproductive toxicity found no adverse effects on the fertility of rats exposed by inhalation to 10-fold higher concentrations of 1,2-dichloroethane in a one-generation reproduction study (Rao et al. 1980). In the absence of an apparent explanation for the discrepancy, greater credence should be given to the well-designed and reported study. One- and two-generation reproduction studies found no chemical-related effects on fertility indices in long-term oral studies in mice and rats (Alumot et al. 1976; Lane et al. 1982), but exposure to higher oral doses caused increases in non-surviving implants and resorptions in rats that also experienced maternal toxicity (30% decreased body weight gain) (Payan et al. 1995). Histological examinations of the testes, ovaries, and other male and female reproductive system tissues were performed in intermediate- and chronic-duration inhalation and oral animal studies with negative results (Cheever et al. 1990; Daniel et al. 1994; Morgan et al. 1990; NCI 1978; NTP 1991; van Esch et al. 1977), although reproductive performance was not evaluated in these studies. An inhalation study on male mice exposed to high concentrations revealed decreases in sperm concentration, motility, and progressive motility (Zhang et al. 2017).

The study was well designed, examining effects from a wide range of doses over acute and intermediate durations. While the study identified reproductive toxicity in male mice characterized by effects on sperm parameters and morphological abnormalities in spermatozoa, the effects across generations was not examined (Zhang et al. 2017).

***Developmental.*** A data need to conduct additional developmental studies via inhalation, oral, and dermal exposure has been identified. The only studies regarding developmental effects in humans are epidemiologic investigations of adverse birth outcomes. These studies found increased OR for exposure to 1,2-dichloroethane in public drinking water and major cardiac defects (but not neural tube defects) (Bove 1996; Bove et al. 1995), and for residence within the census tract of NPL sites contaminated with 1,2-dichloroethane and neural tube defects (but not heart defects) (Croen et al. 1997). Increased ORs were seen for maternal residential proximity to industrial air emissions of 1,2-dichloroethane and birth defects, neural tube defects, and congenital heart defects (Brender et al. 2014). Primary routes of exposure in these epidemiologic studies were both oral and inhalation (including inhalation of 1,2-dichloroethane volatilized from household water). In these studies, the study populations were also simultaneously exposed to elevated levels of other contaminants. Because of the mixed chemical exposure, lack of dose-response information, and inconsistency between the findings of the studies, the associations with 1,2-dichloroethane are only suggestive, do not establish a cause-and-effect relationship, and should be interpreted with caution.

The weight of evidence from available inhalation and oral studies in rats, mice, and rabbits indicates that 1,2-dichloroethane is not fetotoxic or teratogenic, although indications of embryo and fetal lethality at maternally toxic doses have been reported (Kavlock et al. 1979; Lane et al. 1982; Payan et al. 1995; Rao et al. 1980). The reliability of the reports of increased embryo and pup mortality following intermediate-duration inhalation of lower (not maternally toxic) concentrations of 1,2-dichloroethane (Vozovaya 1977; Zhao et al. 1989) is uncertain, due to the lack of statistical analysis, inadequate description of methods, and uncertainties in the reported results. The possibility of induction of cardiac malformations by 1,2-dichloroethane, as suggested by the epidemiologic data, was not adequately addressed in the animal studies because their conventional teratology protocols did not include detailed examinations of dissected hearts. Given the suggestive evidence of an association between exposure to 1,2-dichloroethane in drinking water and major cardiac defects in human offspring, and evidence of heart malformations in epidemiology and animal cardiac teratogenicity studies of dichloroethylene and

trichloroethylene (Dawson et al. 1993; Goldberg et al. 1990), which are metabolized to some of the same reactive intermediates as is 1,2-dichloroethane, it would be informative to have studies specifically designed to investigate the potential for induction of developmental heart malformations by 1,2-dichloroethane. In addition, neurodevelopmental effects need to be investigated since human case studies and laboratory animal data identified 1,2-dichloroethane as a neurotoxin in adult humans and adult animals.

***Cancer.*** Epidemiological studies that have investigated associations between occupational or oral exposure to 1,2-dichloroethane and increased incidences of cancer are inadequate for assessing carcinogenicity of 1,2-dichloroethane in humans due to complicating co-exposures to various other chemicals, as discussed in the section on epidemiology. The carcinogenic potential of 1,2-dichloroethane has been examined in rats and mice following inhalation, oral, and dermal exposure.

The positive and suggestive carcinogenicity results from animal bioassays (Nagano et al. 2006; NCI 1978; Stoner 1991; Suguro et al. 2017; Theiss et al. 1977; Van Duuren et al. 1979), along with data indicating that 1,2-dichloroethane and certain metabolites are mutagenic and capable of forming DNA adducts as discussed in the preceding section, provide sufficient evidence to suggest that 1,2-dichloroethane is a probable human carcinogen.

***Genotoxicity.*** A data need to conduct additional genotoxicity studies has been identified. Only one oral exposure study examined genotoxicity and no information regarding the genotoxicity of 1,2-dichloroethane in humans following oral, dermal, or parenteral exposure is available (Cheng et al. 2000). The study has several other limitations, such as not properly observing lifestyle factors, including alcohol consumption, and the small age range of subjects limited examination of an age-related response.

However, a great deal of data are available regarding the genotoxic effects of 1,2-dichloroethane in human cells *in vitro*; prokaryotic organisms, fungi, and nonhuman mammalian cells in vitro; and insects, rats, and mice *in vivo*.

Although genotoxicity in humans could be investigated directly by examining peripheral lymphocytes obtained from exposed workers for clastogenic effects, the utility of such studies is likely to be limited due to the workers' exposures to other chemicals. Additional *in vivo* studies

examining the importance of the route of administration on 1,2-dichloroethane-induced quantitative genotoxicity data (i.e., adducts) in animals are needed since the available information indicates route-dependent effects (inhalation doses are less potent than oral gavage) (Storer et al. 1984). DNA adduct and monoclonal antibody dosimetry work also are needed to provide quantitative genotoxicity data, and perhaps could be used as a biomarker of exposure to 1,2-dichloroethane.

**Epidemiology and Human Dosimetry Studies.** Most of the available information on the adverse noncancer effects of 1,2-dichloroethane in humans comes from cases of acute poisoning by inhalation or ingestion (Chen et al. 2015; Dang et al. 2019; Garrison and Leadingham 1954; Hubbs and Prusmack 1955; Hueper and Smith 1935; Liu et al. 2010; Lochhead and Close 1951; Martin et al. 1969; Nouchi et al. 1984; Schönborn et al. 1970; Yodaiken and Babcock 1973; Zhan et al. 2011; Zhou et al. 2015) and epidemiological studies of exposure to drinking water contaminants, residence near hazardous waste sites, or employment in the chemical industry (discussed later in this section). Limitations inherent in the case studies include unquantified exposure and the high-dose nature of the exposures. Despite their inadequacies, the available human case studies indicate that 1,2-dichloroethane can cause neurotoxicity, nephrotoxicity, gastrointestinal toxicity, and hepatotoxic effects, and death due to cardiac arrhythmia. These observations are similar to those in high-dose animal studies, but other, more sensitive effects seen in animals at low levels of exposure have not been investigated in humans.

Epidemiologic investigations of adverse birth outcomes found an increased OR for exposure to 1,2-dichloroethane in public drinking water and major cardiac defects (but not neural tube defects) (Bove 1996; Bove et al. 1995), an increased OR for residence within the census tract of NPL sites contaminated with 1,2-dichloroethane and neural tube defects (but not heart defects) (Croen et al. 1997), and an increased adjusted OR for maternal proximity to industrial facilities using 1,2-dichloroethane and neural tube defects and spina bifida (Brender et al. 2014). The study populations also were simultaneously exposed to elevated levels of other contaminants. Because of the mixed chemical exposure, lack of dose-response information, and inconsistency between the findings of the two studies, the associations with 1,2-dichloroethane are only suggestive, and do not establish a cause-and-effect relationship. The animal data do not indicate that 1,2-dichloroethane is teratogenic, but conventional teratology protocols were used that do not include detailed examinations of dissected hearts. Increased rates of premature births were reported in workers exposed in a Chinese synthetic fiber factory (Zhao et al. 1989). This study was generally deficient in reporting of study design and accounting for possible confounders, including other chemicals in the factory.

Epidemiological studies of workers in the chemical industry suggest that exposure to chemical manufacturing processes that involve 1,2-dichloroethane is associated with formation of cerebral edema (Chen et al. 2015; Dang et al. 2019; Liu et al. 2010; Zhan et al. 2011; Zhou et al. 2015), an increased incidence of brain tumors (Austin and Schnatter 1983a, 1983b; Reeve et al. 1983; Teta et al. 1989; Waxweiler et al. 1983), significant neuropsychological impairment (Bowler et al. 2003; Ruffalo et al. 2000), nonlymphatic leukemia (Ott et al. 1989), stomach cancer, and leukemia (Hogstedt et al. 1979), and with increased deaths due to pancreatic cancer and lymphatic and hematopoietic cancers (Benson and Teta 1993) among chemical plant workers. Increased risk of breast cancer was reported among men working at jobs associated with exposure to gasoline or gasoline combustion products containing 1,2-dichloroethane (Hansen 2000), and the risk of several cancer types was increased in residents living proximal to a Montreal municipal waste site that emitted volatile organic substances including 1,2-dichloroethane (Goldberg et al. 1995). These studies involved exposure to other chemicals and did not deal with 1,2-dichloroethane exposure exclusively. Isacson et al. (1985) reported an association between the presence of 1,2-dichloroethane in drinking water and an increased incidence of colon and rectal cancer in men aged ≥55 years old, but other organic chemicals were present in the drinking water. Studies in animals are adequate to support the determination that 1,2-dichloroethane may reasonably be anticipated to be a human carcinogen.

Well-controlled epidemiological studies of people living in areas where 1,2-dichloroethane has been detected in water or near industries or hazardous waste sites releasing 1,2-dichloroethane, and/or of people exposed in the workplace, could add to and clarify the existing database on 1,2-dichloroethane induced human health effects. Previous studies of 1,2-dichloroethane from hazardous waste sites or drinking water have not been able to establish anything more than a weak association between a health effect and 1,2-dichloroethane due to the presence of many other chemicals at the sites or in the water, small numbers of cases with the health effect, and difficulties in controlling for all of the variables that may confound the results for a general population study. At present, the only known health effects of 1,2-dichloroethane in humans, seen in cases of acute-duration high exposure, are neurotoxicity, nephrotoxicity, hepatotoxicity, and effects on the cardiovascular system. A particularly sensitive endpoint of acute-duration inhalation or gavage exposure to 1,2-dichloroethane in mice (but not rats) is immunological effects. No data regarding this endpoint are available for humans.

**Biomarkers of Exposure and Effect.** A data need has been identified for biomarkers of exposure. Proposed biomarkers for exposure to 1,2-dichloroethane include levels of parent compound in

the breath, blood, urine, and breast milk; levels of thioethers in the urine; and levels of thiodiglycolic acid in the urine (Igwe et al. 1988; Payan et al. 1993; Spreafico et al. 1980; Urusova 1953). However, use of the parent compound as a biomarker would only be possible at a known time since exposure, and the other proposed biomarkers are not specific for 1,2-dichloroethane. If epidemiological studies are conducted in which there is a correlation between 1,2-dichloroethane exposure time and time to specific adverse health effects, then it may be possible to correlate these health effects quantitatively with changes in tissue and/or body levels of 1,2-dichloroethane.

Biomarkers of effect for 1,2-dichloroethane include serum enzyme levels indicative of liver damage (ALT, AST, SDH), increased liver or kidney weight (size), and DNA adduct formation for liver and kidney effects (Brondeau et al. 1983; Inskeep et al. 1986; Nouchi et al. 1984; Prodi et al. 1986). Another potential biomarker would be tests for immunosuppression, but immune effects have been demonstrated only in mice in acute-duration exposure studies (Munson et al. 1982; Sherwood et al. 1987). Because they have not been seen in humans, rats, or even mice exposed for an intermediate duration, the relevance of these effects to humans is uncertain. None of these biomarkers are specific for 1,2-dichloroethane. These biomarkers are indicative of effects, but dosimetry has not been worked out for any of them. Because immunological effects of 1,2-dichloroethane have been seen only in mice, it is uncertain whether immunosuppression would occur in humans exposed to this chemical.

**Absorption, Distribution, Metabolism, and Excretion.** A data need to assess the toxicokinetics of 1,2-dichloroethane following inhalation, oral, and dermal exposure has been identified. Case reports of toxic effects subsequent to inhalation or oral exposure suggest that 1,2-dichloroethane is absorbed following exposure by these routes (Garrison and Leadingham 1954; Hueper and Smith 1935; Lochhead and Close 1951; Martin et al. 1969; Nouchi et al. 1984; Schönborn et al. 1970; Yodaiken and Babcock 1973). Inhalation exposure of lactating women in the workplace resulted in distribution of 1,2-dichloroethane to their milk (Urusova 1953). Animal studies were sufficient to characterize the rate and extent of absorption following inhalation, oral, and dermal exposure (Morgan et al. 1991; Reitz et al. 1980, 1982; Spreafico et al. 1980). Distribution, metabolism, and excretion have also been well studied in animals exposed by the inhalation or oral routes (D'Souza et al. 1987, 1988; Reitz et al. 1982; Spreafico et al. 1980; Sweeney et al. 2008) and are qualitatively similar across these routes. Metabolism is saturable in animals, but the precise levels at which saturation phenomena come into play have not been determined and appear to differ between gavage and inhalation exposures (Reitz et al. 1982). Additional studies investigating the saturation of CYP metabolism by inhaled and ingested 1,2-dichloroethane, as well as the roles of the oxidative and glutathione conjugation metabolic pathways in 1,2-dichloroethane toxicity and

mutagenicity/carcinogenicity, would enable better understanding of the metabolism of this compound. Based on the elimination of virtually all radiolabel from inhalation or gavage administration of 1,2-dichloroethane to rats within 48 hours, Reitz et al. (1982) concluded that the potential for 1,2-dichloroethane to accumulate with repeated exposure is minimal. The rate of elimination of the parent compound from adipose tissue was similar to that from blood following gavage administration to rats, but was slower following a single inhalation exposure or intravenous injection (Spreafico et al. 1980; Withey and Collins 1980), raising the possibility that 1,2-dichloroethane may accumulate to some extent in adipose tissue and in breast milk of nursing women. In the past, 1,2-dichloroethane has been detected in human milk (EPA 1980; Urusova 1953), indicating that developing children could possibly be exposed to 1,2-dichloroethane from breastfeeding mothers. However, historic data likely reflect exposures from former use patterns that are no longer relevant today. Thus, the importance of this route of developmental exposure is unclear because current data on the concentration of 1,2-dichloroethane in breast milk are not available. More quantitative information on the presence of 1,2-dichloroethane in fat and breast milk would be useful to assess the ability of 1,2-dichloroethane to accumulate in fat and the potential hazard to nursing infants. Further study into the long-term fate of low-level 1,2-dichloroethane exposure in humans and animals and the potential for accumulation in humans would also provide valuable information.

