Toxicological Profile for 1,2-Dichloroethane

Draft for Public Comment

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Agency for Toxic Substances and Disease Registry

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FOREWORD

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

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

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

Each profile includes the following:

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

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

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

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. ATSDR plans to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

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

Written comments may also be sent to: Agency for Toxic Substances and Disease Registry
Office of Innovation and Analytics
Toxicology Section
1600 Clifton Road, N.E.
Mail Stop S102-1
Atlanta, Georgia 30329-4027

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

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

Patrick N. Breysse, Ph.D., CIH
Director, National Center for Environmental Health and
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

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

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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, Rockville, MD

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

PEER REVIEWERS

1. Jordan N. Smith, Ph.D., Joint Appointment, Department of Environmental and Molecular Toxicology (EMT), Oregon State University
2. John C. Lipscomb, Ph.D., D.A.B.T, F.A.T.S, Lipscomb and Associates, PLLC, Sherwood, Arkansas
3. James V. Buckner, Ph.D., Professor, Department of Pharmaceutical & Biomedical Sciences, University of Georgia, Athens, Georgia

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 composed of two carbon atoms bound to each other, with each atom also bound to one chlorine atom and two hydrogen atoms, and is produced by chlorination of ethylene using a catalyst.. 1,2-Dichloroethane 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 added to leaded gasoline (for aviation and off-road racing), used as a dispersant in rubber and plastics, and as a solvent in organic synthesis. 1,2-Dichloroethane was previously used as an insect and soil fumigant. 1,2-Dichloroethane is produced by chlorination of ethylene using a catalyst.

1,2-Dichloroethane is a widespread contaminant 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 about 73 days (Arnts et al. 1989; Atkinson 1986). 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 1.18×10^{-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, 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, as well as exposure from accidental spills. 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. Occupational exposure to 1,2-dichloroethane occurs through inhalation and dermal contact with the compound at workplaces where it is produced or used. Children are expected to be exposed to 1,2-dichloroethane by the same routes as adults. 1,2-Dichloroethane has been detected in human milk, indicating that infants could possibly be exposed to 1,2-dichloroethane from breast-feeding mothers. The importance of this route of child exposure is unclear because current data on the concentration of 1,2-dichloroethane in breast milk are not available.

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 slightly higher near point sources such as factories, treatment

plants, and hazardous waste sites. The estimated daily intake of 1,2-dichloroethane in Japan attributed to food ingestion is 0.004 mg/day, a level well below ATSDR's intermediate oral Minimal Risk Level (MRL) of 0.2 mg/kg/day for 1,2-dichloroethane (Miyahara et al. 1995). Since the levels of 1,2-dichloroethane in food products of Japan are similar to those in the United States, the daily intake value may also be similar. 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-Dichloroethane is included in the priority list of hazardous substances identified by ATSDR and the Environmental Protection Agency (EPA), and has been found in at least 585 of the 1,854 current or former National Priorities List (NPL) sites (ATSDR 2017). However, the total number of NPL sites evaluated for 1,2-dichloroethane is not known. As more sites are evaluated, the sites at which 1,2-dichloroethane is found may increase.

1.2 SUMMARY OF HEALTH EFFECTS

Acute, intermediate, and chronic health effects can result from inhalation or ingestion of, or dermal contact with 1,2-dichloroethane. Main targets of mammalian toxicity include the liver, kidneys, and neurological, cardiovascular, and immune systems. A limited amount of information is available regarding effects in humans, most coming from case reports of people who died following acute exposure to high levels by inhalation or ingestion. Symptoms and signs in these people included central nervous system depression, nausea and vomiting, corneal opacity, bronchitis, respiratory distress, lung congestion, myocardial lesions, hemorrhagic gastritis and colitis, increased blood clotting time, hepatocellular damage, renal necrosis, and histopathological changes in brain tissue. Death was most often attributed to cardiac arrhythmia. Inhalation and oral studies in experimental animal studies have found similar effects to those seen in human case studies, as well as immunological, genotoxic, and carcinogenic effects. 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. Animal data further indicate that 1,2-dichloroethane is unlikely to cause reproductive or developmental toxicity at doses below those that are maternally toxic. Route-related differences in some toxic and carcinogenic responses have been observed between gavage and drinking water or inhalation exposure in animal studies of 1,2-dichloroethane. The differences in response may be due to saturation of the detoxification/excretion mechanism due to bolus gavage dosing. Effects of 1,2-dichloroethane in various tissues appear to be largely mediated by reactive intermediates formed by conjugation with glutathione. The reaction of 1,2-dichloroethane and glutathione results in activation rather than detoxification. Toxicity may occur when the biotransformation processes are saturated, thereby allowing higher levels of 1,2-dichloroethane to

circulate throughout the body and conjugate with glutathione instead of being detoxified and eliminated. Therefore, even though certain health effects might be expected in humans ingesting sufficient doses of 1,2-dichloroethane, it is uncertain whether the effects would occur following typical drinking water and inhalation exposures.

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

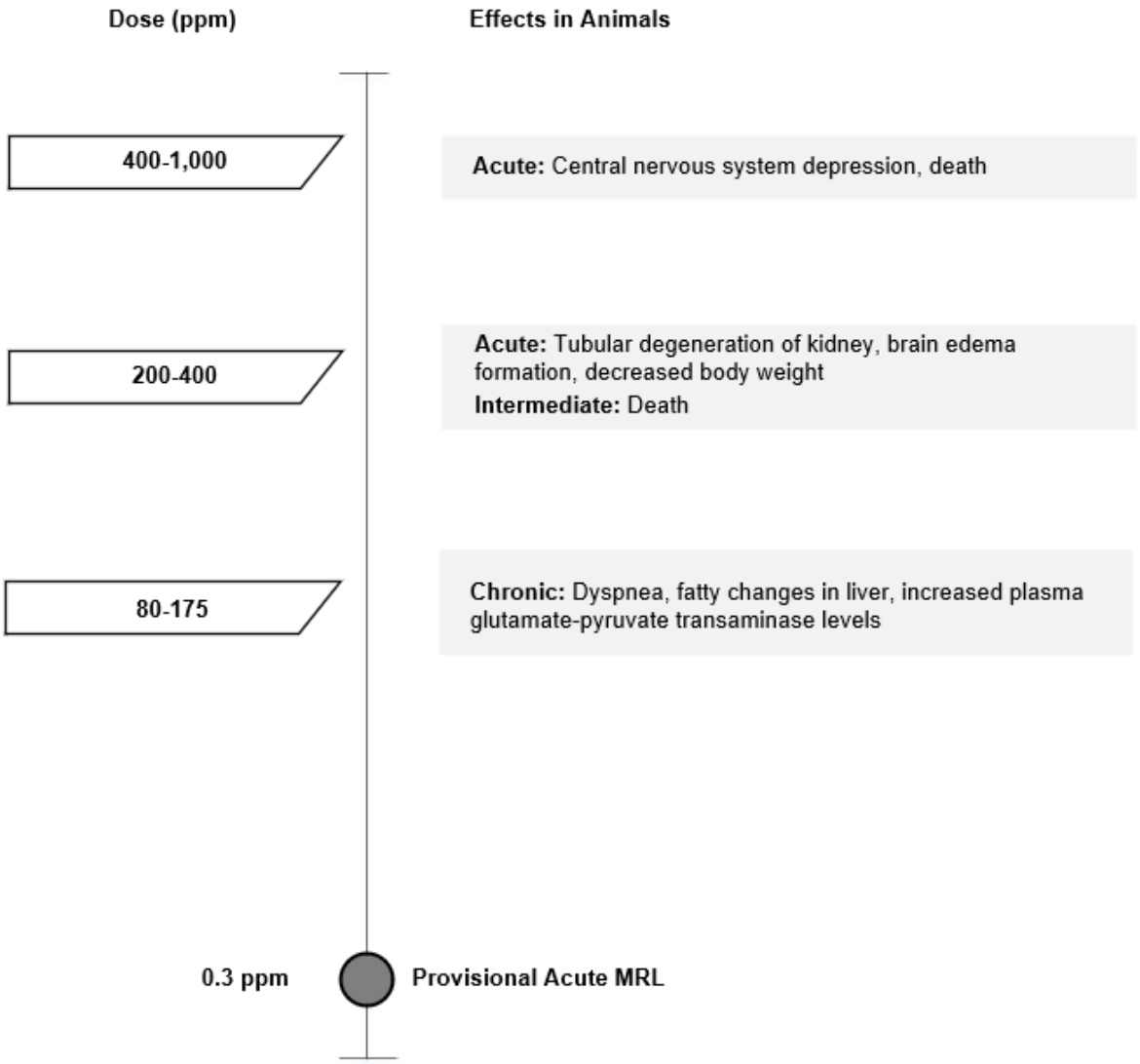


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to 1,2-Dichloroethane

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 exposure were respiratory distress, lung congestion, pulmonary edema, dyspnea, and bronchitis. Respiratory effects seen in experimental animals were limited to the acute duration for both inhalation and ingestion. The effects include nasal olfactory degeneration/necrosis, histopathologic alterations to the olfactory mucosa, pulmonary congestion, and pulmonary edema. Additionally, a 26-week dermal study produced cancerous and non-cancerous tumors in the lungs of mice. The effects in animals were not limited to any specific route of exposure and support the conclusion that the lung is a target organ for 1,2-dichloroethane. For inhalation exposure, the lowest concentration reported to produce respiratory effects was 100 ppm for up to 8 hours. For oral exposure, the lowest dose producing respiratory effects was a single dose of 136 mg/kg by gavage. Nasal epithelium degeneration/necrosis was used to derive the acute-duration MRL for inhalation exposure to 1,2-dichloroethane as discussed in Section 1.3 and in more detail in Appendix A.

Hepatic Effects. Liver effects have been observed in cases of humans who died following acute inhalation or ingestion of 1,2-dichloroethane. In one case study, hepatotoxicity was indicated by elevated serum markers used to assess liver injury, enlarged liver, and extensive centrilobular necrosis in a man who was exposed to concentrated 1,2-dichloroethane vapors for 30 minutes and subsequently died. When parenchymal liver cells are damaged, aminotransferases leak from the liver into the blood, resulting in elevated levels of enzymes marking liver dysfunction in the bloodstream. Similar increases in serum markers used to assess liver injury, in addition to mild liver lesions, were observed in three workers exposed to unknown air concentrations of 1,2-dichloroethane, with one worker dying 10 days later. Necrosis and cirrhosis were reported in people following acute high-level oral exposure to 570 mg/kg/day. Evidence from animal studies supports the conclusion that the liver is a target organ for 1,2-dichloroethane. Hepatic effects in exposed animals were not limited to any specific route or duration of exposure and included increased levels of serum markers of liver injury, increased liver weight, and fatty degeneration. For inhalation exposure, the lowest concentrations producing hepatic effects were approximately 222 ppm for acute-duration exposure and approximately 86 ppm for intermediate-duration exposure. For oral exposure, the lowest dose producing hepatic effects was 18 mg/kg/day for intermediate-duration exposure, however this dose was administered via gavage, which could have led to lower effective doses due to possibly bolus saturation of the detoxification/excretion mechanism. The lowest oral dose producing hepatic effects not using gavage administration was 60 mg/kg/day for intermediate-duration exposure.

Renal Effects. 1,2-Dichloroethane is acutely nephrotoxic in humans following both inhalation and ingestion. Renal effects observed in individuals who died following acute high-level exposure were diffuse necrosis, tubular necrosis, and kidney failure. Renal effects seen in experimental animals include increased kidney weight, cloudy swelling of the tubular epithelium, tubular degeneration and regeneration, karyomegaly, dilatation, protein casts, and mineralization. The effects in animals were not limited to any specific route or duration of exposure and support the conclusion that the kidney is a target organ for 1,2-dichloroethane. For inhalation exposure, the lowest concentration reported to produce renal effects was 400 ppm for durations of 8–12 days and 8 months. For oral exposure, the lowest dose producing renal effects was 58 mg/kg/day for 13 weeks. Increased kidney weight, considered to be an early-stage adverse effect because it leads to histopathological changes at higher doses, was used to derive the intermediate-duration MRL for oral exposure to 1,2-dichloroethane as discussed in Section 1.3 and in more detail in Appendix A.

Immunological and Lymphoreticular Effects. Immunological effects have not been reported in humans exposed to 1,2-dichloroethane. In mice, however, this chemical had immunosuppressive effects following both acute inhalation exposure and acute 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 end points were found in rats after single inhalation exposures with longer durations and higher doses. Effects observed in mice following acute oral 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). The immune system was the most sensitive target for short-term exposure to 1,2-dichloroethane by both the inhalation and oral routes in mice. Because of the apparent interspecies differences in immunotoxicity, it is unclear whether the immune system could be a target of 1,2-dichloroethane in humans following acute exposure by inhalation or ingestion. Immune function has not been evaluated in intermediate- or chronic-duration inhalation studies of 1,2-dichloroethane nor in chronic-duration oral studies. Leukocyte counts were not affected in intermediate duration drinking water and gavage studies in rats, and intermediate and chronic oral exposures did not produce histological changes in immune system tissues in rats and mice. Although immunological effects might be expected in humans ingesting sufficient doses of undiluted 1,2-dichloroethane, it is not known whether the effects would occur in people exposed via drinking water from wells located near hazardous waste sites.

Neurological Effects. Neurological symptoms and signs in people acutely exposed to high levels of 1,2-dichloroethane by inhalation or ingestion included headache, irritability, drowsiness, tremors, partial paralysis, and coma. Autopsies of people who died after acute 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. Similar symptoms are reported for intermediate and chronic exposures to 1,2-dichloroethane. 1,2-Dichloroethane induced toxic encephalopathy, primarily characterized by cerebral edema, is also commonly observed in workers exposed for longer periods of time. The results of experimental animal inhalation studies confirm that the central nervous system is a target of high concentrations of 1,2-dichloroethane. Symptoms similar to those reported in humans, such as tremors, abnormal posture, uncertain gait, and narcosis were observed after high-level acute vapor exposures in experimental animal studies. 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. 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, and no brain lesions were seen in rats intermittently exposed for 2 years. The effects seen in the gavage study might be attributable to the method of 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.

Cardiovascular Effects. Cardiac arrhythmia was given as the cause of death of a man briefly exposed to 1,2-dichloroethane as a concentrated vapor. Autopsy revealed diffuse degenerative changes in the myocardium (fragmentation, interstitial edema, loss of nuclei from myocardial fibers). In addition, cardiovascular insufficiency and hemorrhage were major factors contributing to death in people following acute high-level oral exposure to 570 mg/kg/day. In laboratory animals, myocardial inflammation was reported following acute inhalation of lethal concentrations, and fatty infiltration of the myocardium was observed in guinea pigs that died following exposure to 200 ppm for 25 weeks and in monkeys that survived the same exposure regimen. These findings in animals were based upon a very limited number of observations and in some cases did not include comparison to controls. More complete animal studies did not report cardiovascular histopathologic effects following high-level intermediate-duration oral exposure or low-level chronic-duration inhalation exposure. Overall, the data suggest that the heart could be a target of 1,2-dichloroethane following acute high-level oral exposure and possibly longer-term inhalation exposure as well.

Developmental Effects. Development effects of 1,2-dichloroethane exposure have been studied in humans with epidemiologic investigations of adverse birth outcomes. A population-based case-control study suggests birth defects such as neural tube defects, spina bifida, cleft palate, and congenital heart defects are associated with maternal residential proximity to industrial air emissions of 1,2-dichloroethane. Another set of studies found exposure to 1,2-dichloroethane in public drinking water was

associated with increased odds of major cardiac defects (but not neural tube defects), and residence within the census tract of NPL sites contaminated with 1,2-dichloroethane was associated with neural tube defects (but not heart defects). In all of these studies, the study populations were also simultaneously exposed to elevated levels of other contaminants and lifestyle factors that could also lead to birth defects. Because of the mixed chemical exposure, lack of dose-response information, and inconsistency between the findings of the epidemiologic studies, the associations with 1,2-dichloroethane are only suggestive and do not establish a cause-and-effect relationship. 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 lethality at maternally toxic doses have been reported. (There are reports of increased embryo and pup mortality following intermediate-duration inhalation of lower [not maternally toxic] concentrations of 1,2-dichloroethane, but the reliability of the results is uncertain due to the lack of statistical analysis and inadequate description of methods.) The possibility of induction of cardiac malformations in human offspring by exposure to 1,2-dichloroethane, as suggested by the epidemiologic data, was not confirmed in available animal studies because the teratology protocols did not include detailed examinations of dissected hearts. Studies of dichloroethylene and trichloroethylene, which are metabolized to some of the same reactive intermediates as 1,2-dichloroethane, have also shown evidence of heart malformations in humans as well as animal cardiac teratogenicity. Overall, the available information does not indicate that 1,2-dichloroethane is a developmental toxicant in animals at doses below those that cause other toxic effects.

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. A well-designed study in male mice reported male reproductive toxicity after intermediate inhalation exposure to 1,2-dichloroethane, including significant pathological changes in the testes, decreases in sperm concentration, decreases in sperm motility and progressive motility, and non-cell specific apoptosis of germ cells in the testes. 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 in these studies. Additionally, results of experimental animal studies indicate that 1,2-dichloroethane is unlikely to cause reproductive impairment at doses that are not maternally toxic in females. Some inhalation studies found that exposure of rat dams to 1,2-dichloroethane prior to mating and continuing into gestation caused pre-implantation loss and embryo lethality in rats, although the study methods were not well reported, and the reliability of the data is uncertain. In contrast to these findings, 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. One- and two-generation reproductive 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. The overall indication of the data is that 1,2-dichloroethane appears to induce embryotoxic effects in rats and to cause reproductive toxicity in male mice at doses as low as 25 ppm for 4 weeks, but it is unlikely to impair reproduction at doses that do not also cause other toxic manifestations in females.

Cancer. The Department of Health and Human Services (DHHS) 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 EPA has classified 1,2-dichloroethane as a Group B2 carcinogen (probable human carcinogen). 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, due to complicating co-exposures to various other chemicals. There have been mixed results in animal studies of tumor incidence after 1,2-dichloroethane exposure via inhalation, though the studies in mice and rats that failed to find 1,2-dichloroethane induced carcinogenic effects after chronic exposure had limitations that may explain the lack of these effects. A more recent study found a dose-dependent increase in benign and malignant tumors in rats of both sexes and female mice after chronic inhalation exposure to 1,2-dichloroethane. 1,2-Dichloroethane induced a clear positive carcinogenic response in animals after gavage administration, causing 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. Other animal bioassays provide supportive or suggestive evidence for the carcinogenicity of 1,2-dichloroethane. One study showed compound-related lung papillomas following lifetime dermal exposure of female mice. Another study found an increase in bronchioloalveolar adenomas and adenocarcinomas in mice of both sexes after intermediate dermal exposure. Two additional studies found that pulmonary adenomas were induced in mice by intraperitoneal injection.

1.3 MINIMAL RISK LEVELS (MRLS)

The inhalation database was considered adequate for derivation of a provisional acute -duration inhalation MRL for 1,2-dichloroethane, and inadequate for derivation of intermediate- and chronic-duration MRLs,

as the most sensitive endpoints are represented by serious effects for these durations. The respiratory endpoint was considered a sensitive target following inhalation exposure to 1,2-dichloroethane. Immunological and neurological endpoints also have sensitive endpoints 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 MRLs. Data were insufficient to derive an acute-duration provisional 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. Data were insufficient for the derivation of a chronic-duration provisional oral MRL as the most sensitive endpoint was represented by a serious effect. As presented in Figure 1-4., immunological, hematological, and renal endpoints are sensitive targets of 1,2-dichloroethane toxicity. The provisional MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

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

Exposure duration	Provisional MRL	Critical Effect	Point of Departure/ Human Equivalent Concentration	Uncertainty/ Modifying Factor	Reference
Inhalation exposure (ppm)					
Acute	**0.3**	Degeneration, with necrosis, olfactory epithelium in rats	$BMCL_{10}$: 57 ($BMCL_{HEC}$: 9.2)	UF: 30	Hotchkiss et al. 2010
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg 1,2 dichloroethane /kg/day)					
Acute	Insufficient data for MRL derivation				
Intermediate	**0.2**	Increase in kidney weight in rats	LOAEL: 58	UF: 300	NTP 1991
Chronic	Insufficient data for MRL derivation				

[a]See Appendix A for additional information.

$BMCL_{10}$ = benchmark concentration lower confidence limit 10%; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; UF = uncertainty factor

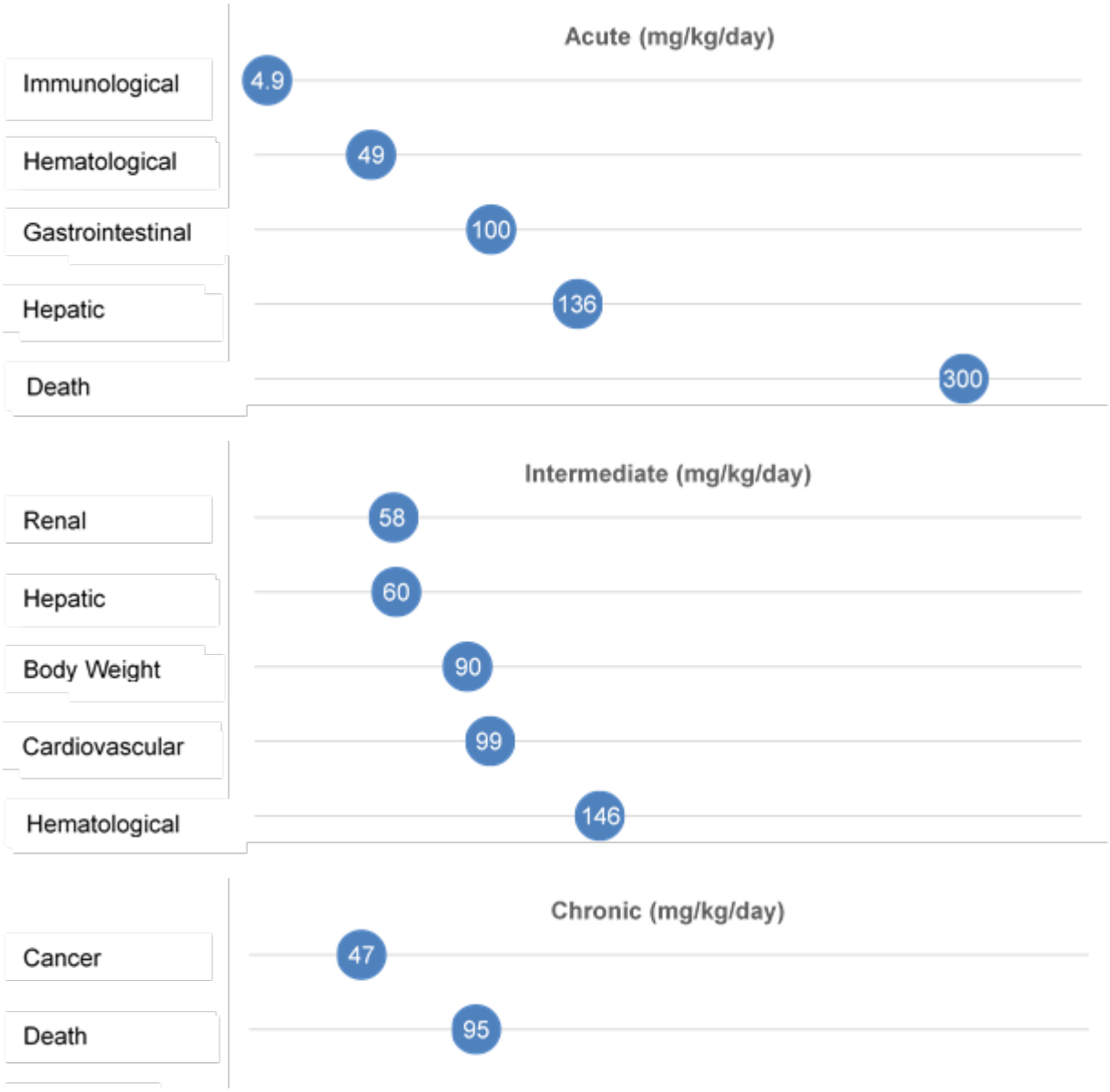
Figure 1-3. Summary of Sensitive Target of 1,2-Dichloroethane – Inhalation

The reproductive and cancer endpoints are the most sensitive targets of 1,2-dichloroethane inhalation exposure.

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

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

The immunological endpoint is the most sensitive target of 1,2-dichloroethane oral exposure. Numbers in circles are the lowest LOAELs for all health effects in animals. No reliable dose response data were available for humans.



*Lower doses related to renal and hepatic effects were observed in intermediate gavage studies but were not included in Figure 1-4 as the low effective doses could be due to possible bolus saturation of the detoxification/excretion mechanism of 1,2-dichloroethane after administration by gavage.

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.

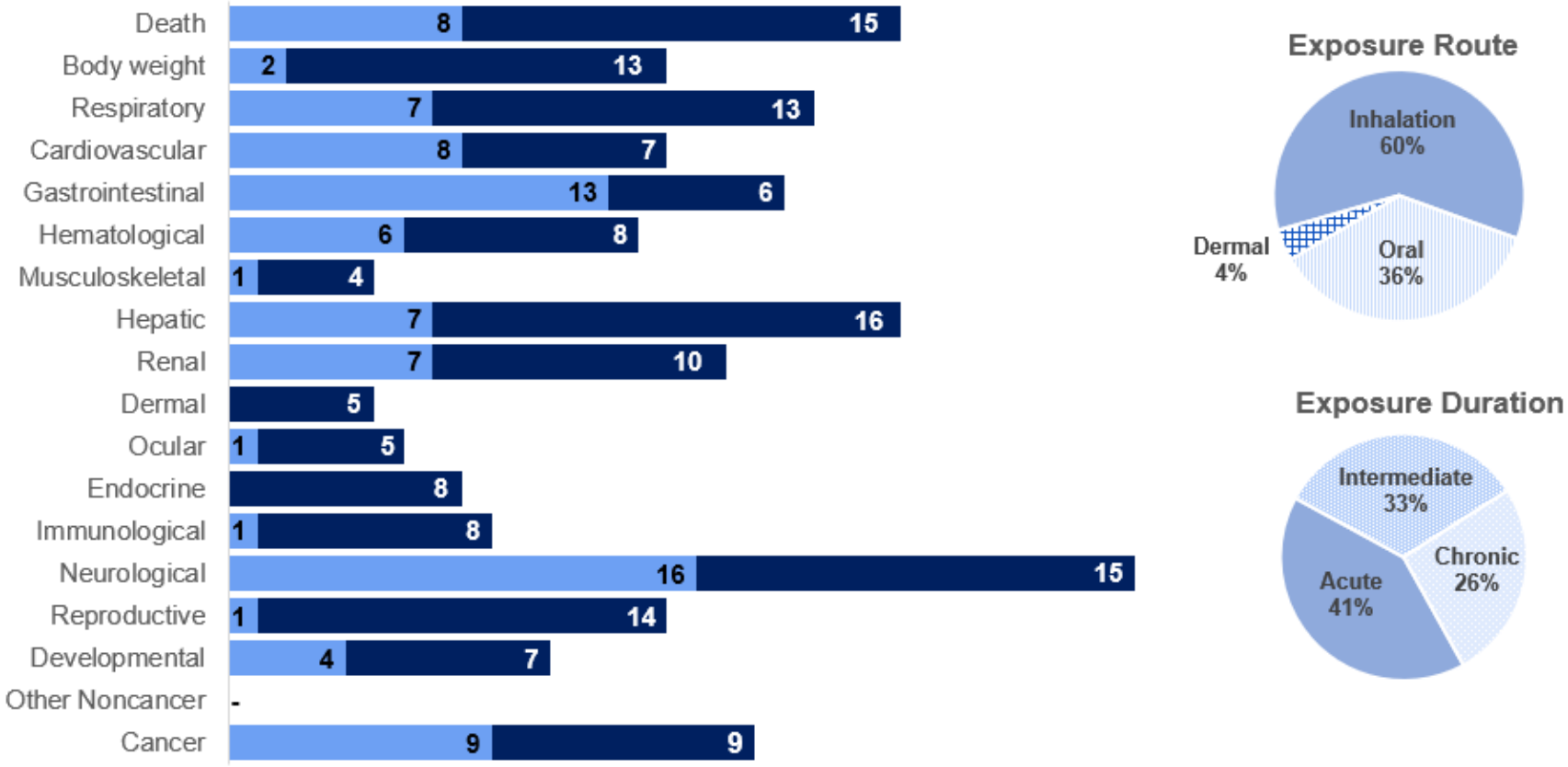
Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects 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.

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

Most studies examined death, neurological, hepatic, and respiratory effects of 1,2-dichloroethane.
Fewer studies evaluated health effects in **humans** than in **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 multple endpoints.

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
ACUTE EXPOSURE									
1	MONKEY (Rhesus) 2M	7 hrs/day, 5 days/wk, 8 to 12 days	0, 100, 400	BW OW GN HP HE CS	Hemato	100 M	400 M		increased clotting time
					Hepatic	100 M	400 M		fatty degeneration
					Renal	100 M	400 M		tubular degeneration
Spencer et al. 1951									
2	RAT 16-30F	7 hrs/day, 10 days Gd 6-15	0, 100, 300	BW OW FI WI CS MX DX LE	Death			300 F	2/3 died
Schlacter et al. 1979									
3	RAT (Sprague-Dawley) 16M	5 hrs	0, 100, 200	IX	Immuno	200			
Sherwood et al. 1987									
4	RAT (Sprague-Dawley) 16M	5 hrs/day, 5 days/wk, 12 days	0, 10, 20, 50, 100	IX	Immuno	100			
Sherwood et al. 1987									
5	RAT (Wistar) 20M,20F	7 hrs/day, 2 to 3 days	0, 400	BW OW N HP BC	Death			400	24/40 died
Spencer et al. 1951									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
6	RAT (Wistar) 54B	0.1 hrs to 8 hrs	300, 600, 800, 1000, 1500, 3000, 12000, 20000	CS BC LE BW GN HP OW	Death			1000	LC50
Spencer et al. 1951									
7	RAT (Sprague-Dawley) 8M	4 hrs	0, 618, 850, 1056, 1304	BC BI OR	Hepatic	618 M		850 M	38% increase in GDH, 100% increase in AST, 67% increase in ALT, 140% increase in SDH
Brondeau et al. 1983									
8	RAT (Sprague-Dawley) 8M	6 hrs/day, 2 or 4 days	0, 850	BC OR	Hepatic		850		increased levels AST, ALT, SDH, GDH (not otherwise described)
Brondeau et al. 1983									
9	RAT (Wistar) 8M,21F	7 hrs/day, 5 days	1500	GN HP CS	Death			1500	29/29 died
Heppel et al. 1945									
10	RAT (NS) 26 NS	7 hrs/day, 5 days/wk, 2 wks	1000	GN HP CS LE	Death			1000	20/26 died
Heppel et al. 1946									
11	RAT (Sprague-Dawley) 16-30F	7 hrs/day, 9 days Gd 6-15	0, 100, 300	BW FI CS LE	Death			300	10/16 died

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
Rao et al. 1980									
12	RAT 16-30F	7 hrs/day, 10 days Gd 6-15	0, 100, 300	BW OW FI WI CS MX DX LE	Bd wt		300 F		12% decrease in body weight loss
					Other noncancer	100 F			
Schlacter et al. 1979									
13	RAT (Fischer-344) 40M, 40F	4 hrs	0, 200, 600, 2000	NX	Neuro	200	600		Increased urination as marker for CNS depression
Hotchkiss et al. 2010									
14	RAT (Fischer-344) 25M, 25F	8 hrs, 4 hrs for 50ppm	0, 50, 100, 150	CS, BW, HP, OW	Resp	50	100[b]		Very slight unilateral, focal/multifocal, olfactory epithelium degeneration with necrosis in dorsal meatus (1/5 males, 3/5 females) ($BMCL_{10}$ = 57.42 ppm)
Hotchkiss et al. 2010									
15	RAT (Sprague-Dawley) 48M, 48F	6 hrs	0, 618, 1235, 2471	HP	Neuro	618		1235	Increased water content in cortex, brain edema
Zhang et al. 2011									
16	RAT (Sprague-Dawley) 48M 48F	0 hrs, 2 hrs, 4 hrs, or 6 hrs	1235, 2471	HP	Neuro			2471	Increased cortex water content after 2 hours
Zhang et al. 2011									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
17	RAT (Sprague-Dawley) 30M	1.5 hrs or 4 hrs	988, 2965	NX, HP	Neuro			988 M	Lesions with brain edema in the white matter in both brain hemispheres
Zhou et al. 2016									
18	MOUSE (NS) 20 NS	7 hrs	1500	GN HP CS LE	Death			1500	20/20 died
Heppel et al. 1945									
19	MOUSE (CD-1) 158F	3 hrs/day, 5 days	0, 2.3	IX	Immuno	2.3			
Sherwood et al. 1987									
20	MOUSE (Kunming albino) 50F	3.5 hrs/day, 3 days	296	BW, NX, HP	Bd wt			296 F	21% decrease in bodyweight was observed in rats acutely exposed to 1,2-dichloroethane
					Neuro			296 F	Brain edema formation; body tremor and forelimb flexure seen after 2 days, and severe after 3
Jin et al. 2018a									
21	MOUSE (albino) 20F	3.5 hrs/day, 1, 2 or 3 days	296	NX, HP	Neuro			296 F	Increased brain water contents and increased blood brain barrier permeability after 2 or 3 days exposed
Jin et al. 2018b									
22	MOUSE (albino) 32F	3.5 hrs/day, up to 10 days	0, 56, 111, 222	BI	Hepatic	56 F	111 F		~15% increased microsomal CYP2E1 protein activity and ~100% increased CYP2E1 protein expression intensity
Sun et al. 2016									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
23	MOUSE (albino) 48F	3.5 hrs/day, 10 days	0, 222	BI	Hepatic		222 F		29% increased serum ALT activities; 34% increased malondialdehyde levels in liver; 18% decreased SoD activities in liver; 29% decreased nonprotein sulfhydryl levels in liver
Sun et al. 2016									
24	MOUSE (albino) 40F	3.5 hrs/day, 3 days	0, 272, 296, 321	HP	Death			296 F	
					Neuro	272 F		296 F	Water content in cerebral tissues; morphological characteristics of brain edema
Wang et al. 2014									
25	MOUSE (albino) 80F	3.5 hrs/day, 1 day, 2 days, and 3 days	296	BI	Immuno		296 F		Increased levels of aquaporin 9 and matrix metalloproteinase 9 in the brain after 2 days; increased levels of matrix metalloproteinase 2 in the brain after 3 days
Wang et al. 2014									
26	MOUSE (albino) 100F	3.5 hrs/day, 1, 2, or 3 days	296	BI	Neuro		296 F		Decreased Na+-K+-ATPase and ATP content after 3 days exposure; increased lactic acid content after 3 days exposure; decreased Ca2+-ATPase activity, ZO-1, and occludin after 2 days of exposure; increased intracellular free Ca2+ concentrations after 2 days of exposure
Wang et al. 2018									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
27	MOUSE (Swiss-Webster) 280M	6 hrs/day, 1 wk	0, 25, 86, 173	RX	Repro	86 M		173 M	Decreased sperm concentration, motility, progressive motility. Increased sperm body abnormalities, and total abnormalities.
Zhang et al. 2017									
28	MOUSE (albino) 32F	3.5 hrs/day, 10 days	0, 56, 111, 222	BI, NX	Neuro		56 F		33% increase in glutamate in the brain as a marker for disturbed neurotransmitters; 34% increase in inducible nitric oxide synthase activity in brain
Wang et al. 2013									
29	GN PIG 12 NS	7 hrs	1500	GN HP CS LE	Death			1500	6/12 died
Heppel et al. 1945									
30	GN PIG 2M	7 hrs/day, 5 days/wk, 1 to 14 days	0, 400	BW OW GN HP BC	Hepatic		400 M		slight parenchymal degradation
					Renal		400 M		increased kidney weight, swelling of tubular epithelium
Spencer et al. 1951									
31	GN PIG 9M	7 hrs/day, 4 days	1500	GN HP CS LE	Death			1500	9/9 died
Heppel et al. 1945									
32	GN PIG 16 NS	7 hrs/day, 4 days	1000	GN HP CS LE	Death			1000	16/16 died
Heppel et al. 1946									
33	DOG 3M	7 hrs/day, 6 days	1500		Death			1500	2/3 died