Toxicity data in humans and animals suggest similar target organs in each. Toxicokinetic studies have not been performed in humans. The database with regard to comparative toxicokinetics across species is limited as most studies have been performed in rats (D'Souza et al. 1987, 1988; Morgan et al. 1991; Reitz et al. 1980, 1982; Spreafico et al. 1980). Only one set of studies included mice (D'Souza et al. 1987, 1988), and these studies were conducted to validate PBPK modeling, primarily for levels of the direct glutathione conjugate in selected tissues of concern for carcinogenicity (liver and lung). More information on the toxicokinetics of 1,2-dichloroethane in other animal species would be useful for more fully assessing interspecies differences and the implications for human exposure. The database with regard to comparative toxicokinetics across routes does include comparative toxicokinetics across acute-duration inhalation and gavage (oil) administration (Reitz et al. 1980; Spreafico et al. 1980). The vehicle used in oral administration studies appears to play a role in the time course of absorption. Withey et al. (1983) reported that 1,2-dichloroethane is absorbed more rapidly by the gastrointestinal tract following gavage administration in water than in corn oil; the estimated area under the curve (based on data for up to 300 minutes post-dosing) was also much greater for the water than the corn oil vehicle. Information on toxicokinetics for repeated or longer-term continuous exposure is not available.

**Comparative Toxicokinetics.** Toxicity data in humans and animals suggest similar target organs in each. Toxicokinetic studies have not been performed in humans. The database with regard to comparative toxicokinetics consists primarily of studies in rodents (D'Souza et al. 1987, 1988; Morgan et al. 1991; Reitz et al. 1980, 1982; Spreafico et al. 1980; Sweeney et al. 2008). More information on the toxicokinetics of 1,2-dichloroethane in other animal species, including humans, would be useful for more fully assessing interspecies differences and the implications for human exposure.

**Children's Susceptibility.** Data needs related to both prenatal and childhood exposures, and developmental effects expressed whether prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

**Physical and Chemical Properties.** The physical and chemical properties of 1,2-dichloroethane are well characterized to permit estimation of its environmental fate (see Chapter 4). No additional studies are needed at this time.

**Production, Import/Export, Use, Release, and Disposal.** Production methods for 1,2-dichloroethane are known and there does not appear to be a need for further information. The use pattern of 1,2-dichloroethane is known. Detailed information on the uses of 1,2-dichloroethane in industry and consumer products is available from Chemical Data Reporting (EPA 2012a, 2016). Additional data on the uses of 1,2-dichloroethane are not needed. TRI contains data on releases to air, water, and soil from facilities that produce 1,2-dichloroethane. There does not appear to be a need for additional data on releases of 1,2-dichloroethane. More information regarding the amount of 1,2-dichloroethane that is disposed of at hazardous waste sites or abandoned would be useful. No current data are available on the amount of 1,2-dichloroethane disposed of annually. Methods for disposing of 1,2-dichloroethane are described in the literature.

**Environmental Fate.** The partitioning of 1,2-dichloroethane into air, water, and soil is well established (Brüggemann et al. 1991; Chiou et al. 1980; Dilling 1977; Dilling et al. 1975; EPA 1981, 1985; Jeng et al. 1992; Jury et al. 1990; Pearson and McConnell 1975; Wilson et al. 1981). 1,2-Dichloroethane is highly mobile in soil and is expected to leach into groundwater. Available laboratory data are sufficient to estimate its atmospheric lifetime, but information on degradation rates in soil and water are limited. Recent data indicate that 1,2-dichloroethane will biodegrade slowly in soil, water, and groundwater under both aerobic and anaerobic conditions. Additional data regarding the degradation rates of 1,2-dichloroethane in soil and water would be helpful in assessing its environmental fate.

**Bioavailability from Environmental Media.** 1,2-Dichloroethane has been measured in the breath, blood, urine, adipose tissue, and breast milk of humans (Barkley et al. 1980; EPA 1980, 1982; Wallace et al. 1984). Thus, it can be concluded that 1,2-dichloroethane is bioavailable from the environment. Good quantitative data that correlate varying levels in the environment with levels in the body and associated health effects are lacking. Data are lacking regarding the extent to which 1,2-dichloroethane can be absorbed from various media (e.g., soil).

The health effects observed in humans following exposure to 1,2-dichloroethane are those generally associated with exposure to chlorinated hydrocarbons. Therefore, it may not be possible to correlate the exact levels of 1,2-dichloroethane in the environment with observed health effects in humans. The methodology to predict exposure levels of 1,2-dichloroethane from observed health effects is lacking.

**Food Chain Bioaccumulation.** The limited experimental data on bioconcentration of 1,2-dichloro-ethane in aquatic organisms (Banerjee and Baughman 1991; Farrington 1991) and the physical and chemical properties of this compound indicate that bioconcentration and biomagnification are not likely to occur. However, experimental data on food chain biomagnification will aid in determining the potential for human exposure to 1,2-dichloroethane.

**Exposure Levels in Environmental Media.** 1,2-Dichloroethane has been detected at low levels (ppb) in ambient urban and rural air (Class and Ballschmiter 1986; Cohen et al. 1989; EPA 1988, 1991; Jüttner 1986; Kelly et al. 1994; Pellizzari et al. 1986; Singh et al. 1982, 1992), outdoor and indoor air samples of residences located near hazardous waste disposal sites (Andelman 1985; Barkley et al. 1980; Heavner et al. 1996; LaRegina et al. 1986), surface water (Brown et al. 1984; EPA 1977; Yamamoto et al. 1997), groundwater (Barbee 1994; Brown et al. 1984; Lesage et al. 1990; Plumb 1987; Westrick et al. 1984), drinking water (Barkley et al. 1980; Clark et al. 1986; Iowa DWAW 1985; Krill and Sonzogni 1986; Lam et al. 1994; Steichen et al. 1988; Suffet et al. 1980), sediment (Bianchi et al. 1991; Oliver and Pugsley 1986), and food stuffs (Gold 1980; Heikes and Hopper 1986, Heikes 1987; Miyahara et al. 1995; Rembold et al. 1989). Data on estimated human intake from all media have not been located.

Reliable monitoring data for the levels of 1,2-dichloroethane in contaminated media at hazardous waste sites are needed so that the information obtained on environmental levels of 1,2-dichloroethane can be used in combination with the known body burden of 1,2-dichloroethane to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

**Exposure Levels in Humans.** Recent estimates of the size of the population occupationally exposed to 1,2-dichloroethane are not available, and monitoring data on workplace exposure levels are 30–40 years old and generally inadequate. General population exposure estimates have been prepared by the EPA (1985) for inhalation of the compound in ambient air, which is believed to be the most important route of exposure. However, the general population may also be exposed to low concentrations of 1,2-dichloroethane through ingestion of contaminated water and/or food. The use of old consumer products that contained 1,2-dichloroethane represents a possible, but most likely inconsequential potential exposure route. Quantitative information about the size of the exposed populations and the levels of exposure are generally incomplete. This information is necessary for assessing the need to conduct health studies on these populations.

**Exposures of Children.** There is no information available on the exposure of children to 1,2-dichloroethane under the age of 12 years. Children are most likely to be exposed to 1,2-dichloroethane via inhalation of ambient air. Ingestion of drinking water and food may also yield childhood exposures. Contact with older household products that contained 1,2-dichloroethane is possible but is unlikely to be a major source of exposure since 1,2-dichloroethane is no longer used in most consumer products. Children are unlikely to be exposed to 1,2-dichloroethane from pica. Accurate data on the levels of 1,2-dichloroethane in children are needed to identify ways to reduce the potential exposure risks.

## 6.3 ONGOING STUDIES

No relevant ongoing studies were identified in the National Institute of Health (NIH) RePORTER (2024) database.

# CHAPTER 7. REGULATIONS AND GUIDELINES

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

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

| Agency | Description | Information | Reference |
|---|---|---|---|
| | **Air** | | |
| EPA | RfC | Not evaluated | IRIS 1987 |
| | Provisional peer-reviewed toxicity values | | EPA 2010 |
| | Provisional chronic RfC | 0.007 mg/m$^3$ (0.0017 ppm) | |
| | Provisional subchronic RfC | 0.07 mg/m$^3$ (0.017 ppm) | |
| WHO | Air quality guidelines | 0.7 mg/m$^3$ [a] | WHO 2000 |
| | **Water & Food** | | |
| EPA | Drinking water standards and health advisories | | EPA 2018c |
| | 1-Day health advisory (10-kg child) | 0.7 mg/L | |
| | 10-Day health advisory (10-kg child) | 0.7 mg/L | |
| | Lifetime health advisory | No data | |
| | $10^{-4}$ Cancer risk | 0.04 mg/L | |
| | National primary drinking water regulations | | EPA 2009 |
| | MCL | 0.005 mg/L | |
| | MCLG | 0 mg/L | |
| | RfD | Not evaluated | IRIS 1987 |
| | Provisional peer-reviewed toxicity values | | EPA 2010 |
| | Provisional subchronic RfD | 0.02 mg/kg/day | |
| WHO | Drinking water quality guidelines | 0.03 mg/L | WHO 2022 |

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

| Agency | Description | Information | Reference |
|---|---|---|---|
| FDA | Allowable level in bottled water | 0.005 mg/L | FDA 2017 |
| | Concentration limit in pharmaceutical products | 5 ppm | FDA 2018 |
| | Substances added to food (formerly EAFUS) | Allowed under certain color, food additive and food contact substance regulations with limitations | FDA 2022 |
| | Food additive levels | Not to exceed: | |
| | Residues from use as solvent in extraction process of: | | |
| | Whole fish protein concentrate | 5 ppm | FDA 2021a |
| | Modified hop extract | 150 ppm | FDA 2021a |
| | Spice oleoresins | 30 ppm | FDA 2021b |
| | Animal byproducts for use in animal feeds | 300 ppm | FDA 2021c |
| | Use in flume water for washing sugar beets | 0.2 ppm | FDA 2021b |
| | **Cancer** | | |
| HHS | Carcinogenicity classification | Reasonably anticipated to be a human carcinogen | NTP 2021 |
| EPA | Carcinogenicity classification | B2[b] | IRIS 1987 |
| | Inhalation unit risk | $2.6 \times 10^{-5}$ per µg/m$^3$ | |
| | Oral slope factor | $9.1 \times 10^{-2}$ per mg/kg/day | |
| IARC | Carcinogenicity classification | Group 2B[c] | IARC 1999 |
| | **Occupational** | | |
| OSHA | PEL (8-hour TWA) for general industry, shipyards, and construction | 50 ppm[d] | OSHA 2021a, 2021b, 2021c |
| | Ceiling concentration for general industry | 100 ppm[e], 200 ppm (peak) | OSHA 2021a |
| NIOSH | REL (up to 10-hour TWA) | 1 ppm[d] | NIOSH 2019 |
| | STEL | 2 ppm | |
| | IDLH | 50 ppm | |
| | **Emergency Criteria** | | |
| EPA | AEGLs-air | No data | EPA 2018d |

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

| Agency | Description | Information | Reference |
|---|---|---|---|
| DOE | PACs-air | | DOE 2018a |
| | PAC-1[f] | 50 ppm | |
| | PAC-2[f] | 200 ppm | |
| | PAC-3[f] | 300 ppm | |

[a]24-hour TWA.
[b]B2: probable human carcinogen.
[c]Group 2B: possibly carcinogenic to humans.
[d]Potential occupational carcinogen.
[e]Not to exceed this concentration at any time during an 8-hour shift, except for up to 5 minutes in any 3 hours, up to the acceptable peak concentration.
[f]Definitions of PAC terminology are available from 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; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; STEL = short-term exposure limit; 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 S106-5, Atlanta, Georgia 30329-4027.