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
Heppel et al. 1945									
34	RABBIT 4F,1M	7 hrs/day, 5 days	1500	CS LE	Death			1500	4/5 died
Heppel et al. 1945									
35	RABBIT 6 NS	7 hrs	3000	GN HP CS	Death			3000	12/16 died
Heppel et al. 1945									
INTERMEDIATE EXPOSURE									
36	CAT 6 NS	7 hrs/day, 5 days/wk, 11 wks	1000	GN HP CS LE	Death			1000	2/6 died
Heppel et al. 1946									
37	MONKEY 2M	7 hrs/day, 5 days/wk, 25 wk	200	GN HP CS	Resp	200			
					Cardio		200		fatty degeneration of myocardium
					Hepatic		200		fatty degeneration in liver
					Renal	200			
					Endocr		200		adrenal calcification
Heppel et al. 1946									
38	MONKEY 2NS	7 hrs/day, 5 days/wk, 9 wks	1000	GN HP CS	Death			1000	2/2 died
Heppel et al. 1946									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
39	RAT (Wistar) 15M,15F	7 hrs/day, 5 days/wk, 198 to 212 days	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									
40	RAT 15M,15F	7 hrs/day, 14 to 56 days	0, 400	BW OW GN HP BC CS	Death			400	30/30 died
Spencer et al. 1951									
41	RAT 15M,1F	7 hrs/day, 5 days/wk, 14 wks	0, 400	GN HP CS	Death			400	9/16 died
Heppel et al. 1946									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
42	RAT (Wistar) 23M,16F	7 hrs/day, 5 days/wk, 15 wks	0, 100	GN HP CS	Resp	100			
					Cardio	100			
					Hepatic	100			
					Renal	100			
					Endocr	100			
Heppel et al. 1946									
43	RAT (Sprague-Dawley) 20M,20F	6 hrs/day, 7 days/wk, 1 gen	0, 25, 75, 150	BW OW FI GN HP	Repro	150			
Rao et al. 1980									
44	MOUSE 19NS	7 hrs/day, 5 days/wk, 4 wks	0, 100	GN HP CS	Resp	100			
					Cardio	100			
					Hepatic	100			
					Renal	100			
					Endocr	100			
Heppel et al. 1946									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
45	MOUSE (Swiss-Webster) 30M	6 hrs/day, 28 days	0, 86, 173	BI, BC, BW, HP, OW	Bd wt	86 M	173 M		25% decrease in body weight gain after 28 days
					Hemato		86 M		20% decrease in blood glucose, 296% increase in blood triglycerides, and 171% increase in blood free fatty acids
					Hepatic		86 M		~10% increase in liver/body weight ratio; ~20% increase in serum AST; ~40% increase in glycogen content in liver; ~50% increase in free fatty acid content in liver
Wang et al. 2017									
46	MOUSE (Swiss-Webster) 280M	6 hrs/day, 4 wks	0, 25, 86, 173	BW, RX	Bd wt	86 M	173 M		~15% decrease in body weight
					Repro			25 M	Total sperm abnormalities
Zhang et al. 2017									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
47	GN PIG 8M,8F	7 hrs/day, 5 days/wk, 170 to 246 days	0, 100, 200	BW OW GN HP BC CS	Bd wt	200			
					Resp	200			
					Cardio	200			
					Hemato	200			
					Hepatic		100		increased liver weight, fatty degeneration
					Renal	200			
					Endocr	200			
Spencer et al. 1951									
48	GN PIG 8M,8F	7 hrs/day, 5 days/wk, 14 to 32 days	0, 400	BW OW GN HP BC	Death			400	16/16 died
Spencer et al. 1951									
49	GN PIG 12M,2F	7 hrs/day, 5 days/wk, 25 wks	0, 200	GN HP CS	Death			200	5/14 died
Heppel et al. 1946									
50	GN PIG 10M,2F	7 hrs/day, 5 days/wk, 14 wks	0, 400	GN HP CS	Death			400	7/12 died
Heppel et al. 1946									
51	DOG 6F	7 hrs/day, 5 days/wk, 9 wks	1000	GN HP CS BC UR LE	Death			1000	2/6 died
Heppel et al. 1946									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
52	DOG 6F	7 hrs/day, 5 days/wk, 8 mos	0, 400	GN HP CS HE BC UR	Resp	400			
					Cardio	400			
					Hemato	400			
					Hepatic		400		fatty degeneration
					Renal		400		fatty changes
					Endocr	400			
Heppel et al. 1946									
53	DOG 6F	7 hrs/day, 5 days/wk, 8 mos	0, 400	CS	Neuro	400			
Heppel et al. 1946									
54	RABBIT 2M,3F	7 hrs/day, 5 days/wk, 20 wks	0, 400	GN HP CS	Death			400	5/5 died
Heppel et al. 1946									
55	RABBIT 2M,1F	7 hrs/day, 5 days/wk, 232 to 248 days	0, 100, 400	BW OW GN HP CS BC	Bd wt	400			
					Resp	400			
					Cardio	400			
					Hemato	400			
					Hepatic	400			
					Renal	400			
					Endocr	400			
Spencer et al. 1951									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
56	RABBIT 6NS	7 hrs/day, 5 days/wk, 13 wks	1000	GN HP CS	Death			1000	5/6 died
Heppel et al. 1946									
57	RABBIT 5M	7 hrs/day, 5 days/wk, 25 wks	0, 200	GN HP CS HE	Resp	200			
					Cardio	200			
					Hemato	200			
					Hepatic	200			
					Renal	200			
					Endocr	200			
Heppel et al. 1946									
CHRONIC EXPOSURE									
58	RAT (Sprague-Dawley) 50M,50F	7 hrs/day, 5 days/wk, 2 yrs	0, 50	BW OW FI WI GN HP CS	Immuno	50			
Cheever et al. 1990									
59	RAT (Sprague-Dawley) 50M,50F	7 hrs/day, 5 days/wk, 2 yrs	0, 50	BW OW FI WI GN HP CS	Neuro	50			
Cheever et al. 1990									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
60	RAT (Sprague-Dawley) 50M,50F	7 hrs/day, 5 days/wk, 2 yrs	0, 50	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			
Cheever et al. 1990									
61	RAT (Sprague-Dawley) 50M,50F	7 hrs/day, 5 days/wk, 2 yrs	0, 50	BW OW FI WI GN HP CS	Renal	50			
Cheever et al. 1990									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
62	RAT (Fischer-344) 200M, 200F	6 hrs/day, 5 days/wk, 104 wks. 6 weeks of age	0, 10, 40, 160	BC, BW, CS, FI, HE, HP, LE, OW, UR	Bd wt	160			
					Cancer	40		160	CEL: Increase in combined total of adenoma, fibroadenoma, and adenocarcinoma Increase in subcutis fibroma; increase in adenoma of the mammary glands; increase in fibroadenoma of the mammary glands; increase in combined adenoma and fibroadenoma total in mammary glands
Nagano et al. 2006									
63	MOUSE (B6D2F1) 200M, 200F	6 hrs/day, 5 days/wk, 104 wks. 6 weeks of age	0, 10, 30, 90	BC, BW, CS, FI, HE, HP, LE, OW, UR	Bd wt	90			
					Cancer	10 M		30 M	CEL: Increase in hemangiosarcoma of the liver
Nagano et al. 2006									

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

[b]Used to derive an acute inhalation Minimal Risk Level (MRL) of 0.3 ppm 1,2-dichloroethane calculated using benchmark dose analysis. The BMCL10 of 57.42 ppm was multiplied by the RGDR of 0.16 to obtain the $BMCL_{HEC}$ of 9.2 ppm, which was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment, and 10 for human variability). See Appendix A for details.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BC = blood chemistry; Bd wt or BW = body weight; BUN = blood urea nitrogen; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; (F) = feed; F = female(s); FI = food intake; G = gavage; Gastro = gastrointestinal; GDH = glutamate dehydrogenase; GGT = gamma-glutamyl transferase; GN = gross necropsy; (GO) = gavage in oil vehicle; HE = hematology; Hemato = hematological; HP = histopathological; Immuno = immunological; LOAEL = lowest-

observed-adverse-effect level; LD50 = lethal dose, 50% kill; M = male(s); Musc/skel = muscular/skeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OW = organ weight; Repro = reproductive; Resp = respiratory; RX = reproductive toxicity; SDH = sorbitol dehydrogenase: UR = urinalysis; WI = water intake

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

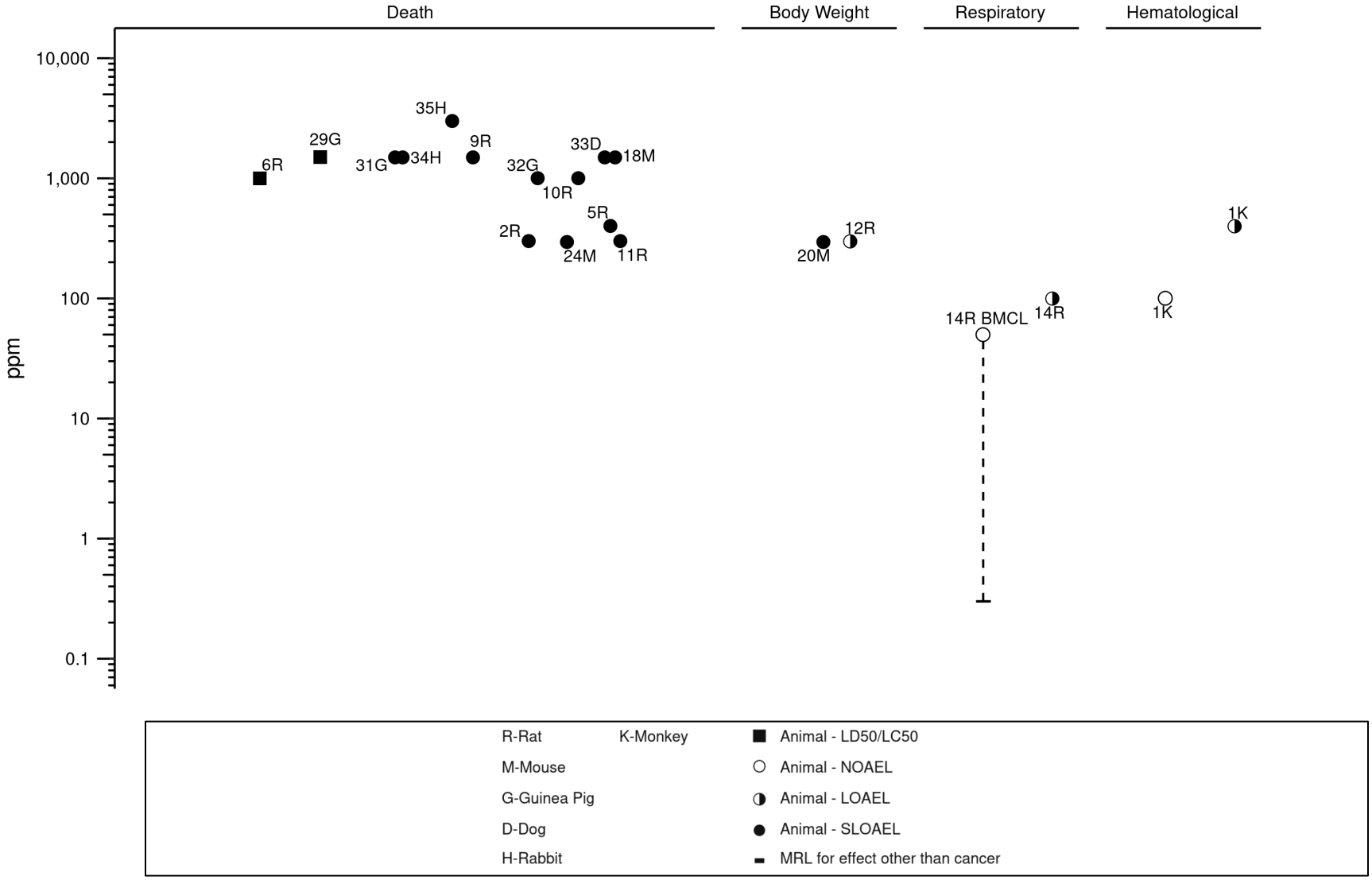


Figure 2-2. Levels of Significant Exposure to 1,2-Dichloroethane – Inhalation
Acute (≤14 days)

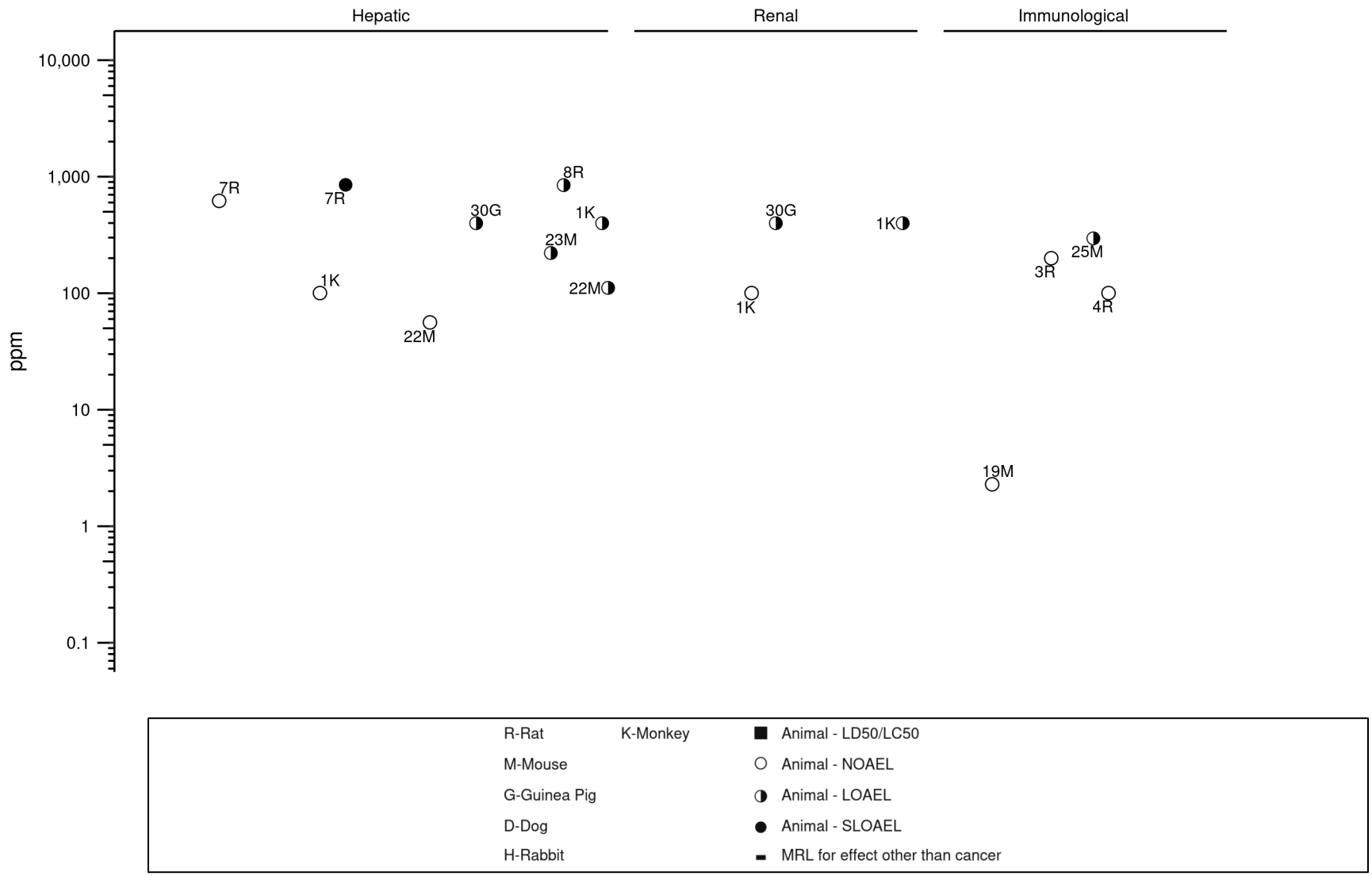


Figure 2-2. Levels of Significant Exposure to 1,2-Dichloroethane – Inhalation
Acute (≤14 days)

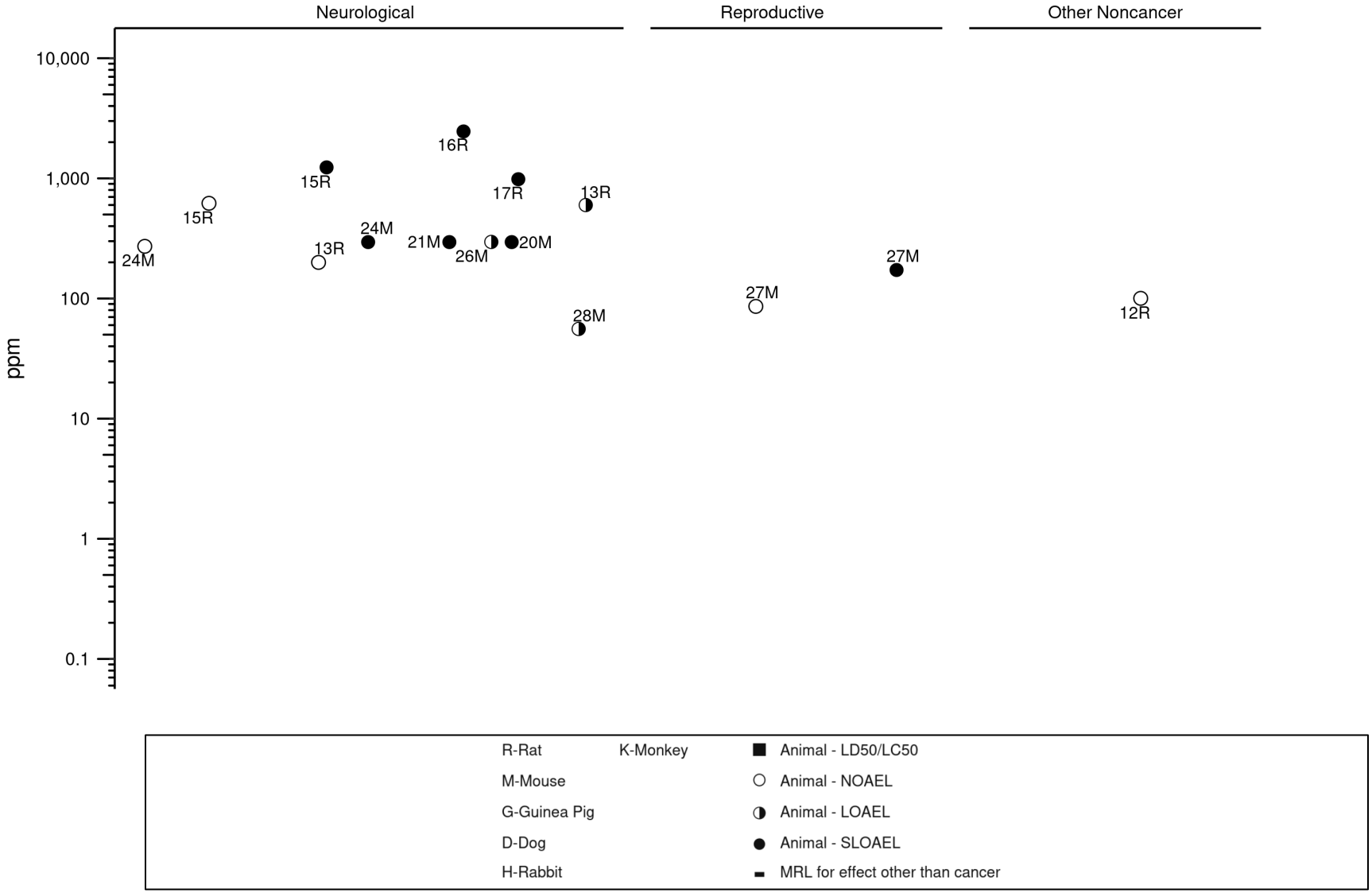


Figure 2-2. Levels of Significant Exposure to 1,2-Dichloroethane – Inhalation
Intermediate (15-365 days)

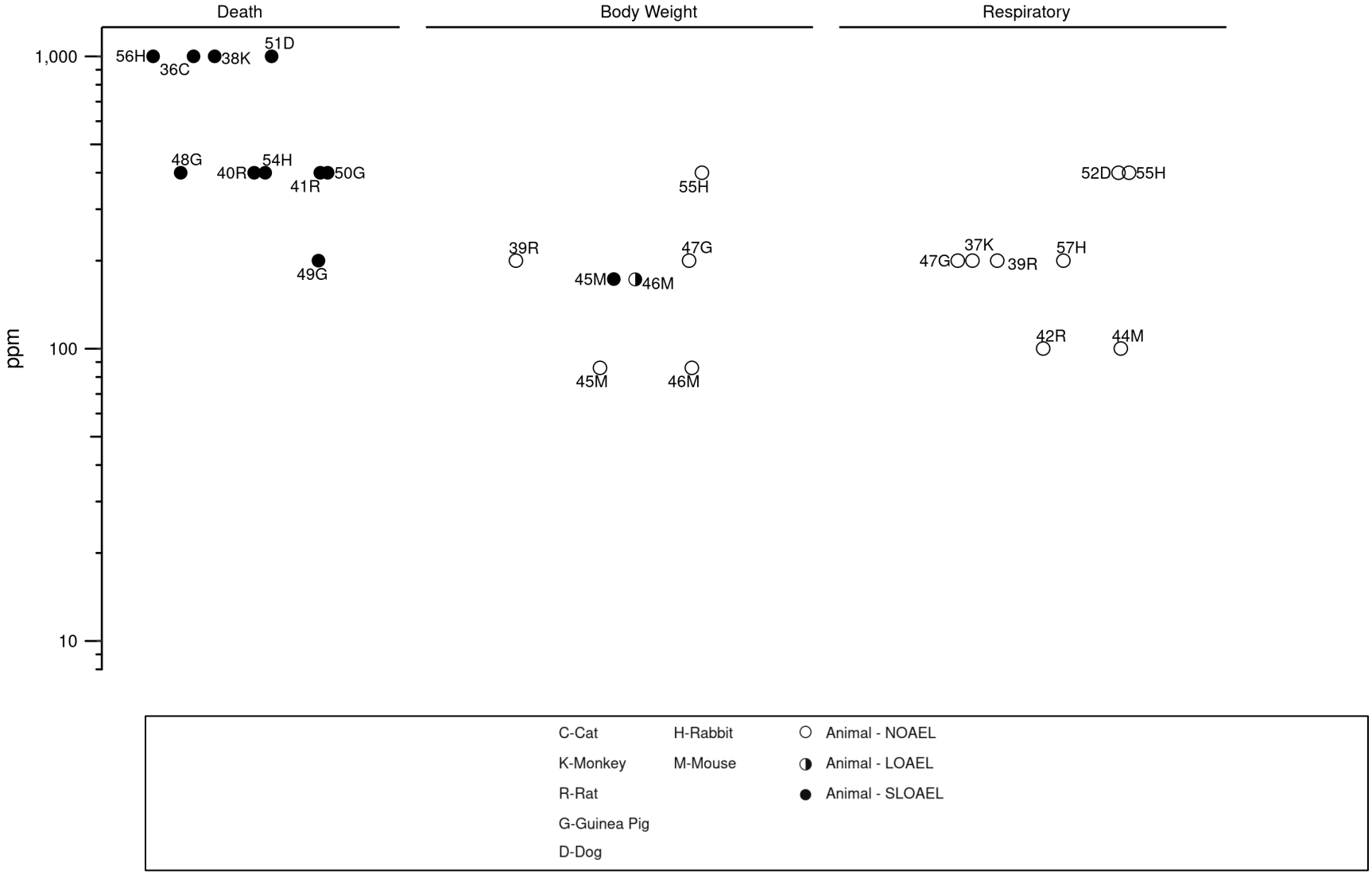


Figure 2-2. Levels of Significant Exposure to 1,2-Dichloroethane – Inhalation
Intermediate (15-365 days)

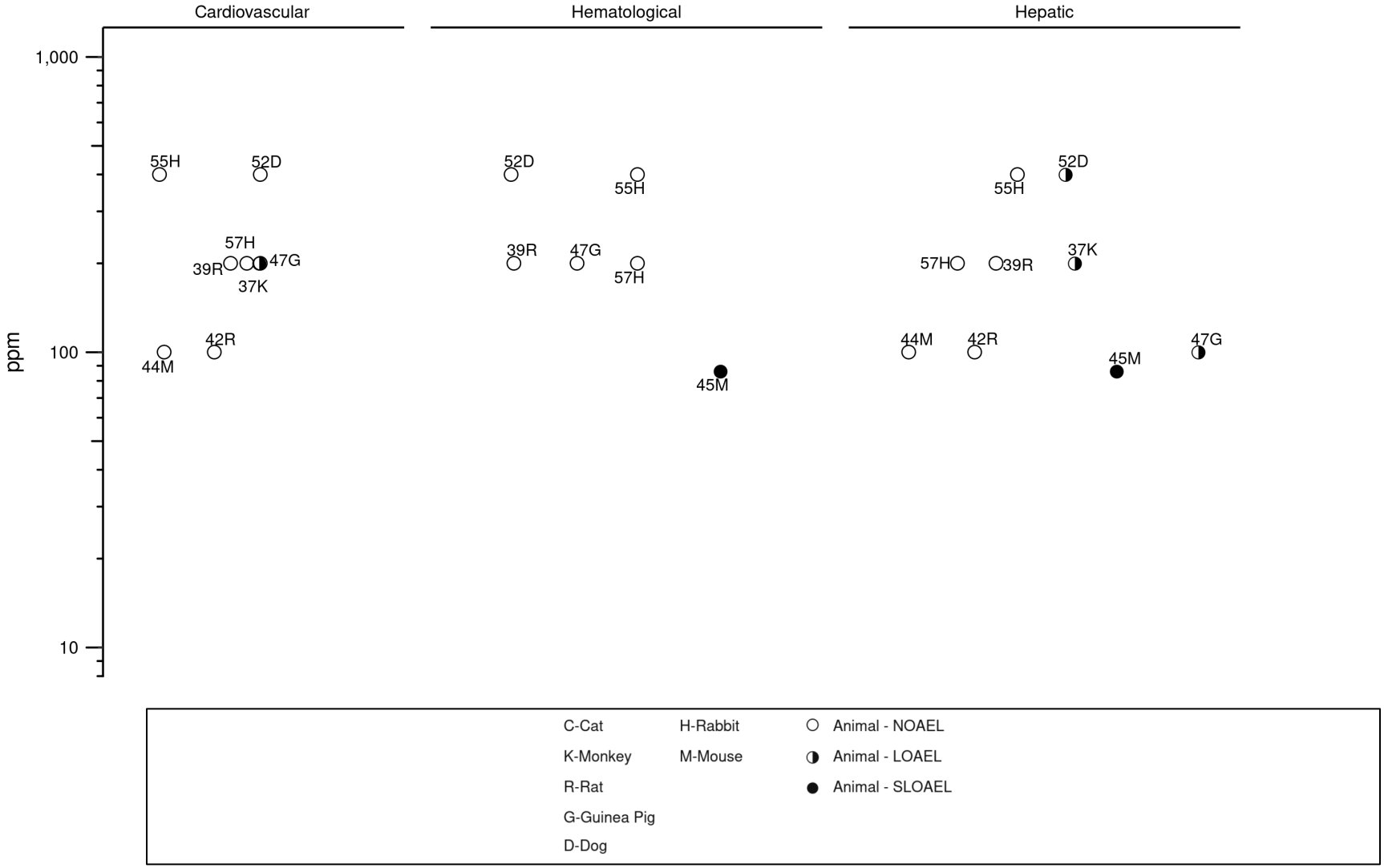


Figure 2-2. Levels of Significant Exposure to 1,2-Dichloroethane – Inhalation
Intermediate (15-365 days)

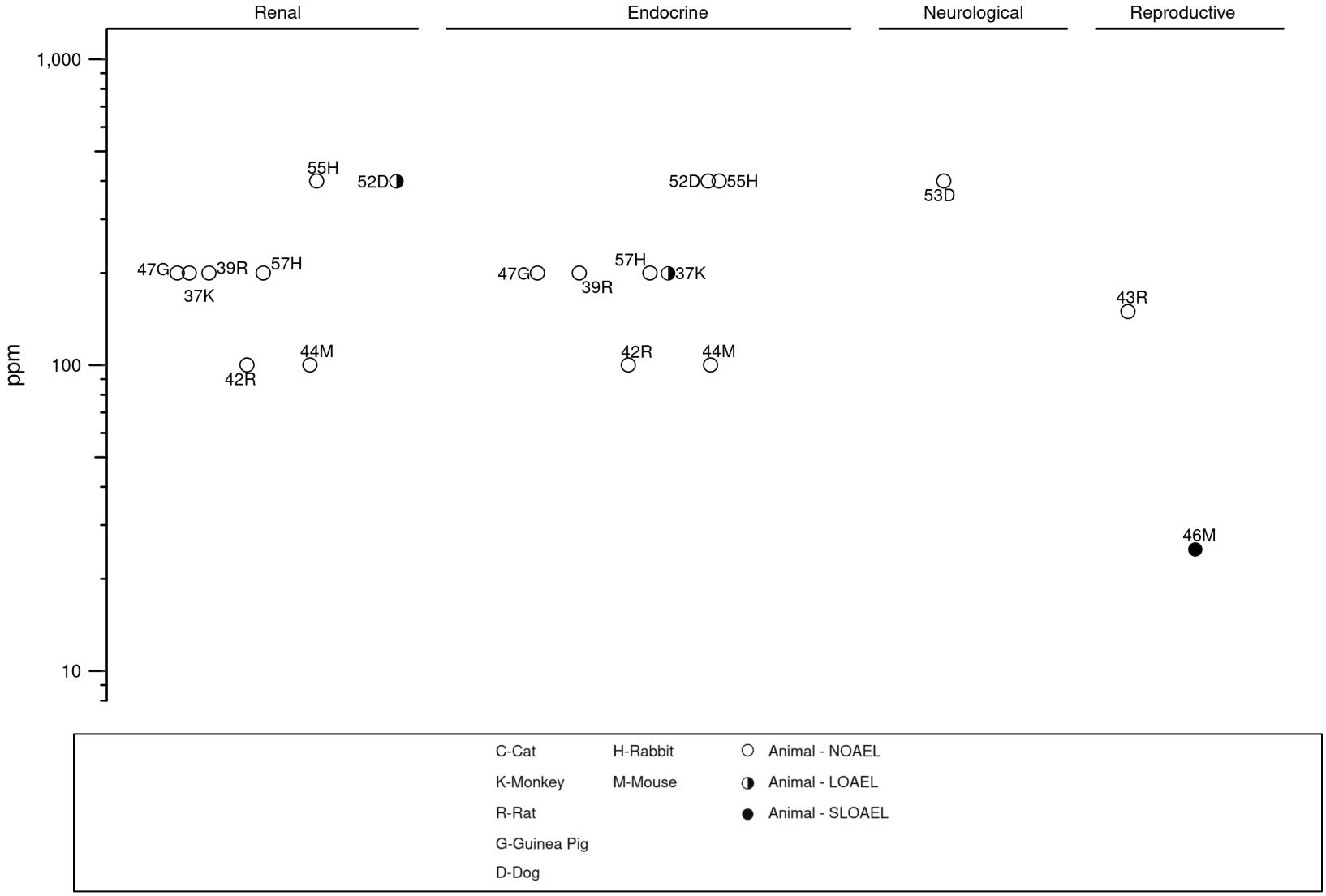


Figure 2-2. Levels of Significant Exposure to 1,2-Dichloroethane – Inhalation
Chronic (>365 days)

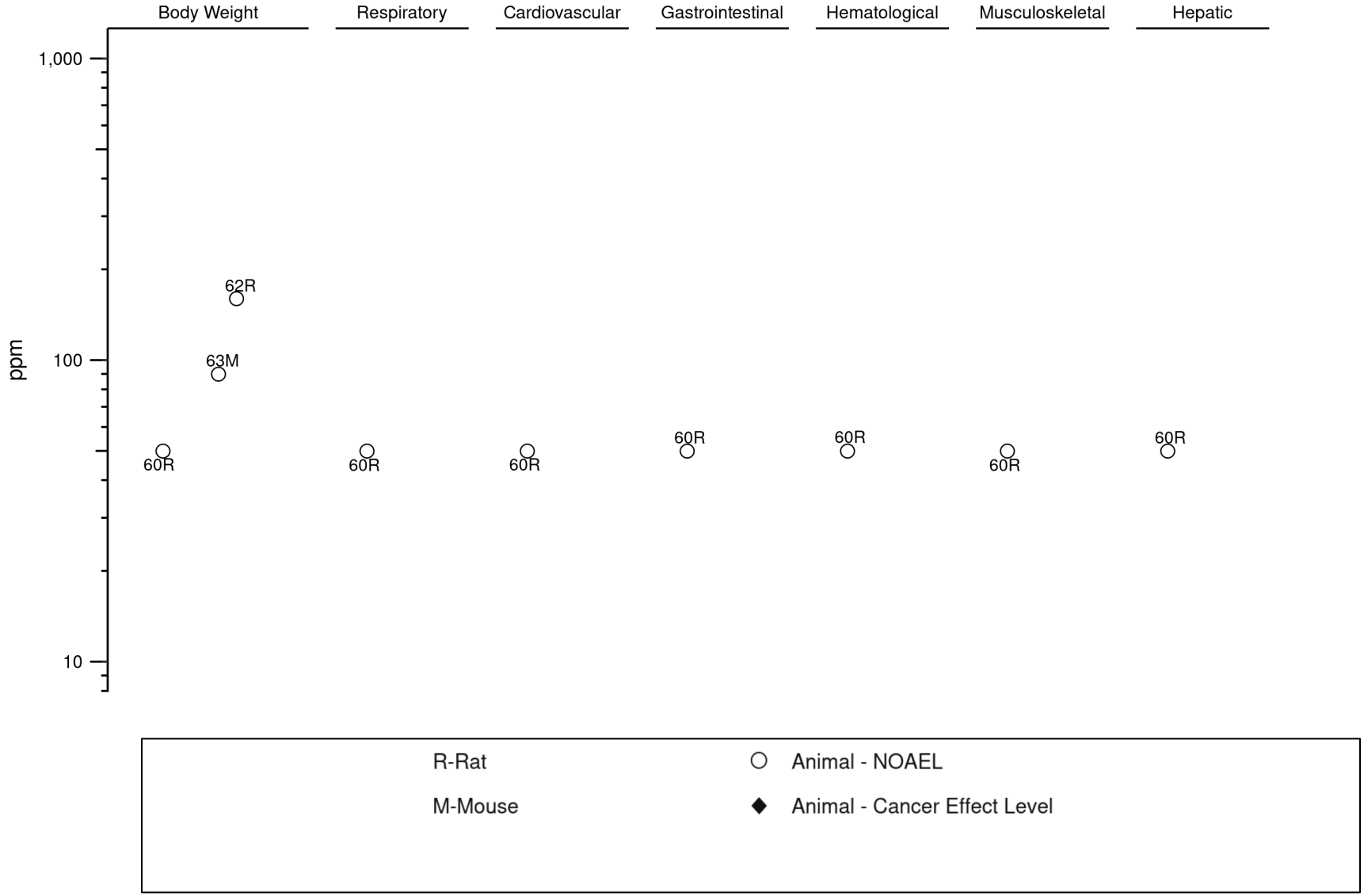


Figure 2-2. Levels of Significant Exposure to 1,2-Dichloroethane – Inhalation
Chronic (>365 days)

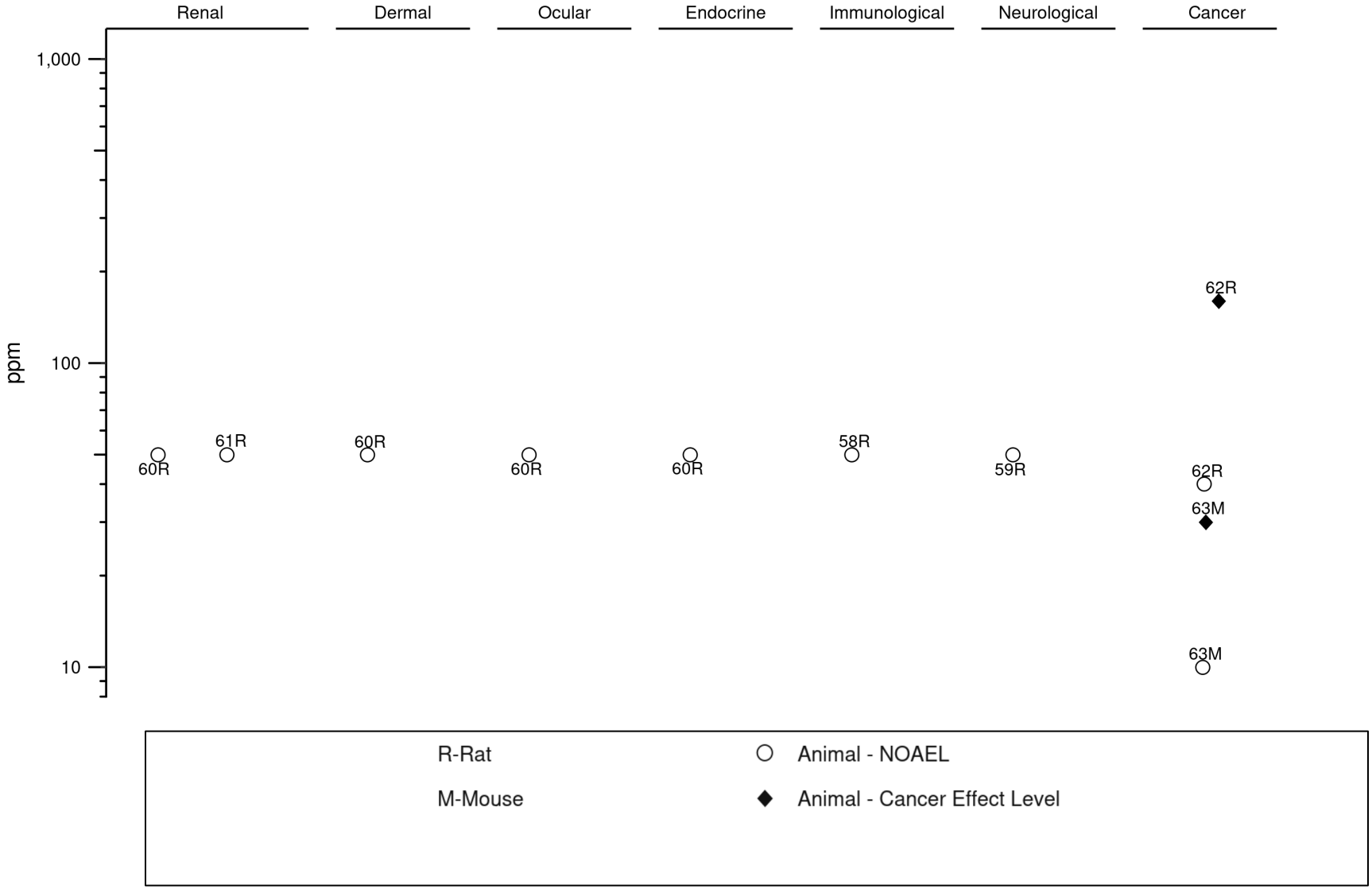


Table 2-2. Levels of Significant Exposure to 1,2-Dichloroethane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
ACUTE EXPOSURE									
1	HUMAN 3M	Once	214-286, 714	GN HP CS LE HE	Death			714 M	death
Schonborn et al. 1970									
2	HUMAN 3M	Once	214-286, 714	GN HP HE LE	Cardio		714		decreased coagulation factors circulatory bradycardia
					Gastro		714		necrosis and hemorrhagic enteritis
					Hemato		714		decreased coagulation factors
					Hepatic		714		necrosis
					Renal		714		bleeding; hyperemia
Schonborn et al. 1970									
3	HUMAN 1M	Once	570	GN HP BC CS LE HE	Resp		570		congestion and edema
					Cardio			570	cardiac arrest
					Gastro		570		gastrointestinal hemorrhage
					Hemato			570	uncoagulable blood
					Hepatic			570	severe atrophy of liver
Martin et al. 1969									
4	RAT (albino) 80B	1 day (G)	NS		Death			680	LD50
McCollister et al. 1956									
5	RAT (Sprague-Dawley) 20F	Once (IN)	628	BI	Hepatic		628 F		Increased levels of alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase
Cottalasso et al. 2002									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
6	RAT (Wistar) 80M	Once (GO)	136	HP	Hepatic		136 M		Increased activities of lactate dehydrogenase, alkaline phosphatase, acid phosphatase, superoxide dismutase, catalase, and glutathione peroxidase. Increased content of malondialdehyde in lung homogenate.
Salovsky et al. 2002									
7	RAT (Sprague-Dawley) 50M 50F	Once/day, 10 days (GO)	0, 10, 30, 100, 300	BI BW CS DX GN HE HP IX LE NX OW	Death			300	8/10 F and 10/10 M
					Bd wt	100			
					Resp	100		300	gross pathologic changes in 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			
Daniel et al 1994									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
8	RAT (Wistar) 30M 30F	Once/day, 5 days/wk, 14 days (G)	0, 100, 300	BW CS DX GN HE HP IX LE NX OW	Death			300	6/6 died
					Bd wt	100			
					Resp	100			
					Hemato	100			
					Hepatic	100			
					Renal	100			
					Endocr	100			
van Esch et al. 1977									
9	MOUSE (CD-1) 18-30F	7 days, Gd 7-14 ad lib (W)	0, 1, 3 9, 20, 51, 67, 170, 198, 510	BW OW	Develop	510			
Kavlock et al. 1979									
10	MOUSE 10-12M	Once/day, 14 days (G)	0, 4.9, 49	BC BI OW BW	Immuno		4.9		~30% decrease in immune response
Munson et al. 1982									
11	MOUSE (CD-1) 10-12M	Once/day, 14 days (G)	0, 4.9, 49	BC BI OW BW	Resp	49			
					Hemato	4.9	49		30% decrease in leukocytes
					Hepatic	49			
					Renal	49			
Munson et al. 1982									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
12	MOUSE (CD-1) NS	1 day (G)	NS		Death			413 F	LD50
					Death			489 M	LD50
Munson et al. 1982									
INTERMEDIATE EXPOSURE									
13	RAT 6M,6F	2 x/day, 5-7 wks (F)	0, 15, 30, 80	OW BI	Hepatic	30	80		(fatty liver)
Alumot et al. 1976									
14	RAT (F344/N) 10-20M,10F	13 wks (W)	M:0, 49, 86, 147, 259, 515 F:0, 58, 102, 182, 320, 601	BW OW FI WI GN HP BC CS	Death	601			
					Bd wt	320 F	601 F		7% decrease in bodyweight gain
					Bd wt	147 M	259 M		8% decrease in bodyweight gain
					Resp	601			
					Cardio	320 F	601 F		6% increase in relative heart weight
					Cardio	147 M	259 M		5% decrease in absolute heart weight
					Gastro	601			
					Hemato	147 M	259 M		4% decrease in mean corpuscular hemoglobin after 90 days
					Musc/skel	601			
					Hepatic	86 M	147 M		15% increase in absolute liver weight; 17% increase in relative liver weight
					Renal		58 F[b]		10% increase in right kidney absolute weight

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Renal	49 M	86 M		16% increase in absolute kidney weight; 18% increase in relative kidney weight
					Dermal	601			
					Ocular	601			
					Endocr	601			
					Immuno	601			
					Neuro	601 F			
					Neuro	147 M	259 M		9% increase in relative brain weight
					Repro	147 M	259 M		10% increase in relative weight of right testis
NTP 1991									
15	RAT (Sprague-Dawley) 10-20M,10F	13 wks (W)	M:0, 60, 99, 165, 276, 518 F:0, 76, 106, 172, 311, 531	BW OW FI WI GN HP BC CS	Death	531			
					Bd wt	531 F			
					Bd wt	276 M	518 M		8% decrease in body weight gain
					Resp	531			
					Cardio	531 F			
					Cardio	60 M	99 M		12% increase in absolute heart weight
					Gastro	531			
					Hemato	276 M	531 M		4% decrease in mean corpuscular hemoglobin after 90 days
					Musc/skel	531			
					Hepatic	311 F	531 F		13% increase in relative liver weight

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Hepatic		60 M		9% increase in relative liver weight
					Renal		76 F		13% increase in absolute kidney weight; 8% increase in relative kidney weight
					Renal	60 M	99 M		7% increase in relative kidney weight
					Dermal	531			
					Ocular	531			
					Endocr	531			
					Immuno	531			
					Neuro	531 F			
					Neuro	276 M	518 M		9% increase in relative brain weight
					Repro	518 M			
NTP 1991									
16	RAT (Osborne-Mendel) 10-20M,10F	13 wks (W)	M:0, 54, 88, 146, 266, 492 F:0,82, 126, 213, 428, 727	BW OW FI WI GN HP BC CS	Death	727			
					Bd wt	727 F			
					Bd wt	266 M	492 M		11% decrease in body weight gain
					Resp	727			
					Cardio	727			
					Gastro	727			
					Hemato	88 M	146 M		5% decrease in mean corpuscular hemoglobin at 45 days
					Musc/skel	727			
					Hepatic	727 F			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Hepatic	54 M	88 M		30% increase in absolute liver weight; 16% increase in relative liver weight
					Renal		82 F		14% increase in absolute kidney weight; 12% increase in relative kidney weight
					Renal	54 M	88 M		16% increase in absolute kidney weight
					Dermal	727			
					Ocular	727			
					Endocr	727			
					Immuno	727			
					Neuro	727			
					Repro	492 M			
NTP 1991									
17	RAT (F344/N) 10-20M,10F	Once/day, 5 days/wk, 13 wks (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	9/10 died
					Death			240 M	10/10 died
					Bd wt	150			
					Resp	150 F	300 F		Dyspnea
					Resp	120 M	240 M		Dyspnea
					Cardio	37 F	75 F		10% increase in absolute heart weight
					Cardio	120 M			
					Gastro	300 F			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Gastro	120 M	240 M		forestomach hyperplasia and inflammation
					Hemato		120 M		2% decrease in blood hemoglobin after 45 days
					Musc/skel	480			
					Hepatic		18 F		9% increase in absolute liver weight; 9% increase in relative liver weight
					Hepatic	60 M	120 M		14% increase in absolute liver weight; 14% increase in relative liver weight
					Renal	37 F	75 F		12% increase in absolute right kidney weight; 10% increase in relative right kidney weight
					Renal		30 M		9% increase in absolute right kidney weight
					Dermal	480			
					Ocular	480			
					Endocr	150 F	300 F		Necrosis of thymus
					Endocr	240 M		480 M	Necrosis of thymus
					Neuro	240 F	300 F		Tremors, abnormal postures, ruffled fur
					Neuro	120 M	240 M		Tremors, abnormal postures, ruffled fur
					Repro	120 M			
NTP 1991									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
18	RAT (Sprague-Dawley) 40M 40F	Once/day, 90 days (GO)	0, 37.5, 75, 150	BI BW CS DX GN HE HP IX LE NX OW	Bd wt	75	150		17% reduced body weight gain
					Resp	150			
					Cardio	150			
					Gastro	150			
					Hemato	150			
					Musc/skel	150			
					Hepatic	150			
					Renal	37.5	75		Increased relative kidney weight
					Dermal	150			
					Ocular	150			
					Endocr	150			
					Immuno	150			
					Neuro	150			
					Repro	150			
Daniel et al 1994									
19	RAT (Wistar) 40M 40F	Once/day, 5days/wk, 90 days (GO)	0, 10, 30, 90	BW CS DX GN HE HP IX LE NX OW	Bd wt	90 F			
					Bd wt	30 M		90 M	22% decreased body weight gain
					Resp	90			
					Cardio	90			
					Gastro	90			
					Hemato	90			
					Musc/skel	90			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Hepatic	90			
					Renal	30	90		Increased relative kidney weight
					Endocr	90			
					Neuro	90			
					Repro	90			
van Esch et al. 1977									
20	MOUSE (B6C3F1) 10M,10F	13 wks (W)	M:0, 249, 448, 781, 2710, 4207 F:0, 244, 647, 1182, 2478, 4926	BW OW FI WI GN HP CS	Death			4926 F	9/10 died
					Bd wt	4926 F			
					Bd wt	2710 M	4207 M		10% decrease in body weight gain
					Resp	4926			
					Cardio	4926 F			
					Cardio	781 M	2710 M		17% increase in relative heart weight
					Gastro	4926			
					Hemato	4926			
					Musc/skel	4926			
					Hepatic	244 F	647 F		7% increase in relative liver weight
					Hepatic		249 M		11% increase in relative liver weight
					Renal		244 F		18% increase in absolute kidney weight; 18% increase in relative kidney weight

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Renal	249 M	448 M	4207 M	6% increase in absolute kidney weight; 12% increase in relative kidney weight at 448 mg/kg/day karyomegaly, mineralization, tubular dilation, protein casts at 4207 mg/kg/day
					Dermal	4926			
					Ocular	4926			
					Endocr	1182 F	2478 F		15% decrease in absolute thymus weight
					Immuno	4926			
					Neuro	4926 F			
					Neuro	2710 M	4207 M		14% increase in relative brain weight
					Repro		4207 M		6% decrease in absolute weight of right testis; 10% increase in relative weight of right testis
NTP 1991									
21	MOUSE (ICR Swiss) 10M,30F	49 wks, 2 gen ad lib (W)	0, 5, 15, 50	BW WI	Repro	50			
Lane et al. 1982									
22	MOUSE (ICR Swiss) NS	18 days ad lib (W)	0, 5, 15, 50	BW WI	Develop	50			
Lane et al. 1982									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
23	MOUSE (ICR Swiss) NS	24 wks, F/1B gen ad lib (W)	0, 5, 15, 50		Repro	50			
Lane et al. 1982									
24	MOUSE (CD-1) 16M	90 days ad lib (W)	0, 3, 24, 189	BW BC WI	Immuno	189			
Munson et al. 1982									
25	MOUSE (CD-1) 16M	90 days ad lib (W)	0, 3, 24, 189	GN BC BW	Resp	189			
					Hemato	189			
					Hepatic	189			
					Renal	189			
Munson et al. 1982									
26	MOUSE (B6C3F1) 5M,5F	Once/day, 5 days/wk, 6 wks (GO)	0, 159, 251, 398, 631, 1000	BW	Death			631 F	5/5 died
NCI 1978									
CHRONIC EXPOSURE									
27	RAT 18M,18F	2x/day, 2 yrs (F)	0, 12.5 25	BW FI CS	Hepatic	25			
					Renal	25			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
Alumot et al. 1976									
28	RAT 18M,18F	2 x/day, 2 yrs (F)	0, 12.5 25	BW BI	Repro	25			
Alumot et al. 1976									
29	RAT (Osborne-Mendel) 50M,50F	Once/day, 5 days/wk, 78 wks (GO)	0, 47, 95	BW HP CS	Death			95	42/50 died
NCI 1978									
30	RAT (Osborne-Mendel) 50M,50F	Once/day, 5 days/wk, 78 wks (GO)	0, 47, 95	BW GN HP CS	Cancer			47	CEL: hemangiosarcoma of the spleen, liver, adrenal gland, pancreas, and other organs
NCI 1978									
31	MOUSE (B6C3F1) 50M,50F	Once/day, 5 days/wk, 78 wk s (GO)	M:0, 97 195;F:0 149, 299	BW HP CS	Death			299	36/50 died
NCI 1978									
32	MOUSE (B6C3F1) 50M,50F	Once/day, 5 days/wk, 78 wks (GO)	M:0, 97 195 F:0 149, 299	BW GN HP CS	Cancer			149	CEL: pulmonary adenoma, mammary gland adenocarcinoma, and combined endometrial polyps and sarcoma
NCI 1978									

[a]The number corresponds to entries in Figure 2-3.

[b]Used to derive an intermediate oral Minimal Risk Level (MRL) of 0.2 mg/kg/day; the LOAEL dose of 58 mg/kg/day was divided by an uncertainty factor of 300 (10 for extrapolation from animals to humans, 10 for human variability, and 3 for use of a LOAEL). See Appendix A for details.

BC = blood chemistry; Bd wt or BW = body weight; BUN = blood urea nitrogen; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; (F) = feed; F = female(s); FI = food intake; G = gavage; Gastro = gastrointestinal; GGT = gamma-glutamyl transferase; GN = gross necropsy; (GO) = gavage in oil vehicle; HE = hematology; Hemato = hematological; HP = histopathological; Immuno = immunological; LOAEL = lowest-observed-adverse-effect level; LD50 = lethal dose, 50% kill; M = male(s); Musc/skel = muscular/skeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OW = organ weight; Repro = reproductive; Resp = respiratory; RX = reproductive toxicity; UR = urinalysis; WI = water intake

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

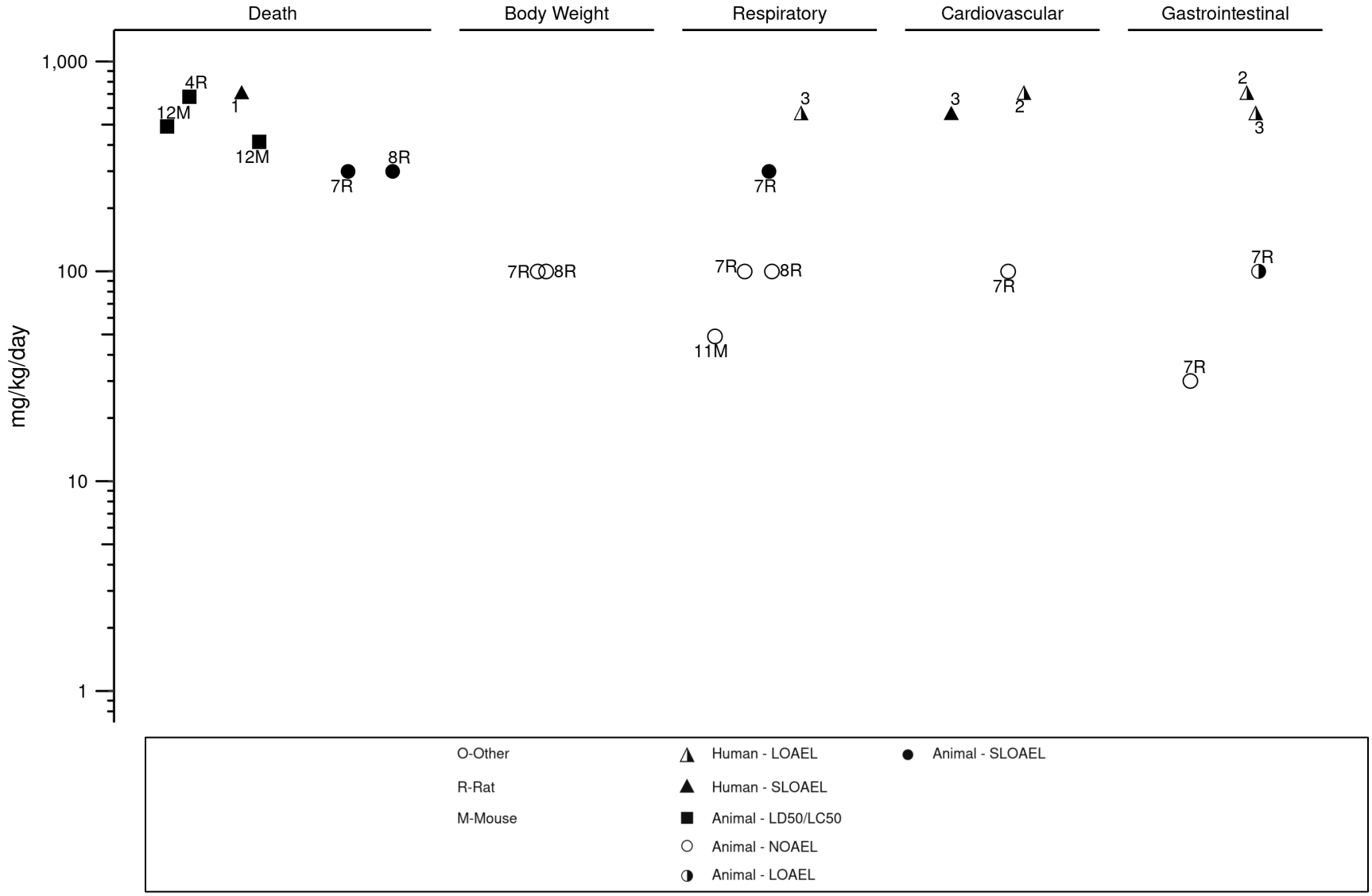


Figure 2-3. Levels of Significant Exposure to 1,2-Dichloroethane – Oral
Acute (≤14 days)

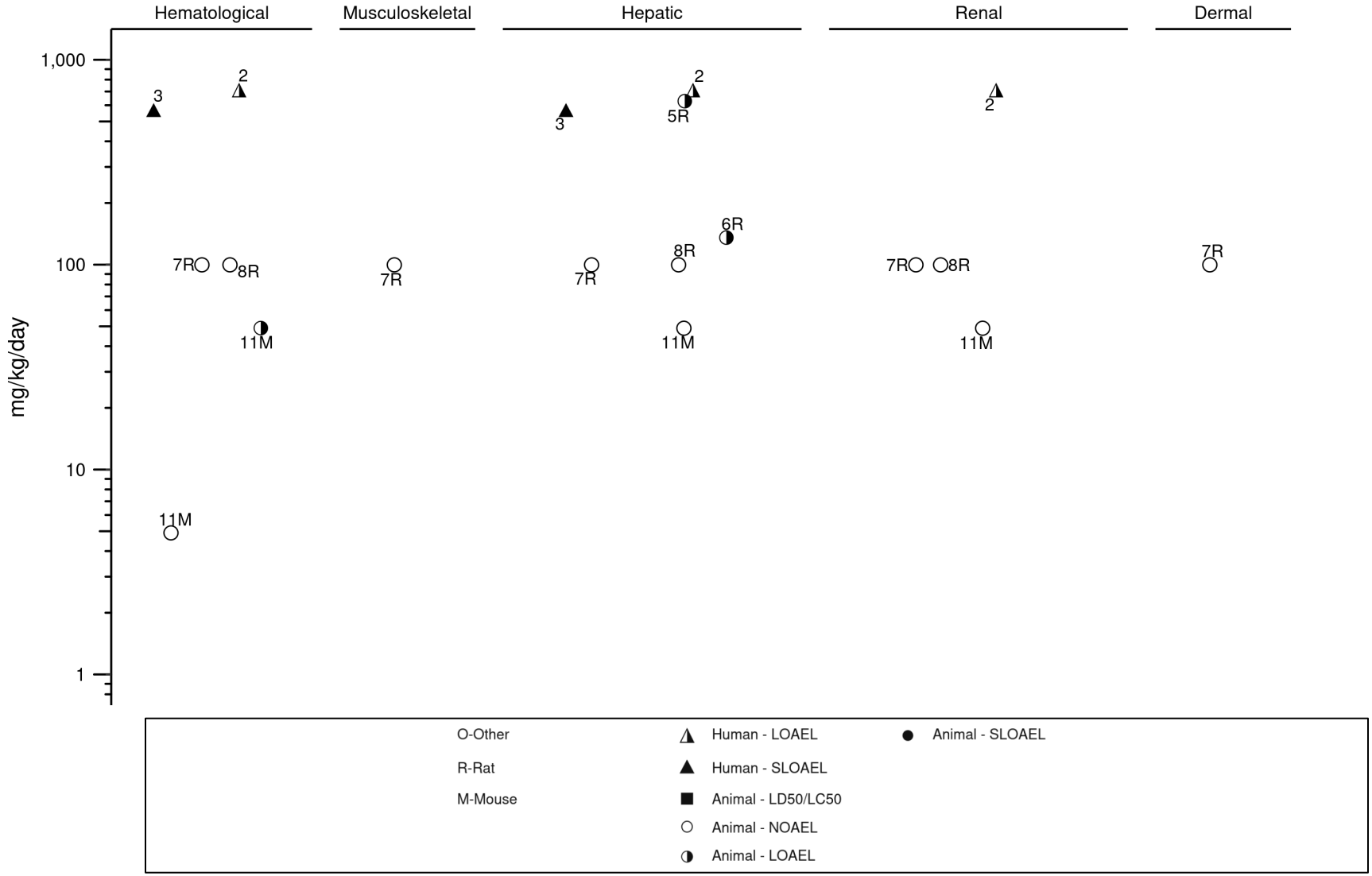


Figure 2-3. Levels of Significant Exposure to 1,2-Dichloroethane – Oral
Acute (≤14 days)

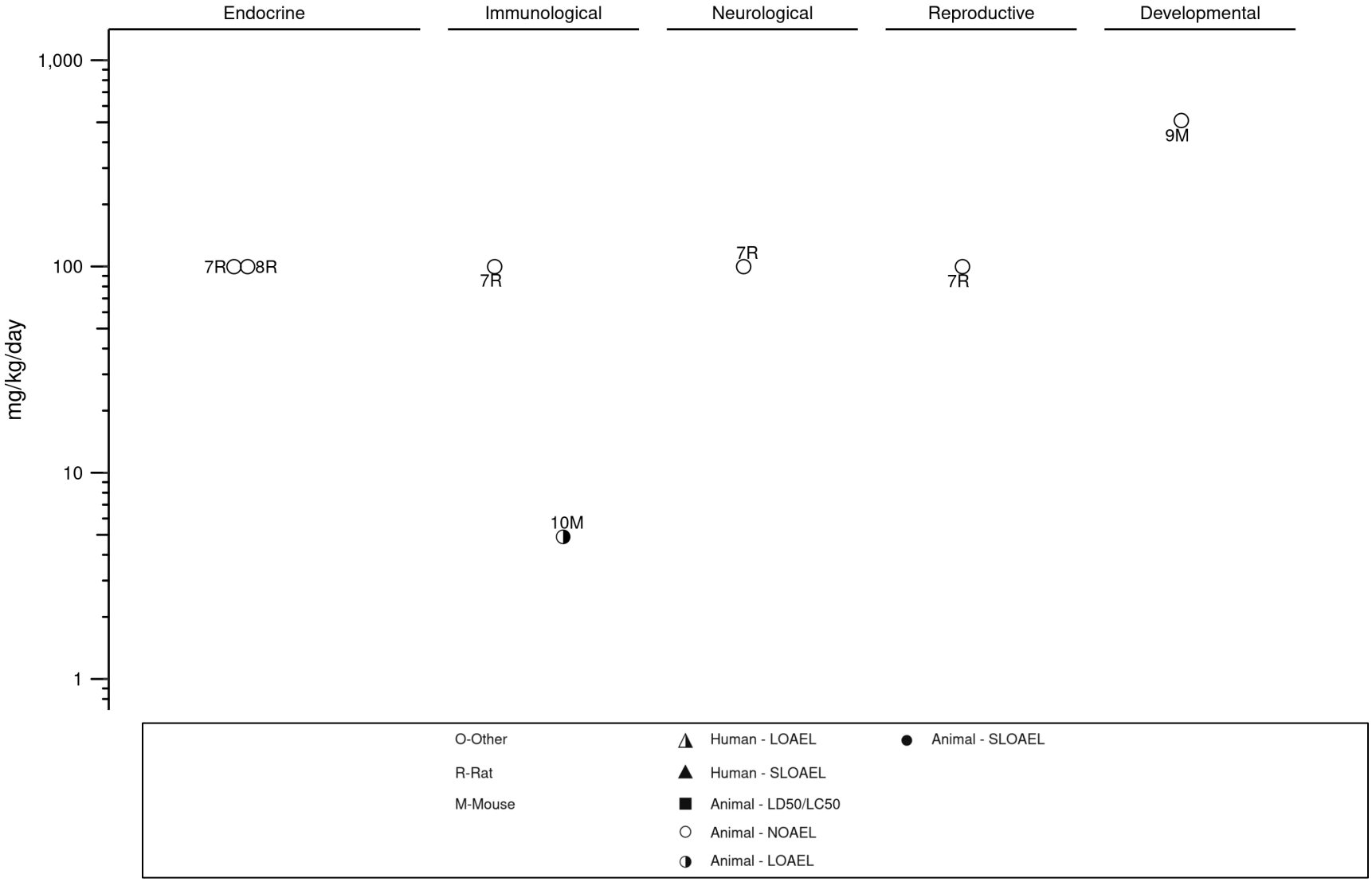


Figure 2-3. Levels of Significant Exposure to 1,2-Dichloroethane – Oral
Intermediate (15-364 days)

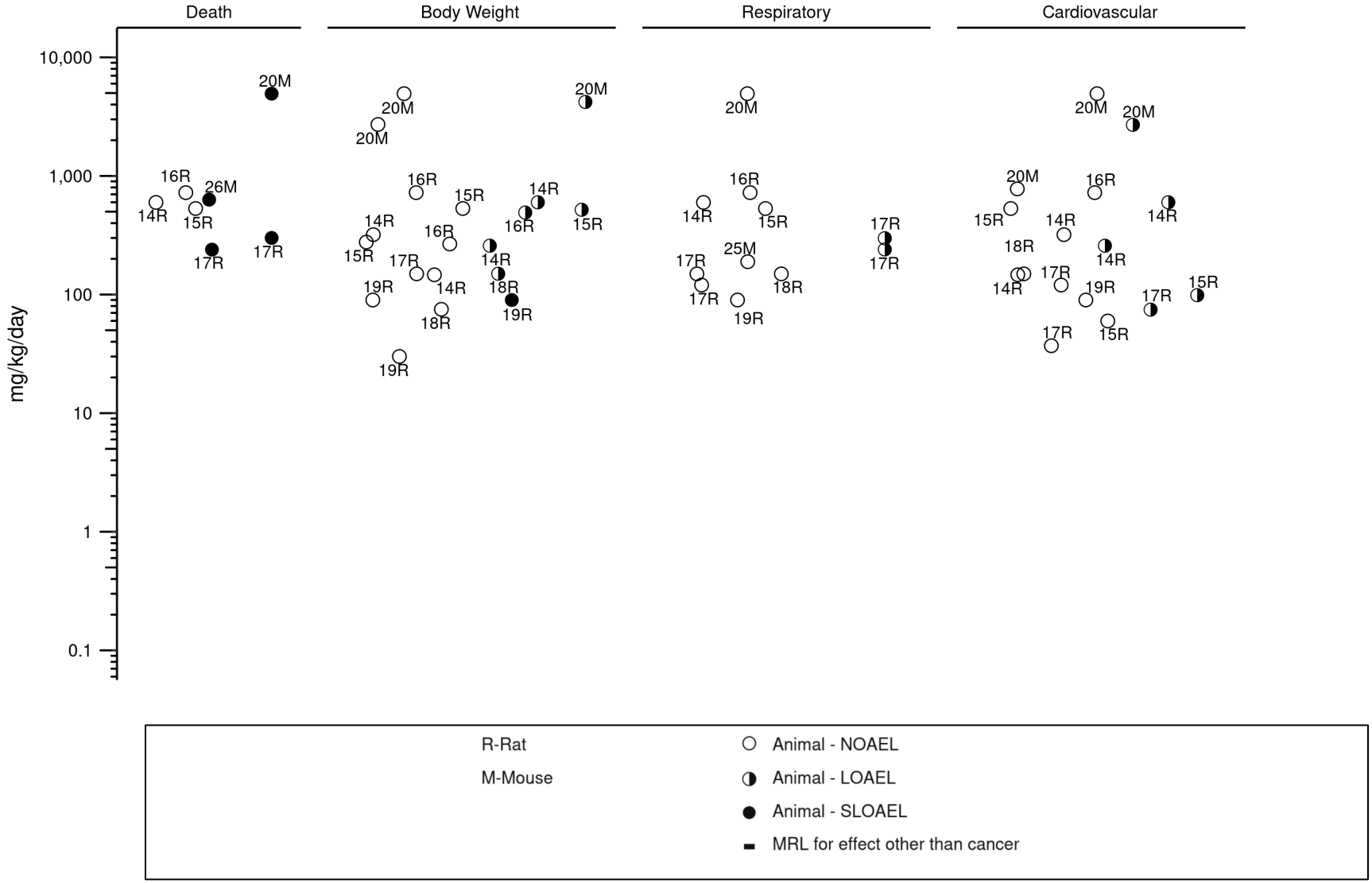


Figure 2-3. Levels of Significant Exposure to 1,2-Dichloroethane – Oral
Intermediate (15-364 days)

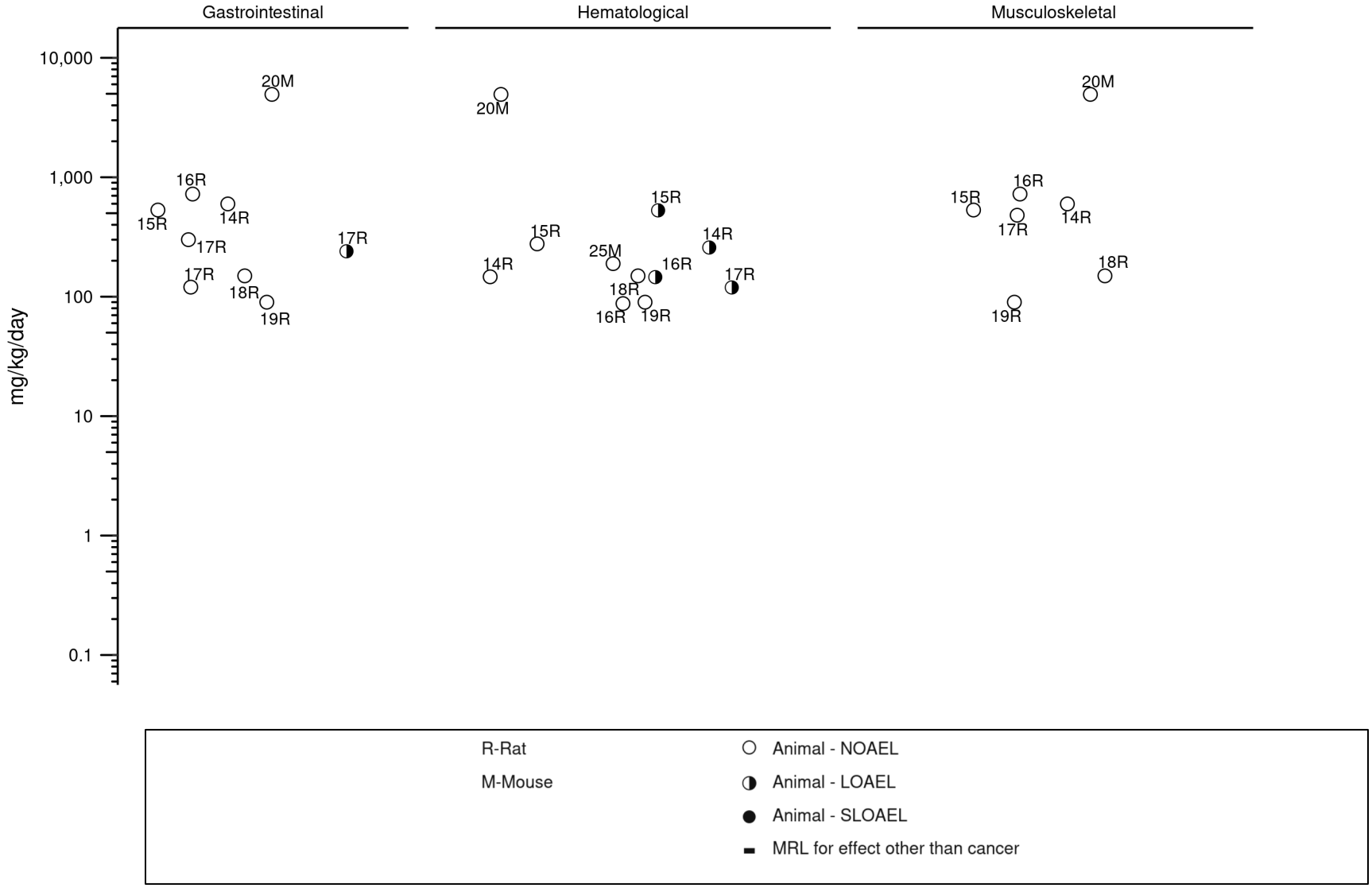


Figure 2-3. Levels of Significant Exposure to 1,2-Dichloroethane – Oral
Intermediate (15-364 days)

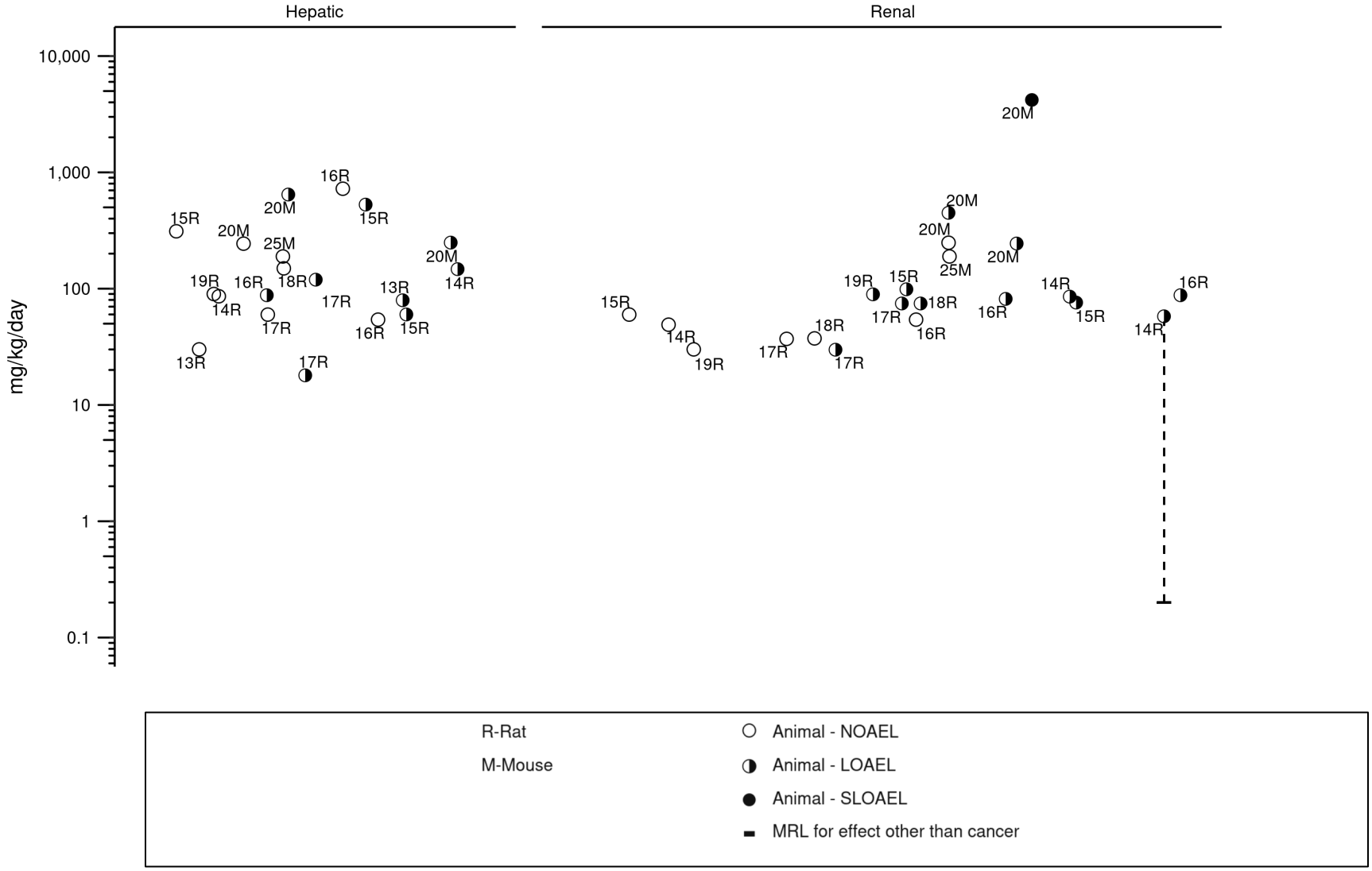


Figure 2-3. Levels of Significant Exposure to 1,2-Dichloroethane – Oral
Intermediate (15-364 days)