APPENDIX A

# MINIMAL RISK LEVEL (MRL) WORKSHEET

| | |
|---|---|
| ***Chemical Name*:** | 1,2-Dichloroethane |
| ***CAS Numbers:*** | 107-06-2 |
| ***Date:*** | July 2024 |
| ***Profile Status:*** | Final |
| ***Route:*** | Inhalation |
| ***Duration:*** | Acute |
| ***MRL:*** | 0.1 ppm (0.4 mg/m$^3$) |
| ***Critical Effect:*** | Degeneration, with necrosis, olfactory epithelium |
| ***Reference:*** | Hotchkiss et al. 2010 |
| ***Point of Departure:*** | $BMCL_{10}$ of 57.62 ppm ($BMCL_{HEC}$ of 3.84 ppm) |
| ***Uncertainty Factor:*** | 30 |
| ***LSE Graph Key:*** | 5 |
| ***Species:*** | Rat |

***MRL Summary:*** An acute-duration inhalation MRL of 0.1 ppm was derived for 1,2-dichloroethane based on an increased incidence of nasal epithelium degeneration/necrosis in rats administered 1,2-dichloroethane via inhalation (Hotchkiss et al. 2010). The MRL is based on a $BMCL_{10}$ of 57.62 ppm converted to human equivalent concentration ($BMCL_{HEC}$) of 3.84 ppm and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

***Selection of the Critical Effect:*** A number of studies have evaluated the toxicity of 1,2-dichloroethane following acute-duration inhalation exposure; these studies examine a wide range of endpoints including neurotoxicity (Heppel et al. 1945; Hotchkiss et al. 2010; Jin et al. 2018a, 2018b; Niu et al. 2009; Wang et al. 2013, 2014, 2018; Zhang et al. 2011; Zhou et al. 2016), liver and kidney effects (Hotchkiss et al. 2010; Spencer et al. 1951), respiratory effects (Chan et al. 2002; Hotchkiss et al. 2010), immunotoxicity (Sherwood et al. 1987), developmental toxicity (Schlacter et al. 1979), reproductive toxicity (Zhang et al. 2017), gastrointestinal toxicity (Heppel et al. 1945), and hematotoxicity (Spencer et al. 1951). The LOAELs for these studies range from 50 to 3,000 ppm; a summary of the lowest NOAEL and LOAEL values is presented in Table A-1. To provide a consistent basis for comparison across species, the NOAELs and LOAELs were adjusted for intermittent exposure and converted to human equivalent concentrations (HECs) following EPA (1994a) methodology. For systemic (extrarespiratory) effects, the HEC is calculated by multiplying the duration-adjusted animal NOAEL or LOAEL by the ratio of the blood:gas partition coefficients in animals and humans. Gargas et al. (1989) estimated a blood:air partition coefficient of 19.5±0.7 for 1,2-dichloroethane in humans; however, a blood:air partition coefficient for mice was not located. The default value of 1 was used for the ratio in calculating the HEC values for reduced locomotor activity in mice (Wang et al. 2013). For effects on the respiratory tract, the regional gas dose ratio (RGDR) corresponding to the part of the respiratory tract that is affected was used. Thus, the RGDR for extrathoracic effects was used for nasal lesions and the $RGDR_{ET}$ (extrathoracic) value for rats (0.20) was calculated as follows:

$$RGDR_{ET} = \frac{V_{E_a}}{SA_a} \div \frac{V_{E_h}}{SA_h}$$

where:

$V_{E_a}$ = ventilation rate for male and female F344 rats = 0.211 L/minute (EPA 1994a)
$SA_a$ = surface area of the extrathoracic region in rats = 15 cm$^2$ (EPA 1994a)

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

| Species | Duration | NOAEL (ppm) | LOAEL or SLOAEL (ppm) | $NOAEL_{ADJ}$ (ppm)[a] | $LOAEL_{ADJ}$ (ppm)[a] | $NOAEL_{HEC}$ (ppm) | $LOAEL_{HEC}$ (ppm) | Effect | Reference |
|---|---|---|---|---|---|---|---|---|---|
| Respiratory effects | | | | | | | | | |
| Rat/ Fischer 344 | 8 hours | 50 | 100 | 17 | 33 | 3.3 | 6.6 | Olfactory epithelium degeneration/necrosis | Hotchkiss et al. 2010 |
| Neurological effects | | | | | | | | | |
| Mouse/ Albino | 3.5 hours/day 10 days | 56 | 111 | 8.2 | 16.2 | 8.2 | 16.2 | Reduced locomotor activity | Wang et al. 2013 |
| Reproductive effects | | | | | | | | | |
| Mouse (Swiss-Webster) | 6 hours/day, 7 days | 25 | 86 (SLOAEL) | 6.25 | NA | 6.25 | NA | Increased abnormal sperm[b] | Zhang et al. 2017 |

[a]NOAEL and LOAEL values were adjusted from intermittent daily exposures to the equivalent of 24-hour continuous exposure. The duration adjusted values were calculated as:

$$Adjusted\ daily\ dose = Intermittent\ dose \times \frac{hours\ per\ day\ exposed}{24\ hours} \times \frac{days\ per\ week\ exposed}{7\ days}$$

[b]Histopathological effects at 86 ppm (vacuolar degeneration of germ cells in the seminiferous tubules and sloughing of spermatogenic cells into the lumen of the testes) are considered to be serious adverse effects.

LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; NA = not applicable (MRLs cannot be based on exposure levels that produce serious adverse effects); NOAEL = no-observed-adverse-effect level; $NOAEL_{ADJ}$ = NOAEL adjusted to continuous exposure; $NOAEL_{HEC}$ = $NOAEL_{ADJ}$ converted to human equivalent concentration (HEC; see text); SLOAEL = serious lowest-observed-adverse-effect level

$V_{E_h}$ = ventilation rate for humans = 13.8 L/minute (EPA 1994a)
$SA_h$ = surface area of the extrathoracic region in humans = 200 $cm^2$ (EPA 1994a)

As Table A-1 shows, the lowest $LOAEL_{HEC}$ and $NOAEL_{HEC}$ values were 6.6 and 3.3 ppm, respectively, for nasal epithelial degeneration and necrosis.

***Selection of the Principal Study:*** Hotchkiss et al. (2010) conducted studies evaluating neurological and toxicological effects of 1,2-dichloroethane inhalation in rats. Hotchkiss et al. (2010) demonstrated a dose-response relationship between 1,2-dichloroethane exposure and degeneration of the nasal tissue. The $LOAEL_{HEC}$ and $NOAEL_{HEC}$ values for nasal lesions in the Hotchkiss et al. (2010) study were the lowest among the studies evaluating acute-duration exposure.

***Summary of the Principal Study:***

Hotchkiss JA, Andrus AK, Johnson KA, et al. 2010. Acute toxicologic and neurotoxic effects of inhaled 1,2-dichloroethane in adult Fischer 344 rats. Food Chem Toxicol 48(2):470-481. http://doi.org/10.1016/j.fct.2009.10.039.

Fischer 344 rats were exposed to 0, 200, 600, or 2,000 ppm (or 0.0, 196.4, 607.8, and 2,029 ppm as analytically measured mean concentrations delivered) 1,2-dichloroethane for 4 hours or 0, 50, 100, or 150 ppm (or 0.0, 52.8, 107.5, and 155.8 ppm as analytically measured mean concentrations delivered) for 8 hours. Neurobehavioral and neuropathological effects were assessed using a functional observational battery and by light microscopy, respectively. Acute toxicological effects were assessed by bronchoalveolar lavage and histopathology of the respiratory tract and selected target organs. Neurobehavioral effects consistent with central nervous system depression were observed on day 1, but not at subsequent times (days 8 or 15). No neuropathological changes were reported. Degeneration/ necrosis of the olfactory epithelium was reported at an exposure of 107.5 ppm for 8 hours. Nasal regeneration occurred at 196.4 ppm (4-hour exposure). A decrease in adrenal, kidney, and liver weights occurred at an exposure concentration of 2,029 ppm for 4 hours.

***Selection of the Point of Departure for the MRL:*** Benchmark dose (BMD) modeling was conducted to identify a point of departure (POD) using the data for degeneration/necrosis of nasal epithelium in rats administered 1,2-dichloroethane via inhalation for 8 hours. Combined male and female rat incidence data for nasal degeneration/necrosis were selected for BMD analysis (Table A-2) as the male and female data were deemed to be similar in their response. The data were fit to all available dichotomous models in EPA's Benchmark Dose Software (BMDS, version 3.2.0.1) using a benchmark response (BMR) of 10% extra risk. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, a 95% confidence limit on the BMC (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 was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest Akaike information criterion (AIC) was chosen. BMDS recommended the Multistage-3 model for nasal epithelium degeneration/ necrosis; however, this model yielded a BMCL (36.28 ppm) that was less than the experimental NOAEL (52.88 ppm) and three of four Multistage-3 model parameters were bounded. Evaluation of viable alternate models showed that the Log-Probit model derived a BMCL (57.62 ppm), similar to the experimental NOAEL (52.8 ppm), and provided a better fit than the Multistage 3-degree model with lower residuals near the BMC; therefore, the Log-Probit model was selected as the basis for estimating this MRL. The BMC/BMCL values considered for MRL derivation are presented in Table A-3 and the fit of the selected model is presented in Figure A-1.

## Table A-2. Results from an 8-Hour Exposure to 1,2-Dichloroethane Via Inhalation and Subsequent Incidence of Nasal Epithelium Degeneration/Necrosis

| Analytically measured mean concentration delivered (ppm) | Number (males and females) | Incidence of nasal epithelium degeneration/necrosis | |
|---|---|---|---|
| | | Males | Females |
| 0.0 | 10 | 0/5 | 0/5 |
| 52.8 | 10 | 0/5 | 0/5 |
| 107.5 | 10 | 1/5 | 3/5 |
| 155.8 | 10 | 4/5 | 5/5 |

Source: Hotchkiss et al. (2010)

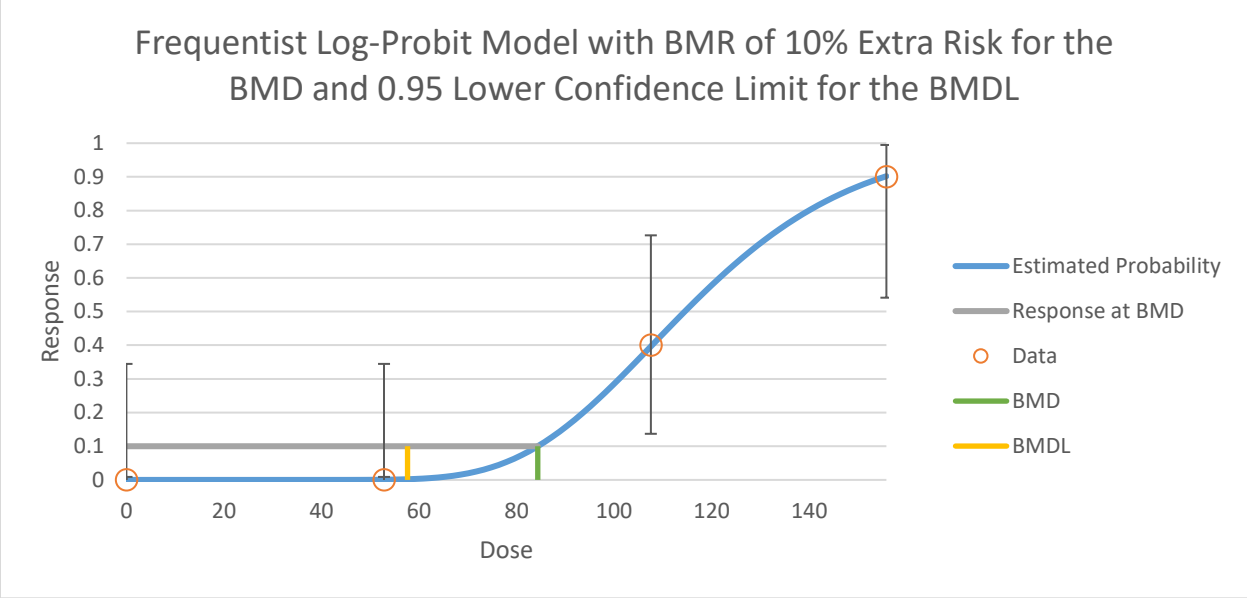
## Table A-3. Model Predictions for Increased Incidence of Nasal Epithelium Degeneration/Necrosis in Male and Female (Combined) Rats Following Inhalation Exposure to 1,2-Dichloroethane for 8 Hours (Hotchkiss et al. 2010)

| Model | $BMC_{10}$[a] (ppm) | $BMCL_{10}$[a] (ppm) | p-Value[b] | AIC | Scaled residuals[c] | |
|---|---|---|---|---|---|---|
| | | | | | Dose below BMC | Dose above BMC |
| Dichotomous Hill | | | NA | 27.96 | -0.01 | $8.68 \times 10^{-5}$ |
| Gamma[d] | 83.06 | 55.73 | 0.98 | 24.01 | -0.15 | 0.07 |
| Log-Logistic[e] | 84.68 | 57.42 | 0.83 | 26.04 | -0.19 | 0.07 |
| Multistage Degree 3[f] | 60.32 | 36.28 | 0.77 | 23.80 | -0.86 | -0.31 |
| Multistage Degree 2[f] | 42.87 | 25.40 | 0.36 | 26.87 | -0.0004 | -1.32 |
| Multistage Degree 1[f] | | | 0.02 | 34.86 | -0.0004 | -1.96 |
| Weibull[d] | 78.44 | 50.57 | 0.61 | 26.39 | -0.42 | 0.27 |
| Logistic | 81.81 | 53.84 | 0.85 | 24.46 | -0.42 | 0.26 |
| **Log-Probit[g]** | **84.32** | **57.62** | **0.997** | **23.97** | **-0.08** | **0.02** |
| Probit | 81.49 | 52.26 | 0.91 | 24.26 | -0.33 | 0.24 |

[a]BMC and BMCLs values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional $\chi^2$ goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]All models provided an adequate fit to the data except for the Dichotomous Hill and Multistage 1-degree models. BMCLs were sufficiently close (differed by <3-fold). The BMDS recommended the model with the lowest AIC (3-degree Multistage); however, three of the four parameters were bounded and the resulting BMCL (36.28) was lower than the experimental NOAEL (52.8 ppm). The Log-Probit model derived a BMCL value (57.62 ppm) similar to the experimental NOAEL and provided a better fit near the BMC with lower residuals; therefore, the Log-Probit model was selected.

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); BMDS = Benchmark Dose Software

**Figure A-1. Fit of Log-Probit Model to Data on Incidence of Nasal Degeneration/Necrosis in Male and Female Rats (Combined) Administered 1,2-Dichloroethane via Inhalation for 8 Hours**




***Adjustment for Intermittent Exposure:*** The rats from the Hotchkiss et al. (2010) study were exposed for a total of 8 hours in a single day. Therefore, the $BMCL_{10}$ was adjusted for intermittent exposure as follows:

$$BMCL_{10ADJ} = BMCL_{10} \times \frac{8\ hours}{24\ hours} = 57.62\ ppm \times \frac{8\ hours}{24\ hours} = 19.21\ ppm$$

***Human Equivalent Concentration:*** The $BMCL_{10ADJ}$ was converted to a HEC by multiplying the $BMCL_{10}$ by the rat-specific regional gas dose ratio that corresponds with the extrathoracic region ($RGDR_{ET}$), as nasal epithelium degeneration/necrosis is a localized-portal of entry effect (EPA 2012b). This $RGDR_{ET}$ is calculated using the following equation as defined by EPA (1994a):

$$RGDR_{ET} = \frac{V_{E_a}}{SA_a} \div \frac{V_{E_h}}{SA_h}$$

where:
$V_{E_a}$ = ventilation rate for male and female F344 rats = 0.211 L/minute (EPA 1994a)
$SA_a$ = surface area of the extrathoracic region in rats = 15 $cm^2$ (EPA 1994a)
$V_{E_h}$ = ventilation rate for humans = 13.8 L/minute (EPA 1994a)
$SA_h$ = surface area of the extrathoracic region in humans = 200 $cm^2$ (EPA 1994a)

Applying this equation results in an RGDR of 0.20 and the HEC was calculated as:

$$BMCL_{10HEC} = BMCL_{10ADJ} \times RGDR = 3.84\ ppm$$

***Uncertainty Factor:*** The $BMCL_{HEC}$ is divided by a total uncertainty factor (UF) of 30:

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

This resulted in the following MRL:

$$MRL = \frac{BMCL_{HEC}}{UFs} = \frac{3.84\ ppm}{30} = 0.13\ ppm, which\ rounds\ to\ 0.1\ ppm$$

***Other Additional Studies or Pertinent Information that Lend Support to this MRL:*** Few studies of animals exposed to 1,3-dichloroethane by inhalation evaluated histopathology of the nasal turbinates. A chronic-duration study in rats exposed to 1,2-dichloroethane via inhalation also observed a NOAEL of 50 ppm for respiratory toxicity (Cheever et al. 1990). No histological alterations were observed in respiratory tracts, including nasal turbinates, of rats in this study. In another chronic-duration study, Nagano et al. (2006) evaluated a wide range of endpoints including clinical chemistry, hematology, gross pathology, organ weights, and histopathology; however, the publication does not specify the tissues examined for histopathology. The observation that the NOAELs were identical after acute- and chronic-duration exposure suggests that the nasal lesions may occur when exposure exceeds a concentration threshold.