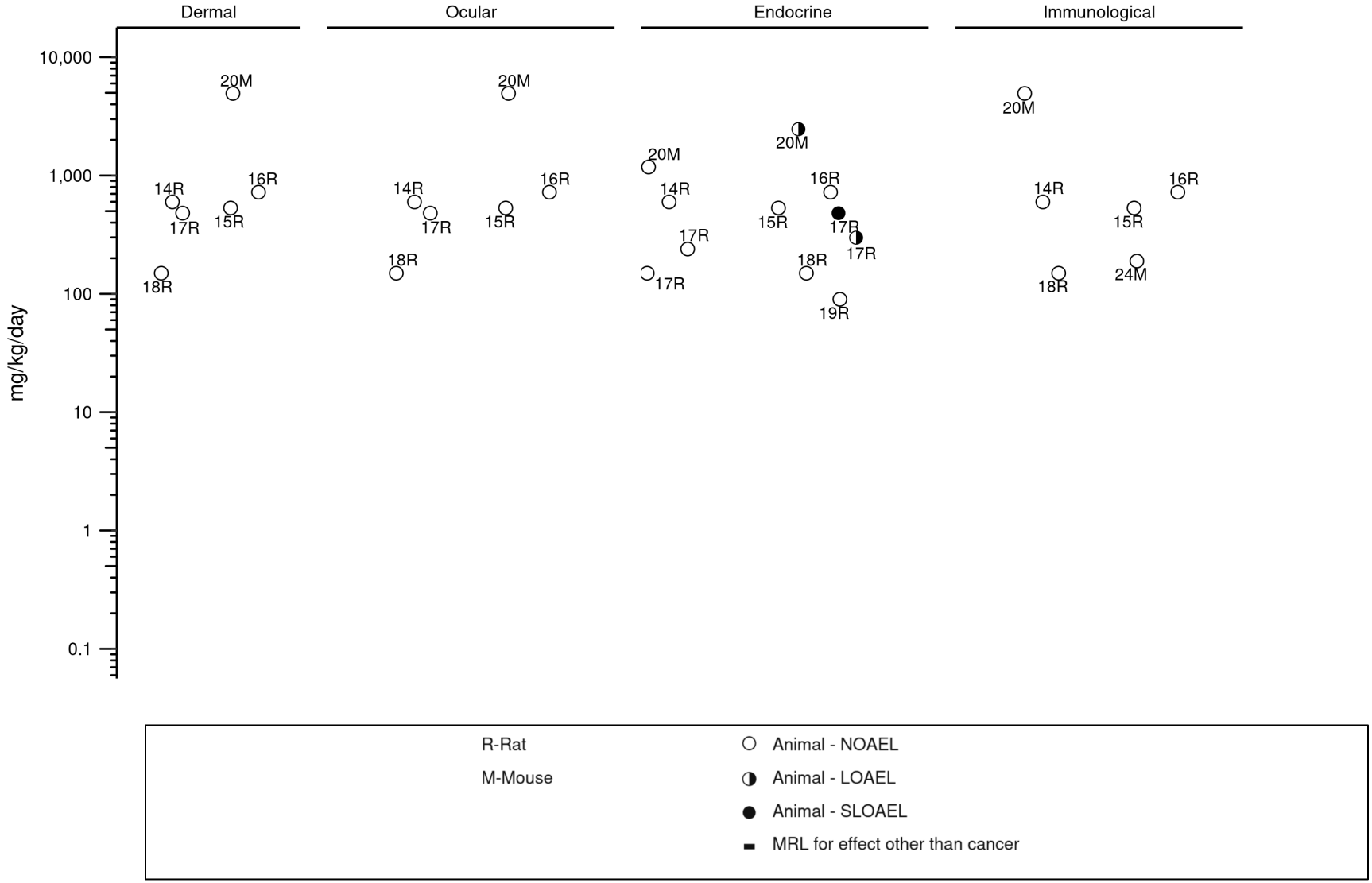


Figure 2-3. Levels of Significant Exposure to 1,2-Dichloroethane – Oral
Intermediate (15-364 days)

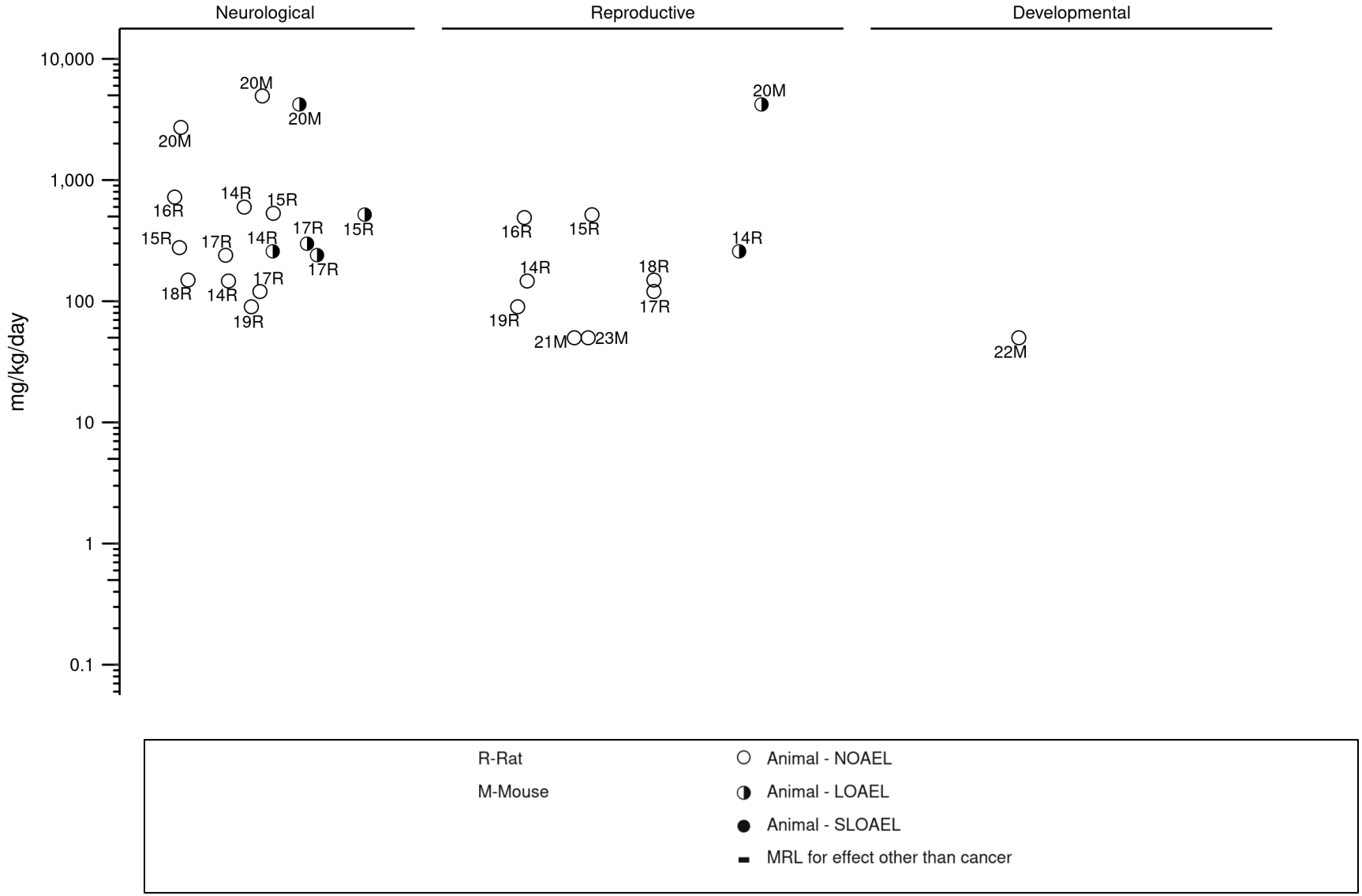


Figure 2-3. Levels of Significant Exposure to 1,2-Dichloroethane - Oral
Chronic (≥365 days)

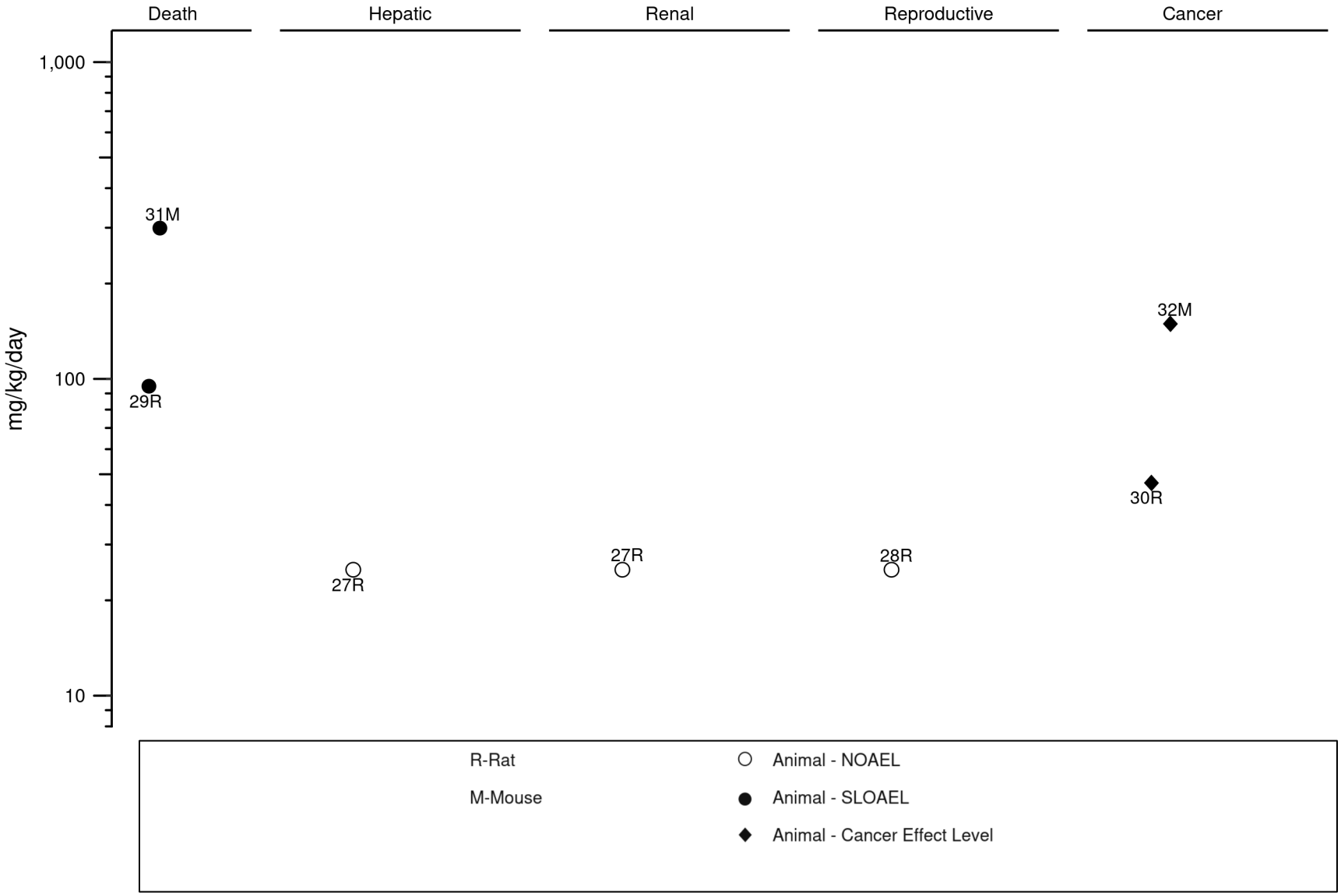


Table 2-3. Levels of Significant Exposure to 1,2-Dichloroethane – Dermal

	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
INTERMEDIATE EXPOSURE									
	MOUSE (rasH2) 40M 40F	3 x/wk, 26 wks	126 mg	BW, CS, GN, WI	Bd wt		126 mg F		~10% decrease in bodyweight following 18 weeks of exposure
					Resp			126 mg F	280% increase in absolute lung weight; 390% increase in relative lung weight
					Renal		126 mg		Increased distal tubular mild karyomegaly and tubular degeneration, as well as slight increased kidney weight (not specified).
					Cancer			126 mg	CEL: Increase in incidence and multiplicity of bronchioloalveolar adenomas, adenocarcinomas, and bronchiolo-alveolar hyperplasia
Suguro et al. 2017									

BW = body weight; CS = clinical signs; F = female(s); GN = gross necropsy; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect-level; WI = water intake

2.2 DEATH

Inhalation

Inhalation of concentrated 1,2-dichloroethane vapor can be lethal to humans. A 51-year-old man who inhaled concentrated vapor for only 30 minutes died 5 days later from cardiac arrhythmia (Nouchi et al. 1984). The exposure concentration could not be determined, and it was only 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.

Occupational exposure to 1,2-dichloroethane through inhalation may lead to lethal lung damage. A 45-year-old female patient 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, and 1,2-dichloroethane exposure is suspected to have caused lung damage leading to death, but further examination of the patient was not possible (Liu et al. 2010).

In animals, acute inhalation exposure to 1,2-dichloroethane in sufficient concentrations also causes death. 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 200 ppm, in rabbits at 400 ppm, and in monkeys at 1,000 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). An 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. High mortality (10/16 died) was seen in rat dams exposed to 300 ppm for 7 hours/day on 9 consecutive days during gestation (Rao et al. 1980; Schlacter et al. 1979). No death has been recorded for mice exposed to concentrations of 1,2-dichloroethane as high as 2,000 ppm for 4 hours, and as high as 150 ppm for 8 hours (Hotchkiss et al. 2010).

Intermediate-duration intermittent exposures (6–25 weeks) 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). Necropsy of these animals showed liver, kidney, heart, and lung effects similar to those observed following acute exposure. In a chronic inhalation study, there was no exposure-related effect on survival in rats that were intermittently exposed to 50 ppm of 1,2-dichloroethane for 2 years (Cheever et al. 1990). Chronic inhalation exposure of 2 years (104 weeks) 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 ppm and 90 ppm, respectively, compared to non-exposed groups (Nagano et al. 2006). Among female mice, significant decreases in survival rates were seen at 30 ppm and greater over 2 years.

The LC_{50} value and LOAEL values from each reliable study for death in each species and duration category are presented in Table 2-1, and plotted in Figure 2-2.

Oral

Ingestion of large amounts of 1,2-dichloroethane may be lethal to humans. 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 after 10 hours (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). Another man who drank 50 mL of 1,2-dichloroethane died 22 hours later of circulatory failure (Hueper and Smith 1935). 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 two other cases of 1,2-dichloroethane poisoning, the patients drank 15–20 mL of Marament; they suffered gastrointestinal disorders and were discharged from the hospital in a few days (Schönborn et al. 1970). These patients received prophylactic heparinization 3–4 days before the appearance of blood coagulation disorders. Only crude estimates of ingested dose were available, limiting the value of the data.

Death has also occurred in animals following oral exposure to 1,2-dichloroethane. An acute oral LD_{50} value of 680 mg/kg has been reported for rats (McCollister et al. 1956); treatment was by gavage, but the dosage levels tested and the time of death after administration were not reported. 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). Munson et al. (1982) determined LD_{50} values of 1,2-dichloroethane administered by single gavage of 489 and 413 mg/kg for male and female mice, respectively; the mice died over a 48-hour period following gavage.

Intermediate-duration studies in animals indicate that 1,2-dichloroethane is much more lethal by gavage than by ingestion in drinking water. Complete mortality occurred at 398 mg/kg/day in male mice and at 631 mg/kg/day in female mice 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 (NTP 1991). However, much higher dose levels were required to produce death following drinking water exposure. No deaths occurred among rats exposed to doses <725 mg/kg/day in the drinking water for 13 weeks (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 (NTP 1991). The mortality in the NTP (1991) drinking water studies began to increase during the first 2 weeks of exposure and approached or reached 100% after 13 weeks (NTP 1991). In the 13-week gavage study, 240 and 480 mg/kg/day produced 100% mortality in male rats within 13 weeks and 3 days, respectively (NTP 1991). Morgan et al. (1990) presents the same information, as it is a more specific publication of the larger results contained within NTP (1991).

Chronic exposure to 1,2-dichloroethane by gavage reduced survival in rats and mice. Treatment with 95 mg/kg/day for 78 weeks caused 84% mortality in rats (NCI 1978). The mortality was seen as early as week 2 and became substantial after 15 weeks. 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). The data suggest that the dose levels tested might be lethal to rats under both acute and chronic conditions, though the percentage of rats killed with acute exposure may vary compared to chronic exposure at the same dose.

The LD_{50} values and all LOAEL values from each reliable study for death in each species and duration category are presented in Table 2-2 and plotted in Figure 2-3.

Dermal

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

2.3 BODY WEIGHT

Inhalation

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. However, the period over which the weight was lost relative to the exposure period was not specified (McNally and Fostvedt 1941).

Significant decreases in bodyweight were observed in rats acutely exposed to 1,2-dichloroethane for 1.2 g/m^3 (296 ppm) for 3.5 hours per day, for 3 consecutive days (Jin et al. 2018a). A dose-responsive change in body weight was observed in male and female rats, with body weight loss most observed after inhalation exposure to 600 and 2000 ppm of 1,2-dichloroethane for 4 hours (Hotchkiss et al. 2010).

Intermediate exposure to 0.7 ppm of 1,2-dichloroethane resulted in significant decreases in body weight of mice (Wang et al. 2017; Zhang et al. 2017). Mice exposed to ~173 ppm of aerosol 1,2-dichloroethane for 6 hours for 28 consecutive days, showed a significant decrease in body weight, compared to the control and mice exposed to ~86 ppm of 1,2-dichloroethane (Wang et al. 2017). Zeng et al. (2018) present the same body weight results as Wang et al. (2017), as the two studies use the same underlying data. Similarly, a significant mean body weight decrease of 3.32 grams in male mice was observed on the 28th day of daily 6-hour exposure to 1,2-dichloroethane. Body weight gain was observed in mice exposed to ~24.7 and ~86 ppm of 1,2-dichloroethane (Zhang et al. 2017). Adverse changes in body weight (decreased gain or weight loss) occurred in maternal rats that were intermittently exposed to 300 or 329 ppm of 1,2-dichloroethane during gestation, although these effects were not observed at 100 or 254 ppm (Payan et al. 1995; Rao et al. 1987; Schlacter et al. 1979).

No changes in body weight gain were caused by intermittent exposures to 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), or 50 ppm for 2 years in rats (Cheever et al. 1990).

The highest NOAEL values and all LOAEL values from each reliable study for body weight effects in each species and duration category are recorded in Table 2-1, and plotted in Figure 2-2.

Oral

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

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), although gavage treatment with 198 mg/kg/day (but not 158 mg/kg/day) for 14 days during pregnancy 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; NTP 1991; van Esch et al. 1977),

rats and mice exposed to 259 and 4,210 mg/kg/day, respectively, in drinking water for 90 days (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).

Dermal

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

Following intermediate dermal exposure of 1,2-dichloroethane for 18 weeks, significant decreases in body weight were observed in female mice (Suguro et al. 2017). Dorsal skin of mice was exposed to a mixture of 126 mg of 1,2-dichloroethane in 200 µl of acetone, 3 times a week for 26 weeks. No significant changes in bodyweight were observed for male mice in the same study (Suguro et al. 2017).

2.4 RESPIRATORY

Inhalation

Short-term exposure to concentrated 1,2-dichloroethane in air may produce adverse respiratory effects in humans. In the case study reported by Nouchi et al. (1984), respiratory distress was reported 20 hours after the initial exposure; autopsy revealed that the lungs were severely congested and edematous. 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), but the authors regarded the symptoms as transitory.

Nasal tissue was the most sensitive target site following acute inhalation exposure to 1,2-dichloroethane in rats, characterized by nasal olfactory degeneration/necrosis (Hotchkiss et al. 2010). The no-observed adverse effect concentration for nasal olfactory degeneration/necrosis was 50 ppm of 1,2-dichloroethane for up to 8 hours in rats, and the lowest-observed adverse effect level was 100 ppm. Histopathologic alterations to the olfactory mucosa in rats were present at exposure to 200 ppm and up to 2000 ppm of 1,2-dichloroethane. 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 (Hotchkiss et al. 2010). In the affected sites, the nuclei of olfactory cells were slightly pyknotic and the amount of cytoplasm was decreased. Bronchoalveolar lavage was performed 1 day after 1,2-dichloroethane exposure and found no treatment related effect on pulmonary inflammatory cells, no markers of lung injury present, nor any changes in phagocytic activity of pulmonary alveolar macrophages (Hotchkiss et al. 2010).

Using a NOAEL of 50 ppm for nasal epithelium degeneration/necrosis in rats, and subsequent benchmark dose modeling, an MRL of 0.3 ppm was developed for acute-duration inhalation exposure to 1,2-dichloroethane as shown in Table 1-1, and discussed in greater detail in Appendix A.

In animals, acute 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 produced 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 intermittently for 4–15 weeks, rabbits and monkeys exposed to 200 ppm intermittently for 25 weeks, or dogs exposed to 400 ppm intermittently 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 intermittent 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 intermittent exposure to 50 ppm of 1,2-dichloroethane for 2 years caused no histological alterations in the respiratory tract of rats (Cheever et al. 1990).

The highest NOAEL values and all LOAEL values from each reliable study for respiratory effects in each species and duration category are recorded in Table 2-1, and plotted in Figure 2-2.

Oral

The respiratory effects exhibited by individuals who died following acute oral exposure to 1,2-dichloroethane include 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.

One study demonstrates early mild-to-moderate transitory toxic injury of the lung in rats following oral exposure to 1,2-dichloroethane (Salovsky et al. 2002). Rats were orally administered a single dose of 136 mg/kg of 1,2-dichloroethane and observed over 30 days. Histological examinations showed congestion and edema as signs of pneumonitis, and lung interstitial inflammatory changes, especially after the first day and until day 5 of exposure. Additionally, increased lipid peroxidation and levels of key antioxidant enzymes in lung tissue were seen at the earliest days of exposure (Salovsky et al. 2002). This study

suggests toxic damage to the lung from 1,2-dichloroethane likely occurs immediately following exposure, as effects on the respiratory system seen immediately after 5 days of expsoure were not observed at the end of longer duration exposures (15 and 30 days). Gross and histological examinations of rats treated with 100 mg/kg/day for 10 or 14 days showed no effects in the respiratory tract following gavage exposure (Daniel et al. 1994; van Esch et al. 1977), rats treated with 480 mg/kg/day for 90 days (Daniel et al. 1994; 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 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 (NTP 1991). The histological examinations performed by NTP (1991) were more complete than those reported in other studies because they included the nasal cavity and turbinates in addition to the lungs and bronchi. Other studies in mice found no changes in lung weight or gross appearance following exposure to 49 mg/kg/day by gavage for 14 days or 189 mg/kg/day in drinking water for 90 days (Munson et al. 1982), but these results are limited by lack of histological examinations.

Dermal

Histopathological changes in the lung of mice have been observed following 26-week dermal exposure to a 1,2-dichloroethane-acetone mixture (Suguro et al. 2017). Incidence and multiplicity of both bronchioloalveolar adenomas and adenocarcinomas were significantly increased in 1,2-dichloroethane treated mice of both sexes, and bronchioloalveolar hyperplasia significantly increased in female mice (Suguro et al. 2017). In 1,2-dichloroethane treated male mice, lung tumors were primarily solid adenomas, while large bronchioloalveolar adenocarcinomas were predominant in female mice (see Cancer 2.18). Additionally, discolored spots/areas or nodules in the lungs were most prominent in female mice, and lung weights were significantly increased compared to controls.

2.5 CARDIOVASCULAR

Inhalation

Autopsy findings in a 51-year-old man 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. Blood pressure was normal in one shoe-making factory employee and two packing plant employees subsequent to repeated occupational exposures to unreported air

concentrations of 1,2-dichloroethane over 6 years and 2- or 5-month periods, respectively (Chen et al. 2015; McNally and Fostvedt 1941).

Cardiac lesions have been reported in animals exposed to 1,2-dichloroethane. Acute lethal concentrations produced myocarditis in rats, dogs, and monkeys (Heppel et al. 1946). Guinea pigs died following intermittent 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 2 monkeys intermittently exposed to 200 ppm 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 intermittently exposed to 100 ppm for 4–15 weeks, in rabbits intermittently exposed to 200 ppm for 25 weeks, or in dogs intermittently exposed to 400 ppm for 8 months (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 few animals. Similarly, there were no histopathological changes in the heart following intermittent 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 study, intermittent exposure to 50 ppm of 1,2-dichloroethane for 2 years failed to produce cardiovascular lesions in rats (Cheever et al. 1990).

The highest NOAEL values and all LOAEL values from each reliable study for cardiovascular effects in each species and duration category are recorded in Table 2-1, and plotted in Figure 2-2.

Oral

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).

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; 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 (NTP 1991).

Dermal

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

2.6 GASTROINTESTINAL

Inhalation

Vomiting has been reported following multiple 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 immediately following exposure and died 5 days later (Nouchi et al. 1984). Nausea and vomiting were reported shortly 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 to 5 months experienced periods of epigastric pain, nausea, and vomiting (McNally and Fostvedt 1941). Nausea and vomiting were reported by factory workers occupationally exposed to unknown concentrations of 1,2-dichloroethane, who sought medical attention following the onset of symptoms. Exposure ranged from 2 months to 1 year, and worker ages from 20 to 43 years; 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).

In animal studies, gastrointestinal effects, including emesis and passing of red watery stools, preceded death in dogs intermittently exposed to 1,500 ppm of 1,2-dichloroethane 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).

The highest NOAEL values and all LOAEL values from each reliable study for gastrointestinal effects in each species and duration category are recorded in Table 2-1, and plotted in Figure 2-2.

Oral

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).

Gastrointestinal lesions have also been found in animals given bolus doses of 1,2-dichloroethane. Forestomach lesions developed in rats given gavage doses of 100 mg/kg/day for 10 days (minimal mucosal and submucosal inflammation), 240 mg/kg/day for 13 weeks (mild hyperplasia and inflammation), or 47 mg/kg/day for 78 weeks (acanthosis and hyperkeratosis) (Daniel et al. 1994; NCI 1978; 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 (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). The incidences of non-neoplastic lesions of the stomach, large intestine, and colon were also not increased in mice intermittently 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.

Dermal

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

2.7 HEMATOLOGICAL

Inhalation

Transient leukocytosis was reported 5 days subsequent to 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 cells counts in the cerebrospinal fluid of workers occupationally exposed to unknown concentrations of 1,2-dichloroethane for at least 10 months (Chen et al. 2015).

Few studies provided any indication of hematological effects in animals. Increased plasma prothrombin clotting time was reported in 2 monkeys exposed to 400 ppm of 1,2-dichloroethane intermittently for 8–12 days (Spencer et al. 1951). This study was limited because only two monkeys were examined, and one moribund monkey was killed after eight exposures. Intermediate-duration studies of 1,2-dichloroethane found no hematological changes in rats, guinea pigs, rabbits, or dogs following intermittent exposures to

200–400 ppm for 32–35 weeks (Heppel et al. 1946; Spencer et al. 1951). Chronic 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 ppm or 160 ppm, respectively of 1,2-dichloroethane for 2 years (Nagano et al. 2006). No further information on examined hematological parameters was given.

The highest NOAEL values and all LOAEL values from each reliable study for hematological effects in each species and duration category are recorded in Table 2-1, and plotted in Figure 2-2.

Oral

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). These are only crude estimates of the ingested doses. The alterations in coagulation parameters described above may have been associated to some degree with liver dysfunction. The liver plays an important role in blood clotting homeostasis, and hepatic disorders may result in abnormalities in coagulation tests. 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.

Similar 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. Mice that ingested 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 (NTP 1991). In order 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. 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), 480

mg/kg/day by gavage for 90 days (Daniel et al. 1994; NTP 1991; van Esch et al. 1977), or 492 mg/kg/day in drinking water for 90 days (NTP 1991).

Dermal

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

2.8 MUSCULOSKELETAL

Inhalation

Limb weakness was one of several reported symptoms in one female occupationally exposed by inhalation to an unknown concentration of 1,2-dichloroethane for 3 months (Dang et al. 2019). The patient also exhibited dizziness, and many neurological symptoms, all of which were 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.

Histological examination of skeletal muscle and skin showed no effects in rats that were intermittently exposed to 50 ppm of 1,2-dichloroethane for 2 years (Cheever et al. 1990).

The highest NOAEL values and all LOAEL values from each reliable study for musculoskeletal effects in each species and duration category are recorded in Table 2-1, and plotted in Figure 2-2.

Oral

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

There is no indication that ingested 1,2-dichloroethane produces musculoskeletal effects in animals. 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; 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 (NTP 1991).

Dermal

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

2.9 HEPATIC

Inhalation

The liver may be a target of 1,2-dichloroethane toxicity following inhalation exposure in humans. Nouchi et al. (1984) found an enlarged liver, high serum levels of lactate and ammonia, and increased serum levels of aspartate aminotransferase (AST; also known as glutamic oxaloacetic transaminase [SGOT]) and alanine aminotransferase (ALT; also known as glutamic pyruvic transaminase [SGPT]), 2 enzymes routinely used as indicators of liver damage, 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 to what degree this condition was preexisting. Mixed workplace exposure to 1,2-dichloroethane and vinyl chloride (exposure levels ranging up to 5.3 and 23.5 ppm, respectively, by area sampling, and up to 334 and 6.2 ppm, respectively, by personal sampling) was associated with a combined exposure-related increase in the prevalence of abnormal levels of ALT in a group of 251 male workers in a vinyl chloride manufacturing facility (Cheng et al. 1999); the contribution of 1,2-dichloroethane to the observed effect is uncertain. Mild liver lesions and increased serum levels of ALT were observed in 3 workers occupationally exposed to unknown air concentrations of 1,2-dichloroethane, who presented for medical attention following onset of symptoms (Chen et al. 2015). One worker died 10 days after admission. Chen et al. (2015) suggest liver function changes identified by abnormal liver blood biochemistry tests may be an early sign of 1,2-dichloroethane induced toxic-encephalopathy.

In animals, acute inhalation exposure has resulted in 1,2-dichloroethane induced liver damage. Mice exhibiting high level expressions of cytochrome P450 E1 (CYP2E1) exhibit enhanced metabolism of 1,2-dichloroethane to reactive intermediates, resulting in enhanced susceptibility to cytotoxic effects (Sun et al. 2016). Mice exposed to ~111 ppm and ~222 ppm of 1,2-dichloroethane by inhalation for 3.5 hours per day for 10 days had significantly increased microsomal CYP2E1 protein expression and activity. In mice exposed to ~222 ppm, serum ALT activities and hepatic malondialdehyde (MDA) levels (which helps evaluate 1,2-dichloroethane's ability to generate free radicals) significantly increased. In the same group, hepatic superoxide dismutase (SOD) activities and nonprotein sulfhydryl (NPSH) levels decreased, which suggests oxidative stress (Sun et al. 2016). Altogether, Sun et al. (2016) suggest acute exposure to ~222 ppm 1,2-dichloroethane can enhance the expression of CYP2E1 in the liver and result in obvious oxidative damage in mice. No effects to liver weight attributable to 1,2-dichloroethane inhalation were seen in rats acutely exposed to <600 ppm of 1,2-dichloroethane (Hotchkiss et al. 2010). While decreased liver weight was seen in male rats exposed to 2000 ppm, increased liver weight was seen in female rats exposed to 600 and 2000 ppm. The authors concluded the effects on body weight was likely due to

decreased feed consumption in male rats, which was not attributed to 1,2-dichloroethane exposure (Hotchkiss et al. 2010).

Wang et al. (2017) observed that intermediate 1,2-dichloroethane exposure increased hepatic CYP2E1 mRNA and protein expression in mice exposed to ~86 and ~173 ppm of 1,2-dichloroethane by inhalation 6 hours per day for 28 days. The authors noted that the increments in CYP2E1 expression induced by 1,2-dichloroethane were relatively mild compared to findings reported by Sun et al. but still suggest the CYP2E1 pathway as a mechanism of 1,2-dichloroethane induced hepatotoxicity (Wang et al. 2017). Increased serum AST and serum ALT activity, indicators of hepatic damage, were observed in mice exposed to ~86 and ~173 ppm of 1,2-dichloroethane (Wang et al. 2017).

Intermediate exposure of 28 days to 1,2-dichloroethane can significantly disrupt hepatic glucose and lipid homeostasis in mice (Wang et al. 2017). All mice exposed to 1,2-dichloroethane had a significant increase in liver free fatty acid (FFA) and triglycerides, and a significant decrease in blood glucose levels, compared to control groups (Wang et al. 2017). Hepatic glucose and lipid homeostasis may result from the down regulation of liver glycogen phosphorylase (PYGL) and glucose-6-phosphatase catalytic subunit (G6PC), expression genes associated with hepatic glucose metabolism (Wang et al. 2017), though this may be primarily mediated by a 1,2-dichloroethane metabolite rather than 1,2-dichloroethane. Zeng et al. (2018) present the same hepatic results as Wang et al. (2017), as the two studies use the same underlying data.

Longer-term exposure to 1,2-dichloroethane vapor produced hepatic effects in guinea pigs, dogs, and monkeys. Guinea pigs intermittently exposed to 100 ppm of 1,2-dichloroethane 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 intermittently exposed to concentrations of 100–400 ppm for 4–30 weeks (Heppel et al. 1946; Spencer et al. 1951). There were a number of deficiencies in the studies of 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).

In the only chronic inhalation study of 1,2-dichloroethane, groups of 50 male and 50 female rats were intermittently exposed to 50 ppm for 2 years (Cheever et al. 1990). No histological changes were found in the liver, bile duct, or any other tissues, indicating that the exposure concentration is a NOAEL of 50 ppm.

The highest NOAEL values and all LOAEL values from each reliable study for hepatic effects in each species and duration category are recorded in Table 2-1, and plotted in Figure 2-2.

Oral

1,2-Dichloroethane has been implicated as a hepatotoxin in humans after acute oral poisoning (Przezdziak and Bakula 1975). 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 pre-existing 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).

Studies in orally exposed animals have not found serious liver effects like those reported in humans. 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). Histological examinations were not performed, although liver weight was unchanged. The NOAEL for liver changes in Alumot et al. (1976) was 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. The increase over controls was significant at 18–150 mg/kg/day in females and 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 weight increases were noted at 60 mg/kg/day in rats (liver-to-body-weight ratio was significantly elevated at 60–518 mg/kg/day in Sprague-Dawley males without corresponding decreases in body weight), and at 249 mg/kg/day in mice (liver-to-body-weight ratio was significantly elevated in a dose-related manner at 249–4,210 mg/kg/day in males without corresponding decreases in body weight). Morgan et al. (1990) present the same information, as it is a more specific publication of the larger results contained within NTP (1991). 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). Daniel et al. (1994) also found no significant hepatic effects in rats administered 100 mg/kg/day by gavage for 10 days. 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.

1,2-Dichloroethane increased liver toxicity in rats, following chronic ethanol consumption (Cottalasso et al. 2002). Rats were treated daily with liquid ethanol in their diets for 8 weeks, and then administered a single dose of 628 mg of 1,2-dichloroethane/kg-bodyweight, by oral intubation. In-vitro experiments were also conducted on isolated hepatocytes from rats chronically exposed to ethanol, and 25 µl was added to the closed system. In-vitro and in-vivo experiments found concomitant chronic administration of ethanol enhances 1,2-dichloroethane hepatotoxicity by further increasing levels of ALT and AST and lactate dehydrogenase (LDH) (Cottalasso et al. 2002). While the hepatic effects observed cannot be directly attributed to 1,2-dichloroethane, it does suggest the liver may be a target organ for 1,2-dichloroethane toxicity in animals.

Other animal studies of 1,2-dichloroethane did not find hepatic effects. No changes in liver weight were observed in mice exposed to 49 mg/kg/day by gavage for 14 days or 189 mg/kg/day in drinking water for 90 days (Munson et al. 1982); histology was not evaluated. Rats administered single gavage doses (80 mg/kg) of 1,2-dichloroethane showed no effect on liver triglyceride, sorbitol dehydrogenase (SDH), and ALT levels (Aragno et al. 1992; Danni et al. 1992). Chronic 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). In this chronic feeding study, the animals were not evaluated grossly or microscopically for liver lesions. 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. 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).

Dermal

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

2.10 RENAL

Inhalation

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

Acute-duration inhalation exposure to 1,2-dichloroethane also produced renal effects in animals. 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 intermittent exposure to 400 ppm for 8–12 days (Spencer et al. 1951). No renal effects were noted in monkeys exposed to 100 ppm for 8–12 days (Spencer et al. 1951). A statistically significant increase in mean absolute kidney weight was observed in rats exposed to 2000 ppm of 1,2-dichloroethane vapor for 4 hours (Hotchkiss et al. 2010). Male mice had slightly increased basophilia of the renal tubular epithelium; female mice exhibited this effect and degeneration with individual cell necrosis of a segmental portion of the nephron (outer stripe, outer zone of medulla) of the kidney. These effects are likely associated with changes in absolute and relative kidney weight in rats (Hotchkiss et al. 2010). A no adverse effect level for renal effects from inhalation of 1,2-dichloroethane vapor in rats was 600 ppm (Hotchkiss et al. 2010).

Kidney lesions have also been reported following longer-term exposure of animals to 1,2-dichloroethane. Dogs intermittently exposed to 400 ppm 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 intermittently exposed to 100–400 ppm of 1,2-dichloroethane for 4–30 weeks (Heppel et al. 1946; Spencer et al. 1951). In all of these studies, a limited number of animals were exposed, and only a few of those were examined for histopathology. In a chronic study, no histopathological changes developed in the kidneys of rats exposed to 50 ppm of 1,2-dichloroethane intermittently for 2 years (Cheever et al. 1990).

The highest NOAEL values and all LOAEL values from each reliable study for renal effects in each species and duration category are recorded in Table 2-1, and plotted in Figure 2-2.

Oral

Acute renal damage resulting from ingestion of 1,2-dichloroethane has been observed in humans. Bleeding and hyperemia of the kidney were observed in an 18-year-old man who ingested 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 of 1,2-dichloroethane (Hubbs and Prusmack 1955). Observations upon microscopic examination included swelling, vacuolation, and degeneration of the renal tubule epithelial cells and sloughing of the glomerular capsular epithelium, and nearly complete loss of the bladder epithelium (Hubbs and Prusmack 1955). In one case study, renal damage that resulted from acute oral poisoning of a 25-year-old man was not considered severe or permanent, and the patient fully recovered (Przezdziak and Bakula 1975). The amount of 1,2-dichloroethane ingested was not reported. However, individuals who died following ingestion of 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). These are only crude estimates of ingested dose.

Renal effects reported in animals were limited to increases in kidney weight and minimal-to-moderate histopathological changes after longer-term exposures. Relative kidney weight was 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). An NTP (1991) 13-week gavage study in rats found significant dose-related increases in kidney weight and kidney-to-body-weight ratio at 30–120 mg/kg/day in males and 75–150 mg/kg/day in females (kidney weight was not measured in higher-dose animals because of mortality). Exposure to 1,2-dichloroethane in the drinking water for 13 weeks caused significant dose-related increases in kidney weight and kidney-to-body-weight ratio in female rats at 58 mg/kg/day and female mice at 244 mg/kg/day (NTP 1991). The increase in kidney weight is considered to be an early-stage adverse effect in a known target tissue because renal histopathological changes occurred at higher doses. Histopathological examination of the animals in the drinking water study showed dose-related increased incidences of minimal-to-moderate renal regeneration in female rats at 102 mg/kg/day and male mice at 249 mg/kg/day. These changes are indicative of previous tubular injury with subsequent repair. More severe renal effects including karyomegaly, dilation, protein casts, and mineralization occurred in male mice exposed at 4,210 mg/kg/day. Based on these results, NTP (1991) concluded that the kidney was a target organ for 1,2-dichloroethane in mice. Morgan et al. (1990) presents the same information, as it is a more specific publication of the larger results contained within NTP (1991). Using a LOAEL of 58 mg/kg/day based on kidney effects from NTP (1991), an intermediate-duration oral MRL of 0.2 mg/kg/day was calculated as described in Table 1-1 and in Appendix A.

Other studies in animals failed to find evidence of kidney damage produced by 1,2-dichloroethane. Acute (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 or exposure to 189 mg/kg/day in drinking water for 90 days (Munson et al. 1982), and kidney function, as measured by changes in serum levels of urea and uric acid, was normal in rats exposed to 25 mg/kg/day in food for 2 years (Alumot et al. 1976). Histological examination of the kidney was not performed in either of these studies. 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 compound-related renal changes in F344/N rats, whereas Osborne-Mendel rats were tested by NCI (1978); tests of Osborne-Mendel and Sprague-Dawley rats by NTP (1991) were also negative.

Dermal

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

Limited evidence in animals suggests renal effects in animals after dermal exposure to 1,2-dichloroethane. Distal tubular mild karyomegaly was increased in mice of both sexes, following application of a mixture (126 mg of 1,2-dichloroethane dissolved in 200 µl acetone) to dorsal skin for 26 weeks (Suguro et al. 2017). In females, karyomegaly was accompanied by tubular degeneration. Kidney findings may be associated with a slight increase in relative kidney weight (Suguro et al. 2017).

2.11 DERMAL

Inhalation

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

Histological examinations showed no changes in the skin of rats exposed to 50 ppm of 1,2-dichloroethane intermittently for 2 years (Cheever et al. 1990).

The highest NOAEL values and all LOAEL values from each reliable study for dermal effects in each species and duration category are recorded in Table 2-1, and plotted in Figure 2-2.

Oral

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

Histological examinations showed no changes 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; 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 (NTP 1991).

The highest NOAEL values and all LOAEL values from each reliable study for dermal effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-3.

Dermal

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

A single animal study was located that investigated dermal effects following direct application of 1,2-dichloroethane to the skin as a liquid. In guinea pigs, dermal exposure to unspecified amounts for 4 hours applied to the skin under a cover slip 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.

2.12 OCULAR

Inhalation

Blurred vision was a reported symptom in one male occupationally exposed by inhalation to an unknown concentration of 1,2-dichloroethane for 1 year (Dang et al. 2019). The patient also exhibited many neurological symptoms, including headache, and all symptoms were gone following treatment with steroids and/or mannitol and 1-year follow-up. The patient's ocular changes were likely due to encephalopathy brought on by acute 1,2-dichloroethane exposure. No further information was found to elucidate ocular effects of 1,2-dichloroethane on humans.

Ocular effects reported in animals acutely exposed to 1,2-dichloroethane by inhalation were corneal clouding and lacrimation (Heppel et al. 1945, 1946). These effects probably resulted from direct ocular contact with 1,2-dichloroethane vapor and are discussed in more detail in Section 3.2.3. In a chronic study, rats that were exposed to 50 ppm of 1,2-dichloroethane intermittently for 2 years had no histological changes in the eyes (Cheever et al. 1990).

The highest NOAEL values and all LOAEL values from each reliable study for ocular effects in each species and duration category are recorded in Table 2-1, and plotted in Figure 2-2.

Oral

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

Ophthalmoscopic examinations showed no effects in rats that were treated with 150 mg/kg/day of 1,2-dichloroethane by gavage in a 90-day study; the exams were performed prior to treatment and during the last week of the study (Daniel et al. 1994). Other 90-day 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 (NTP 1991).

The highest NOAEL values and all LOAEL values from each reliable study for ocular effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-3.

Dermal

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

Studies in animals reported direct-contact effects following exposure to 1,2-dichloroethane as a vapor in the air. Dogs exposed to 1,2-dichloroethane as a vapor in the air developed corneal opacity. This corneal clouding was observed in 3 dogs that died following intermittent exposure to 1,500 ppm for 6 days (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 in air intermittently for 4 days (Heppel et al. 1945).

2.13 ENDOCRINE

Inhalation

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

Endocrine function has not been evaluated in inhalation 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 intermittent exposure to 1,2-dichloroethane caused congestion of the adrenal cortex in guinea pigs exposed to 1,500 ppm 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 1 of 2 monkeys intermittently exposed to 200 ppm for 25 weeks (Heppel et al. 1946), but the evidence for this effect is inconclusive because only 2 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 intermittent exposures to 100 ppm 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.

The only chronic inhalation study of 1,2-dichloroethane found that intermittent exposure to 50 ppm 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, the effect was induced in only one sex (females), additional exposure levels were not tested, and the study was designed to evaluate carcinogenicity.

The highest NOAEL values and all LOAEL values from each reliable study for endocrine effects in each species and duration category are recorded in Table 2-1, and plotted in Figure 2-2.

Oral

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

Endocrine function has not been evaluated in oral 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. 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), in rats administered 480 mg/kg/day by gavage for 90 days (Daniel et al. 1994; 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 90 days (NTP 1991), or in 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) studies were the most extensive and included tissues from the adrenal, pancreas, pituitary, thyroid, and parathyroid glands.

Dermal

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

2.14 IMMUNOLOGICAL

Inhalation

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

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

There is evidence that acute exposure to 1,2-dichloroethane affects the ability to fight infection arising from inhaled microbial pathogens in animals. 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 in the exposed mice (Sherwood et al. 1987); male mice were not evaluated. No effect was observed at 2.3 ppm. Additionally, 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 (female rats were not evaluated); mortality following S. zooepidemicus challenge was not evaluated in rats. In addition, no effects on lymphocyte function (as indicated by blastogenesis to T- and B-cell mitogens) were seen in rats exposed to 100 ppm 5 hours/day for 12 days. Results reported in Sherwood et al. (1987) suggest 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. The relevance of the immunological effects in mice to human immunotoxicity is uncertain, since the massive bacterial challenges given to mice in the study are unlikely to be representative of normal immunological challenges in humans. In addition, Sherwood et al. (1987) concluded that the interspecies differences in immunotoxicity observed in the study suggest against extrapolating from animals to humans.

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), to 400 ppm for 232–248 days in rabbits (Spencer et al. 1951), or to 50 ppm for 2 years in rats (Cheever et al. 1990).

The highest NOAEL values and all LOAEL values from each reliable study for immunological effects in each species and duration category are recorded in Table 2-1, and plotted in Figure 2-2.

Oral

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

Evidence from animal studies suggests that the immune system is a target of 1,2-dichloroethane toxicity after oral exposure. In 5-week-old mice exposed for 14 days by gavage to 4.9 and 49 mg/kg/day, there was a significant dose-related reduction in humoral immunity (measured by immunoglobulin M [IgM] response to sheep erythrocytes), and a significant, but not dose-related, reduction in cell-mediated immunity (measured by delayed-type hypersensitivity response to sheep erythrocytes) (Munson et al. 1982). In mice given 49 mg/kg/day, these effects were accompanied by a 30% decrease in total leukocyte number.

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). The authors suggested that the conflicting results in mice treated by gavage and those exposed to 1,2-dichloroethane in drinking water may reflect differences in compound administration and exposure duration, as discussed earlier (see the discussion of hematological effects in Section 2.7). 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).

Immune system function tests were not included in intermediate- and chronic-duration studies conducted by NTP (1991). However, immune system tissues were examined for histopathological lesions in some of these studies. Thymic necrosis was observed in rats given 240 mg/kg/day of 1,2-dichloroethane by gavage for 13 weeks (NTP 1991). Because this lesion was found only in moribund animals, the study authors concluded that it was a result of generalized stress rather than a target organ effect. 1,2-Dichloroethane did not produce lesions in immune system tissues in rats and mice exposed to 492 mg/kg/day and 4,210 mg/kg/day, respectively, in drinking water for 13 weeks (NTP 1991), in rats exposed by gavage to 150 mg/kg/day for 90 days (Daniel et al. 1994), or in rats and mice exposed to 95 and 299 mg/kg/day, respectively, by gavage for 78 weeks (NCI 1978).

Dermal

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

2.15 NEUROLOGICAL

Inhalation

Inhalation of high concentrations of 1,2-dichloroethane can affect the nervous system of humans. It has been reported that 1,2-dichloroethane is an anesthetic narcotic in humans, and that it is as potent an anesthetic as gasoline, benzene, carbon tetrachloride, and chloroform when inhaled for periods of an hour or more (Garrison and Leadingham 1954). A 51-year-old sailor exposed to a concentrated vapor of 1,2-dichloroethane for 30 minutes suffered central nervous system effects, such as irritability and periodic vomiting, immediately following exposure (Nouchi et al. 1984). Twenty hours later, he was drowsy and became delirious and tremulous; he lapsed into a coma 4 hours later, with a generalized continuous clonic jerk. His electroencephalogram showed slow wave abnormality. He died 5 days after exposure. Upon autopsy, the Purkinje cell layer of his cerebellum showed a shrunken appearance with pyknotic nuclei. A 31-year old worker exposed to 1,2-dichloroethane over 6 years, presented with dizziness, headache, memory impairment, high intracranial pressure, increased white blood cells in the cerebrospinal fluid; 10 days after admission, he entered into a coma and was pronounced brain dead (Chen et al. 2015).

Weakness, dizziness, and trembling were reported shortly 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). Headaches, dizziness, seizures (including generalized tonic-clonic), recent amnesia and a slow response to verbal commands have been seen in male and female workers exposed to unknown 1,2-dichloroethane concentrations by inhalation for 3 months to 1 year (Dang et al. 2019; Liu et al. 2010; Zhan et al. 2011).

1,2-Dichloroethane induced toxic encephalopathy, primarily characterized by cerebral edema, is commonly observed in workers intermediately or chronically exposed. Five cases of 1,2-dichloroethane induced toxic encephalopathy were seen in factory workers who were exposed to concentrations in air at 370 ppm over 2- or 5-months or 6-year periods (Chen et al. 2015). Brain edema was the main cause of intracranial hypertension in patients and likely progressed to toxic encephalopathy. Imaging showed other usual signs of edema including abnormal signal intensities in the cerebellar dentate nucleus, basal ganglia, and white matter in the bilateral cerebral hemispheres (Chen et al. 2015). Additionally, increased white blood cell count was seen in cerebrospinal fluid of all workers, suggesting nonspecific inflammation in the central nervous system (CNS) also occurred. Due to its high lipid solubility, 1,2-dichloroethane can accumulate in lipid-rich tissues of the brain resulting in irreversible damage to the CNS (Chen et al. 2015). Similarly, 5 female workers, exposed to unknown concentrations, presented with 1,2-dichloroethane induced toxic encephalopathy, and showed extensive edema in subcortical white matter, bilateral globus pallidus, and/or dentate nucleus (Liu et al. 2010); all patients recovered from neurological symptoms. 1,2-dichloroethane induced toxic encephalopathy was seen in 4 workers intermediately exposed (3 months – 1 year) to unknown concentrations (Dang et al. 2019). Severe mixed edema was the primary edema, with extensive edema in white matter, nucleus dentatus, globus pallidus, and bilateral cortex among the patients. Brain biopsies of 2 patients revealed extensive severe neural edema, extensive glial cell necrosis, and extensive edema in glial cytoplasm and neurites (Dang et al. 2019); all patients recovered.

Apparent diffusion coefficient (ADC) values from 4.5 to 5.5×10^{-4} mm^2/s are a suggested threshold marker for irreversible damage from cerebral edema. A case study of a male worker exposed to 1,2-dichloroethane for 6 months, exhibited an ADC of 5.066×10^{-4} mm^2/s 4 days after seeking medical attention for symptoms, suggesting brain edema was mainly cytotoxic. Neuronal necrosis and white matter demyelination were also observed in the patient to some degree (Zhan et al. 2011). Toxic leukoencephalopathy, a type of encephalopathy primarily affecting white matter, was suspected in a 20-year old female occupationally exposed (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 seen in 121 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 on either a daily basis, more than twice a month, less than twice a month or never. Significant impairment was demonstrated on tests of attention, non-verbal processing speed, verbal memory and learning, and motor strength and speed. High motor impairment and neuropsychological impairment had a significant dose-response relationship with 1,2-dichloroethane (Bowler et al. 2003). Significant intellectual and memory impairment were measured in workers exposed for >41 months, compared to workers exposed for 6 months (Ruffalo et al. 2000). Performance in measures of attention and problem solving were in the "impaired" range for the higher level exposed group, compared to "normal" scores by the lower level exposed workers.

Acute-duration exposure to concentrated 1,2-dichloroethane also produces neurological effects in animals. Uncertain gait, narcosis, prostration, or unconsciousness were seen in rats, guinea pigs, and rabbits exposed once to 3,000 ppm for 7 hours, but were not reported at 1,500 ppm; 7-hour exposures to 1,500 ppm on 5 consecutive days induced transitory tremors, convulsions, or coma in rats and dogs (Heppel et al. 1945). Forelimb flexion and body tremors, indicators of cerebral injury, were observed in 1,2-dichloroethane exposed mice (Jin et al. 2018a). No exposure related histopathologic observations were reported in the central or peripheral nervous systems of rats exposed to less than 2000 ppm for 4 hours (Hotchkiss et al. 2010). Treatment-related lesions found in the peripheral nervous system were limited to regeneration of the olfactory mucosa 14 days after exposure to 1,2-dichloroethane concentrations ≥200 ppm for 4 hours.

Brain lesions, particularly brain edema, are seen in animals acutely exposed to 1,2-dichloroethane by inhalation (Jin et al. 2018a, 2018b; Wang et al. 2014, 2018; Zhang et al. 2011; Zhou et al. 2016). Mice exposed to concentrations as low as ~296 ppm of 1,2-dichloroethane 3.5 hours/day for 3 days presented formation of brain edema, indicated by significantly increased brain water contents and typical morphological changes of brain edema in mice (Jin et al. 2018a, Wang et al. 2014). 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 (Jin et al. 2018a, Wang et al. 2014). These effects were not seen in mice exposed to ~272 ppm of 1,2-dichloroethane for up to 3 days (Wang et al. 2014). Edema characteristics, including increased brain water contents, were apparent in rats exposed to ~1235 ppm of 1,2-dichloroethane by inhalation for 6 hours, and severity increased with exposure duration, compared to controls (Zhang et al. 2011). Slight brain dropsy, characterized by loose

tissues and enlarged spaces surrounding the cells, also appeared at this concentration, and became more severe at ~2471 ppm, where "vacuolous and spongy structures" appeared. Lesions with brain edema in the white matter in both hemispheres of the brain were seen in rats exposed to ~988 ppm of 1,2-dichloroethane by inhalation (Zhou et al. 2016). Low ADC and fractional anisotropy (FA) reflect axonal damage in exposed rats, and acute ADC reduction likely reflects trauma-induced cytotoxic edema and inflammation (Zhou et al. 2016). A model of acute occupational exposure was developed in rats, where 1,2-dichloroethane induced edema found in autopsies of workers was duplicated in rats by inhalation exposure to an unknown 1,2-dichloroethane exposure concentration (Niu et al. 2009). This duplication resulted in brain lesions, including edema, necrosis, and hemorrhage (Niu et al. 2009). Microscopic photographs demonstrated 1,2-dichloroethane induced toxic encephalopathy showing gaps between widened cells and vessels; electronic microscope observation showed that nerve fibers were demyelinated, and the axis cylinder was pushed sideward (Niu et al. 2009).

The pathogenesis underlying 1,2-dichloroethane induced brain edema following acute exposure is not clarified. CYP2E1 mediated metabolism of 1,2-dichloroethane likely contributes to oxidative damage in the brain through the increased activity of NADPH oxidase and subsequent generation of reactive oxygen species and is possibly an underlying mechanism of 1,2-dichloroethane induced brain edema (Jin et al. 2018a). Exposure to ~296 ppm of 1,2-dichloroethane increased protein and mRNA levels of CYP2E1 in the brains of mice, which was upregulated transcriptionally (Jin et al. 2018a). At the same dose, 1,2-dichloroethane may also activate the p38 signaling pathway, involved in the course to brain edema in mice (Jin et al. 2018b). Brain water content and brain-blood barrier permeability increased significantly, indicating disruption of the blood brain barrier integrity which can lead to edema (Jin et al. 2018b). At inhalation exposure to ~296 ppm of 1,2-dichloroethane, up-regulation of MMP2 and MMP9 proteins in cerebral tissue can occur, after 2 days of exposure, and may play a key role in the breakdown of the blood brain barrier, which can lead to vasogenic edema (Wang et al. 2014). In Wang et al. (2018), authors concluded that calcium overload and depressed expression of tight junction associated proteins, such as ZO-1 and occludin, may play an important role in the early phase of brain edema formation. In mice, suppressed Ca^{2+} ATPase activity may lead to calcium overload, disturbing calcium homeostasis in brain cells, thereby causing an energy metabolism disorder (Wang et al. 2018).

Oxidative stress is indicated in mice exposed to 1,2-dichloroethane by inhalation, which may contribute to brain edema formation (Jin et al. 2018a; Wang et al. 2013). Wang et al. (2013) found oxidative stress occurred at a low dose 3.5 hours daily for 10 consecutive days, but not in higher doses for the same frequency and duration. Significantly increased malondialdehyde (MDA) levels were observed at ~56 ppm and indicated overproduction, or accumulation of oxidants in the brain of mice. At inhalation of

~222 ppm, MDA increased, but superoxide dismutase (SOD) also increased and is considered essential in protecting cells against oxidative damage (Wang et al. 2013). Oxidative stress was also indicated in mice exposed to ~296 ppm of 1,2-dichloroethane for 3.5 hours/day for 3 days, as indicated by increased expression of a transcription factor and heme oxygenase-1 (HO-1) enzyme (Jin et al. 2018a).

Acute inhalation exposure to 1,2-dichloroethane produces neurobehavioral effects in animals (Hotchkiss et al. 2010; Wang et al. 2013; Zhou et al. 2016). Central nervous system (CNS) depression and intoxication was indicated at concentrations >200 ppm in mice after a 1 day, 4-hour exposure (Hotchkiss et al. 2010). This observation was not seen past 8 days of exposure. Hotchkiss et al. (2010) determined a no-observed adverse effect concentration by inhalation for behavioral neurotoxicity in mice of 200 ppm of 1,2-dichloroethane. Mice exhibited CNS excitability when exposed to ~56 ppm of 1,2-dichloroethane, as evidenced by enhancement of the exploratory behavior and general motor activities of mice (Wang et al. 2013). Conversely, CNS inhibition by depression was seen in mice exposed to ~222 ppm. This suggests low doses may result in behavioral excitement, while high doses may result in behavioral inhibition (Wang et al. 2013). Disturbed contents of amino acid neurotransmitters in the brain is a mechanism of induced neurotoxic effects that may explain changed behavior in mice. Significantly higher glutamate was observed in 1,2-dichloroethane exposed mice, which may cause excitotoxicity, an overstimulation of the postsynaptic receptors (Wang et al. 2013). In female rats, motor activity across time points significantly decreased following exposure to 2000 ppm 1,2-dichloroethane for 4 hours; this effect was not seen in male rats (Hotchkiss et al. 2010).

Longer-term exposure to lower concentrations of 1,2-dichloroethane did not appear to produce neurological effects, although sensitive indicators of subtle neurological effects were not examined. Negative results were obtained by physical examination (without histopathology) of dogs intermittently exposed to 400 ppm for 8 months (Heppel et al. 1946) and by histopathological examination of the brain from rats intermittently exposed to 50 ppm for 2 years (Cheever et al. 1990). The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 2-1, and plotted in Figure 2-2.

Oral

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). Morphological alterations in the nervous system were observed in patients who died of acute oral poisoning by 1,2-dichloroethane. These alterations included 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). The morphological changes observed in the cerebellum may affect the coordination of muscular movements.

Neurological effects have also been observed in animals exposed to 1,2-dichloroethane by ingestion. 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 (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. Intermittent gavage exposure to 90 mg/kg/day in female rats over a 90-day period induced a slight increase in relative brain weight (+8%) in female rats, but no clinical signs or histological changes in the brain or spinal cord were observed, and no neurological effects of any kind were seen in males dosed at 90 mg/kg/day or in either sex at lower exposure levels (van Esch et al. 1977). Similarly, gavage administration of 75 and 150 mg/kg/day induced a significant increase in brain weight (+8 and +22%, respectively) in male rats without increases in the incidences of neurological clinical signs or lesions of the brain or sciatic nerve; no neurological effects of any kind were reported in females at 75 mg/kg/day or in either sex at lower exposure levels (Daniel et al. 1994). In the Daniel et al. (1994) study, the increase in relative brain weight may have been due to an observed dose-related decrease in body weight in the male rats and may not necessarily be due to an actual change in brain weight; absolute organ weights were not reported. Exposure to 1,2-dichloroethane in the drinking water for 13 weeks did not produce increased brain weights, abnormal clinical signs, or lesions in nervous system tissues in rats (492 mg/kg/day) or mice 4,210 mg/kg/day) (NTP 1991). (See the discussion of hematological effects in Section 3.2.2.2 regarding why effects that occur following bolus exposure might not occur following drinking water exposure). A 10-day gavage exposure to up to 100 mg/kg/day did not induce an increase in brain weight or an increase in the incidences of gross or microscopic lesions in nervous system tissues of rats (Daniel et al. 1994), and 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).

Dermal

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

2.16 REPRODUCTIVE

Inhalation

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 female workers and in wives of male workers who were exposed in a Chinese synthetic fiber factory (Zhao et al. 1989). Concentrations of 1,2-dichloroethane ranged from 0.4 to 384 ppm 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. These results should be treated with caution because the study evaluated a small number of subjects (44 male and 54 female exposed workers), the authors indicated that co-exposure to other chemicals occurred in most cases, and the study was generally deficient in reporting the study design including accounting for possible confounding environmental and behavioral factors.

Some studies in rodents (Vozovaya 1974, 1977; Zhao et al. 1989) found that inhalation exposure to 1,2-dichloroethane either prior to mating and continuing into gestation or throughout gestation caused pre-implantation loss and embryo lethality, although the reliability of these studies is unclear because of deficiencies in reporting study design and results. Pre-implantation loss was reportedly increased (31.0% compared to 10.2% in controls, $p<0.05$) in unspecified rodents that were exposed to 51.9 ppm "during the entire pregnancy period"; one account of the study indicated that a 2-week pre-mating exposure also occurred (Zhao et al. 1997), although this could not be corroborated from the original study (Zhao et al. 1989). Intermittent exposure of rats to 4.7±7 ppm for 4 months prior to the mating period, followed by inhalation exposure during pregnancy, produced a statistically significant ($p<0.01$) increase in embryo mortality (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 intermittently exposed to 14 ppm of 1,2-dichloroethane over a period of 6 months (Vozovaya 1974). In contrast to the studies summarized above, 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 intermittently exposed to 150 ppm for 60 days pre-mating, then throughout mating, gestation, and lactation (excluding gestation day 21 through postpartum day 40). No gross or histopathological lesions were observed in reproductive organs of rats exposed to 50 ppm intermittently for 2 years (Cheever et al. 1990).

1,2-Dichloroethane significantly inhibited the cyclic adenosine monophosphate (cAMP)-response element binding (CREB) protein and the cAMP-response element modulator (CREM), subsequently inducing apoptosis, and reproductive toxicity in male mice (Zhang et al. 2017). CREM testis mRNA expression decreased significantly in male mice exposed to ~173 ppm of 1,2-dichloroethane for 1-and-4-weeks, and to ~86 ppm for 4 weeks. CREB mRNA expression decreased significantly in mice after 1-week exposure to ~86 and ~173 ppm, or after 4-week exposure to ~25, 86, and 173 ppm to 1,2-dichloroethane (Zhang et al. 2017). Significant pathological changes in mice testes were present at exposures of ~86 ppm and ~173

ppm of 1,2-dichloroethane for 4-weeks; after 1-week at both doses, pathological changes in mice testes were observed to a lesser extent. Effects on sperm parameters and morphological abnormalities in spermatozoa occurred in mice exposed to ~173 ppm of 1,2-dichloroethane by inhalation for 1 week, and significantly after 4 weeks of exposure to ~86 and 173 ppm; sperm concentration, motility and progressive motility all decreased (Zhang et al. 2017). Comet assay revealed no genetic damage to sperm DNA in any exposure groups and no significant effects on male reproductive toxicity in mice were observed at ~25 ppm. 1,2-Dichloroethane induced non-cell specific apoptosis in the germ cells in seminiferous tubules in the testes of mice after 4 weeks of inhalation exposure to ~86 and 173 ppm of 1,2-dichloroethane (Zhang et al. 2017).

The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects in each species and duration category are recorded Table 2-1, and plotted in Figure 2-2.

Oral

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

Studies in animals suggest that reproductive effects of 1,2-dichloroethane may be induced at oral doses that are maternally toxic. 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). Similarly, 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). In a study using higher doses of 1,2-dichloroethane, rats that were treated with 198 mg/kg/day for 14 days during gestation 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 number of implantation sites or live fetuses per litter were observed.

Histological examinations showed no changes 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; 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 (NTP 1991), or in rats and mice exposed to 95 and 299 mg/kg/day, respectively, by gavage for 78 weeks (NCI 1978). Reproductive performance was not evaluated in these studies.

Dermal

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

2.17 DEVELOPMENTAL

Inhalation

Limited evidence suggests inhalation of 1,2-dichloroethane can result in developmental effects in humans. One population-based case-control study, using adjusted odds ratios (aOR), suggests birth defects in offspring as a result of maternal environmental exposure to 1,2-dichloroethane in air (Brender et al. 2014). Maternal residential proximity to industrial air emissions of 1,2-dichloroethane was strongly associated to neural tube defects (aOR=1.28) and spina bifida (aOR=1.64) in offspring. The association with neural tube defects and spina bifida were more pronounced when maternal age was <35 years (aOR=1.31 and aOR=1.70, respectively) (Brender et al. 2014). Weak associations were seen with cleft palate (aOR=1.10) and congenital heart defects (aOR=1.03; aOR=1.06). Brender et al. (2014) had a large sample size with over 60,000 case-mothers, but other factors that can lead to birth defects could not be properly adjusted for, such as number of maternal offspring and other lifestyle factors; smoking was suspected to be underreported (Brender et al. 2014). No further evidence elucidates the relationship between maternal inhalation exposure to 1,2-dichloroethane and birth defects in offspring.

The overall evidence from inhalation studies in rats and rabbits indicates that 1,2-dichloroethane is not a developmental toxicant. 1,2-Dichloroethane was not fetotoxic or teratogenic in the offspring of rats that were intermittently exposed to 100 ppm on days 6–15 of gestation (Rao et al. 1980; Schlacter et al. 1979). Exposure to 300 ppm produced high maternal mortality with fetolethality, and one rat had a total resorption of the litter. Another study similarly found that exposure to 1,2-dichloroethane during gestation days 6–20 was not fetotoxic or teratogenic to rats at concentrations as high as those producing maternal toxicity (329 ppm) (Payan et al. 1995). 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, although maternal body weight gain was 24% reduced at 329 ppm; no maternal effects occurred at lower concentrations (150–254 ppm). Developmental toxicity was reported in one study in rats, but the reliability of the data is unclear (Vozovaya 1977). Exposure to 4.7±7 ppm of 1,2-dichloroethane for 4 months before mating followed by exposure during pregnancy was embryotoxic and caused hematomas in the head and neck region and anterior extremities of the fetuses. The reliability of the Vozovaya (1977) data cannot be assessed due to lack of statistical analysis and uncertainties in the reported results. Zhao et al. (1984) reported no developmental changes in F1 and F2 generations of mice

after the parental dams were exposed by inhalation for 4 hours per day to up to 62.5 ppm on gestation days 6–15, or to 250 ppm on gestation days 9 and 10. The F1 generation was not postnatally exposed to 1,2-dichloroethane. No changes were observed in the following parameters: fetal survival, length, or weight; external, skeletal, or visceral appearance; pup survival; onset of pup physical changes and reflex acquisition; or pup weight gain. In spite of reporting deficiencies leading to critical uncertainties in the adequacy of the study design, the results are suggestive that 1,2-dichloroethane is not developmentally toxic in mice under reported study conditions.

Rabbits that were intermittently exposed to 100 or 300 ppm of 1,2-dichloroethane on days 6–18 of gestation experienced some maternal deaths, but there were no chemical-related fetotoxic or teratogenic effects as indicated by pregnancy and resorption incidences, litter size, fetal body measurements, and soft-tissue and skeletal examinations (Rao et al. 1980).

The highest NOAEL values from each reliable study for developmental effects in each species and duration category are recorded in Table 2-1, and plotted in Figure 2-2.

Oral

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 odds ratio increased to 2.81 when exposure was recategorized as detected versus not detected. Croen et al. (1997) reported an increased crude odds ratio (OR=2.8; 95% 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, concurrent mixed chemical exposures indicate that the results are only suggestive, do not

establish a cause-and-effect relationship, and should be interpreted with caution. Primary routes of exposure in these epidemiological studies may have been both oral and inhalation (including inhalation of 1,2-dichloroethane volatilized from household water).

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 gestation days 0–18 (Lane et al. 1982) or 510 mg/kg/day on gestation days 7–14 (Kavlock et al. 1979). Rats that were treated with 198 mg/kg/day by gavage on gestation days 6–20 showed 30% reduced body weight gain and some embryo-lethal effects (increased non-surviving implants and resorption sites per litter), but no fetotoxicity or teratogenicity as indicated by fetal sex ratio, fetal body weight, and incidences of visceral and skeletal variations and malformations (Payan et al. 1995).

Dermal

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

2.18 CANCER

Inhalation

Specific evidence associating inhalation exposure to 1,2-dichloroethane with the occurrence of cancer in humans was not found in the literature reviewed. 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 the increased deaths due to pancreatic cancer and lymphatic and hematopoietic cancers in a cohort of workers in chlorohydrin production plants where 1,2-dichloroethane was a production byproduct (Benson and Teta 1993). Increased risk of primary breast cancer (odds ratio [OR]=2.2; 95% confidence interval [CI]=1.4–3.6; no latency) was observed in Danish men who were occupationally exposed to unreported levels of gasoline and combustion products containing 1,2-dichloroethane, compared to workers who were not exposed (according to job type and trade code) (Hansen 2000). The OR increased to 2.5 (95% CI=1.3–4.5) among workers with a latency of >10 years (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 increased risk of stomach cancers (relative risk [RR]=1.3; 95% CI=1.0–1.5), liver and

intrahepatic bile duct cancers (RR=1.3; 95% CI=0.9–1.8), and cancers of the trachea, bronchus, and lung (RR=1.1; 95% CI=1.0–1.2) (Goldberg et al. 1995). Female residents showed increased risk of stomach cancer (RR=1.2; 95% CI=0.9–1.5) and cervix uteri cancer (RR=1.2; 95% CI=1.0–1.5). None of these epidemiology studies dealt with 1,2-dichloroethane exposure exclusively, and the concurrent exposure to other chemicals or solvents confounded the results.

The carcinogenicity of inhaled 1,2-dichloroethane has been evaluated in chronic experiments in both rats and mice. Nagano et al. (2006) exposed F344 rats for to 1,2-dichloroethane concentrations of 10, 40 or 160 ppm for 6 hours/day, 5 days/week, for 104 weeks (2 years), and exposed BDF1 mice to 10, 30, or 90 ppm for the same frequency and duration. A dose-dependent increase in benign and malignant tumors was observed in rats of both sexes and female mice; peritoneal mesothelioma in male rats, fibroadenomas and adenocarcinomas in female rats, and subcutaneous fibromas and mammary gland fibroadenomas in both sexes. Increased incidence of bronchioloalveolar adenomas and carcinomas, endometrial stromal polyps, mammary gland adenocarcinoma, and hepatocellular adenomas was also dose-dependent in female mice (Nagano et al. 2006). The mice and rat survival rates were consistent among all exposure groups and the study design was strong. In rats, increased incidence of tumors appeared at 40 ppm of exposure to 1,2-dichloroethane, and at 90 ppm in female mice. Previous studies on mice and rats failed to find 1,2-dichloroethane induced carcinogenic effects following chronic exposure (Maltoni et al. 1980; Cheever et al. 1990). Maltoni et al. (1980) exposed Sprague-Dawley rats and Swiss mice to 1,2-dichloroethane at concentrations of 5, 10, 50 or 150-250 ppm 7 hours/day, 5 days/week, for 78 weeks. This study was limited due to 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 (Maltoni et al. 1980). Cheever et al. (1990) exposed rats to 50 ppm of 1,2-dichloroethane intermittently for 2 years, and was limited by its use of a single dose level, which was seemingly too low to demonstrate tumor induction (the relatively low exposure concentration of 50 ppm was chosen because it was the U.S. occupational standard at the time the experiment was initiated).

Oral

Little information is available concerning 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. A statistically significant association was observed between the presence of 1,2-dichloroethane in drinking water and an increased incidence of colon (p=0.009) and rectal (p=0.02) cancer in men aged 55 years or older. However, it is highly likely that the study population was concomitantly exposed to other chemicals.

1,2-Dichloroethane was found to be carcinogenic in rats and mice that were exposed by gavage for up to 78 weeks (NCI 1978). Statistically significant increases in multiple tumor types (malignant and benign) were noted in treated animals of both species. An increased incidence 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 of both exposure groups (47 and 95 mg/kg/day). In the high-dose group (95 mg/kg/day), 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 incidence of hepatocellular carcinomas and pulmonary adenomas 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 pulmonary adenomas, adenocarcinomas of the mammary gland, and endometrial polyps and sarcomas. In conclusion, 1,2-dichloroethane administered by gavage produced tumors in rats and mice in tissues distant from the site of administration. 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. Despite these study limitations, it is prudent to consider the possibility of tumor induction when the chemical is administered via other routes and absorbed into systemic circulation as well.

In another study, 1,2-dichloroethane was administered to $B6C3F_1$ mice in their drinking water using a two-stage (initiation/promotion) treatment protocol; no increase in tumorigenicity was found (Klaunig et al. 1986). In this study, mice were initiated with diethyl nitrosamine (DENA) for 4 weeks and subsequently treated with 159 or 475 mg/kg/day 1,2-dichloroethane for 52 weeks. 1,2-Dichloroethane did not increase the incidence of lung or liver tumors either alone or as a tumor promoter following DENA initiation. However, severe study limitations (including short duration, high liver-tumor incidence in untreated controls [20%] and in DENA-initiated [100%] mice after 52 weeks, lack of positive controls, and failure to specify the compound purity) invalidate any conclusions about the lack of carcinogenicity of 1,2-dichloroethane. A shorter-term initiation/promotion study in rats, based on the use of enzyme-altered liver foci as a marker for preneoplastic changes, also failed to confirm the carcinogenic potential of 1,2-dichloroethane (Milman et al. 1988), but was limited by use of a single dose level (100 mg/kg), short exposure duration (single dose in initiation study and 7 weeks in promotion study), and monitoring of an end point not firmly established as proof of carcinogenicity.

In another two-stage oral cancer assay (Pott et al. 1998), a 16-week co-administration of 1,2-dichloroethane and arsenic (in drinking water) with vinyl chloride and trichloroethylene (administered by gavage) (all of which are chemicals commonly found at hazardous waste sites) produced dose-related inhibition of the promotion of preneoplastic hepatic lesions and bronchoalveolar hyperplasia and pulmonary adenomas in male Fisher 344 rats, after a 4-week initiation with a series of three broad-spectrum initiators. The drinking water concentrations of 1,2-dichloroethane ranged from 3 ppm (approximately 0.47 mg/kg/day) in the low exposure group (with relatively low levels of the other test substances) to 300 ppm (approximately 47 mg/kg/day) in the high exposure group (with relatively high levels of the other test substances). The study has limited usefulness for understanding lifetime risk of cancer from 1,2-dichloroethane exposure because of co-exposure with other known carcinogens, the use of a short promotion exposure period (16 weeks), small numbers of test animals (15 per exposure group), and evaluation of effects to only one sex (males).

CEL values from the chronic NCI (1978) study in rats and mice are recorded in Table 2-2 and plotted in Figure 2-3.

EPA has derived a slope (potency) factor (q_1*) of 0.091 $(mg/kg/day)^{-1}$ for cancer risk associated with oral exposure to 1,2-dichloroethane based on the study by NCI (1978) in rats (EPA 1987c). This slope factor corresponds to a drinking water unit risk of $2.6x10^{-6}$ $(\mu g/L)^{-1}$ and an inhalation unit risk of $2.6x10^{-5}$ $(\mu g/m^3)^{-1}$. Based on this potency factor, oral doses of 1,2-dichloroethane associated with excess human lifetime cancer risks are: $1x10^{-3}$ mg/kg/day with a risk of 10^{-4}, $1x10^{-4}$ mg/kg/day with a risk of 10^{-5}, $1x10^{-5}$ mg/kg/day with a risk of 10^{-6}, and $1x10^{-6}$ mg/kg/day with a risk of 10^{-7}. A risk level of 10^{-4} corresponds to one excess cancer death in 10,000, a risk level of 10^{-5} corresponds to one excess cancer death in 100,000, a risk level of 10^{-6} corresponds to one excess cancer death in 1 million, and a risk level of 10^{-7} corresponds to one excess cancer death in 10 million persons. These affected population figures are derived based on the assumption that individuals are exposed continuously for their entire lifetime (estimated as 70 years) to these oral doses of 1,2-dichloroethane. The range of doses associated with excess lifetime cancer risks of 10^{-4} to 10^{-7} is plotted in Figure 2-3. The estimated excess cancer risks are upper-bound risks (i.e., the true risks are not likely to exceed the upper-bound risk estimate and may be lower).