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

APPENDIX A

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dichloroethane
***CAS Numbers:*** 107-06-2
***Date:*** July 2024
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Intermediate
***MRL:*** 0.1 ppm (0.40 mg/m$^3$)
***Critical Effect:*** Neurobehavioral changes (altered performance in open field test)
***Reference:*** Zhong et al. 2022
***Point of Departure:*** $BBMCL_{1SD}$ of 14.8 ppm ($BBMCL_{HEC}$ of 3.70 ppm)
***Uncertainty Factor:*** 30
***LSE Graph Key:*** 51
***Species:*** Mouse

***MRL Summary:*** An intermediate-duration inhalation MRL of 0.1 ppm was derived for 1,2-dichloroethane based on altered performance in an open field test of male mice. Mice were exposed to ≤173 ppm 1,2-dichloroethane for 28 days at 6 hours/day, 7 days/week (Zhong et al. 2022). The MRL is based on a Bayesian benchmark response of 1 standard deviation ($BBMCL_{1SD}$) of 14.8 ppm, which was adjusted to continuous duration exposure (6 hour/24 hour) and converted to a $BBMCL_{1SD\text{-}HEC}$ of 3.70 ppm. The $BBMCL_{1SD\text{-}HEC}$ of 3.70 ppm was divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

***Selection of the Critical Effect:*** Review of the intermediate-duration inhalation database shows that the exposure level of 86 ppm is a serious LOAEL for neurological (Zhong et al. 2022) and male reproductive effects (Zhang et al. 2017). Therefore, to determine the critical effect for the intermediate-duration inhalation MRL, the POD must be <86 ppm. Studies with data meeting this criterion were considered for the critical effect (Table A-4).

The lowest exposure level evaluated in the intermediate-duration inhalation database was 25 ppm; this value is a NOAEL for both neurological effects and male reproductive effects. Neurological effects have been evaluated in numerous studies, identifying the neurological system as a target organ for 1,2-dichloroethane toxicity (details provided in Section 2.15). In contrast, male reproductive effects have only been evaluated in a single study (Zhang et al. 2017). Although results of the Zhang et al. (2017) show that 1,2-dichloroethane can produce serious effects to the testes, these findings have not been corroborated. Therefore, neurological effects, with the more extensive database, were identified as the critical effects for the intermediate-duration inhalation MRL (Liang et al. 2021; Zhong et al. 2022). Given that NOAELs for reproductive and neurological effect are the same (25 ppm), an MRL based on neurological effects should be protective of reproductive effects.

**Table A-4. Summary of Possible Critical Effect for Derivation of the Intermediate-Duration Inhalation Exposure MRL for 1,2-Dichloroethane**

| Reference | Species | Exposure | Effect | NOAEL/LOAEL/SLOAEL |
|---|---|---|---|---|
| Liang et al. 2021 | Mouse | 28 days,<br>7 days/week,<br>6 hours/day (WB)<br>0, 25, 86, 173 ppm | Neurological: vacuolization in the cerebral cortex[a] | NOAEL: 25 ppm<br>LOAEL: 86 ppm |

**Table A-4. Summary of Possible Critical Effect for Derivation of the Intermediate-Duration Inhalation Exposure MRL for 1,2-Dichloroethane**

| Reference | Species | Exposure | Effect | NOAEL/LOAEL/SLOAEL |
|---|---|---|---|---|
| Zhong et al. 2022 | Mouse | 28 days,<br>7 days/week,<br>6 hours/day (WB)<br><br>0, 25, 86, 173 ppm | Neurological: altered behavior in open field (decreased distance and time in central area); vacuolization and demyelination in the cerebral cortex | NOAEL: 25 ppm<br>SLOAEL: 86 ppm |
| Zhang et al. 2017 | Mouse | 28 days,<br>7 days/week,<br>6 hours/day (WB)<br><br>0, 25, 86, 173 ppm | Reproductive SLOAEL: histopathological alterations to the testes and dose-related increases in abnormal sperm | NOAEL: 25 ppm<br>SLOAEL: 86 ppm |

[a]Behavioral effects and demyelination were not assessed.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; SLOAEL = serious lowest-observed-adverse-effect level; WB = whole-body exposure

***Selection of the Principal Study:*** Neurological effects following intermediate-duration inhalation exposure to 1,2-dichloroethane were observed in studies by Zhong et al. (2022) and Liang et al. (2021), both with the same NOAEL value of 25 ppm. Results of open field tests by Zhong et al. (2022) showed decreased central distance/total distance (%) and decreased time in the central area of the test site; histopathological evaluations showed vacuolization and demyelination in the cerebral cortex at a concentration of 86 ppm. Taken together, these effects were considered to be a serious LOAEL. However, no neurological effects were observed at 25 ppm. Liang et al. (2021) reported increased vacuolization in the cerebral cortex at 86 ppm, with no effects at 25 ppm; neurobehavior was not evaluated in this study. Endpoints from both studies were further evaluated to determine the basis of the MRL. As discussed below, further analyses identified the lowest POD for central distance/total distance (%). Therefore, Zhong et al. (2022) was selected as the principal study.

***Summary of the Principal Study:***

Zhong, Y, Liang, B, Meng H, et al. 2022. 1,2-Dichloroethane induces cortex demyelination by depressing myelin basic protein via inhibiting aquaporin 4 in mice. Ecotoxicol Environ Saf 231:113180.

Groups of 20 male CD-1 mice were exposed to 0, 25, 86, and 173 ppm 1,2-dichloroethane (whole body) for 6 hours/day for 28 consecutive days. In addition to CD-1 mice, the experiments also included aquaporin 4 knock-out mice to provide mechanistic data (not discussed in this summary). After the last exposure, mice were evaluated in open field tests for total distance traveled, distance traveled in the central area relative to the total distance traveled (%), time spent in the central area, and mean speed. Additional assessments included histopathological examination of the cerebral cortex and brain-water content measurement from five additional mice exposed under the same conditions.

Results of open field tests showed dose-dependent decreases in the distance traveled in the central area relative to the total distance traveled and time spent in the central area in mice exposed to 86 and 173 ppm; no decreases were observed relative to control at 25 ppm. The total distance traveled was decreased in mice exposed to 173 ppm, but not at 25 or 86 ppm. Mean speed was similar between

controls and the three treatment groups. Histopathological examination of the cerebral cortex found dose-related increases in vacuolization and demyelination in mice exposed to 86 and 173 ppm. Brain water content was increased in the 173-ppm group. Based on results of this study, the NOAEL and SLOAEL were identified as 25 and 86 ppm, respectively.

***Selection of the Point of Departure for the MRL:*** Neurological effects data from the Zhong et al. (2022) and Liang et al. (2021) studies were considered as the possible basis for derivation of the intermediate-duration inhalation MRL. Data sets for distance traveled in the central area relative to the total distance traveled, mean time in the central area, and vacuolization in the cerebral cortex are summarized in Table A-5. All data were presented graphically; therefore, GrabIt® software was used to convert graphic data to numeric data.

**Table A-5. Data Considered as the Critical Effect for the Intermediate-Duration Inhalation MRL**

| | | | Exposure concentration (ppm) | | | |
|---|---|---|---|---|---|---|
| Reference | Endpoint | Number | 0 | 25 | 86 | 173 |
| Liang et. al 2021 | Vacuolization area cerebral cortex (%) | 5 | 21.39±1.18[a] | 21.98±0.59 | 29.11±1.19[b] | 34.46±0.59[b] |
| Zhong et al. 2022 | Central distance/total distance (%) | 20 | 18.71±7.74 | 12.9±5.81 | 9.35±5.81[b] | 6.13±3.71[b] |
| Zhong et al. 2022 | Mean time in the central area (seconds) | 20 | 36.99±23.23 | 25.81±12.9 | 13.76±15.49[b] | 9.46±4.3[b] |
| Zhong et al. 2022 | Vacuolization area cerebral cortex (%) | 5 | 1.81±0.82 | 2.13±0.89 | 5.00±1.07[b] | 5.6±1.09[b] |

[a]Values are mean±standard deviation; estimated from graphically presented data using GrabIt! or DigitizeIt 2.5.9 Software.
[b]ANOVA and LSD multiple comparison test, $p<0.05$.

ANOVA = analysis of variance; LSD = least significant difference

All data sets were modeled using EPA's Benchmark Dose Software (BMDS, version 3.2.0.1). None of the models for these endpoints provided adequate fit. Therefore, data were run using the Bayesian Benchmark Dose (BBMD) modeling online software [Bayesian BMD (benchmarkdose.com)]. Data for distance/total distance and mean time in central area were fitted to all continuous models using a $BBMCL_{1SD}$. Data for vacuolization were also fitted to all continuous models but used a Bayesian benchmark response of 10% relative deviation ($BBMCL_{10\%RD}$). To obtain a model averages, Bayesian benchmark concentration (BBMC) weighted the Exponential 2, Exponential 3, Exponential 4, Exponential 5, Hill, Power, Michaelis-Menten, and linear models equally (i.e., 12.5% each) as recommended by EPA (2020b). The resulting average $BBMCL_{1SD}$ values for distance/total distance and mean time in central area were 14.763 and 20.073 ppm, respectively, and the $BBMCL_{10\%RD}$ for vacuolization data obtained for Liang et al. (2021) was 15.523 ppm. Vacuolization data from Zhong et al. (2022) could not be appropriately modeled because of the wide uncertainty on each of the dose groups which was due to the small response, small sample size (n=5), and high variability between the animals. ATSDR considered the NOAEL of 25 ppm for Zhong et al. (2022) vacuolization data for a potential POD. However, the lowest model-averaged BBMCL value of 14.763 ppm for central distance/total distance (%) was selected as the POD. The posterior model probabilities were 0.318, 0.0.83, 0.284,

0.052, 0.069, 0.016, 0.110, and 0.07 for the Exponential 2, Exponential 3, Exponential 4, Exponential 5, Hill, Power, Michaelis-Menten, and linear models, respectively (Table A-6). Model results are presented graphical in Figure A-2.

***Adjustment for Intermittent Exposure:*** Mice in the Zhong et al. (2022) study were exposed for 6 hours/day for 28 consecutive days. Therefore, the $BBMCL_{1SD}$ was adjusted for intermittent exposure as follows:

$$BBMCL_{ADJ} = BBMCL_{1SD} \times \frac{6\ hours}{24\ hours} = 14.8\ \text{ppm} \times \frac{6\ \text{hours}}{24\ hours} = 3.70\ ppm$$

***Human Equivalent Concentration:*** For systemic (extrarespiratory) effects, the HEC is calculated by multiplying the duration-adjusted animal $BBMCL_{ADJ}$ by the ratio of the blood:gas partition coefficients in animals and humans. Gargas et al. (1989) estimated a blood:air partition coefficient of 19.5±0.7 for 1,2-dichloroethane in humans; however, a blood:air partition coefficient for mice was not located. Therefore, the default value of 1 was used for the ratio, resulting in the $BBMCL_{HEC}$ of 3.70 ppm.

***Uncertainty Factor:*** The $BBMCL_{HEC}$ was divided by a total uncertainty factor (UF) of 30:

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

This results in the following MRL:

$$\text{MRL} = \frac{BBMCL_{HEC}}{\text{UFs}} = \frac{3.70\ \text{ppm}}{30} = 0.123\ \text{ppm, which rounds to } 0.1\ \text{ppm}$$

***Other Additional Studies or Pertinent Information that Lend Support to this MRL:*** The intermediate-duration inhalation oral MRL is based on neurological effects identified in open field tests. ATSDR considers results of open field and maze tests to be valid indicators of adverse neurological effects and has used results from these tests to derive MRLs for other chemicals (e.g., 1-bromopropane, bromomethane, cypermethrin, permethrin, and fuel oil #2). Studies in humans and animals identify the neurological system as a target for inhaled 1,2-dichloroethane. In animals, acute- and intermediate-duration inhalation exposure studies have observed neurological effects. Acute effects of inhalation exposure have been observed at concentrations of 111–1,235 ppm; effects include decreased motor activity and response to stimuli (Hotchkiss et al. 2010; Wang et al. 2013; Yang et al. 2021), tremor (Jin et al. 2018a, 2018b, 2019), cerebral edema (Jin et al. 2019; Zhang et al. 2011), vacuolization in the cerebral cortex (Zhong et al. 2020), and brain lesions (Zhou et al. 2016). For intermediate-duration exposure, in addition to neurological effects observed at 86 ppm (Liang et al. 2021; Zhong et al. 2022), damage to cerebellar granular cells (shrunken and hypereosinophilic cytoplasm, nuclear pyknosis, apoptosis) was observed at approximately 180 ppm (Huang et al. 2020).