Dermal

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

The carcinogenicity of 1,2-dichloroethane following dermal exposure has been evaluated in mice (Van Duuren et al. 1979; Suguro et al. 2017). A statistically significant increase ($p<0.0005$) in pulmonary papillomas was observed in mice treated with 126 mg of 1,2-dichloroethane 3 times/week for 428–576 days (Van Duren 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. Bronchioloalveolar adenomas and adenocarcinomas significantly increased in rasH2 mice of both sexes treated dermally with a mixture of 126 mg of 1,2-dichloroethane in 200 µl of acetone daily for 26 weeks (Suguro et al. 2017). Additionally, bronchioloalveolar proliferative lesions were more prominent in female mice. These findings indicate 1,2-dichloroethane is a potential lung carcinogen in mice.

The DHHS has determined that 1,2-dichloroethane is reasonably anticipated to be a human carcinogen (NTP 2016). IARC has placed 1,2-dichloroethane in Group 2B (possibly carcinogenic to humans) (IARC 2016). EPA has classified 1,2-dichloroethane as a Group B2 carcinogen (probable human carcinogen) (EPA 1987c). This EPA category applies to chemical agents for which there is sufficient evidence of carcinogenicity in animals.

2.19 GENOTOXICITY

Inhalation

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 lymphocyte sister chromatid exchange (SCE) frequency (Cheng et al. 2000). Mean duration of employment for all employees ranged from 7.1 to 9.7 years, and workers were characterized into 3 exposure groups: low VCM-low 1,2-dichloroethane, low VCM-moderate 1,2-dichloroethane, and moderate VCM-moderate 1,2-dichloroethane exposure. SCE frequency is used as a parameter to investigate genotoxicity since it is one of the most sensitive markers of DNA damage (Cheng et al. 2000). Statistically significant increases in SCE frequency compared to the control were observed at groups exposed to low VCM-moderate 1,2-dichloroethane (0.69-1.31 ppm) and moderate VCM-moderate 1,2-dichloroethane (0.77 ppm). SCE frequency increase was also associated with smoking, but also increased among non-smoking workers. (Cheng et al. 2000). The study was limited in that it could not properly account for age of workers, due to the limited age range of workers in the study, in addition to other lifestyle factors.

Inhalation of 1,2-dichloroethane has produced genotoxic effects in animals but cannot be concluded to be a genotoxic carcinogen. Exposure to 1,000 ppm for 4 hours produced irreversible deoxyribonucleic acid (DNA) damage in mice as evidenced by single-stranded breaks in hepatocytes, though 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 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-dichloroethane 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). A study of Fischer-344 rats exposed to 200 ppm of 1,2-dichloroethane by inhalation for 6 hours per day, 7 days per week for 28 days, did not find increased DNA damage in mammary epithelial cells (Boverhof et al. 2018). No effect on serum prolactin levels or cell proliferation was seen in mammary epithelial cells, and DNA adduct levels, including the N7-guanylethyl glutathione crosslink adduct, were not considerably high compared to levels in the liver. The authors suggest the results contribute to a weight of evidence of 1,2-dichloroethane as a non-genotoxic carcinogen (Boverhof et al. 2018). In a study investigating the relationship between inhalation exposure to 1,2-dichloroethane and covalent binding to liver and lung DNA, female Fischer-344 rats were 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). The DNA covalent binding index was elevated, compared to controls, after both exposure scenarios. However, in both the liver and the lung, the effect was much greater (approximately 35 times greater) after peak exposure, suggesting that acute exposure to highly concentrated 1,2-dichloroethane may pose a greater genotoxic hazard than protracted low-level exposure. The results of this study support the hypothesis that toxicity of 1,2-dichloroethane is associated with saturation of mixed function oxidation (MFO) enzymes. Also consistent with this hypothesis is the fact that oral doses were more potent than comparable inhalation doses, and that a route-of-administration effect has been reported for 1,2-dichloroethane carcinogenicity.

Oral

No studies were located regarding genotoxicity in humans after oral exposure to 1,2-dichloroethane, although oral exposure has produced genotoxic effects in animals. A single oral dose of 100 mg/kg of 1,2-dichloroethane produced irreversible DNA damage in mice, as revealed by single-stranded breaks in hepatocytes (Storer et al. 1984). Hepatocytic DNA damage was also induced in female rats receiving two oral 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). A single oral dose of 150 mg/kg produced high levels of DNA binding in the liver of rats (Cheever et al. 1990). The level of binding produced was similar in rats that had previously been exposed via inhalation to 50 ppm of 1,2-dichloroethane vapor for 2 years, and in

rats that had served as controls in the 2-year study. No significant increase in lactose operon (lacZ) mutation frequency was seen in the liver of male Muta™ Mice, 7, 14 or 28 days after receiving single oral gavage doses of 75 mg/kg or 150 mg/kg of 1,2-dichloroethane (Hachiya or Motohashi 2000). No increase in lac Z mutation frequency was seen in the testis DNA of the same mice.

Dermal

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

In vivo

The results of in vivo genotoxicity studies by all routes of exposure are summarized in Table 2-4. As indicated in the table, the ability of 1,2-dichloroethane to 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 and oral exposures, in rats (Banerjee 1988; Prodi et al. 1986; Watanabe et al. 2007) and mice (Banerjee 1988; Hellman and Brandt 1986; Prodi et al. 1986; Watanabe et al. 2007) administered a single intraperitoneal injection of 1,2-dichloroethane at dose levels as low as 6.35 μmol/kg (0.00635 mg/kg) (Prodi et al. 1986). Actual 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). DNA damage, in the form of increased DNA adduct levels in the kidney and liver, was not demonstrated following a single intraperitoneal injection of 5 mg/kg-bodyweight in male rats, and male and female mice (Watanabe et al. 2007). No increases in lac Z mutation frequency were observed in the liver and testis of male Muta™ Mice 28 days after receiving successive intraperitoneal injections totaling 200 mg/kg (5 doses of 40 mg/kg) or 280 mg/kg (6 doses of 20 mg/kg + 4 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. In one study, DNA binding was associated with decreased rates of DNA synthesis and transcription (Banerjee 1988). However, the results of this study are questionable. Genotoxicity assays for clastogenic effects obtained mixed results, with a positive effect on sister chromatid exchange (believed to be caused by strand breakage) in mouse 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 45–400 mg/kg (Jenssen and Ramel 1980; King et al. 1979). The only in vivo assay for mutagenicity in mammalian cells produced only a marginal response after a single intraperitoneal

injection of an unreported dose. However, there is abundant evidence that 1,2-dichloroethane produces both somatic and sex-linked recessive lethal mutations in Drosophila melanogaster in vivo.

In vitro

The results of in vitro genotoxicity studies are presented in Table 2-5. The evidence from these studies overwhelmingly indicates that 1,2-dichloroethane is capable of interacting with DNA to produce genotoxic effects in vitro. Results were positive in assays for point mutations in human cells, animal cells, and bacteria, unscheduled DNA synthesis (i.e., DNA repair activity) in human and animal cells, DNA binding in animal cells, and mitotic segregation aberrations leading to aneuploidy in fungi. 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). 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. Mutagenicity was increased in TA100 strain Salmonella typhimurium 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, an analog of the proposed intermediate product of the conjugation of 1,2-dichloroethane with glutathione, was a potent inducer of unscheduled DNA synthesis and micronucleus formation in mammalian cells in vitro (Vamvakas et al. 1988, 1989). S-(2-Chloroethyl)glutathione itself was found to be a potent mutagen in S. typhimurium. Although it produced only intermediate levels of alkylation, the results indicate that the guanyl adduct that is formed appears to be unusually mutagenic (Humphreys et al. 1990). 1,2-Dichloroethane was found to be non-mutagenic in somatic cells and mature spermatozoa in D. melanogaster, further suggesting the lack of genotoxicity through a direct mechanism (Ballering et al. 1993).

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

Species (test system)	End Point	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
Mouse	Micronuclei	-	Jenssen and Ramal 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
Rat liver and kidney	DNA binding	+	Watanabe et al. 2007
Rat liver and lung	DNA binding	+	Baertsch et al. 1991
Rat liver	DNA binding	+	Banerjee 1988
Rat liver	DNA binding	+	Cheever et al. 1990
Mouse liver	DNA damage	+	Storer and Conolly 1983, 1985; Storer et al. 1984
Mouse liver	DNA damage	+	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
Rat bone marrow cells	Chromosomal aberration	+	Lone et al. 2016
Insect assays:			
Drosophila melanogaster/somatic Mutation	Gene mutation	+	Nylander et al. 1978
D. melanogaster/somatic mutation	Gene mutation	+	Chroust et al. 2001; Chroust et al. 2007
D. melanogaster/somatic mutation	Gene mutation	+	Romert et al. 1990
D. melanogaster/somatic mutation	Gene mutation	+	Kramers et al. 1991
D. melanogaster/somatic mutation	Gene mutation	+	Ballering et al. 1994
D. melanogaster/somatic mutation	Gene mutation	+	Vogel and Nivard 1993
D. melanogaster/sex-linked recessive	Gene mutation	+	King et al. 1979
D. melanogaster/sex-linked recessive	Gene mutation	+	Kramers et al. 1991
D. melanogaster/recessive lethal	Gene mutation	+	Ballering et al. 1993

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

Species (test system)	End Point	Results	Reference
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
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

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

Species (test system)	End Point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium	Gene mutation	+	+	Milman et al. 1988
S. typhimurium	Gene mutation	+	+	Barber et al. 1981
S. typhimurium	Gene mutation	+	+	Kanada and Uyeta 1978
S. typhimurium	Gene mutation	+	+	Nestmann et al. 1980
S. typhimurium	Gene mutation	+	+	Rannug et al. 1978
S. typhimurium	Gene mutation	+	+	Van Bladeren et al. 1981
S. typhimurium	Gene mutation	+	No data	Rannug and Beije 1979
S. typhimurium	Gene mutation	+	-	Cheh et al. 1980
S. typhimurium	Gene mutation	+	-	Moriya et al. 1983
S. typhimurium	Gene mutation	-	-	King et al. 1979
S. typhimurium	Gene mutation	No data	+	Thier et al. 1993
S. typhimurium	Gene mutation	No data	+	Simula 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

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

Species (test system)	End Point	Results: With activation	Results: Without activation	Reference
Eukaryotic organisms:				
Fungi:				
A. nidulans	Mitotic segregation aberrations	No data	+	Crebelli et al. 1984
A. nidulans	Aneuploidy induction	No data	+	Crebelli et al. 1988
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	-	Milmann 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

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

3.1 TOXICOKINETICS

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

- Absorption: 1,2-Dichloroethane is well absorbed after inhalation exposure through the lungs (Urusova 1953; EPA 1980; Nouchi et al. 1984), through the gastrointestinal tract after oral exposure (Hueper and Smith 1935; Lochhead and Close 1951; Yodaiken and Babcock 1973), and through the skin after dermal exposure in humans (Urusova 1953; Gajjar and Kasting 2014). In animal studies, equilibrium blood concentrations of 1,2-dichloroethane were obtained 2–3 hours after inhalation exposure (Reitz et al. 1980, 1982; Spreafico et al. 1980), 15–60 minutes after oral exposure (Reitz et al. 1980, 1982; Spreafico et al. 1980), and 1–2 hours after aqueous dermal exposure (Morgan et al. 1991). Absorption probably occurs by passive diffusion for all three routes of exposure.
- Distribution: 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 (Spreafico et al. 1980; Take et al 2013). The liver and lung were shown to have lower equilibrium levels of 1,2-dichloroethane than the blood (Spreafico et al. 1980).
- Metabolism: 1,2-Dichloroethane is readily metabolized in the body (D'Souza et al. 1988; Reitz et al. 1982; Spreafico et al. 1980). The primary metabolic pathways for this chemical are MFO and glutathione conjugation (Reitz et al 1982). Oxidation products include chloroacetaldehyde, 2-chloroethanol, and 2-chloroacetic acid (Yllner 1971; NTP 1991). MFO metabolism of 1,2-dichloroethane appears to be saturable at oral gavage doses ~25 mg/kg and inhalation concentrations of ~150 ppm (.500 mg/kg), both of which correspond to blood levels of 5–10 µg/mL (D'Souza et al.1988; Reitz et al. 1982; Spreafico et al. 1980). Glutathione conjugation becomes relatively more important at larger doses, and increased metabolism by this pathway may be responsible for the toxic effects noted at these high doses (Reitz et al 1982).
- Excretion: Excretion of 1,2-dichloroethane and metabolites is rapid; in animal studies, excretion was essentially complete 48 hours after acute exposure (Reitz et al 1982). Following inhalation exposure to labeled 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 (CO2) in the exhaled air (7%) (Reitz et al. 1982). Following oral exposure to labeled 1,2-dichloroethane, the amount of radioactivity excreted by these routes was reduced, and a large percentage of the dose (29%) was excreted as unchanged 1,2-dichloroethane in the exhaled air (Reitz et al. 1982). The increased exhalation of unchanged 1,2-dichloroethane may reflect the saturation of biotransformation enzymes.

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. 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 (1980a) 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 further evidence that this chemical is readily absorbed through the lungs by humans. However, adverse effects were seen at 20 hours post-exposure, prompting the 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. 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.

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) subsequent to accidental (Hueper and Smith 1935) or intentional (Lochhead and Close 1951; Yodaiken and Babcock 1973) ingestion of 1,2-dichloroethane by humans, 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 [14C]-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 [14C]-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 of 1,2-dichloroethane were about four times higher following oral administration in water than when given in corn oil. This may relate to higher solubility vehicles with regard to the absorption of xenobiotics. Furthermore, the time taken to reach peak levels was approximately three times longer when administered in corn oil, compared to water. 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, and thus, the reliability of these results cannot be assessed. A more recent study conducted by Gajjar et al. (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 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. 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 of neat 1,2-dichloroethane of 6,280 $\mu g/cm^2$-hour and 3,842 $\mu g/cm^2$-hour by each laboratory, respectively. Compared with neat fluxes measured in the same laboratory, flux from saturated aqueous solution was slightly lower. 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.

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, though 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 [14C]-1,2-dichloroethane distribution in maternal rats following a single bolus dose of approximately 160 mg/kg on gestation day 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 less than 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 gestation day 18, the pattern of distribution was similar, except greater accumulation occurred in the developing fetus and placenta. At 48 hours post-exposure (the 20th day of gestation), the majority of 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

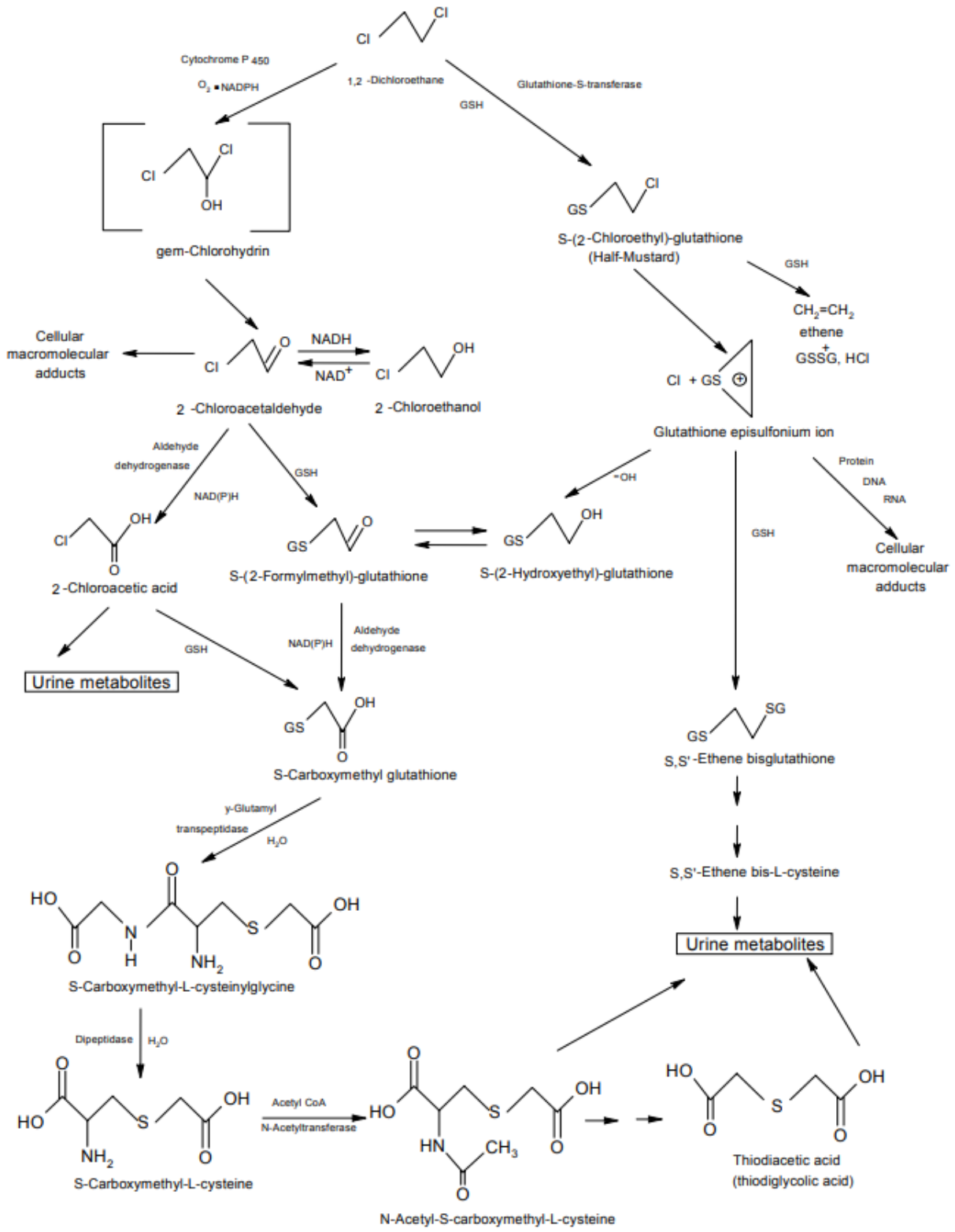
remained in fat longer than in other soft tissues, as indicated by a lower estimated elimination coefficient in fat (0.0088 min-1) relative to other tissues (ranged from 0.0226 to 0.0514 minute-1).

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) (D'Souza et al. 1988; Reitz et al. 1982; Spreafico et al. 1980). Metabolic saturation appears to occur at lower concentrations after oral (gavage) administration than after inhalation exposure. This will be discussed further below. 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).

No studies were located regarding metabolism specifically in children. However, the expression of certain enzymes is known to be developmentally regulated. An N-acetyltransferase (NAT) is thought to be involved in 1,2-dichloroethane metabolism at a step subsequent to a glutathione (GSH) conjugation (see Figure 3-1). There are two NATs (NAT1 and NAT2) that are expressed in humans (Parkinson 1996) and

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



Source: NTP 1991

one, NAT2, is known to be developmentally regulated (Leeder and Kearns 1997). Some NAT2 activity is present in the fetus at 16 weeks. Activity is low in virtually 100% of infants and reaches adult activity at 1 to 3 years of age (Leeder and Kearns 1997).

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 (CA), an oxidative metabolite of DCE. CA is a very potent mutagen *in vitro* (McCann et al. 1975). Several researchers have also presented *in vitro* evidence that DCE is activated to a mutagen by glutathione (GSH) conjugation (Rannug et al. 1978; van Bladeren et al. 1979). Electrophilic episulfonium ions formed via the GSH pathway are believed to bind to DNA and cause genetic damage (Guengerich et al. 1987). Kramer et al. (1987) described the role of GSH-generated episulfonium ions in DCE-induced nephrotoxicity in rats. Results of relatively recent research indicate that oxidative metabolites of DCE 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 [14C]-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 14C was recovered as urinary metabolites and only 2% of the administered 14C 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 2 groups of investigators, 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 [14C]-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 five 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 chloroacetaldehyde by hepatic nuclear cytochrome P-450 (Casciola and Ivanetich 1984). Guengerich et al. (1980) proposed a pathway involving microsomal cytochrome P-450 (in the presence of oxygen and nicotinamide adenine dinucleotide phosphate [reduced form] [NADPH]) and MFO to explain the production of 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 cytochrome P-450 2E1 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). 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).

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 14C-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 14C-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 14C-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 per week for 4 weeks. At 48 hours after administration of the radiolabeled compound, expired volatile metabolites, CO2, excreta (feces and urine), and the carcass accounted for approximately 11.5, 8.2, 69.5, and 7% of administered radioactivity in rats, and 7.7, 18.2, 81.9, and 2.4% of the administered dose in mice.

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) and/or in breast milk of nursing women (Urusova 1953).

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 (PBPD) 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). 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. Figure 3-2. shows a conceptualized representation of the Sweeney et al. (2008) model. 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

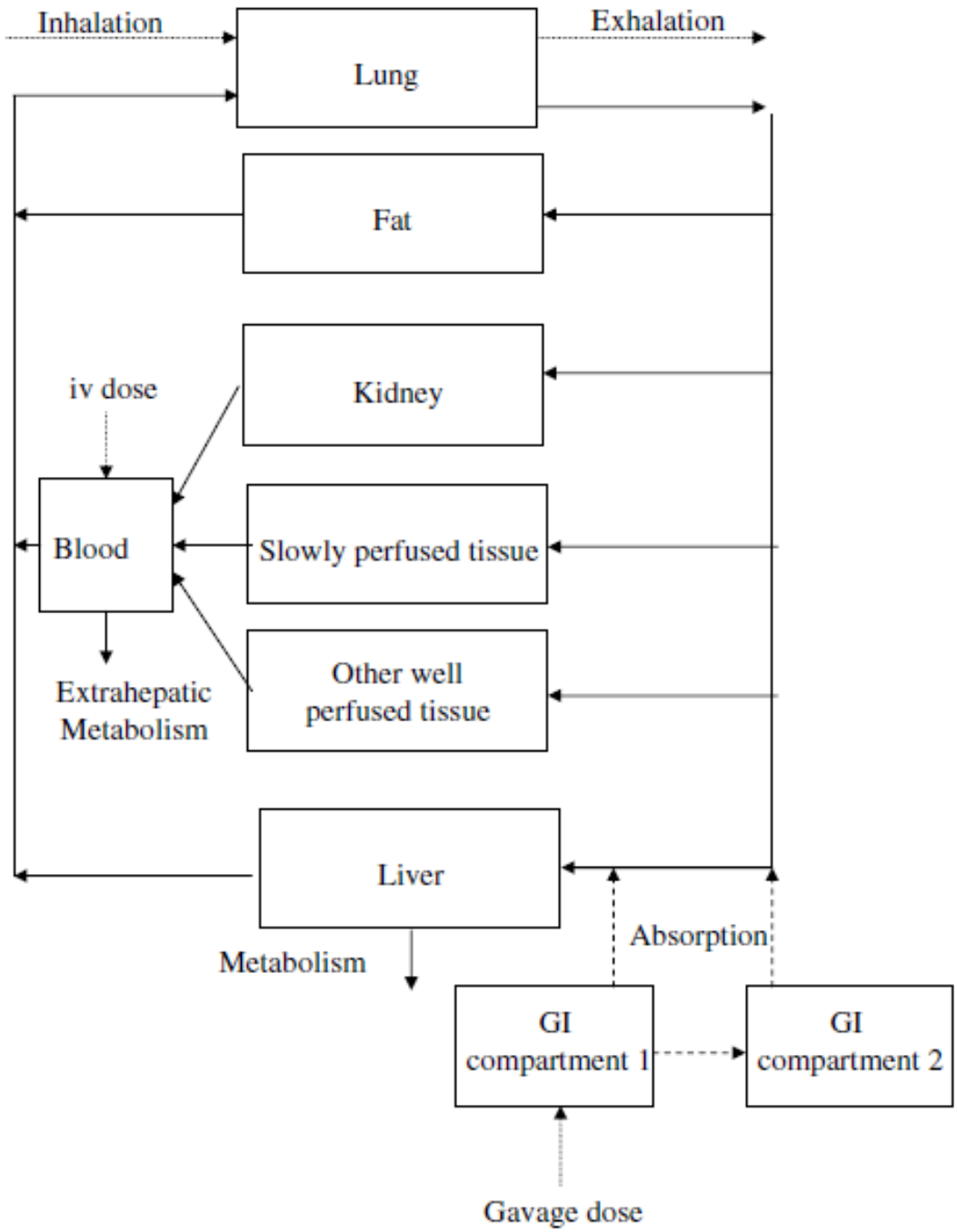
rats. The Sweeney et al. (2008) model was used in Sweeney et al. (2016) to extrapolate the oral NOAEL and LOAEL of existing health effect studies in rats to the inhalation route. However, it is unclear how well the Sweeney et al. (2008) model would perform in extrapolating doses between species, such 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.

Gargas et al. (1989) measured and presented blood:air partition coefficients for chemicals, including 1,2-dichloroethane. 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. These values are used to develop the dose adjustment factor value for category 3 effects (e.g., liver, kidney), which 1,2-dichloroethane produces at exposures relevant for consideration. EPA (2012) used these data to develop a dose adjustment factor (value 1.6) for 1,2-dichloroethane.

Figure 3-2. Compartments and Pathways of 1,2-Dichloroethane in the Sweeney et al. (2008) Model



Source: Sweeney et al. 2008

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 5th 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 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).

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- to 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 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 [14C]-1,2-dichloroethane distribution in maternal rats following a single oral bolus dose of approximately 160 mg/kg on gestation day 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 gestation-day 18 administration than after the gestation-day 12 administration. At 48 hours after the gestation-day 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 GSH 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 to 3 years of age (Leeder and Kearns 1997). It is not clear in NTP (1991), the source of the metabolism

information in Figure 3-1, 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 to 3 months of age exhibited mean levels of the enzyme of about 10% of adult values, infants 3 to 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 (Vieira et al. 1998; Hines 2008). There is less of a consensus about the general ontogeny of GSH in humans (Hines 2008).

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. 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. Cottalasso et al. (2002) found that 1,2-dichloroethane increased liver toxicity in rats, following chronic ethanol consumption. 1,2-Dichloroethane is a known substrate for human CYP2E1 (Gonzalez and Gelboin 1994). CYP 2EI 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.

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).

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.

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.

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, these measurements would have to be made at a known time since exposure, since 1,2-dichloroethane is rapidly eliminated from the body (see Section 3.1.4). In addition, without additional data, it is not possible to establish from such measurements the precise environmental levels of 1,2-

dichloroethane to which these individuals were exposed. 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 2 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 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]) in male Sprague-Dawley rats during a 24-hour post-administration period, 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 end point 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 the halogens.

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 cytochrome P4502E1. The urinary levels of chloroacetic acid increased significantly in the group of mice exposed to 1,2-dichloroethane through inhalation for up to three days, while the intervention group that was also exposed to 1,2-dichloroethane but was fed a substance that inhibits cytochrome P4502E1 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 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 primary targets of 1,2-dichloroethane identified in humans are probably 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; 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; 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 cytochrome P-450 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 cytochrome P-450 enzymes by phenobarbital and/or Aroclor 1254 increases the rate of MFO metabolism of 1,2-dichloroethane 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 cytochrome P-450 2E1, the major MFO enzyme involved in 1,2-dichloroethane metabolism (Guengerich et al. 1991). Since ethanol and 1,2-dichloroethane are both cytochrome P-450 2E1 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-dichloroethane (Sato et al. 1981). At low tissue ethanol concentration, cytochrome P-450 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 five-fold by co-treatment with disulfiram (Cheever et al. 1990). In addition, the amount of 14C 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 cytochrome P-450 2E1, 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 cytochrome P-450 2E1 (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 3 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 et al 2011).

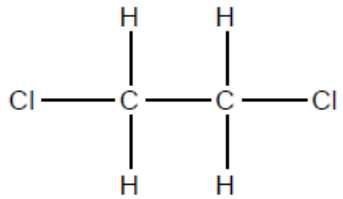
CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

1,2-Dichloroethane is a colorless, oily liquid composed of two carbon atoms each bound to each other, one chlorine atom, and two hydrogen atoms. 1,2-Dichloroethane is primarily used in the production of vinyl chlorides, though it is also added to leaded gasoline, used as a dispersant in rubber and plastics, 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	Reference
Chemical name	1,2-Dichloroethane	PubChem 2021
Synonym(s) and Registered trade name(s)	1,2-Bichloroethane; 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	PubChem 2021
Chemical formula	$C_2H_4Cl_2$	PubChem 2021
Chemical structure		Budavari et al. 1996
CAS registry number	107-06-2	PubChem 2021
NIOSH RTECS	KI0525000	PubChem 2021
EPA hazardous waste	U077	PubChem 2021
DOT/UN/NA/IMO shipping	UN 1184	PubChem 2021
HSDB	65	PubChem 2021

CAS = Chemical Abstracts Service; HSDB = Hazardous Substances Data Bank

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 relatively high vapor pressure. 1,2-Dichloroethane has a very high 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	PubChem 2021
Color	Clear, colorless	PubChem 2021
Physical state	Oily liquid; heavy liquid	PubChem 2021
Melting point(s)	-35.6 °C	PubChem 2021
Boiling point(s)	83.4 °C	PubChem 2021
Critical temperature and pressure	563 K and 5360 kPa	PubChem 2021
Density	1.2454 at 25°C	PubChem 2021
Taste	Sweet	PubChem 2021
Taste threshold:	No data	PubChem 2021
Odor	Pleasant, chloroform-like; sweet	PubChem 2021
Odor threshold:		
Water	20 mg/L	Verschueren 1996
Air	12 ppm 50 ppm 100 ppm	Verschueren 1996 Torkelson and Rowe 1981 Weiss 1980
Solubility:		
Water	8600 mg/L at 25 °C 8690 mg/L at 20 °C	PubChem 2021 Verschueren 1996
Organic solvent(s)	Miscible with alcohol, chloroform, ether; Soluble in acetone, benzene, chloroform	PubChem 2021
Inorganic solvent(s)	No data	PubChem 2021
Partition coefficients:		
Log K_{ow}	1.48	PubChem 2021
Log K_{oc}	33	
Vapor pressure at 25 °C	78.9 mmHg (10.5 kPa)	PubChem 2021
Henry's law constant at 25 °C	1.18×10^{-3} atm-m^3/mole	PubChem 2021
Degradation half-life in air via reaction with OH radicals	2.48×10^{-13} cu cm/molc-sec at 25 °C	PubChem 2021
Dissociation constants:	No data	PubChem 2021
Autoignition temperature	413 °C	PubChem 2021

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

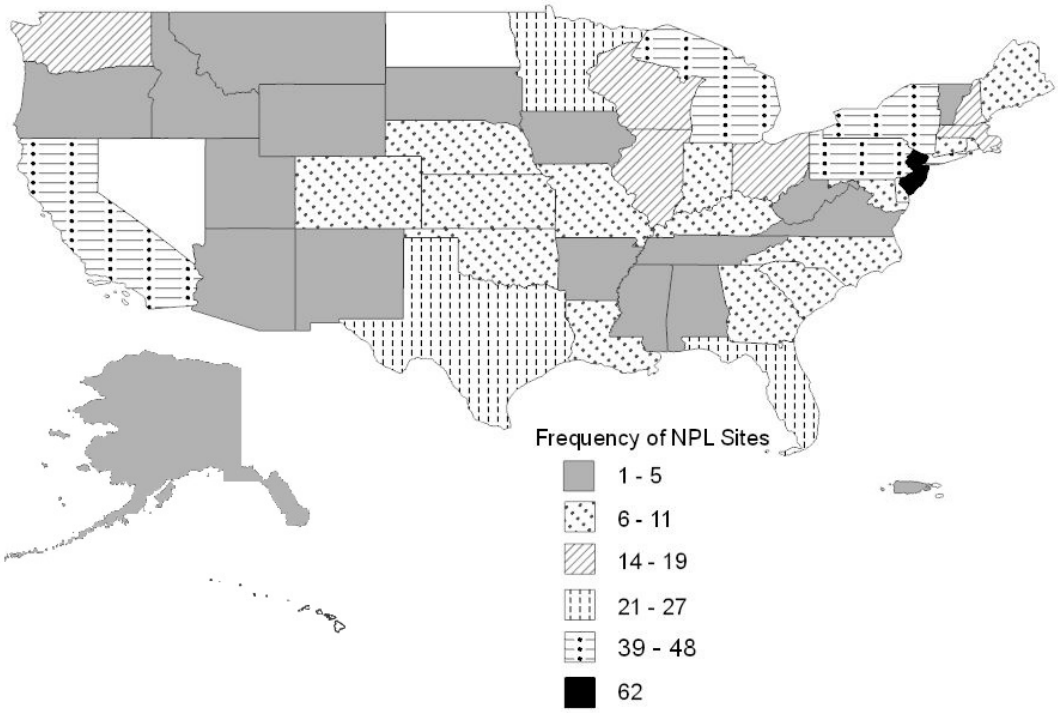
Property	Information	Reference
Flash point	13 °C	PubChem 2021
Flammability limits in air	6.2 – 16% by volume	PubChem 2021
Conversion factors:	1 ppm in air = 4 mg/m^3 ppm(v/v)x4.05=mg/m^3 mg/m^3x0.247=ppm(v/v)	PubChem 2021 Torkelson and Rowe 1981 Torkelson and Rowe 1981
Explosive limits	6.2 – 15.9%	PubChem 2021
Incompatibilities and reactivity	Incompatible with strong oxidizing agents; Violent reaction with aluminum, dinitrogen tetroxide, ammonia, dimethylaminopropylamine	PubChem 2021

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

1,2-Dichloroethane has been identified in at least 585 of the 1,854 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2017). However, the number of sites evaluated for 1,2-dichloroethane is not known. The number of sites in each state is shown in Table 5-1. Of these sites, 583 are located within the United States, and 2 are located in Puerto Rico.

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



Source: ATSDR 2017

- 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 more than 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 (Anonymous 1998; EPA 1985a), as a lead scavenger in leaded aviation gasoline (Henderson et al. 2009), and as a solvent in closed systems (Dow Chemical Company 1989) may result in its release to the environment. The use of 1,2-dichloroethane as a lead scavenger has decreased significantly in the past several decades as leaded gasoline use has declined. 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 TSCA Inventory Update Reporting data details a range from less than 10 workers to 500-999 workers for each of the 17 reporting plants that may be occupationally exposed to 1,2-dichloroethane (CDR 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 et al. 2004). Direct chlorination of ethylene occurs at 40-50º Celsius, usually using small amounts of ferric chloride as a catalyst, and less often aluminum chloride, antinomy pentachloride, and cupric chloride (Snedecor et al. 2004). Oxychlorination of ethylene occurs at

temperatures exceeding 200º Celsius in fixed or fluidized bed reactors in the presence of oxygen and copper chloride catalyst (Al-Zahrani et al. 2001; Snedecor et al. 2004).

The 2016 EPA Chemical Data Reporting dataset (CDR), which contains production and use information by chemical manufacturers and importers, reports that 6 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 (CDR 2016).

According to the Toxic Release Inventory (TRI), 55 facilities in the United States produced, processed or used 1,2-dichloroethane in 2017 (TRI17 2018). Table 5-1 summarizes information on facilities by state that reported manufacturing or processing of 1,2-dichloroethane to TRI in 2017. 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	5	311,000	3,109,995	6, 9, 10, 12
GA	1	--	--	--
IA	1	1,000	9,999	1, 13
IL	1	100,000	999,999	10
KS	1	100	999	12
KY	3	10,011,000	50,109,997	1, 3, 5, 6, 9
LA	14	341,110,000	1,111,100,087	1, 3, 4, 5, 6, 9, 10, 12, 13, 14
MI	1	10,000	99,999	10, 12
MO	2	1,100,000	10,999,998	6, 7, 10
MS	1	100,000	999,999	6
NC	1	1,000,000	9,999,999	10
NE	1	100,000	999,999	12
NY	1	-	99	12
OH	3	21,000	209,997	7, 9, 12
OR	1	10,000	99,999	12
SC	2	1,001,000	10,009,998	1, 5, 12
TX	13	731,131,100	2,161,311,086	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
UT	1	100,000	999,999	12
WA	1	1,000	9,999	14
WI	1	1,000	9,999	10, 11

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]

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

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

Source: TRI17 2018; Data are from 2017

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 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 exports 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

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[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, resins, rubber, and in paint, varnish and finish removers (O'Neil 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 (Vulcan Materials Company 1989; Henderson et al. 2009). Even after the ban of leaded gasoline, 1,2-dichloroethane has been used in leaded fuel for aviation, racing cars, marine engines, and farm equipment (Aronson and Howard 2008). 1,2-Dichloroethane was formerly registered as a fumigant, including as an insect and soil fumigant, for grains and orchards (IARC 1979; O'Neil 2013). 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 2016).

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 (40 CFR §261). The 2016 CDR reports that 1,2-dichloroethane was recycled at 3 facilities that domestically manufacture the chemical (CDR 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 (40 CFR 302, 40 CFR 261) 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 1985a, 1987b).

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 2018). 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's North American Industry Classification System (NAICS) codes is covered under EPCRA Section 313 or is a federal facility; and if their facility manufactures (defined to include importing) or processes any TRI chemical in excess of 25,000 pounds, or otherwise uses any TRI chemical in excess of 10,000 pounds, in a calendar year (EPA 2018).

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	5	2,937	4	21,707	0	0	3,496	21,152	24,648
GA	1	0	0	0	0	0	0	0	0
IA	1	9,294	7	0	0	0	9,301	0	9,301
IL	1	5,550	0	0	0	0	5,550	0	5,550
KS	1	2	0	0	0	0	2	0	2
KY	3	87,837	702	0	0	0	88,539	0	88,539
LA	14	222,723	774	0	1,334	120	223,545	1,406	224,951
MI	1	1,728	58	0	0	0	1,786	0	1,786
MO	2	2,778	5	0	0	0	2,783	0	2,783
MS	1	273	0	0	0	0	273	0	273
NC	1	6,085	0	0	0	728	6,085	728	6,813
NE	1	13	0	0	756	0	13	756	769
NY	1	0	0	0	0	0	0	0	0
OH	3	155	0	0	0	0	155	0	155
OR	1	8	0	0	16,470	0	16,478	0	16,478
SC	2	15,274	0	0	0	599,760	15,274	599,760	615,034
TX	13	79,893	759	3,923	8,414	20	84,575	8,435	93,010
UT	1	6	0	0	0	0	6	0	6
WA	1	0	0	0	0	0	0	0	0
WI	1	250	0	0	0	0	250	0	250
Total	55	434,807	2,309	25,630	26,974	600,628	458,112	632,236	1,090,349

RF = Reporting Facilities; UI = Underground Injection

[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 by a given facility.
[f] The sum of on-site surface water discharges, and off-site transfers to wastewater treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g] The sum of on-site and off-site disposal to underground injection wells (Class I wells and Class II-V).

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

[h] The sum of on-site and off-site disposal to: Resource Conservation and Recovery Act (RCRA) subtitle C landfills, other landfills, RCRA subtitle C surface impoundments, other surface impoundments, land treatment, other land disposal.
[i] Includes the sum of off-site transfers to: storage only, solidification/stabilization (metals only) disposal, other off-site management, waste broker for disposal, unknown.
[j] Total on-site disposal or other releases of the chemical including emissions to air, surface water discharges, land and underground injection wells.
[k] Total amount of chemical transferred off-site for disposal or other releases, including to POTWs.

Source: TRI17 2018; Data are from 2017

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 434,807 pounds (~197 metric tons) of 1,2-dichloroethane to the atmosphere from 47 domestic manufacturing and processing facilities in 2017 accounted for about 40% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2018). These releases are summarized in Table 5-2.

1,2-Dichloroethane has been identified in air samples collected at 32 of the 585 NPL hazardous waste sites where it was detected in some environmental media (ATSDR 2017).

5.3.2 Water

Estimated releases of 2,309 pounds (~1 metric ton) of 1,2-dichloroethane to surface water from 19 domestic manufacturing and processing facilities in 2019, accounted for about 0.21% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2018). 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). 1,2-Dichloroethane has been identified in water samples collected at 229 of the 585 NPL hazardous waste sites where it was detected in some environmental media (ATSDR 2017).

5.3.3 Soil

Estimated releases of 26,974 million pounds (~12 metric tons) of 1,2-dichloroethane to soils from 16 domestic manufacturing and processing facilities in 2017, accounted for about 2.5% of the estimated total environmental releases from facilities required to report to the TRI (TRI17 2018). An additional 25,630 million pounds (~12 metric tons), constituting about 2.35% of the total environmental emissions, were released via underground injection (TRI17 2018). These releases are summarized in Table 5-2.

1,2-Dichloroethane has been identified in soil samples at 49 of the 585 NPL hazardous waste sites where it was detected in some environmental media (ATSDR 2017).

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 2015), 1,2-dichloroethane is expected to volatilize from water surfaces, with the rate of volatilization depending on water flow and depth. 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 per 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; Sabljic et al. 1995), 1,2-dichloroethane is not expected to adsorb to suspended solids and sediment in the water column. An experimental bioconcentration factor 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; Sabljic 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 1985a). 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 2.2×10^{-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 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 less than a year 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 examines 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 2.1×10^{-8} second^{-1} and 1.8×10^{-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 4.9×10^{4} years at pH 9 and 15°C (Miyamoto and Urano 1996). Barbash and Reinhard (1989) found that the presence of 5.1×10^{-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 1995).

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 of 1,2-dichloroethane per gram 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.

1,2-Dichloroethane has been detected at low levels (ppb) in ambient urban and rural air, in indoor air samples of residences located near hazardous waste disposal sites, and in surface water, groundwater, and drinking water. Quantitative concentration information is presented in the following sections.

Table 5-3 shows the limit of detections 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	0.02 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	Number of quantitative measures	NPL sites
Water (μg/L)	18.0	47.02	26.2	399	229
Soil (μg/kg)	3.3x10^3	1990	114	70	49
Air (ppbv)	2.00	2.50	36.70	43	32

[a] Concentrations found in ATSDR site documents from 1981 to 2017 for 1,832 NPL sites (ATSDR 2017). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

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) (Juttner 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. According to the 2014 National Air Toxics Assessment, the mean 1,2-

dichloroethane concentration in the United States is 0.000409 μg/m^3 (EPA 2018a). Concentrations ranged from 0 μg/m^3 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 2018a).

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 volatile organic compounds (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 to 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 1988–1990 ranged from 0.070 to 0.28 μg/m^3 (0.017 to 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 detected 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).

Other possible sources of indoor air pollution 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 all concentrations of 1,2-dichloroethane were below ATSDR's media-specific noncancer comparison values for indoor air and vapor intrusion (Burk and Zarus 2013). The 1,2-dichloroethane detected in indoor air at eight of 148 vapor intrusion sites ranged from 0.0049 ppb (0.02 μg/m^3) to 6.7 ppb (27 μg/m^3). The 1,2-dichloroethane groundwater concentrations detected at nine of the vapor intrusion sites ranged from 0.987 μg/L to 150 μg/L.

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 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). Carcinogenic risk levels calculated using concentrations and available unit risk values were significantly higher than the bright-line of 1.0 x 10^{-6} for the integrated lifetime cancer risk in all five functional zones.

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

Year	Number of US locations	25th	50th	75th	95th	Maximum
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 2018c

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 8160 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).

1,2-Dichloroethane was found in drinking water samples from a number of urban and rural locations in the United States. This compound has been detected in drinking water samples from New Orleans, Miami, Philadelphia, and Cincinnati (Clark et al. 1986; Suffet et al. 1980). Private drinking water wells in Wisconsin contained >7 μg/L 1,2-dichloroethane in 2 of 7 wells surveyed (Krill and Sonzogni 1986); in Iowa, 3 public well water supplies contained concentrations of 4–19 μg/L (EPA 1985b), and in Kansas, 1 of 103 farmstead wells contained 1,2-dichloroethane at an average concentration of 1.25 μg/L during 1985–1986 (Steichen et al. 1988). It was also detected at 0.050 μg/L in drinking water samples from three of nine residences surveyed in the Love Canal area of Niagara, New York (Barkley et al. 1980). 1,2-Dichloroethane was detected in 0.5% of the drinking water wells studied between 1984 and 1990 in California at a maximum concentration of 24 μg/L (Lam et al. 1994b).

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 ten most prevalent chemicals found in Superfund sites in North Carolina (Tilley et al. 2017).

5.5.4 Other Media

1,2-Dichloroethane has been used as a lead scavenger in leaded aviation gasoline, and its approximate concentration in gasoline is 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 an 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 volatile organic chemicals (VOCs) with similar properties. Using a numerical model, Ma et al. (2016) concluded that 1,2-dichloroethane could

cause vapor intrusion problems. The model predicted that indoor air concentration of 1,2-dichloroethane can exceed EPA screening levels of 0.011 μg/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, 95th 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 1985a; 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 1985a). The estimated daily intake of 1,2-dichloroethane in Japan attributed to food ingestion is 0.004 mg/day (Miyahara et al. 1995).

The National Occupational Hazard Survey (NOHS), conducted by NIOSH from 1972 to 1974, estimated that 1.35 million workers in 111,222 plants were potentially exposed to 1,2-dichloroethane in the workplace in 1970 (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%). The largest numbers of exposed workers were employed in medical and other health services, automotive dealerships and service stations, and wholesale trade industries. The occupational groups with the largest

numbers of exposed workers were automobile mechanics, registered nurses, heavy equipment mechanics, janitors, and machinists.

Preliminary data from a second workplace survey, the National Occupational Exposure Survey (NOES), conducted by NIOSH from 1980 to 1983, indicated that 77,111 workers (including 32,891 females) in 1,526 plants were potentially exposed to 1,2-dichloroethane in the workplace in 1980 (NIOSH 1984). The largest numbers of exposed workers were employed in the apparel and other textile products, chemical and allied products, business services, and petroleum and coal products industries as machine operators, assemblers, production inspectors, checkers, and examiners. The estimates were based on direct observation by the surveyor of the actual use of the compound (68%) and observation of the use of trade name products known to contain 1,2-dichloroethane (32%).

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).

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 Total Exposure Assessment Methodology (TEAM) studies measured personal and outdoor exposures of about 800 people to 25 volatile organic compounds, 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 year) blood samples collected by the National Health and Nutrition Examination Survey (NHANES), though most of the values collected were below the limit of detection of 10 pg/mL (CDC 2015). A summary of 1,2-dichloroethane levels found in children and adults in the United States are summarized in Table 5-7.

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 been detected in human milk at concentrations ranging from 0.195 to 0.63 mg/100 mL of milk (EPA 1980; Urusova 1953). Therefore, it is possible that children may be exposed to 1,2-dichloroethane from breast-feeding mothers, although no details of the analytical methodology were reported and, the sample size was not provided in this study. Current data on the concentration of 1,2-dichloroethane in breast milk are not available. 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.

Table 5-7. Geometric Mean and Selected Percentiles of 1,2-Dichloroethane in Blood (in pg/mL) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) (CDC 2015)*

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% Confidence Interval) 50th	75th	90th	95th	Sample Size
Total	13-14	7.22 (7.16, 7.27)	7.10	7.10	7.10	7.10	3,203
	15-16	7.20 (7.13, 7.26)	7.00	7.00	7.00	7.00	3,035
Age Group							
12-19 years	13-14	7.13 (7.10, 7.16)	7.10	7.10	7.10	7.10	599
12-19 years	15-16	7.08 (7.02, 7.14)	7.00	7.00	7.00	7.00	532
20-59 years	13-14	7.23	7.10	7.10	7.10	7.10	1,792

Table 5-7. Geometric Mean and Selected Percentiles of 1,2-Dichloroethane in Blood (in pg/mL) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) (CDC 2015)*

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% Confidence Interval) 50th	75th	90th	95th	Sample Size
		(7.17, 7.29)					
	15-16	7.20 (7.12, 7.29)	7.00	7.00	7.00	7.00	1,661
60 years and older	13-14	7.23 (7.06, 7.41)	7.10	7.10	7.10	7.10	812
	15-16	7.24 (7.12, 7.36)	7.00	7.00	7.00	7.00	842
Sex							
Females	13-14	7.23 (7.16, 7.30)	7.10	7.10	7.10	7.10	1,546
	15-16	7.14 (7.06, 7.22)	7.00	7.00	7.00	7.00	1,498
Males	13-14	7.20 (7.14, 7.26)	7.10	7.10	7.10	7.10	1,657
	15-16	7.25 (7.17, 7.34)	7.00	7.00	7.00	7.00	1,537
Race/Ethnicity							
Mexican-Americans	13-14	7.22 (7.09, 7.35)	7.10	7.10	7.10	7.10	504
	15-16	7.25 (7.09, 7.42)	7.00	7.00	7.00	7.00	555
Other Hispanics	13-14	7.17 (7.03, 7.31)	7.10	7.10	7.10	7.10	305
	15-16	7.15 (7.06, 7.25)	7.00	7.00	7.00	7.00	409
Non-Hispanic Whites	13-14	7.20 (7.13, 7.27)	7.10	7.10	7.10	7.10	1,305
	15-16	7.18 (7.10, 7.27)	7.00	7.00	7.00	7.00	983
Non-Hispanic Blacks	13-14	7.38 (7.26, 7.49)	7.10	7.10	7.10	7.10	615
	15-16	7.25 (7.13, 7.38)	7.00	7.00	7.00	7.00	627
Other Races	13-14	7.15 (7.10, 7.20)	7.10	7.10	7.10	7.10	474
	15-16	7.19 (6.94, 7.44)	7.00	7.00	7.00	7.00	461

*The limit of detection (LOD) for 1,2-dichloroethane in blood in both NHANES 2013-2014 and 2015-2016 is 10.0 pg/mL. All values that fell below the LOD were recorded as the LOD divided by the square root of 2. The majority of the data points in both years were recorded at value of the LOD over the square root of 2, which rounds to 7 pg/mL.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Human exposure to 1,2-dichloroethane is expected to be highest among certain occupational groups (e.g., chemical and allied products industry workers) (NIOSH 1984) and members of the general population

living in the vicinity of industrial point emission sources (EPA 1985a) 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; Juttner 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.

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).

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.

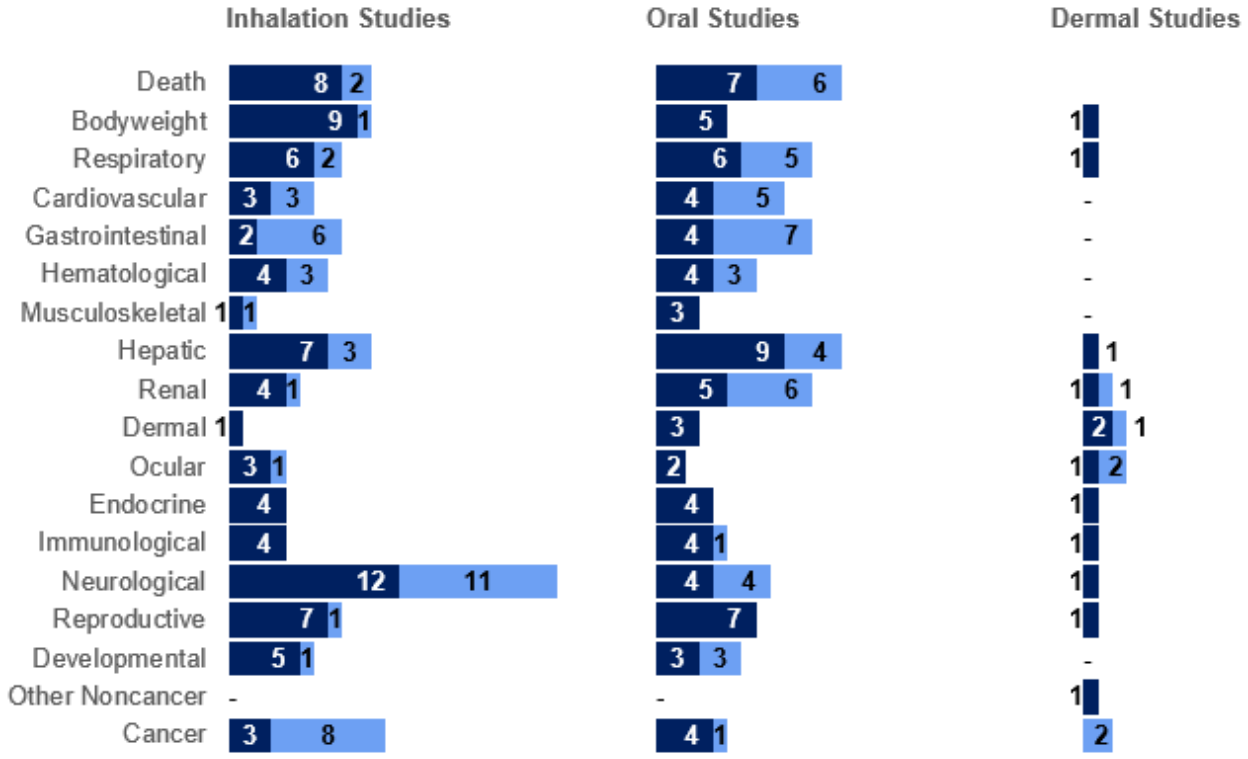
6.1 EXISTING INFORMATION ON HEALTH EFFECTS

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. Hepatic and neurological endpoints were the most commonly studied endpoints. Studies on inhalation and oral exposure to humans were limited to case studies of occupationally exposed individuals. Dermal studies were limited to laboratory animals and focus on only 6 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 inhalation exposure in animals (versus humans).



*Includes studies discussed in Chapter 2; the number of studies includes 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 available acute oral database was inadequate for deriving an MRL. Information on 1,2-dichloroethane toxicity in humans is limited as it comes primarily from case reports of humans who died following acute exposure to high levels of 1,2-dichloroethane by ingestion. Human and animal data were sufficient to identify the central nervous system, liver, kidney, and respiratory system as sensitive targets from both oral and inhalation exposure. Limitations include the lack of examination of low dose levels that demonstrate a NOAEL for oral exposure. Additional studies are needed to characterize the thresholds for acute immunologic effects and for other end points (e.g., central nervous system, liver, kidney, cardiovascular) to determine the most sensitive effects of oral exposure and to investigate whether the immunologic effects observed in mice can be extrapolated across species. The additional data would establish the most appropriate basis for deriving an acute oral MRL. The database provided enough data to derive an acute-duration inhalation MRL.

Intermediate-Duration MRLs. The available intermediate inhalation database was inadequate for deriving an MRL. The most sensitive endpoint for deriving an intermediate inhalation MRL is related to morphological abnormalities in sperm in mice. Since effects on sperm are always considered serious effects, this precludes the derivation of an intermediate inhalation MRL (Pohl et al. 2005; ATSDR 2018). Additional studies are needed to characterize less serious health effects for lower-level doses. 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 oral and inhalation databases were inadequate for deriving an MRL. Limitations include the lack of examination on sensitive targets including the kidneys, liver, central nervous, and reproductive systems following oral exposure. The one oral study on rats and mice was primarily designed to assess carcinogenicity, which is not applicable to MRL derivation. A chronic dermal study on mice also examined carcinogenicity and not any noncancer endpoints. Chronic oral toxicity studies are needed to identify critical targets that may be different than those identified at acute- and intermediate-durations, since chronic toxicity levels may be considerably lower. Similarly, there were only two chronic inhalation studies, one of which found no adverse effects for any of the

studied outcomes, while the other study was primarily designed to assess carcinogenicity, which is not applicable to MRL derivation. Carcinogenic effects were observed at exposure levels that were lower than the noncancer NOAELs, which suggests a need for further examination of the toxicity of chronic inhalation exposure.

Health Effects. Studies demonstrate that 1,2-dichloroethane readily absorbs dermally through human (Urusova 1953) and animal skin (Morgan et al. 1991; Jakobson et al. 1982). Dermal exposure to workers can occur in occupational settings (Bowler et al. 2003). Currently there are no studies examining health effects in human 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. Hepatic and neurological endpoints have been identified as the most toxic endpoints, but no dermal studies examine these endpoints. Studies examining dermal exposure would further elucidate potential toxicity to humans occupationally exposed to 1,2-dichloroethane. Additionally, toxicity studies that include doses relevant to human exposures would be useful in providing information toward a further understanding of the potential health implications of current human exposure patterns.

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 (Nouchi et al. 1984; McNally and Fostvedt 1941) 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 (Hotchkiss et al. 2010; Chan et al. 2002; Heppel et al. 1945) resulted from inhalation. There is an identified data need for 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 inhalation and acute 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 twelve 5-hour exposures to 100 ppm (Sherwood et al. 1987). Other immune function end points studied in the rats were also negative. The relevance of the end point (lethality due to massive streptococcal challenge) in mice to immune function is known, but its suitability as a basis for MRL derivation is uncertain.

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 end points 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 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; NCI 1978; NTP 1991). Leukocyte counts were not affected in intermediate-duration drinking water and gavage studies in rats (NTP 1991). The acute 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 exposure by inhalation or ingestion.

The mechanism by which 1,2-dichloroethane may produce immunological effects is not known, but it is possible that these effects were produced by reactive intermediates resulting from conjugation with glutathione (Reitz et al. 1982). Glutathione conjugation and MFO metabolism are the two primary pathways of 1,2-dichloroethane metabolism. It has been shown that MFO metabolism of 1,2-dichloroethane is saturable and that direct glutathione conjugation occurs to a much greater extent after saturation of MFO metabolism. Gavage administration, which involves the placement of large bolus doses in the stomach that are absorbed at one time, could lead to saturation of MFO metabolism and the subsequent expression of toxicity. Drinking water exposure, which results in multiple daily ingestions of small doses, may not provide large enough doses to saturate MFO metabolism, even when the aggregate daily dose is fairly large. Therefore, even though immunological effects might be expected in humans ingesting large doses of undiluted 1,2-dichloroethane, it is uncertain whether immunological effects would occur in humans exposed to 1,2-dichloroethane in the drinking water at hazardous waste sites.

Another possible explanation for the different outcomes of acute and intermediate 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. An additional possibility, related to age of the mice at the time of immune function testing, was mentioned in the section on acute exposure and is discussed in detail in the section on children's susceptibility.

Both the oral and the inhalation acute immunotoxicity studies found immunosuppressive effects at levels of 1,2-dichloroethane low enough to enable identification of the immune system as the most sensitive target for acute exposure by both routes of exposure, but neither study provided the data sufficient for deriving an MRL (the lethality assay in the inhalation study was not considered suitable, and the oral study showed a dose-response in only one end point and was limited by use of gavage). In addition, dose-response information for other potential targets of toxicity was not adequate. Additional studies are needed to determine the immunologic potential of acute inhalation and oral (drinking water) exposure and to better characterize the threshold for immunologic effects by both routes of exposure relative to thresholds for other effects in order to provide the data needed to establish the most appropriate basis for deriving acute inhalation and oral MRLs (Hubbs and Prusmack 1955; Hueper and Smith 1935; Lochhead and Close 1951; Nouchi et al. 1984). The results of animal studies confirm that the central nervous system is a target of high concentrations of 1,2-dichloroethane. Symptoms similar to those reported in humans, such as tremors, abnormal posture, uncertain gait, and narcosis, were observed after high-level acute vapor exposures (Heppel et al. 1945; 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 (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 (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; 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).

Although 1,2-dichloroethane appears to have induced embryotoxic effects in one adequate animal study conducted by the oral route, the overall indication of the data is that this chemical is unlikely to impair reproduction at doses that are not highly toxic. No data are available regarding the potential reproductive toxicity of dermal exposure, so there is a need for studies.

Developmental. A data need to conduct additional developmental studies via inhalation, oral, and dermal exposure has been identified. Additionally, there is a data need concerning vertical transmission of 1,2-dichloroethane and potential exposure risk of the fetus and infant through breast milk or placental transfer. 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 OR was 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). The OR for cardiac defects for 1,2-dichloroethane (detected versus not detected in drinking water) was 2.8 (95% CI 1.11–6.65; 6 exposed cases) (Bove 1996; Bove et al. 1995). The crude odds ratio for neural tube defects was 2.8 (95% CI 1.0–7.2; 14 exposed cases) (Croen et al. 1997), and the adjusted odds ratio for neural tube defects was 1.28 (95% CI 1.01 – 1.62, 85 exposed cases) (Brender et al. 2014). 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. Benign and malignant tumors were produced in rats and mice exposed to 1,2-dichloroethane via inhalation and found to be dose-dependent in female mice (Nagano et al. 2006). Strengths of this study included the use of appropriate doses, including ones comparable to human occupational exposure levels, and consistent survival rates among all exposure groups (Nagano et al. 2006). Conversely, no tumors were produced in rats and mice exposed via inhalation (Cheever et al. 1990; Maltoni et al. 1980). Limitations of the inhalation studies included the use of a single, subthreshold exposure level in one study (Cheever et al. 1990), and exceedance of the maximum tolerated dose in rats, less-than-lifetime study duration, and poor survival in mice in the other study (Maltoni et al. 1980).

1,2-Dichloroethane was carcinogenic after gavage administration (of 97–195 mg/kg/day to rats and 97–299 mg/kg/day to mice), inducing 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). Limitations of this oral study include the non-natural method of administration (gavage) and dosage adjustments during the study.

1,2-Dichloroethane is a potential lung carcinogen in mice following lifetime dermal exposure of female mice (Suguro et al. 2017; Van Duuren et al. 1979). An apparent dose-response relationship, with statistical significance at the high dose, was observed for 1,2-dichloroethane induced lung papillomas following lifetime dermal exposure of female mice (Van Duuren et al. 1979). Dermal life-time exposure in mice significantly increased bronchioloalveolar adenomas and adenocarcinomas in both sexes, and bronchioloalveolar adenocarcinomas in all female mice exposed to 1,2-dichloroethane (Suguro et al. 2017). These studies appear adequate to demonstrate the carcinogenic potential of dermal exposure to 1,2-dichloroethane. In addition, pulmonary adenomas have been induced in mice by intraperitoneal injection (Stoner 1991; Theiss et al. 1977), and, as discussed previously, by oral administration of 1,2-dichloroethane.

It has been suggested that the route-related differences in carcinogenicity between inhalation and oral exposure may be associated with saturation of the detoxification/excretion mechanism by gavage dosing. Reitz et al. (1982) proposed that 1,2-dichloroethane-induced toxicity occurred when the biotransformation processes were saturated, thereby allowing higher levels of 1,2-dichloroethane to circulate throughout the body instead of being detoxified and eliminated. The 1,2-dichloroethane inhalation study, therefore, may

not have produced peak blood levels that were high enough to saturate the detoxification mechanisms and produce a detectable incidence of tumors. Metabolic saturation apparently occurs at lower doses after oral administration (particularly by gavage) than after inhalation exposure. Additional information on 1,2-dichloroethane from well-conducted animal bioassays using the natural routes of exposure expected for populations surrounding hazardous waste sites (i.e., drinking water ingestion and inhalation exposure) are needed to better predict the likelihood of carcinogenicity in humans.

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. Because oral, dermal, and intraperitoneal exposure of experimental animals to 1,2-dichloroethane is associated with the induction of tumors remote from the site of administration, 1,2-dichloroethane should be considered potentially carcinogenic by the inhalation route of exposure as well. The DHHS has determined that 1,2-dichloroethane is reasonably anticipated to be a human carcinogen (NTP 2016). IARC has placed 1,2-dichloroethane in Group 2B (possibly carcinogenic to humans) (IARC 2001). EPA has classified 1,2-dichloroethane as a Group B2 carcinogen (probable human carcinogen) (EPA 1987). This EPA category applies to chemical agents for which there is sufficient evidence of carcinogenicity in animals.

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. Occupational exposure to low levels of 1,2-dichloroethane in air (~1 ppm) corresponded to significantly greater sister chromatid exchange frequency in blood (Cheng et al. 2000). The workers were simultaneously exposed to vinyl-chloride and likely other manufacturing chemicals which could not be fully distinguished, therefore increased SCE frequency cannot not be solely attributed to 1,2-dichloroethane exposure. 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. The ability of 1,2-dichloroethane to bind to DNA in rats and mice in vivo has been well established, not only in the liver, but also in other organs such as the kidney and lung (Baertsch et al. 1991; Banerjee 1988; Cheever et al. 1990; Hellman and Brandt 1986; Inskeep et al. 1986; Prodi et al. 1986; Watanabe et al. 2007). DNA binding has also been reported in D. melanogaster in vivo (Fossett et

al. 1995). DNA damage has been demonstrated in vivo in mice (Lone et al. 2016; Sasaki et al. 1998; Storer and Conolly 1983, 1985; Taningher et al. 1991). Genotoxicity assays for clastogenic effects in mice in vivo obtained mixed results, with a positive effect on sister chromatid exchange in bone marrow cells (Giri and Hee 1988), but no effect on micronucleus formation (Armstrong and Galloway 1993; Jenssen and Ramel 1980; King et al. 1979), and in D. melanogaster, gave positive results for chromosomal aberration (Ballering et al. 1993) and a marginally positive response for chromosomal recombination (Rodriguez-Arnaiz 1998). Negative results were obtained in a cell transformation assay (Milman et al. 1988).

The only in vivo assay for the mutagenicity of 1,2-dichloroethane in mammalian cells (mouse/spot test) produced a marginal response (Gocke et al. 1983), and a mouse host-mediated assay produced negative results in Escherichia coli (King et al. 1979). However, 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. 1994; Chourst et al. 2001, 2007; King et al. 1979; Kramers et al. 1991; Nylander et al. 1978; Romert et al. 1990; Vogel and Nivard 1993). In addition, in vitro studies provide strong support for the mutagenicity of 1,2-dichloroethane. Results of in vitro assays for point mutations were positive in human cells (Crespi et al. 1985; Ferreri et al. 1983), marginally positive in a single assay in animal cells (Tan and Hsie 1981), and positive in nearly all of the assays in bacteria, with or without metabolic activation (Barber et al. 1981; Brem et al. 1974; Buijs et al. 1984; Cheh et al. 1980; Hemminki 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 results of these 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).

Additional evidence from in vitro studies supports the in vivo results regarding the DNA binding, DNA damaging, and clastogenic effects of 1,2-dichloroethane. Results were positive for DNA binding in animal cells (Banerjee 1988; Banerjee and Van Duuren 1979; Banerjee et al. 1980; Prodi et al. 1986), unscheduled DNA synthesis (i.e., DNA repair activity) in human (Perocco and Prodi 1981) and animal cells (Milman et al. 1988; Williams et al. 1989), and mitotic segregation aberrations leading to aneuploidy in fungi (Crebelli et al. 1984). Negative results were obtained for intrachromosomal recombination in a single assay in animal cells (Zhang and Jenssen 1994), but positive results were reported for micronucleus formation in human cells (Doherty et al. 1996; Tafazoli et al. 1998). Thus, both in vitro and in vivo genotoxic effects of 1,2-dichloroethane include gene mutations, DNA binding and damage, and clastogenic effects.

The DNA binding is an alkylation of DNA that occurs following biotransformation of 1,2-dichloroethane. Inhalation exposure of rats to very high concentrations of 1,2-dichloroethane for short durations produced greater amounts of DNA binding in liver and lung than did longer-duration inhalation to low concentrations (Baertsch et al. 1991), and oral gavage doses were more potent in causing DNA damage in the liver than were comparable inhalation doses in mice (Storer et al. 1984). These observations are consistent with the hypothesis that the toxicity of 1,2-dichloroethane is associated with saturation of MFO enzymes. The major identified DNA adduct is S-[2-(N^7-guanyl)ethyl]glutathione in rat liver following a single intraperitoneal injection of ^{14}C-1,2,-dichloroethane, and it is one of several DNA adducts found in the kidney, after a single intraperitoneal injection (Inskeep et al. 1986).

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. A data need has been identified. 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; Zhan 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 neurotoxic, nephrotoxic, gastrotoxic, 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 aOR 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). The study included women exposed throughout pregnancy and unexposed wives of men exposed for at least 1 year before their wives became pregnant and included relatively small numbers of exposed workers. This study was generally deficient in reporting of study design and accounting for possible confounders, including other chemicals in the factory. In general, the adequate one- and two-generation reproductive studies in animals did not report effects except at high, maternotoxic exposure levels.

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 or older, 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 high exposure, are neurotoxicity, nephrotoxicity, hepatotoxicity, and effects on the cardiovascular system. A particularly sensitive end point of acute inhalation or gavage exposure to 1,2-dichloroethane in mice (but not rats) is immunological effects. No data regarding this end point are available for humans.

Biomarkers of Exposure and Effect.

Exposure. A data need has been identified. 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.

Effect. 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 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 oral (gavage) and inhalation exposures (Reitz et al. 1982). Additional studies investigating the saturation of MFO metabolism by inhaled and ingested 1,2-dichloroethane, as well as the roles of the oxidative and GSH 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. 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 GSH 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 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. Production methods for 1,2-dichloroethane are known and there does not appear to be a need for further information. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The TRI, which contains this information, became available in 2001. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Use. 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 (CDR 2012, 2016). Additional data on the uses of 1,2-dichloroethane are not needed.

Release. 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.

Disposal. 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.

Regulatory Information. Sufficient information exists on regulations pertaining to 1,2-dichloroethane. 1,2-Dichloroethane is regulated according to the Emergency Planning and Community Right-to-Know Act of 1986.

Environmental Fate. The partitioning of 1,2-dichloroethane into air, water, and soil is well established (Brüeggemann et al. 1991; Chiou et al. 1980; Dilling 1977; Dilling et al. 1975; EPA 1981, 1985a; 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 indicates 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, 1982a; 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; Juttner 1986; Kelly et al. 1994; Pellizzari et al. 1986; Singh et al. 1982, 1992), in 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), and in 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; Kelley 1985; Krill and Sonzogni 1986; Lam et al. 1994b; Steichen et al. 1988; Suffet et al. 1980), sediment (Bianchi et al. 1991; Oliver and Pugsley 1986), and food stuffs (Draft 1988, 1989, 1991; 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 (NIOSH 1984) are generally inadequate and out of date. General population exposure estimates have been prepared by the EPA (1985a) 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 ongoing studies were identified for 1,2-dichloroethane.

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.

The Permissible Exposure Limit (PEL) listed in Table 7-1, enforced by OSHA, is measured by a time-weighted average during an 8-hour work shift of a 40-hour workweek. PELs are intended to be enforceable limits on exposure to workers, however PELs are generally considered outdated due to the legislative time and other issues involved with the update process and therefore, potentially inadequate for ensuring protection of worker health. The PEL for 1,2-dichloroethane is 50 ppm. There are ceiling and maximum peak regulations in addition. The ceiling value of 100ppm should not be exceeded unless certain criteria are met. The maximum peak above ceiling concentration for an 8-hour shift is 200ppm. An exposure can be between 100 ppm and 200 ppm if the duration of exposure is under 5 minutes in any 3 hours.

Alternatively, the NIOSH Recommended Exposure Limit (REL) listed in Table 7-1 is measured by a time-weighted average during a 10-hour work shift of a 40-hour workweek. RELs are developed to recommend standards to OSHA, and are considered to be the more current, evidence based values than the OSHA PELs, though they are non-enforceable limits. The REL of 1,2-dichloroethane is 1 ppm. The NIOSH Short-Term Exposure Limit (STEL) is 2 ppm. NIOSH recommends limiting occupational exposures while further research is done on the carcinogenicity of 1,2-dichloroethane in humans. Steps should be taken to limit exposures to as few employees as possible while engineering and work practice controls are used to minimize exposure levels (NIOSH 1978).

The WHO continuous exposure air quality guideline of 0.7 mg/m^3 (0.2 ppm) listed in Table 7-1 is a time-weighted average over a 24-hour day. They stated that since present environmental levels are below this threshold, that exposures are not a health concern. Therefore, this guideline relates to accidental release episodes or indoor pollution problems (WHO 2000).

EPA has a 1-day and 10-day health advisory value for 1,2 dichloroethane which are both 0.7 mg/L, based on a 10-kg child ingesting 1 liter of drinking water per day (EPA 2018b). There is no longer-term health

advisory value for 1,2-dichloroethane developed by EPA (EPA 2018b). There are no derived final RfD or RfC values, though EPA established a subchronic provisional RfD (0.02 mg/kg-day) and both a chronic and subchronic provisional RfC (0.007 mg/m^3 and 0.07 mg/m^3, respectively) for 1,2-dichloroethane. There is a maximum contaminant level (MCL) at 0.005 mg/L that is based on the derived oral cancer slope factor of 9.2 x 10^{-2} per mg/kg-day (EPA 1987), as well as a maximum contaminant level goal(MCLG) at 0 mg/L (EPA 2018b).

Lastly, Table 7-1 states the FDA tolerance of 30 ppm of residue in spice oleoresins for 1,2-dichloroethane. The regulation caveats that if residues of other chlorinated solvents are present, the total residues shall not exceed 30 ppm. This caveat comes in 21 CFR 173.230 which was included in the results of the FDA Substances added to food database (FDA 2019a).

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

Agency	Description	Information	Reference
	Air		
EPA	RfC	No data	EPA 1987
	PPRTV Chronic provisional RfC Subchronic provisional RfC	 0.007mg/m^3 0.07 mg/m^3	 EPA 2010 EPA 2010
WHO	Air quality guidelines (continuous exposure)	0.7 mg/m^3	WHO 2000
	Water & Food		
EPA	Drinking water standards One-day health advisory for a 10-kg child Ten-day health advisory for a 10-kg child Longer-term health advisory for a 10-kg child MCL MCLG DWEL	0.7 mg/L 0.7 mg/L No data 0.005 mg/L 0 mg/L No data	EPA 2018b
	RfD	No data	EPA 1987
	Subchronic provisional RfD	0.02 mg/kg-day	EPA 2010
FDA	Substances added to food (formerly EAFUS)[a] Residues from use as solvent in extraction process of: Whole fish protein concentrate Modified hop extract Spice oleoresins Use in flume water for fruit and vegetable peeling: Sugar Beets	Shall not exceed: 5 ppm (5 mg/kg) 150 ppm (150 mg/kg) 30 ppm (30 mg/kg) 0.2 ppm (0.2 mg/kg)	FDA 2019b
	Polyethylenimine reaction product used as fixing material in the manufacture of beer and high fructose corn syrup	1 ppm (1 mg/kg)	FDA 2019c

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

Agency	Description	Information	Reference
	Residues from use as a solvent in the extraction process of animal-by-products for use in animal feeds	300 ppm (300 mg/kg)	FDA 2019a
	Residues from use as a solvent in the manufacture of drug substances	5 ppm (5 mg/kg)	FDA 2017
WHO	Drinking water quality guidelines	0.03 mg/L	WHO 2003
	Cancer		
EPA	Carcinogenicity classification	Group B2[b]	EPA 1987
IARC	Carcinogenicity classification	Group 2B[c]	IARC 2016
NTP-HHS	Carcinogenicity classification	Reasonably anticipated to be a human carcinogen	NTP 2016
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction	50 ppm (202 mg/m^3)	NIOSH 2018
NIOSH	REL (Up to 10-hour TWA)	1 ppm (4.05 mg/m^3)	NIOSH 2018
	Emergency Criteria		
EPA	AEGLs-air	No data	
AIHA	ERPG-1 ERPG-2 ERPG-3	50 ppm (202 mg/m^3) 200 ppm (809 mg/m^3) 300 ppm (1214 mg/m^3)	AIHA 2015
DOE	PAC	No data other than ERPGs	DOE 2016b

[a]The list of substances added to food contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[b]Classification B2: Probable human carcinogen.
[c]Group 2B: Possibly carcinogenic to humans.
[d]Definitions of ERPG terminology are available from NOAA (NOAA 2019).
[e]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2016a).

AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; CFR = Code of Federal Regulations; HHS = Department of Health and Human Services; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; GRAS = Generally Recognized As Safe; IARC = International Agency for Research on Cancer; 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; PPRTV= Provisional Peer-Reviewed Toxicity Values; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

AIHA. 2015. Current ERPG values (2015). AIHA Guideline Foundation.