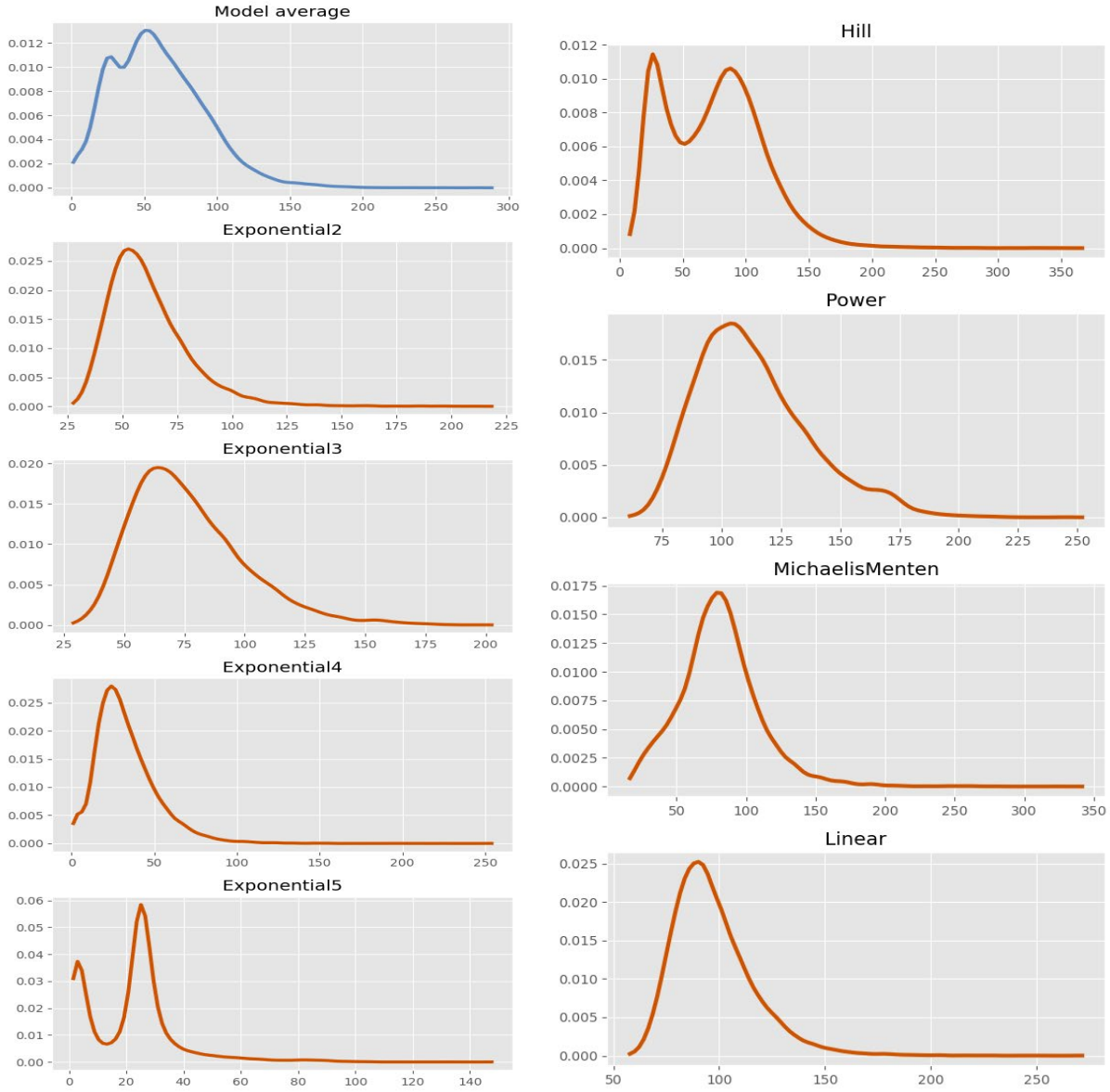
Relevance of neurological effects observed in animals to humans is supported by numerous case reports of individuals who inhaled 1,2-dichloroethane (Chen et al. 2015, Dang et al. 2019; Liu et al. 2010; Zhan et al. 2011). Effects included drowsiness, delirium, and headache; tremors; slow response to verbal commands; encephalopathy and cerebral edema; and neuronal necrosis and white matter demyelination. Autopsies of individuals who died following exposure showed morphological alterations in the nervous system including vascular disorders, diffuse changes in cerebellar cells, parenchymatous changes in the brain and spinal cord, myelin degeneration, and hyperemia, swelling, edema, and hemorrhage of the brain (Hubbs and Prusmack 1955; Hueper and Smith 1935; Lochhead and Close 1951). An occupational

**Table A-6. BBMD Model Predictions for Central Distance/Total Distance (%) in Male Mice Following 28-Day Inhalation Exposure to 1,2-Dichloroethane (Zhong et al. 2022)**

| Statistic | Model average | Exponential 2 | Exponential 3 | Exponential 4 | Exponential 5 | Hill | Power | Michaelis Menten | Linear |
|---|---|---|---|---|---|---|---|---|---|
| Prior model weight | N/A | 0.125 | 0.125 | 0.125 | 0.125 | 0.125 | 0.125 | 0.125 | 0.125 |
| Posterior model weight | N/A | 0.312 | 0.080 | 0.284 | 0.053 | 0.065 | 0.015 | 0.126 | 0.065 |
| Fraction with BMDs | 99.7% | 100.0% | 100.0% | 99.5% | 97.0% | 99.6% | 100.0% | 100.0% | 100.0% |
| BMD (median) | 55.814 | 58.347 | 72.517 | 29.552 | 24.197 | 75.847 | 109.656 | 79.796 | 93.986 |
| BMDL ($5^{th}$ percentile) | 14.763 | 38.897 | 46.033 | 9.588 | 2.105 | 21.876 | 81.229 | 35.408 | 72.990 |
| $25^{th}$ percentile | 34.964 | 49.106 | 59.691 | 20.606 | 6.994 | 39.699 | 96.090 | 63.696 | 84.162 |
| Mean (SD) | 59.101 (32.913) | 61.845 (18.584) | 76.768 (23.704) | 33.172 (19.079) | 22.044 (15.871) | 74.517 (39.174) | 113.655 (24.152) | 81.165 (29.207) | 97.483 (19.388) |
| $75^{th}$ percentile | 79.044 | 70.683 | 89.736 | 42.112 | 27.497 | 100.076 | 127.109 | 96.015 | 107.108 |
| $95^{th}$ percentile | 114.375 | 96.155 | 121.097 | 67.658 | 49.466 | 136.830 | 161.300 | 130.349 | 132.593 |

BBMD = Bayesian benchmark dose; BMD = benchmark dose; BMDL = lower confidence limit on the BMD; SD = standard deviation

**Figure A-2. Bayesian Benchmark Dose (BBMD) Model Predictions for Central Distance/Total Distance (%) in Male Mice Following 28-Day Inhalation Exposure to 1,2-Dichloroethane (Zhong et al. 2022)**



exposure study in 221 workers reported impaired attention, nonverbal processing speed, verbal memory and learning, and motor strength and speed (Bowler et al. 2003). Reliable exposure estimates for 1,2-dichloroethane in humans were not reported.

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

APPENDIX A

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dichloroethane
***CAS Numbers:*** 107-06-2
***Date:*** July 2024
***Profile Status:*** Final
***Route:*** Inhalation
***Duration:*** Chronic

***MRL Summary:*** There are insufficient data for derivation of a chronic-duration inhalation MRL. The two available studies identified effect levels (LOAELs and NOAELs) for noncancer effects that are higher than both the POD for the acute-duration inhalation MRL (36.28 ppm) and the serious LOAEL for intermediate-duration inhalation exposure (25 ppm), precluding derivation of an MRL.

***Rationale for Not Deriving an MRL:*** An MRL has not been derived for chronic-duration inhalation exposure to 1,2-dichloroethane. As summarized in Table A-7, there are only two studies that investigate the effects of chronic-duration inhalation exposure to 1,2-dichloroethane. Cheever et al. (1990) monitored for a number of health effects in rats exposed to 50 ppm of 1,2-dichloroethane for 7 hours/day, 5 days/week, for 2 years. No increased cancer incidences were observed, and the only noncancer effect noted was an increased incidence of unspecified testicular lesions (24 versus 10% in controls) observed at gross necropsy. Histopathology examination did not show increased incidences of testicular lesions. Nagano et al. (2006) found significantly increased tumor incidences in rats and mice exposed to 1,2-dichloroethane for 6 hours/day, 5 days/week, for 104 weeks, but did not report any noncancer effects, resulting in freestanding noncancer NOAELs of 160 and 90 ppm in rats and mice, respectively. All of the available effect levels are higher than the POD used for derivation of the acute-duration inhalation MRL (36.28 ppm) and the serious LOAEL of 25 ppm for sperm abnormalities in mice exposed for 4 weeks (Zhang et al. 2017). Neither Cheever et al. (1990) nor Nagano et al. (2006) evaluated sperm parameters. Therefore, a chronic-duration MRL could not be derived.

**Table A-7. Summary of Relevant NOAEL and LOAEL Values Following Chronic-Duration Inhalation Exposure to 1,2-Dichloroethane**

| Species | Duration | NOAEL ($NOAEL_{ADJ}$)[a] (ppm) | LOAEL ($LOAEL_{ADJ}$)[a] (ppm) | Effect | Reference |
|---|---|---|---|---|---|
| Rat Sprague-Dawley | 7 hours/day 5 days/week 2 years | | 50 (10) | Increased testicular lesions (not further specified) | Cheever et al. 1990 |
| Rat Fischer 344 | 6 hours/day 5 days/week 104 weeks | 160 (28.6) | | NOAEL without LOAEL | Nagano et al. 2006 |
| Mouse B6D2F1 | 6 hours/day 5 days/week 104 weeks | 90 (16) | | NOAEL without LOAEL | Nagano et al. 2006 |

[a]Adjusted daily dose = $Intermittent\ dose \times \frac{Exposure\ hours}{24\ hours} \times \frac{Exposure\ days}{7\ days}$

ADJ = adjusted; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

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

APPENDIX A

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dichloroethane
***CAS Numbers:*** 107-06-2
***Date:*** July 2024
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Acute

***MRL Summary:*** The available data are insufficient for derivation of an acute-duration oral MRL for 1,2-dichloroethane.

***Rationale for not deriving an MRL:*** The database of acute-duration oral toxicity studies of 1,2-dichloroethane consists of one 14-day study in rats (van Esch et al. 1977), one 14-day study in mice (Munson et al. 1982), one 14-day developmental toxicity study in rats (Payan et al. 1995), one 10-day study in rats (Daniel et al. 1994), and two lethality studies (McCollister et al. 1956; Munson et al. 1982). With limited data reporting, the lethality studies were excluded from consideration. All of the remaining studies used gavage administration. van Esch et al. (1977) identified hepatic effects of fatty degeneration in rats at 300 mg/kg/day, the same dose at which 100% mortality occurred. In the study by Daniel et al. (1994), due to high mortality in the 300 mg/kg/day group, the highest dose evaluated was 100 mg/kg/day. Inflammation of the forestomach was observed at 100 mg/kg/day. No other effects were reported in Daniel et al. (1994). In the developmental toxicity study (Payan et al. 1995), a LOAEL of 198 mg/kg/day was identified for decreased maternal weight gain. The lowest dose from an acute-duration study was in Munson et al. (1982). Mice were administered doses of 0, 4.9, or 49 mg/kg/day for 14 days. The lowest dose at which an effect was observed was a LOAEL of 4.9 mg/kg/day based on reduced humoral and cell-mediated immune responses (Munson et al. 1982). As the LOAEL was the lowest dose tested, no NOAEL was determined. Male mice had a dose-related reduction in humoral immune response (IgM response to sheep erythrocytes). The number of antibody-forming cells (AFCs) were reduced in a dose-related manner, significant at both doses, and adjusted AFC/$10^6$ cells were reduced in a dose-related manner, significant at 49 mg/kg/day. Cell-mediated immune response (delayed-type hypersensitivity response to sheep erythrocytes) was significantly reduced in both dose groups but was not dose-related. Decreased serum leukocytes were observed at 49 mg/kg/day.

As Munson et al. (1982) was a gavage study, it is important to emphasize that there is a notable difference in toxicokinetics between gavage and drinking water administration (see Section 3.1). With gavage administration, bolus dosing leads to saturation of the detoxification/excretion mechanism and exacerbates toxicity. In an intermediate-duration, 90-day study by the same study authors, mice administered up to 189 mg/kg/day 1,2-dichloroethane in the drinking water did not exhibit immune suppression (Munson et al. 1982). As the critical effect from the acute-duration gavage study was not observed at higher doses in the drinking water, it is not appropriate to derive an acute-duration oral MRL.

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

APPENDIX A

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dichloroethane
***CAS Numbers:*** 107-06-2
***Date:*** July 2024
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Intermediate
***MRL:*** 0.7 mg/kg/day
***Critical Effect:*** Kidney tubule regeneration, increased kidney weight
***References:*** Morgan et al. 1990; NTP 1991
***Point of Departure:*** $BMDL_{10}$ 70.08 mg/kg/day
***Uncertainty Factor:*** 100
***LSE Graph Key:*** 10
***Species:*** Rat

***MRL Summary*:** An intermediate-duration oral MRL of 0.7 mg/kg/day was derived for 1,2-dichloroethane based on an increase in kidney lesions (tubule regeneration) in rats administered 1,2-dichloroethane via drinking water (Morgan et al. 1990; NTP 1991). The MRL is based on a $BMDL_{10}$ of 70.08 mg/kg/day and a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

***Selection of the Critical Effect:*** A number of studies have evaluated the toxicity of 1,2-dichloroethane following intermediate-duration oral exposure; these studies examined a wide range of endpoints including kidney and liver effects (Alumot et al. 1976; Cottalasso et al. 2002; Daniel et al. 1994; Morgan et al. 1990; Munson et al. 1982; NTP 1991; van Esch et al. 1977), neurotoxicity (Daniel et al. 1994; Morgan et al. 1990; NTP 1991; van Esch et al. 1977), gastrointestinal toxicity (Morgan et al. 1990; NTP 1991; van Esch et al. 1977), hematotoxicity (Daniel et al. 1994; Morgan et al. 1990; Munson et al. 1982; NTP 1991; van Esch et al. 1977), and reproductive toxicity (Charlap 2015; Daniel et al. 1994; Lane et al. 1982; Morgan et al. 1990; NTP 1991; van Esch et al. 1977). The LOAELs for these studies range from 75 to 448 mg/kg/day.

The available data suggest that nephrotoxicity is the most sensitive endpoint following intermediate-duration oral exposure. The lowest LOAELs and NOAELs for renal effects are shown in Table A-8. In female F344/N rats exposed via drinking water, increased absolute and relative kidney weights and renal tubule degeneration were observed at doses >102 mg/kg/day (Morgan et al. 1990; NTP 1991). Increased relative kidney weight was also seen in rats treated with 75 or 90 mg/kg/day by gavage for 90 days (Daniel et al. 1994; NTP 1991; van Esch et al. 1977); however, it is important to emphasize that there is a notable difference in toxicokinetics between gavage and drinking water administration (see Section 3.1). With gavage administration, bolus dosing leads to saturation of the detoxification/excretion mechanism and exacerbates toxicity. Renal effects (e.g., increased kidney weight and/or histopathological lesions) were also found in in mice exposed via drinking water at doses $\geq$448 mg/kg/day and in rats following acute- and intermediate-duration inhalation exposure (Heppel et al. 1946; Hotchkiss et al. 2010; Morgan et al. 1990; NTP 1991; Spencer et al. 1951).

**Table A-8. Summary of NOAEL and LOAEL Values for Sensitive Targets of Intermediate-Duration Drinking Water Exposure to 1,2-Dichloroethane**

| Species | Duration | NOAEL (mg/kg/day) | LOAEL (mg/kg/day) | Effect | Reference |
|---|---|---|---|---|---|
| Renal effects | | | | | |
| F344 rat | 13 weeks 7 days/week | 58 F | 102 F | Tubular regeneration, increase in absolute and relative kidney weight | Morgan et al. 1990; NTP 1991 |
| CD-1 mouse | 90 days | 189 | ND | None | Munson et al. 1982 |
| B6C3F1 mouse | 13 weeks 7 d/week | 249 | 448 | Tubular regeneration, increased absolute and relative kidney weight | Morgan et al. 1990; NTP 1991 |
| Sprague-Dawley rat | 1-generation (90–120 days) 7 days/week | 300 | ND | None | Charlap 2015 |
| Sprague-Dawley rat | 13 weeks 7 days/week | 531 | ND | None | Morgan et al. 1990; NTP 1991 |
| Osborne-Mendel rat | 13 weeks 7 days/week | 727 | ND | None | Morgan et al. 1990; NTP 1991 |
| Body weight effects | | | | | |
| Osborne-Mendel rat | 13 weeks 7 days/week | 126 M | 266 M | 12% decrease in terminal body weight of males | Morgan et al. 1990; NTP 1991 |
| Sprague-Dawley rat | 1-generation (90–120 days) | 150 M | 300 M | Decreased body weight by 10% | Charlap 2015 |
| Sprague-Dawley rat | 13 weeks 7 days/week | 531 | ND | None | Morgan et al. 1990; NTP 1991 |
| F344 rat | 13 weeks 7 days/week | 601 | ND | None | Morgan et al. 1990; NTP 1991 |
| B6C3F1 mouse | 13 weeks 7 days/week | 2,710 M | 4,207 M | 16% decrease in terminal body weight | Morgan et al. 1990; NTP 1991 |

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

Alumot et al. (1976) reported increased fat content in the livers of rats exposed via feed at a dose of 80 mg/kg/day for 7 weeks. However no hepatic effects were seen in rats or mice at much higher doses and for longer durations in the remaining studies (Charlap 2015; Daniel et al. 1994; Morgan et al. 1990; NTP 1991; van Esch et al. 1977; Munson et al. 1982); thus, hepatic effects were not considered for use in MRL derivation.

Body weight effects were reported in several drinking water studies of 1,2-dichloroethane, as shown in Table A-9. The lowest LOAEL for body weight effects in a drinking water study was 266 mg/kg/day in the 13-week study of Osborne-Mendel rats (Morgan et al. 1990; NTP 1991). This LOAEL is higher than the LOAEL of 102 mg/kg/day for renal effects in F344 rats exposed by drinking water; therefore, renal effects were selected as the critical effect.

***Selection of the Principal Study:*** F344/N rats, Sprague-Dawley rats, Osborne-Mendel rats, and B6C3F1 mice were exposed to drinking water containing 1,2-dichloroethane (Morgan et al. 1990; NTP 1991). Dose-related effects on the kidney (i.e., increased weight and renal tubule regeneration) were observed in female F344/N rats and male B6C3F1 mice only. Rats were more sensitive to these effects than mice, with significantly lower NOAEL and LOAEL values; therefore, the drinking water experiment in F344/N rats was selected as the principal study.

***Summary of the Principal Studies:***

Morgan DL, Bucher JR, Elwell MR. 1990. Comparative toxicity of ethylene dichloride in F344/N, Sprague-Dawley and Osborne-Mendel rats. Food Chem Toxicol 28(12):839-845.

NTP. 1991. NTP technical report on the toxicity studies of 1,2-dichloroethane (ethylene dichloride) in F344/N rats, Sprague Dawley rats, Osborne-Mendel rats, and B6C3F1 mice (drinking water and gavage studies) (CAS No. 107-06-2). Research Triangle Park, NC: National Toxicology Program. NTP Tox 4. NIH Publication No. 91-3123.

Groups of F344/N rats (10 /sex) were exposed to drinking water containing 0, 500, 1,000, 2,000, 4,000, or 8,000 ppm of 1,2-dichloroethane for 13 weeks. The high concentration was close to the solubility limit for 1,2-dichloroethane in water. Reported estimates of intake from the water were 0, 49, 86, 147, 259, and 515 mg/kg/day in male rats and 0, 58, 102, 182, 320, and 601 mg/kg/day in female rats. Signs of toxicity, body weight, food and water consumption, hematology, and serum chemistry were evaluated throughout the study, and comprehensive gross and histological examinations were performed at the end of the exposure period.

Dose-related decreased water consumption occurred in both sexes. There was >10% reduction in body weight gain at 259 mg/kg/day in male F344/N rats. There were no significant reductions in body weight gain in female rats. In female rats, absolute and relative kidney weights were increased at doses >102 mg/kg/day. Renal tubular regeneration, described as one or more foci of basophilic-staining tubules lined by closely packed tubular epithelium in the cortex or outer medulla (minimal-to-mild in severity), was observed in female rats administered 601 mg/kg/day. Thus, dose-related changes in kidney weight were not correlated with renal lesions. Absolute and relative kidney weight increases were also observed in male rats at doses >86 mg/kg/day; however, the dose-related change in organ weight was not correlated with renal lesions, which occurred in 9/10 rats in all groups including controls. No effects were observed in other organs of male or female rats.

***Selection of the Point of Departure for the MRL*:** BMD modeling was conducted to identify a POD using the kidney weight and histopathological lesion data from female rats in the drinking water study (see Table A-9).

**Table A-9. Kidney Weights and Incidence of Tubule Regeneration in Female F344 Rats Exposed to 1,2-Dichloroethane in Drinking Water for 13 Weeks**

| Dose (mg/kg/day) | 0 | 58 | 102 | 182 | 320 | 601 |
|---|---|---|---|---|---|---|
| Body weight (% of control) | | 101 | 102 | 99 | 97 | 93 |
| Water intake (g/day) | 19 | 18 | 16 | 14 | 12 | 11 |
| Absolute kidney weight[a] (mg) | 739±26 | 814±16[b] (↑10) | 885±16[c] (↑20) | 845±17[c] (↑14) | 932±15[c] (↑26) | 923±15[c] (↑25) |
| Relative kidney weight[a] (%) | 3.8±0.13 | 4.1±0.07 (↑8%) | 4.2±0.17[b] (↑11%) | 4.3±0.07[c] (↑13%) | 4.8±0.09[c] (↑26%) | 5.0±0.04[c] (↑32%) |
| Tubule regeneration[d] | 0/10 | 0/10 | 1/10 | 2/10 | 3/10 | 9/10[c] |

[a]Organ weights reported as mean±standard error; n=10.
[b]p<0.5.
[c]p<0.01.
[d]Tubule regeneration was characterized as one or more foci of basophilic-staining tubules lined by closely packed tubular epithelium in the cortex or outer medulla of the kidney of minimal-to-mild severity.

Source; NTP (1991)

BMD modeling of dichotomous data (renal lesions in Female F344 rats) was conducted with EPA's BMDS (version 3.2.0.1). For these data, the Dichotomous Hill, Gamma, Logistic, Log Logistic, Log Probit, Multistage, Probit, and Weibull dichotomous models available within the software were fit using a BMR of 10% extra risk. Adequacy of model fit was judged by four criteria: the $\chi 2$ goodness-of-fit p-value (p>0.1), magnitude of scaled residuals for the dose group nearest to the BMD (absolute value <2.0), BMDL that is not 10 times lower than the lowest non-zero dose, and visual inspection of the model fit. Among all models providing adequate fit, the BMDL from the model with the lowest AIC is selected as a potential POD if the BMDLs are sufficiently close (<3-fold); if the BMDLs are not sufficiently close (>3-fold), model-dependence is indicated, and the model with the lowest reliable BMDL is selected. All models provided an adequate fit to the data ($\chi 2$ goodness-of-fit p-value >0.1). The BMDLs were marginally over the 3-fold difference (~3.1-fold) suggested rule; therefore, the model with the lowest BMDL (1-degree Multistage model) was recommended by the BMDS. Visual inspection of the dose-response of the 1-degree Multistage model, however, indicates that there is a poor visual fit in the low-dose region of the predicted curve. A poorer fit is also indicated by the scaled residual near the BMD of -1.03, which is higher when compared to the viable alternative models. Because the difference in BMDLs was marginally close and because there was a relatively poor visual fit of the 1-degree Multistage model in the low-dose region of the curve, the model with the lowest AIC was chosen as a viable alternative (2-degree Multistage). The predicted $BMD_{10}$ and $BMDL_{10}$ values for this dataset are 139.26 and 70.08 mg/kg-day, respectively (see Table A-10 and Figure A-3).

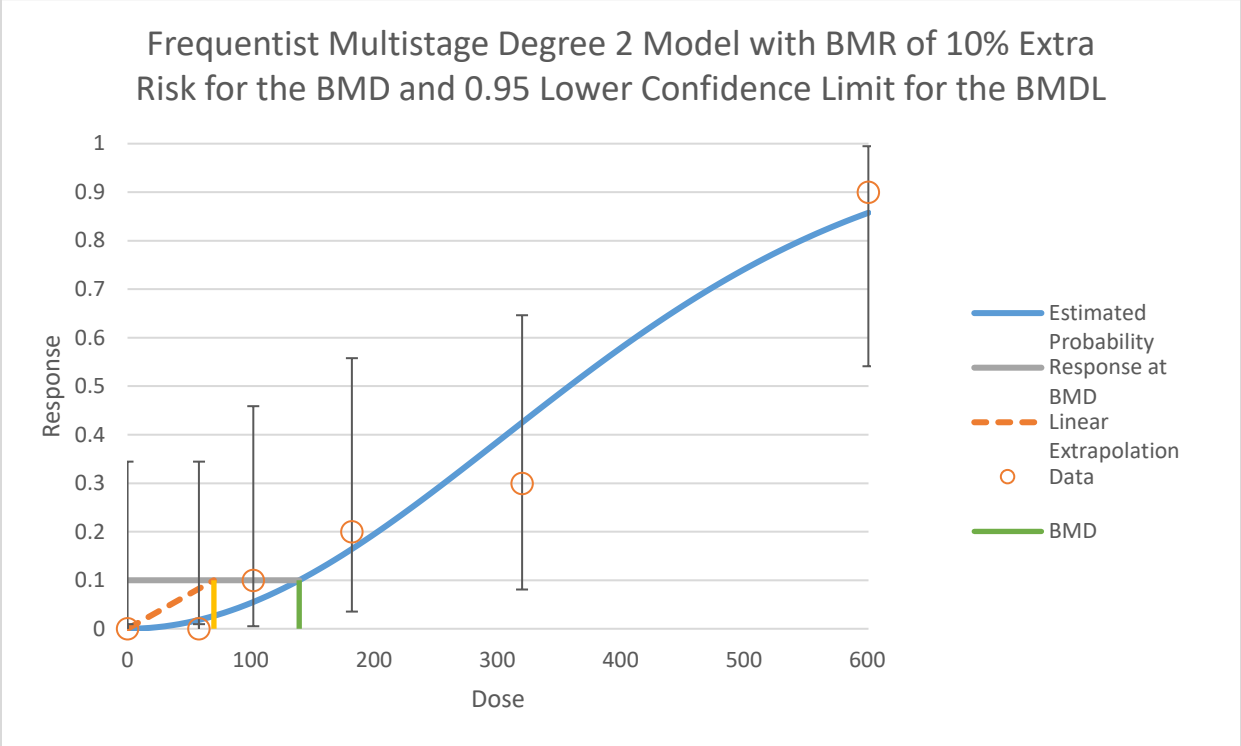
## Table A-10. Model Predictions for Increased Incidence of Renal Lesions in Female F344 Rats Following Exposure to 1,2-Dichloroethane in Drinking Water for 13 Weeks (NTP 1991)

| Model | $BMD_{10}$[a] (mg/kg/day) | $BMDL_{10}$[a] (mg/kg/day) | p-Value[b] | AIC | Scaled residuals[c] | |
|---|---|---|---|---|---|---|
| | | | | | Dose below BMD | Dose above BMD |
| Dichotomous Hill | 142.02 | 80.55 | 0.29 | 45.75 | 0.81 | 0.24 |
| Gamma[d,e] | 138.68 | 75.97 | 0.75 | 41.23 | 0.72 | 0.21 |
| Log-Logistic[e] | 142.02 | 80.55 | 0.66 | 41.75 | 0.81 | 0.24 |
| Multistage Degree 5[f] | 131.14 | 59.37 | 0.86 | 42.34 | 0.32 | 0.42 |
| Multistage Degree 4[f] | 132.74 | 61.03 | 0.84 | 42.42 | 0.33 | 0.45 |
| Multistage Degree 3[f] | 137.24 | 64.48 | 0.80 | 42.55 | 0.39 | 0.46 |
| **Multistage Degree 2[f,g]** | **139.26** | **70.08** | **0.83** | **40.83** | **0.62** | **0.30** |
| Multistage Degree 1[f] | 61.10 | 40.50 | 0.28 | 45.91 | -1.03 | -0.53 |
| Weibull[d] | 142.44 | 77.67 | 0.68 | 42.82 | 0.69 | 0.35 |
| Logistic | 178.79 | 124.15 | 0.81 | 41.34 | 0.52 | 0.73 |
| Log-Probit | 135.39 | 81.04 | 0.45 | 43.90 | 0.82 | 0.04 |
| Probit | 166.93 | 115.93 | 0.84 | 41.08 | 0.57 | 0.64 |

[a]BMD and BMDL values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional $\chi^2$ goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMD.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Recommended model. All models provided adequate fit to the data. The BMDLs were marginally >3-fold; however, the model with the lowest BMDL (1-degree Multistage) provided a relatively poor fit to the low-dose region of the curve. After exclusion of the 1-degree Multistage model, the remaining BMDLs were within 3-fold; therefore, the model with the lowest AIC was selected (2-degree Multistage).

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

**Figure A-3. Fit of 2-Degree Multistage Model to Incidence Data for Renal Lesions in Female F344 Rats Following Exposure to 1,2-Dichloroethane in Drinking Water for 13 Weeks (NTP 1991)**




BMD modeling of continuous data (absolute and relative kidney weight) was conducted with the EPA's BMDS (version 3.2.0.1). For these data, the Exponential, Hill, Linear, Polynomial, and Power continuous models available within the software were fit employing a BMR of 1 standard deviation (SD). An adequate fit was judged based on the $\chi 2$ goodness-of-fit p value ($p>0.1$), magnitude of the scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. In addition to these three criteria for judging adequacy of model fit, a determination was made as to whether the variance across dose groups was constant. If a constant variance model was deemed appropriate based on the statistical test provided in BMDS (i.e., Test 2; p-value >0.1), the final BMD results were estimated from a constant variance model. If the test for homogeneity of variance was rejected (p-value <0.1), the model was run again while modeling the variance as a power function of the mean to account for this nonconstant variance. If this nonconstant variance model did not adequately fit the data (i.e., Test 3; p-value <0.1), the data set was considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest BMDL was selected if the BMDLs estimated from different models varied >3-fold; otherwise, the BMDL from the model with the lowest AIC was selected. For absolute kidney weight, the constant variance model provided an adequate fit to the full dataset; however, none of the models provided adequate fit to the means (p-value <0.1). For relative kidney weight, neither the constant variance nor the nonconstant variance model provided an adequate fit to the variance data. Therefore, the kidney weight datasets were not amenable to BMD modeling.

The selected POD for intermediate-duration oral exposure was the $BMDL_{10}$ value of 70.08 mg/kg/day for renal lesions (tubule regeneration) in female rats.

***Adjustment for Intermittent Exposure:*** Not applicable.

***Uncertainty Factor:*** The $BMLD_{10}$ of 70.08 mg/kg/day was divided by a total uncertainty factor (UF) of 100 (10 for human variability and 10 for extrapolation from animals to humans.

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

This resulted in the following MRL:

$MRL = BMLD_{10} \div UF$
$MRL = 70.08 \text{ mg/kg/day} \div (10x10) = 0.7 \text{ mg/kg/day}$

***Other Additional Studies or Pertinent Information:*** Renal effects (e.g., increased kidney weight and/or tubular epithelial regeneration) were also found in mice exposed via drinking water at doses >448 mg/kg/day and in animals following acute- and intermediate-duration inhalation exposure (Heppel et al. 1946; Hotchkiss et al. 2010; Spencer et al. 1951) and intermediate-duration dermal exposure (Suguro et al. 2017).

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

APPENDIX A

# MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dichloroethane
***CAS Numbers:*** 107-06-2
***Date:*** July 2024
***Profile Status:*** Final
***Route:*** Oral
***Duration:*** Chronic

***MRL Summary:*** The available data are insufficient for derivation of a chronic-duration oral MRL for 1,2-Dichloroethane.

***Rationale for not deriving an MRL:*** The database of chronic-duration oral toxicity studies for 1,2-dichloroethane consists of one 2-year dietary study in rats (Alumot et al. 1976) and one 78-week gavage study in rats and mice (NCI 1978). Alumot et al. (1976) administered doses of 0, 12.5, or 25 mg/kg/day in feed to rats for 2 years. No effects were observed for any endpoint. This study had several significant limitations including unknown purity of the compound, unclear concentrations of 1,2-dichloroethane in the mash diet and dose consumed, and absence of gross or histological examination of organs or tissues. NCI (1978) administered 1,2-dichloroethane to Osborne-Mendel rats at doses of 0, 47, and 95 mg/kg/day and B6C3F1 mice at doses of 0, 97, and 195 (males) and 0, 149, and 299 mg/kg/day (females) via gavage on 5 days/week for 78 weeks. There was high mortality at the high dose in rats of both sexes and in female mice. The only other health effect observed was cancer. Limitations of the NCI (1978) study include dosage adjustments throughout the exposure period, high mortality, and fewer control animals (20/sex) than exposed (50/sex). Both available studies are via the gavage route, and it is important to emphasize that there is a notable difference in toxicokinetics between gavage and drinking water administration (see Section 3.1). With gavage administration, bolus dosing leads to saturation of the detoxification/excretion mechanism and exacerbates toxicity. Due to the limitations, route, and the fact that the only observed effects were death and cancer, available data were not considered adequate for use in deriving an MRL.

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

# APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR 1,2-DICHLOROETHANE

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-dichloroethane.

## B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for 1,2-dichloroethane. 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-dichloroethane 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-dichloroethane 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-dichloroethane released for public comment in 2022; thus, the literature search was restricted to studies published between January 2019 and June 2022. The following main databases were searched in June 2022:

- 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-dichloroethane. 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-dichloroethane 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** | |
| 06/2022 | (107-06-2[rn] OR "ethylene dichloride"[nm] OR "Ethylene Dichlorides"[mh] OR "1,2-Bichloroethane"[tw] OR "1,2-DCA"[tw] OR "1,2-Dichlorethane"[tw] OR "1,2-Dichloroethane"[tw] OR "1,2-Ethylene dichloride"[tw] OR "1,2-Ethylidene dichloride"[tw] OR "alpha,beta-Dichloroethane"[tw] OR "Dichloro-1,2-ethane"[tw] OR "dichloroethane"[tw] OR "dichloroethanes"[tw] OR "EDC (halocarbon)"[tw] OR "Ethane dichloride"[tw] OR "Ethane, 1,2-dichloro-"[tw] OR "Ethylene chloride"[tw] OR "Ethylene dichloride"[tw] OR "Ethylenedichloride"[tw] OR "Glycol dichloride"[tw] OR "sym-Bichloroethane"[tw] OR "sym-Dichloroethane"[tw] OR "α,β-Dichloroethane"[tw] OR "Borer sol"[tw] OR "Brocide"[tw] OR "Di-chlor-mulsion"[tw] OR "Dichlor-Mulsion"[tw] OR "Dichloremulsion"[tw] OR "Dutch liquid"[tw] OR "Dutch oil"[tw] OR "Freon 150"[tw] OR "HCC 150"[tw]) AND (2019/01/01:3000[mhda] OR 2019/01/01:3000[crdat] OR 2019/01/01:3000[edat] OR 2018:3000[dp]) |
| **NTRL** | |
| 06/2022 | Date Published 2018 to 2022<br>"1,2-Bichloroethane" OR "1,2-DCA" OR "1,2-Dichlorethane" OR "1,2-Dichloroethane" OR "1,2-Ethylene dichloride" OR "1,2-Ethylidene dichloride" OR "alpha,beta-Dichloroethane" OR "Dichloro-1,2-ethane" OR "dichloroethanes" OR "EDC (halocarbon)" OR "Ethane dichloride" OR "Ethane, 1,2-dichloro-" OR "Ethylene chloride" OR "Ethylene dichloride" OR "Ethylenedichloride" OR "Glycol dichloride" OR "sym-Bichloroethane" OR "sym-Dichloroethane" OR "α,β-Dichloroethane" OR "Borer sol" OR "Brocide" OR "Di-chlor-mulsion" OR "Dichlor-Mulsion" OR "Dichloremulsion" OR "Dutch liquid" OR "Dutch oil" OR "Freon 150" OR "HCC 150" OR "Dichloroethane" |
| **Toxcenter** | |
| 06/2022 | FILE 'TOXCENTER' ENTERED AT 19:14:00 ON 13 JUN 2022<br>L1 8364 SEA FILE=TOXCENTER 107-06-2<br>L2 8140 SEA FILE=TOXCENTER L1 NOT TSCATS/FS<br>L3 6930 SEA FILE=TOXCENTER L2 NOT PATENT/DT<br>L4 740 SEA FILE=TOXCENTER L3 AND PY>2017<br>L5 647 SEA FILE=TOXCENTER L3 AND ED>=20190101<br>L6 797 SEA FILE=TOXCENTER L4 OR L5<br>ACT TOXQUERY/Q<br>---------<br>L7 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) |

## Table B-2. Database Query Strings

| Database search date | Query string |
|---|---|
| | L8 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) |
| | L9 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) |
| | L10 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT |
| | L11 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) |
| | L12 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) |
| | L13 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) |
| | L14 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) |
| | L15 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) |
| | L16 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) |
| | L17 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) |
| | L18 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) |
| | L19 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) |
| | L20 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) |
| | L21 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) |
| | L22 QUE (ENDOCRIN? AND DISRUPT?) |
| | L23 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) |
| | L24 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) |
| | L25 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) |
| | L26 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) |
| | L27 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) |
| | L28 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) |
| | L29 QUE (NEPHROTOX? OR HEPATOTOX?) |
| | L30 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?) |
| | L31 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) |
| | L32 QUE L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31 |
| | L33 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE |

## Table B-2. Database Query Strings

| Database search date | Query string |
|---|---|
| | OR PORCINE OR MONKEY? OR MACAQUE?) |
| | L34 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA |
| | OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) |
| | L35 QUE L32 OR L33 OR L34 |
| | L36 QUE (NONHUMAN MAMMALS)/ORGN |
| | L37 QUE L35 OR L36 |
| | L38 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR |
| | PRIMATES OR PRIMATE?) |
| | L39 QUE L37 OR L38 |
| | --- |
| | L40 360 SEA FILE=TOXCENTER L6 AND L39 |
| | L41 25 SEA FILE=TOXCENTER L40 AND MEDLINE/FS |
| | L42 341 DUP REM L40 (19 DUPLICATES REMOVED) |
| | D SCAN L42 |

## Table B-3. Strategies to Augment the Literature Search

| Source | Query and number screened when available |
|---|---|
| **TSCATS via ChemView** | |
| 06/2022 | Compounds searched: 107-06-2 |
| **NTP** | |
| 06/2022 | "107-06-2" "1,2-Dichloroethane" "Dichloroethane" "Ethylene dichloride" "1,2-DCA" "dichloroethanes" "Ethane dichloride" "Ethylene chloride" "Ethylenedichloride" "sym-Dichloroethane"<br>Years 2010-2019, 2020-2022 |
| **Regulations.gov** | |
| 06/2022 | "107-06-2"<br>dichloroethane<br>"ethylene dichloride"<br>Posted date 01/01/2018-06/14/2022; Docket and EPA notices |
| **NIH RePORTER** | |
| 02/2024 | Fiscal Year: Active ProjectsText Search: "1,2-Bichloroethane" OR "1,2-DCA" OR "1,2-Dichlorethane" OR "1,2-Dichloroethane" OR "1,2-Ethylene dichloride" OR "1,2-Ethylidene dichloride" OR "alpha,beta-Dichloroethane" OR "Dichloro-1,2-ethane" OR "dichloroethanes" OR "EDC (halocarbon)" OR "Ethane dichloride" OR "Ethane, 1,2-dichloro-" OR "Glycol dichloride" OR "sym-Bichloroethane" OR "sym-Dichloroethane" OR "α,β-Dichloroethane" OR "Borer sol" OR "Brocide" OR "Di-chlor-mulsion" OR "Dichlor-Mulsion" OR "Dichloremulsion" OR "Dutch liquid" OR "Dutch oil" OR "Freon 150" OR "HCC 150" (advanced)Limit to: Project Title, Project Terms, Project Abstracts |
| **Other** | Identified throughout the assessment process |

The 2022 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 613
- Number of records identified from other strategies: 74
- Total number of records to undergo literature screening: 687

### B.1.2 Literature Screening

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

- 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.

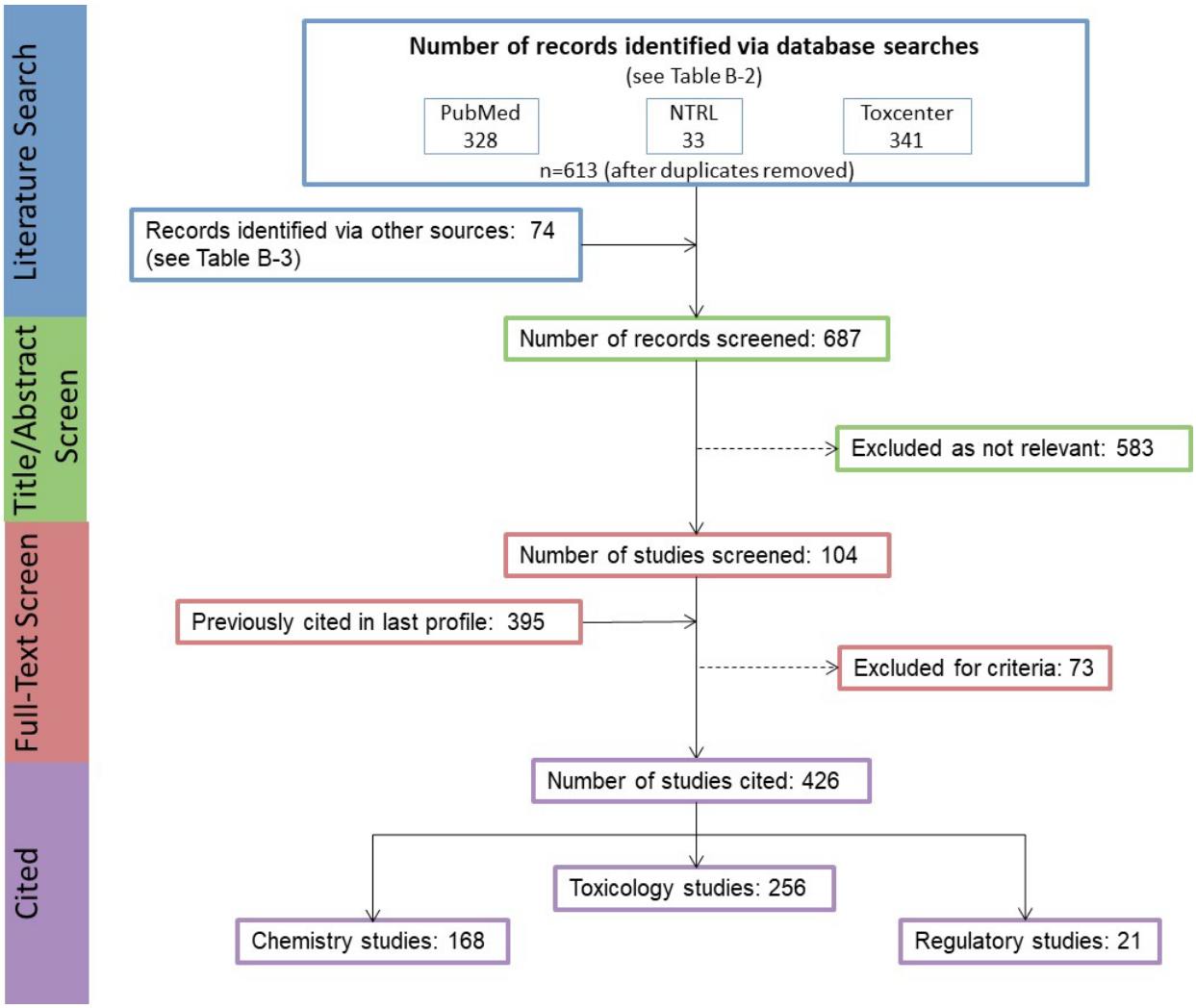
- Number of titles and abstracts screened: 687
- Number of studies considered relevant and moved to the next step: 104

***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: 104
- Number of studies cited in the pre-public draft of the toxicological profile: 395
- Total number of studies cited in the profile: 426

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

## Figure B-1. June 2022 Literature Search Results and Screen for 1,2-Dichloroethane



# APPENDIX C. USER'S GUIDE

## Chapter 1. Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

### Minimal Risk Levels (MRLs)

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

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

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

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

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

## Chapter 2. Health Effects

### Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

**TABLE LEGEND**

**See Sample LSE Table (page C-5)**

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

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

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

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

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

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

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), 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 C-6)**

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(12) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

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

(14) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in $mg/m^3$ or ppm and oral exposure is reported in mg/kg/day.

(15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

APPENDIX C

**Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral** (1)

| Figure key[a] (4) | 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 |
|---|---|---|---|---|---|---|---|---|---|
| (2) **CHRONIC EXPOSURE** | | | | | | | | | |
| 51 (3) | 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 |
| (10) **Aida et al. 1992** | | | | | | | | | |
| 52 | Rat (F344) 78 M | 104 weeks (W) | 0, 3.9, 20.6, 36.3 | CS, BW, FI, BC, OW, HP | Hepatic | 36.3 | | | |
| | | | | | Renal | 20.6 | 36.3 | | Increased incidence of renal tubular cell hyperplasia |
| | | | | | Endocr | 36.3 | | | |
| **George et al. 2002** | | | | | | | | | |
| 59 | Rat (Wistar) 58M, 58F | Lifetime (W) | M: 0, 90 F: 0, 190 | BW, HP | Cancer | | 190 F | | Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided |
| **Tumasonis et al. 1985** | | | | | | | | | |

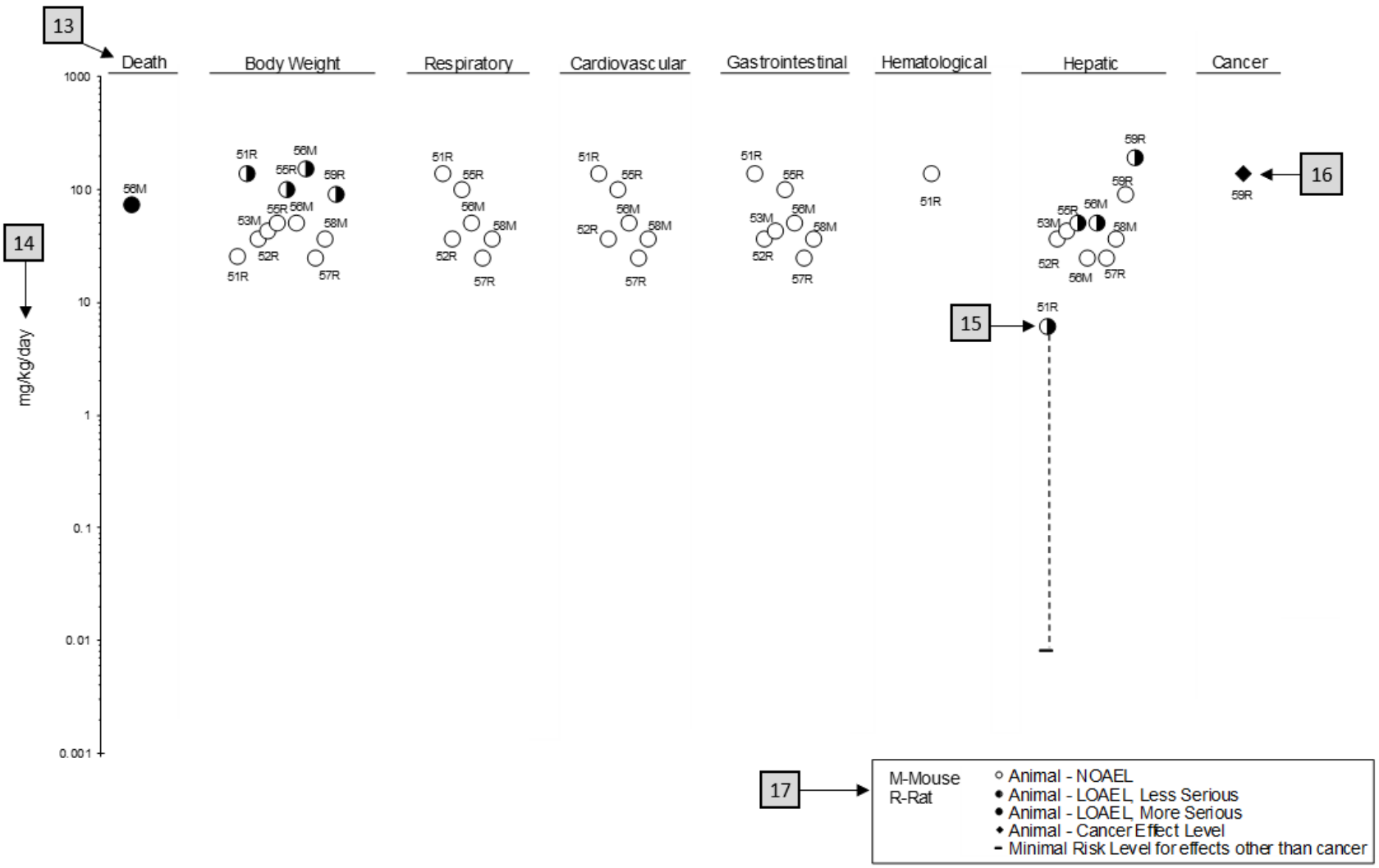
[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

APPENDIX C

**Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral**



# APPENDIX D. 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.

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***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**

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***ATSDR Information Center***

***Phone:*** 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
***Internet***: http://www.atsdr.cdc.gov

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

*Clinician Briefs and Overviews* discuss health effects and approaches to patient management in a brief/factsheet style. They are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/clinician-briefs-overviews.html).

*Managing Hazardous Materials Incidents* is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.html).

*Fact Sheets (ToxFAQs™)* provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

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APPENDIX D

***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/.

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***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 E. 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.

APPENDIX E

**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 exposure level 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 exposure level, 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)—**A National Institute for Occupational Safety and Health (NIOSH) value to protect workers, most often expressed as time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek. RELs may also be expressed as 8-hour TWAs, short-term exposure limits (STELs), or ceiling limits (a concentration that should never be exceeded).

**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) value to protect workers, most often expressed as time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek. RELs may also be expressed as 8-hour TWAs, short-term exposure limits (STELs), or ceiling limits (a concentration that should never be exceeded).

**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 F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

| | |
|---|---|
| AAPCC | American Association of Poison Control Centers |
| ACGIH | American Conference of Governmental Industrial Hygienists |
| ACOEM | American College of Occupational and Environmental Medicine |
| ACMT | American College of Medical Toxicology |
| ADI | acceptable daily intake |
| ADME | absorption, distribution, metabolism, and excretion |
| AEGL | Acute Exposure Guideline Level |
| AIC | Akaike's information criterion |
| AIHA | American Industrial Hygiene Association |
| ALT | alanine aminotransferase |
| AOEC | Association of Occupational and Environmental Clinics |
| AP | alkaline phosphatase |
| AST | aspartate aminotransferase |
| atm | atmosphere |
| ATSDR | Agency for Toxic Substances and Disease Registry |
| AWQC | Ambient Water Quality Criteria |
| BCF | bioconcentration factor |
| BMD/C | benchmark dose or benchmark concentration |
| $BMD_X$ | dose that produces a X% change in response rate of an adverse effect |
| $BMDL_X$ | 95% lower confidence limit on the $BMD_X$ |
| BMDS | Benchmark Dose Software |
| BMR | benchmark response |
| BUN | blood urea nitrogen |
| C | centigrade |
| CAA | Clean Air Act |
| CAS | Chemical Abstract Services |
| CDC | Centers for Disease Control and Prevention |
| CEL | cancer effect level |
| CERCLA | Comprehensive Environmental Response, Compensation, and Liability Act |
| CFR | Code of Federal Regulations |
| Ci | curie |
| CI | confidence interval |
| cm | centimeter |
| CPSC | Consumer Products Safety Commission |
| CWA | Clean Water Act |
| DNA | deoxyribonucleic acid |
| DOD | Department of Defense |
| DOE | Department of Energy |
| DWEL | drinking water exposure level |
| EAFUS | Everything Added to Food in the United States |
| ECG/EKG | electrocardiogram |
| EEG | electroencephalogram |
| EPA | Environmental Protection Agency |
| ERPG | emergency response planning guidelines |
| F | Fahrenheit |
| F1 | first-filial generation |
| FDA | Food and Drug Administration |
| FIFRA | Federal Insecticide, Fungicide, and Rodenticide Act |
| FR | Federal Register |

| | |
|---|---|
| FSH | follicle stimulating hormone |
| g | gram |
| GC | gas chromatography |
| gd | gestational day |
| GGT | γ-glutamyl transferase |
| GRAS | generally recognized as safe |
| HEC | human equivalent concentration |
| HED | human equivalent dose |
| HHS | Department of Health and Human Services |
| HPLC | high-performance liquid chromatography |
| HSDB | Hazardous Substance Data Bank |
| IARC | International Agency for Research on Cancer |
| IDLH | immediately dangerous to life and health |
| IRIS | Integrated Risk Information System |
| Kd | adsorption ratio |
| kg | kilogram |
| kkg | kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton |
| $K_{oc}$ | organic carbon partition coefficient |
| $K_{ow}$ | octanol-water partition coefficient |
| L | liter |
| LC | liquid chromatography |
| $LC_{50}$ | lethal concentration, 50% kill |
| $LC_{Lo}$ | lethal concentration, low |
| $LD_{50}$ | lethal dose, 50% kill |
| $LD_{Lo}$ | lethal dose, low |
| LDH | lactate dehydrogenase |
| LH | luteinizing hormone |
| LOAEL | lowest-observed-adverse-effect level |
| LSE | Level of Significant Exposure |
| $LT_{50}$ | lethal time, 50% kill |
| m | meter |
| mCi | millicurie |
| MCL | maximum contaminant level |
| MCLG | maximum contaminant level goal |
| MF | modifying factor |
| mg | milligram |
| mL | milliliter |
| mm | millimeter |
| mmHg | millimeters of mercury |
| mmol | millimole |
| MRL | Minimal Risk Level |
| MS | mass spectrometry |
| MSHA | Mine Safety and Health Administration |
| Mt | metric ton |
| NAAQS | National Ambient Air Quality Standard |
| NAS | National Academy of Science |
| NCEH | National Center for Environmental Health |
| ND | not detected |
| ng | nanogram |
| NHANES | National Health and Nutrition Examination Survey |
| NIEHS | National Institute of Environmental Health Sciences |

| | |
|---|---|
| NIOSH | National Institute for Occupational Safety and Health |
| NLM | National Library of Medicine |
| nm | nanometer |
| nmol | nanomole |
| NOAEL | no-observed-adverse-effect level |
| NPL | National Priorities List |
| NR | not reported |
| NRC | National Research Council |
| NS | not specified |
| NTP | National Toxicology Program |
| OR | odds ratio |
| OSHA | Occupational Safety and Health Administration |
| PAC | Protective Action Criteria |
| PAH | polycyclic aromatic hydrocarbon |
| PBPD | physiologically based pharmacodynamic |
| PBPK | physiologically based pharmacokinetic |
| PEHSU | Pediatric Environmental Health Specialty Unit |
| PEL | permissible exposure limit |
| PEL-C | permissible exposure limit-ceiling value |
| pg | picogram |
| PND | postnatal day |
| POD | point of departure |
| ppb | parts per billion |
| ppbv | parts per billion by volume |
| ppm | parts per million |
| ppt | parts per trillion |
| REL | recommended exposure limit |
| REL-C | recommended exposure limit-ceiling value |
| RfC | reference concentration |
| RfD | reference dose |
| RNA | ribonucleic acid |
| SARA | Superfund Amendments and Reauthorization Act |
| SCE | sister chromatid exchange |
| SD | standard deviation |
| SE | standard error |
| SGOT | serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST) |
| SGPT | serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT) |
| SIC | standard industrial classification |
| SLOAEL | serious lowest-observed-adverse-effect level |
| SMR | standardized mortality ratio |
| sRBC | sheep red blood cell |
| STEL | short term exposure limit |
| TLV | threshold limit value |
| TLV-C | threshold limit value-ceiling value |
| TRI | Toxics Release Inventory |
| TSCA | Toxic Substances Control Act |
| TWA | time-weighted average |
| UF | uncertainty factor |
| U.S. | United States |
| USDA | United States Department of Agriculture |
| USGS | United States Geological Survey |

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|---|---|
| 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 |