Albano E, Poli G, Tomasi A, et al. 1984. Toxicity of 1,2-dibromoethane in isolated hepatocytes: role of lipid peroxidation. Chem Biol Interact 50(3):255-265.

Alumot E, Nachtomi E, Mandel E, et al. 1976. Tolerance and acceptable daily intake of chlorinated fumigants in the rat diet. Food Cosmet Toxicol 14(2):105-110.

Al-Zahrani SM, Aljodai AM, Wagialla KM. 2001. Modelling and simulation of 1,2-dichloroethane production by ethylene oxychlorination in fluidized-bed reactor. Chemical Engineering Science 56(2):621-626. 10.1016/s0009-2509(00)00268-2.

Andelman JB. 1985. Inhalation exposure in the home to volatile organic contaminants of drinking water. Sci Total Environ 47:443-460. https://doi.org/10.1016/0048-9697(85)90349-3.

Anders M, Livesey J. 1980. Metabolism of 1,2-dihaloethanes. In: Ames B, Infante P, & Reitz R, ed. Ethylene dichloride: A potential health risk? Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 331-341.

Anonymous. 1998. Chemical profile: Ethylene dichloride. Chem Mark Rep.

Ansari GA, Gan JC, Barton BK. 1988. Synergistic inactivation of plasma alpha 1-proteinase inhibitor by aldehydes of cigarette smoke with styrene oxide and 1,2-dichloroethane. Arch Environ Contam Toxicol 17(4):533-536.

Ansari GA, Singh SV, Gan JC, et al. 1987. Human erythrocyte glutathione S-transferase: a possible marker of chemical exposure. Toxicol Lett 37(1):57-62.

Aragno M, Tamagno E, Danni O, et al. 1992. In vivo studies on halogen compound interactions. III. Effect of carbon tetrachloride plus 1,2-dichloroethane on liver necrosis and fatty accumulation. Res Commun Chem Pathol Pharmacol 76(3):341-354.

Armstrong MJ, Galloway SM. 1993. Micronuclei induced in peripheral blood of E mu-PIM-1 transgenic mice by chronic oral treatment with 2-acetylaminofluorene or benzene but not with diethyl-nitrosamine or 1,2-dichloroethane. Mutat Res 302(1):61-70.

Arnts RR, Seila RL, Bufalini JJ. 1989. Determination of room temperature OH rate constants for acetylene, ethylene dichloride, ethylene dibromide, p-dichlorobenzene and carbon disulfide. Japca 39(4):453-460. 10.1080/08940630.1989.10466544.

Aronson D, Howard P. 2008. The environmental behavior of ethylene dibromide and 1,2-dichloroethane in surface water, soil, and groundwater. Regulatory and Scientific Affairs Department, American Petroleum Institute.

Atkinson R. 1986. Kinetics and mechanisms of the gas-phase reactions of the hydroxyl radical with organic compounds. American Institute of Physics.

ATSDR. 2017. 1,2-Dichlorothane. Full SPL data. Substance priority list (SPL) resource page. Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention http://www.atsdr.cdc.gov/SPL/resources. September 22, 2017

ATSDR. 2018. Guidance for the preparation of toxicological profiles. Atlanta, GA https://www.atsdr.cdc.gov/toxprofiles/guidance/profile_development_guidance.pdf.

Austin SG, Schnatter AR. 1983. A case-control study of chemical exposures and brain tumors in petrochemical workers. J Occup Med 25(4):313-320.

Austin SG, Schnatter AR. 1983. A cohort mortality study of petrochemical workers. J Occup Med 25(4):304-312.

Baertsch A, Lutz WK, Schlatter C. 1991. Effect of inhalation exposure regimen on DNA binding potency of 1,2-dichloroethane in the rat. Arch Toxicol 65(3):169-176.

Ballering LA, Nivard MJ, Vogel EW. 1993. Characterization of the genotoxic action of three structurally related 1,2-dihaloalkanes in Drosophila melanogaster. Mutat Res 285(2):209-217.

Ballering LA, Nivard MJ, Vogel EW. 1994. Mutation spectra of 1,2-dibromoethane, 1,2-dichloroethane and 1-bromo-2-chloroethane in excision repair proficient and repair deficient strains of Drosophila melanogaster. Carcinogenesis 15(5):869-875. 10.1093/carcin/15.5.869.

Banerjee S. 1988. DNA damage in rodent liver by 1,2-dichloroethane, a hepatocarcinogen. Cancer Biochem Biophys 10(2):165-173.

Banerjee S, Van Duuren BL. 1979. Binding of carcinogenic halogenated hydrocarbons to cell macromolecules. J Natl Cancer Inst 63(3):707-711. 10.1093/jnci/63.3.707.

Banerjee S, Baughman GL. 1991. Bioconcentration factors and lipid solubility. Environ Sci Technol 25(3):536-539. 10.1021/es00015a024.

Banerjee S, Van Duuren BL, Oruambo FI. 1980. Microsome-mediated covalent binding of 1,2-dichloroethane to lung microsomal protein and salmon sperm DNA. Cancer Res 40(7):2170-2173.

Barbash JE, Reinhard M. 1989. Abiotic dehalogenation of 1,2-dichloroethane and 1,2-dibromoethane in aqueous solution containing hydrogen sulfide. Environ Sci Technol 23(11):1349-1358. 10.1021/es00069a004.

Barbee GC. 1994. Fate of chlorinated aliphatic hydrocarbons in the vadose zone and ground water. Groundwater Monitoring & Remediation 14(1):129-140. 10.1111/j.1745-6592.1994.tb00098.x.

Barber ED, Donish WH, Mueller KR. 1981. A procedure for the quantitative measurement of the mutagenicity of volatile liquids in the Ames Salmonella/microsome assay. Mutat Res 90(1):31-48.

Barkley J, Bunch J, Bursey JT, et al. 1980. Gas chromatography mass spectrometry computer analysis of volatile halogenated hydrocarbons in man and his environment--A multimedia environmental study. Biomed Mass Spectrom 7(4):139-147.

Benson L, Teta M. 1993. Mortality due to pancreatic and lymphopoietic cancers in chlorohydrin production workers. British Journal Industrial Medicine 50:710-716.

Bianchi AP, Varney MS, Phillips J. 1991. Analysis of volatile organic compounds in estuarine sediments using dynamic headspace and gas chromatography—mass spectrometry. Journal of Chromatography A 542:413-450. 10.1016/s0021-9673(01)88779-3.

Blount BC, Kobelski RJ, McElprang DO, et al. 2006. Quantification of 31 volatile organic compounds in whole blood using solid-phase microextraction and gas chromatography–mass spectrometry. J Chromatogr Sci B 832(2):292-301.

Borisover MD, Graber ER. 1997. Specific interactions of organic compounds with soil organic carbon. Chemosphere 34(8):1761-1776. 10.1016/s0045-6535(97)00032-5.

Bosma T, van Aalst-van Leewen M, Geritse J, et al. 1998. Intrinsic dechlorination of 1,2dichloroethane at an industrial site. In: Wickramanayake G & Hinchee R, ed. Natural attentuation: Chlorinated and recalcitrant compounds. Columbus, OH: Battelle Press, 7-11.

Bove FJ. 1996. Public drinking water contamination and birthweight, prematurity, fetal deaths, and birth defects. Toxicol Ind Health 12(2):255-266.

Bove FJ, Fulcomer MC, Klotz JB, et al. 1995. Public drinking water contamination and birth outcomes. Am J Epidemiol 141(9):850-862. 10.1093/oxfordjournals.aje.a117521.

Boverhof DR, Hotchkiss JA, LeBaron MJ, et al. 2018. Investigation of the potential non-genotoxic mode of action for 1,2-dichloroethane (DCE)-induced mammary tumors in female rats. Toxicology Letters 295:S150-S151.

Bowler RM, Gysens S, Hartney C. 2003. Neuropsychological effects of ethylene dichloride exposure. Neurotoxicology 24(4-5):553-562. 10.1016/S0161-813X(03)00027-5.

Brem H, Stein AB, Rosenkranz HS. 1974. The mutagenicity and DNA-modifying effect of haloalkanes. Cancer Res 34(10):2576-2579.

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

Brittebo EB, Kowalski B, Ghantous H, et al. 1989. Epithelial binding of 1,2-dichloroethane in mice. Toxicology 56(1):35-45. 10.1016/0300-483x(89)90210-2.

Brondeau GR BP, Guenier JP, et al. . 1983. Short-term inhalation test for evaluating industrial hepatotoxicants in rats. Toxicol Lett 19:139-146.

Brosseau J, Heitz M. 1994. Trace gas compound emissions from municipal landfill sanitary sites. Atmospheric Environment 28(2):285-293. 10.1016/1352-2310(94)90103-1.

Brown HS, Bishop DR, Rowan CA. 1984. The role of skin absorption as a route of exposure for volatile organic compounds (VOCs) in drinking water. Am J Public Health 74(5):479-484. 10.2105/ajph.74.5.479.

Brüggemann R, Trapp S, Matthies M. 1991. Behavior assessment of a volatile chemical in the Rhine river. Environmental Toxicology and Chemistry 10(9):1097-1103. 10.1002/etc.5620100901.

Budavari S, O'Neil M, Heckelman P. 1996. The Merck index (12th ed.). Whitehouse Station, NJ: Merck and Co., Inc., 646.

Buijs W, van der Gen A, Mohn GR, et al. 1984. The direct mutagenic activity of alpha, omega-dihalogenoalkanes in Salmonella typhimurium. Strong correlation between chemical properties and mutagenic activity. Mutat Res 141(1):11-14.

Bundschuh I HC, Fels LM, et al. 1993. Renal fibronectin excretion as a marker for renal environmental toxins. Contributions to Nephrology 101:177-184.

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

Canter LW, Sabatini DA. 1994. Contamination of public ground water supplies by Superfund sites. International Journal of Environmental Studies 46(1):35-57. 10.1080/00207239408710909.

Capel PD, Larson SJ. 1995. A chemodynamic approach for estimating losses of target organic chemicals from water during sample holding time. Chemosphere 30(6):1097-1107. 10.1016/0045-6535(94)00004-e.

Casciola LAF IK. 1984. Metabolism of chloroethanes by rat liver nuclear cytochrome P-450. . Carcinogenesis (London) 5:543-548.

CDC. 2018. National Health and Nutrition Examination Survey Data. Volatile organic compounds and trihalomethanes/MTBE - Blood (VOCWB_I). from U.S. Department of Health and Human Services, Centers for Disease Control and Prevention https://wwwn.cdc.gov/nchs/nhanes/ContinuousNhanes/Default.aspx?BeginYear=2015.

CDPR. 2019. Output reporting for ethylene dichloride (274). https://apps.cdpr.ca.gov/cgi-bin/label/labq.pl?p_chem=274&activeonly=off. June 19, 2019.

CDR. 2012. Chemical Data Reporting. U.S. Environmental Protection Agency. https://www.epa.gov/chemical-data-reporting/access-cdr-data. May 16, 2019.

CDR. 2016. Chemical Data Reporting. U.S. Environmental Protection Agency. https://www.epa.gov/chemical-data-reporting/access-cdr-data. May 16, 2019.

Chan MH, Chen HH, Lin YR. 2002. Aliphatic chlorinated hydrocarbons alter the contractile responses of tracheal smooth muscle in piglet. J Toxicol Environ Health A 65(3-4):293-304. 10.1080/15287390252800873.

Chang HL, Alvarez-Cohen L. 1996. Biodegradation of individual and multiple chlorinated aliphatic hydrocarbons by methane-oxidizing cultures. Appl Environ Microbiol 62(9):3371-3377.

Cheever KL, Cholakis JM, el-Hawari AM, et al. 1990. Ethylene dichloride: the influence of disulfiram or ethanol on oncogenicity, metabolism, and DNA covalent binding in rats. Fundam Appl Toxicol 14(2):243-261.

Cheh AM, Hooper AB, Skochdopole J, et al. 1980. A comparison of the ability of frog and rat S-9 to activate promutagens in the Ames test. Environ Mutagen 2(4):487-508.

Chen C, Puhakka JA, Ferguson JF. 1996. Transformations of 1,1,2,2-tetrachloroethane under methanogenic conditions. Environ Sci Technol 30(2):542-547. 10.1021/es9502987.

Chen S, Zhang Z, Lin H, et al. 2015. 1,2-Dichloroethane-induced toxic encephalopathy: a case series with morphological investigations. J Neurol Sci 351(1-2):36-40. 10.1016/j.jns.2015.02.020.

Cheng TJ, Huang ML, You NC, et al. 1999. Abnormal liver function in workers exposed to low levels of ethylene dichloride and vinyl chloride monomer. J Occup Environ Med 41(12):1128-1133.

Cheng TJ, Chou PY, Huang ML, et al. 2000. Increased lymphocyte sister chromatid exchange frequency in workers with exposure to low level of ethylene dichloride. Mutat Res 470(2):109-114.

Chiou CT, Freed VH, Peters LJ, et al. 1980. Evaporation of solutes from water. Environment International 3(3):231-236. 10.1016/0160-4120(80)90123-3.

Chroust K, Jowett T, Farid-Wajidi MF, et al. 2001. Activation or detoxification of mutagenic and carcinogenic compounds in transgenic Drosophila expressing human glutathione S-transferase. Mutation Research/Genetic Toxicology and Environmental Mutagenesis 498(1):169-179. https://doi.org/10.1016/S1383-5718(01)00280-7.

Chroust K, Pavlová M, Prokop Z, et al. 2007. Quantitative structure-activity relationships for toxicity and genotoxicity of halogenated aliphatic compounds: wing spot test of Drosophila melanogaster. Chemosphere 67(1):152-159. 10.1016/j.chemosphere.2006.09.020.

Clark RM, Goodrich JA, Deininger RA. 1986. Drinking water and cancer mortality. Sci Total Environ 53(3):153-172.

Class T, Ballschmiter K. 1986. Chemistry of organic traces in air VI: Distribution of chlorinated C1 □ C4 hydrocarbons in air over the northern and southern Atlantic Ocean. Chemosphere 15(4):413-427. 10.1016/0045-6535(86)90535-7.

Clewell HJ III AM. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1:111-113.

Cmarik JL IP, Meredith MJ, et al. 1990. Selectivity of rat and human glutathione Stransferase in activation of ethylene dibromide by glutathione conjugation and DNA binding and induction of unscheduled DNA synthesis in human hepatocytes. Cancer Research 50:2747-2752.

Cohen MA, Ryan PB, Yanagisawa Y, et al. 1989. Indoor/outdoor measurements of volatile organic compounds in the Kanawha Valley of West Virginia. JAPCA 39(8):1086-1093. 10.1080/08940630.1989.10466593.

Cole RH, Frederick RE, Healy RP, et al. 1984. preliminary findings of the priority pollutant monitoring project of the nationwide urban runoff program. Journal (Water Pollution Control Federation) 56(7):898-908.

Conkle JP, Camp BJ, Welch BE. 1975. Trace composition of human respiratory gas. Arch Environ Health 30(6):290-295.

Corapcioglu MY, Hossain MA. 1990. Ground-water contamination by high-density immiscible hydrocarbon slugs in gravity-driven gravel aquifers. Ground Water 28(3):403-412. 10.1111/j.1745-6584.1990.tb02270.x.

Cottalasso D, Domenicotti C, Traverso N, et al. 2002. Influence of chronic ethanol consumption on toxic effects of 1,2-dichloroethane: glycolipoprotein retention and impairment of dolichol concentration in rat liver microsomes and Golgi apparatus. Toxicology 178(3):229-240.

Cox E, McMaster M, Major D, et al. 1998. Natural attenuation of 1,2-dichloroethane and chloroform in groundwater at a superfund site. In: Wickramanayake G & Hinchee R, ed. Natural attentuation: Chlorinated and recalcitrant compounds. Columbus, OH: Battelle Press, 309-314.

Crebelli R, Conti G, Conti L, et al. 1984. Induction of somatic segregation by halogenated aliphatic hydrocarbons in Aspergillus nidulans. Mutat Res 138(1):33-38.

Crebelli R, Benigni R, Franekic J, et al. 1988. Induction of chromosome malsegregation by halogenated organic solvents in Aspergillus nidulans: unspecific or specific mechanism? Mutat Res 201(2):401-411. https://doi.org/10.1016/0027-5107(88)90027-9.

Crespi CL, Seixas GM, Turner TR, et al. 1985. Mutagenicity of 1,2-dichloroethane and 1,2-dibromoethane in two human lymphoblastoid cell lines. Mutat Res 142(3):133-140. 10.1016/0165-7992(85)90053-3.

Croen LA, Shaw GM, Sanbonmatsu L, et al. 1997. Maternal residential proximity to hazardous waste sites and risk for selected congenital malformations. Epidemiology 8(4):347-354.

Daft JL. 1988. Rapid determination of fumigant and industrial chemical residues in food. J Assoc Off Anal Chem 71(4):748-760.

Daft JL. 1991. Fumigants and related chemicals in foods: review of residue findings, contamination sources, and analytical methods. Sci Total Environ 100 Spec No:501-518. https://doi.org/10.1016/0048-9697(91)90390-Z.

Dai H, Jing S, Wang H, et al. 2017. VOC characteristics and inhalation health risks in newly renovated residences in Shanghai, China. Sci Total Environ 577:73-83. 10.1016/j.scitotenv.2016.10.071.

Dang J, Chen J, Bi F, et al. 2019. The clinical and pathological features of toxic encephalopathy caused by occupational 1, 2-dichloroethane exposure. Medicine 98(17).

Daniel FB, Robinson M, Olson GR, et al. 1994. Ten and ninety-day toxicity studies of 1,2-dichloroethane in Sprague-Dawley rats. Drug Chem Toxicol 17(4):463-477. 10.3109/01480549409014312.

Danni O, Aragno M, Tamagno E, et al. 1992. In vivo studies on halogen compound interactions. IV. Interaction among different halogen derivatives with and without synergistic action on liver toxicity. Res Commun Chem Pathol Pharmacol 76(3):355-366.

Dawes VJ, Waldock MJ. 1994. Measurement of volatile organic compounds at UK national monitoring plan stations. Marine Pollution Bulletin 28(5):291-298. 10.1016/0025-326x(94)90153-8.

Dawson BV, Johnson PD, Goldberg SJ, et al. 1993. Cardiac teratogenesis of halogenated hydrocarbon—Contaminated drinking water. Journal of the American College of Cardiology 21(6):1466-1472. 10.1016/0735-1097(93)90325-u.

De Wildeman S, Nollet H, Van Langenhove H, et al. 2001. Reductive biodegradation of 1,2-dichloroethane by methanogenic granular sludge in lab-scale UASB reactors. Advances in Environmental Research 6(1):17-27.

DeMarini DM BH. 1992. Induction of prophage lambda by chlorinated organics: Detection of some single-species/single-site carcinogens. Environ Mol Mutagen 19:98-111.

Dilling WL. 1977. Interphase transfer processes. II. Evaporation rates of chloro methanes, ethanes, ethylenes, propanes, and propylenes from dilute aqueous solutions. Comparisons with theoretical predictions. Environ Sci Technol 11(4):405-409. 10.1021/es60127a009.

Dilling WL, Tefertiller NB, Kallos GJ. 1975. Evaporation rates and reactivities of methylene chloride, chloroform, 1,1,1-trichloroethane, trichloroethylene, tetrachloroethylene, and other chlorinated compounds in dilute aqueous solutions. Environ Sci Technol 9(9):833-838. 10.1021/es60107a008.

DOE. 2016. Table 2: Protective Action Criteria (PAC) Rev. 29 Based on applicable 60-minute AEGLs, ERPGs, or TEELs (Chemicals listed in alphabetical order). https://edms.energy.gov/pac/docs/Revision_29A_Table2.pdf.

DOE. 2016. Protective Action Criteria (PAC) with AEGLs, ERPGs, & TEELs: Rev. 29 for chemicals of concern - May 2016. https://www.energy.gov/ehss/protective-action-criteria-pac-aegls-erpgs-teels-rev-29-chemicals-concern-may-2016.

Doherty AT, Ellard S, Parry EM, et al. 1996. An investigation into the activation and deactivation of chlorinated hydrocarbons to genotoxins in metabolically competent human cells. Mutagenesis 11(3):247-274. 10.1093/mutage/11.3.247.

Dow Chemical Company. 1989. Written communication. Public comment on toxicological profile for 1,2-dichloroethane. Dow Chemical Company, Midland, MI.

Dreher E-L, Beutel KK, Myers JD, et al. 2014. Chloroethanes and Chloroethylenes. In: Ullmann's Encyclopedia of Industrial Chemistry. 1-81.

D'Souza RW, Francis WR, Andersen ME. 1988. Physiological model for tissue glutathione depletion and increased resynthesis after ethylene dichloride exposure. J Pharmacol Exp Ther 245(2):563-568.

D'Souza R FW, Bruce RD, et al. 1987. Physiologically based pharmacokinetic model for ethylene dichloride and its application in risk assessment. In: Pharmacokinetics in risk assessment: Drinking water and health. Washington, DC: National Research Council 8:286-301.

Easley DM, Kleopfer RD, Carasea AM. 1981. Gas chromatographic--mass spectrometric determination of volatile organic compounds in fish. J Assoc Off Anal Chem 64(3):653-656.

Elbir T, Cetin B, Cetin E, et al. 2007. Characterization of volatile organic compounds (VOCs) and their sources in the air of Izmir, Turkey. Environ Monit Assess 133(1-3):149-160. 10.1007/s10661-006-9568-z.

EPA. 1977. Monitoring to detect previously unrecognized pollutants in surface water. Washington, DC Office of Toxic Substances, U.S. Environmental Protection Agency.

EPA. 1980. Acquisition and chemical analysis of mother's milk for selected toxic substances. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticides and Toxic Substances

EPA. 1981. Engineering handbook for hazardous waste incineration. 3-12.

EPA. 1982. Direct measurement of volatile organic compounds in breathing-zone air, drinking water, breath, blood, and urine. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development.

EPA. 1985a. Health assessment document for 1,2-dichloroethane. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment.

EPA. 1985b. Synthetic organic compound sampling survey of public water supplies. Washington, DC: U.S. Environmental Protection Agency.

EPA. 1987a. 1,2-Dichloroethane health advisory. Office of Drinking Water, U.S. Environmental Protection Agency.

EPA. 1987b. Atmospheric persistence of eight air toxics: Project summary. Research Triangle Park, NC: U.S. Environmental Protection Agency, Atmospheric Sciences Research Laboratory.

EPA. 1987c. Integrated Risk Information System (IRIS) chemical assessment summary; 1,2-Dichloroethane; CASRN 107-06-2. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=149.

EPA. 1988. National ambient volatile organic compounds (VOCs) database update. Washington, DC: U.S. Environmental Protection Agency.

EPA. 1989. Interaction between water pollutants: Quantitative electron microscopy of hepatic morphological changes induced by 1,2-dichloroethane (DCE) and 1,1,-dichloroethylene (VDC). Research Triangle Park, NC: Health Effects Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency.

EPA. 1991. 1990 Urban air toxics monitoring program. Research Triangle Park, NC: Office of Air and Radiation, Office of Air Quality Planning and Standards, U.S. Environmental Protection Agency.

EPA. 1992a. Superfund record of decision (EPA region 1). Darling Hill dump, Lyndon, VT. (First remedial action), June 1992. In: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response.

EPA. 1992b. Superfund record of decision: Pacific Coast pipeline, CA. In: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response.

EPA. 1992c. Superfund record of decision (EPA region 5). Clare water supply site, Clare County,Clare, MI. (Second remedial action), September 1992. U.S. Environmental Protection Agency, Office of Emergency and Remedial Response

EPA. 1993. A literature review of atmospheric transformation products of clean air act title III hazardous air pollutants. Research Triangle Park, NC: U.S. Environmental Protection Agency.

EPA. 1994a. Methods for derivation of inhalation reference concentrations and Application of Inhalation Dosimetry. Washington DC EPA/600/8-90/066F.

EPA. 1994b. Method 8010B: Halogenated volatile organics by gas chromatography. U.S. Environmental Protection Agency.

EPA. 1994c. Method 8240B: Halogenated volatile organics by gas chromatography. U.S. Environmental Protection Agency.

EPA. 1996. Drinking water regulations and health advisories. Washington, DC: Office of Water, U.S. Environmental Protection Agency.

EPA. 1997. Special report on environmental endocrine disruption: An effects assessment and analysis. EPA/630/R-96/012.

EPA. 2010. Provisional peer-reviewed toxicity values for 1,2-dichloroethane (CASRN 107-06-2). Cincinnati, OH: EPA/690/R-10/011F.

EPA. 2011. Background indoor air concentrations of volatile organic compounds in North American residences (1990–2005): A compilation of statistics for assessing vapor intrusion. Washington, DC: Office of Solid Waste and Emergency Response, U.S. Environmental Protection Agency.

EPA. 2012. Advances in Inhalation Gas Dosimetry for Derivation of a Reference Concentration (RfC) and Use in Risk Assessment. Washington DC EPA/600/R-12/044.

EPA. 2018. Toxic Chemical Release Inventory reporting forms and instructions: Revised 2017 Version. Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986). U.S. Environmental Protection Agency, Office of Environmental Information.

EPA. 2018a. 2014 NATA: Assessment results. Pollutant specific results: 1,2-Dichloroethane. U.S. Environmental Protection Agency. https://www.epa.gov/national-air-toxics-assessment/2014-nata-assessment-results.

EPA. 2018b. 2018 edition of the drinking water standards and health advisories tables. Washington, DC: Office of Water, U.S. Environmental Protection Agency. EPA822F18001.

EPA. 2018c. Air quality system (AQS): Ethylene dichloride. U.S. Environmental Protection Agency. https://www.epa.gov/aqs. June 5, 2019.

EPA. 2021a. Designation, reportable quantities, and notification. 40 CFR 302. U.S. Environmental Protection Agency. https://www.ecfr.gov/cgi-bin/text-idx?SID=e7ed463134bffdbe475721c16ddbb391&mc=true&node=pt40.30.302&rgn=div5.

EPA. 2021b. Land disposal restrictions. 40 CFR 268. U.S. Environmental Protection Agency. https://www.ecfr.gov/cgi-bin/text-idx?SID=aa1408f99084487a0f110ee4746e945f&mc=true&node=pt40.28.261&rgn=div5.

EPA. 2021c. Identification and listing of hazardous waste. 40 CFR 261. U.S. Environmental Protection Agency. https://www.ecfr.gov/cgi-bin/text-idx?SID=aa1408f99084487a0f110ee4746e945f&mc=true&node=pt40.28.261&rgn=div5.

EPA. 1994a. Methods for Derivation of Inhalation Reference Concent rations and Application of Inhalation Dosimetry. Washington DC EPA/600/8-90/066F.

Erve JC, Deinzer ML, Reed DJ. 1996. Reaction of human hemoglobin toward the alkylating agent S-(2-chloroethyl)glutathione. J Toxicol Environ Health 49(2):127-143.

Farrington JW. 1991. Biogeochemical processes governing exposure and uptake of organic pollutant compounds in aquatic organisms. Environ Health Perspect 90:75-84. 10.1289/ehp.90-1519506.

FDA. 2017. Q3C - Tables and list guidance for industry. Revision 3. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). ://www.fda.gov/media/71737/download.

FDA. 2019. Substances added to food (formerly EAFUS): Ethylene dichloride. Silver Spring, MD: U.S. Food and Drug Administration. https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus. May 14, 2019.

FDA. 2019. Substances added to food (formerly EAFUS): Polyethylenimine Reaction Product W/ 1,2-Dichloroethane. Silver Spring, MD: U.S. Food and Drug Administration. https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus. May 14, 2019.

FDA. 2019. Food additives permitted in feed and drinking water of animals. Code of Federal Regulations. 21 CFR 573.

Ferreri A, Rocchi P, Capucci A, et al. 1983. Induction of diphtheria toxin-resistant mutants in human cells by halogenated compounds. Cancer Res and Clin Oncol 105:111-112.

Först C, Stieglitz L, Roth W, et al. 1989. Quantitative Analysis of Volatile Organic Compounds in Landfill Leachates. International Journal of Environmental Analytical Chemistry 37(4):287-293. 10.1080/03067318908026905.

Fossett N, Byrne B, Tucker A, et al. 1995. Mutation spectrum of 2-chloroethyl methanesulfonate in Drosophila melanogaster premeiotic germ cells. Mutat Res 331:213-224.:213-224.

Frasch HF, Barbero AM, Alachkar H, et al. 2007. Skin penetration and lag times of neat and aqueous diethyl phthalate, 1,2-dichloroethane and naphthalene. Cutan Ocul Toxicol 26(2):147-160. 10.1080/15569520701212274.

Fusillo TV, Hochreiter JJ, Lord DG. 1985. Distribution of volatile organic compounds in a New Jersey coastal plain aquifer system. Ground Water 23(3):354-360. 10.1111/j.1745-6584.1985.tb00780.x.

Gajjar RM, Kasting GB. 2014. Absorption of ethanol, acetone, benzene and 1,2-dichloroethane through human skin in vitro: a test of diffusion model predictions. Toxicol Appl Pharmacol 281(1):109-117. 10.1016/j.taap.2014.09.013.

Gao J, Zhang J, Li H, et al. 2018. Comparative study of volatile organic compounds in ambient air using observed mixing ratios and initial mixing ratios taking chemical loss into account – A case study in a typical urban area in Beijing. Science of The Total Environment 628-629:791-804.

Gargas ML, Burgess RJ, Voisard DE, et al. 1989. Partition coefficients of low-molecular-weight volatile chemicals in various liquids and tissues. Toxicology and Applied Pharmacology 98(1):87-99.

Garrison SC, Leadingham RS. 1954. A fatal case of ethylene dichloride poisoning in an occupational therapy department of a neuropsychiatric hospital. Am J Phys Med 33(4):230-237.

Giri AK, Que Hee SS. 1988. In vivo sister chromatid exchange induced by 1,2-dichloroethane on bone marrow cells of mice. Environ Mol Mutagen 12(3):331-334.

Gocke E, Wild D, Eckhardt K, et al. 1983. Mutagenicity studies with the mouse spot test. Mutat Res 117(1-2):201-212.

Gold LS. 1980. Human exposures to ethylene dichloride. In: Ames BN, Infante P, & Reitz R, ed. Ethylene dichloride: A potential health risk? Banbury report No. 5. Cold Harbor Spring, NY: Cold Harbor Spring Laboratory, 209-225.

Goldberg SJ, Lebowitz MD, Graver EJ, et al. 1990. An association of human congenital cardiac malformations and drinking water contaminants. Journal of the American College of Cardiology 16(1):155-164. https://doi.org/10.1016/0735-1097(90)90473-3.

Goldberg M, Al-Homsi N, Goulet L, et al. 1995. Incidence of cancer among persons living near a municipal solid waste landfill site in Montreal, Quebec. Arch Environ Health 50:416-424.

Gonzalez FJ, Gelboin HV. 1994. Role of human cytochromes P450 in the metabolic activation of chemical carcinogens and toxins. Drug Metab Rev 26(1-2):165-183. 10.3109/03602539409029789.

Guengerich FP, Kim DH, Iwasaki M. 1991. Role of human cytochrome P-450 IIE1 in the oxidation of many low molecular weight cancer suspects. Chem Res Toxicol 4(2):168-179. 10.1021/tx00020a008.

Guengerich FP, Peterson LA, Cmarik JL, et al. 1987. Activation of dihaloalkanes by glutathione conjugation and formation of DNA adducts. Environ Health Perspect 76:15-18.

Guengerich FP, Crawford W, Domoradzki J, et al. 1980. In vitro activation of 1,2-dichloroethane by microsomal and cytosolic enzyme. Toxicol Appl Pharmacol 55:303-317.

Hachiya N, Motohashi Y. 2000. Examination of lacZ mutant induction in the liver and testis of Muta Mouse following injection of halogenated aliphatic hydrocarbons classified as human carcinogens. Ind Health 38(2):213-220. 10.2486/indhealth.38.213.

Hamza M, Tohid H, Maibach H. 2015. Shaving effects on percutaneous penetration: clinical implications. Cutan Ocul Toxicol 34(4):335-343.

Hansen J. 2000. Elevated risk for male breast cancer after occupational exposure to gasoline and vehicular combustion products. Am J Ind Med 37(4):349-352.

Hayes FD, Short RD, Gibson JE. 1973. Differential toxicity of monochloroacetate, monofluoroacetate and monoiodoacetate in rats. Toxicol Appl Pharmacol 26(1):93-102.

Haynes WM. 2015. CRC handbook of chemistry and physics 95th edition. Boca Raton, FL: CRC Press

Heavner DL, Morgan WT, Ogden MW. 1995. Determination of volatile organic compounds and ETS apportionment in 49 homes. Environment International 21(1):3-21. 10.1016/0160-4120(94)00018-3.

Heavner DL, Morgan WT, Ogden MW. 1996. Determination of volatile organic compounds and respirable suspended particulate matter in New Jersey and Pennsylvania homes and workplaces. Environment International 22(2):159-183. 10.1016/0160-4120(96)00003-7.

Heikes DL. 1987. Purge and trap method for determination of volatile halocarbons and carbon disulfide in table-ready foods. J Assoc Off Anal Chem 70(2):215-226.

Heikes DL, Hopper ML. 1986. Purge and trap method for determination of fumigants in whole grains, milled grain products, and intermediate grain-based foods. J Assoc Off Anal Chem 69(6):990-998.

Heikes DL, Jensen SR, Fleming-Jones ME. 1995. Purge and trap extraction with GC-MS determination of volatile organic compounds in table-ready foods. Journal of Agricultural and Food Chemistry 43(11):2869-2875. 10.1021/jf00059a018.

Hellman B, Brant I. 1986. Effects of carcinogenic halogenated aliphatic hydrocarbons on [3H]thymidine incorporation into various organs of the mouse: A comparison between 1,2-dibromoethane and 1,2-dichloroethane. Mutat Res 163:193-199.

Hemminki K, Falck K, Vainio H. 1980. Comparison of alkylation rates and mutagenicity of directly acting industrial and laboratory chemicals: Epoxides, glycidyl ethers, methylating and ethylating agents, halogenated hydrocarbons, hydrazine derivatives, aldehydes, thiouram and dithiocarbamate derivatives. . Arch Toxicol 46:277-285.

Henderson JK, Falta RW, Freedman DL. 2009. Simulation of the effect of remediation on EDB and 1,2-DCA plumes at sites contaminated by leaded gasoline. Journal of Contaminant Hydrology 108(1):29-45.

Henson JM, Yates MV, Cochran JW, et al. 1988. Microbial removal of halogenated methanes, ethanes, and ethylenes in an aerobic soil exposed to methane. FEMS Microbiology Ecology 4(3-4):193-201. 10.1111/j.1574-6968.1988.tb02664.x.

Heppel LA, Neal PA, et al. 1946. The toxicology of 1,2-dichloroethane (ethylene dichloride); the effects of daily inhalations. J Ind Hyg Toxicol 28:113-120.

Heppel LA, Porterfield VT, Sharpless NE. 1947. Toxicology of 1,2-dichloroethane (ethylene dichloride) its detoxication by 1-cystine, dimethionine and certain other sulfur containing compounds. J Pharmacol Exp Ther 91(4):385-394.

Heppel LA, Neal PA, Perrin TL, et al. 1945. The Toxicology Of 1,2-Dichloroethane (Ethylene). III. Its Acute Toxicity And The Effect Of Protective Agents 84(1):53-63.

Hines RN. 2008. The ontogeny of drug metabolism enzymes and implications for adverse drug events. Pharmacol Ther 118(2):250-267.

Hirschorn SK, Dinglasan-Panlilio MJ, Edwards EA, et al. 2007. Isotope analysis as a natural reaction probe to determine mechanisms of biodegradation of 1,2-dichloroethane. Environ Microbiol 9(7):1651-1657. 10.1111/j.1462-2920.2007.01282.x.

Hogstedt C, Rohlen O, Berndtsson BS, et al. 1979. A cohort study of mortality and cancer incidence in ethylene oxide production workers. Br J Ind Med 36(4):276-280. 10.1136/oem.36.4.276.

Holliger C, Schraa G, Stams AJ, et al. 1990. Reductive dechlorination of 1,2-dichloroethane and chloroethane by cell suspensions of methanogenic bacteria. Biodegradation 1(4):253-261. 10.1007/bf00119762.

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. 10.1016/j.fct.2009.10.039.

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

Hu R, Liu G, Zhang H, et al. 2018. Levels, characteristics and health risk assessment of VOCs in different functional zones of Hefei. Ecotoxicol Environ Saf 160:301-307. 10.1016/j.ecoenv.2018.05.056.

Hubbs RS, Prusmack JJ. 1955. Ethylene dichloride poisoning. J Am Med Assoc 159(7):673-675.

Hueper W, Smith C. 1935. Fatal ethylene dichloride [sic] poisoning. Am J Med Sci 189:778-784.

Humphreys WG, Kim DH, Cmarik JL, et al. 1990. Comparison of the DNA-alkylating properties and mutagenic responses of a series of S-(2-haloethyl)-substituted cysteine and glutathione derivatives. Biochemistry 29(45):10342-10350. 10.1021/bi00497a008.

IARC. 1979. 1,2-Dichloroethane. IARC Monographs Volume 71, 501-529. International Agency for Research on Cancer, World Health Organization.

IARC. 2016. Agents Classified by the IARC Monographs , Volumes 1–123. International Agency for Research on Cancer, World Health Organization. https://monographs.iarc.who.int/agents-classified-by-the-iarc/.

Igwe OJ, Que Hee SS, Wagner WD. 1986a. Interaction between 1,2-dichloroethane and disulfiram. I. Toxicologic effects. Fundam Appl Toxicol 6(4):733-746.

Igwe OJ, Que Hee SS, Wagner WD. 1986b. Interaction between 1,2-dichloroethane and tetraethylthiuram disulfide (disulfiram). II. Hepatotoxic manifestations with possible mechanism of action. Toxicol Appl Pharmacol 86(2):286-297.

Igwe OJ, Que Hee SS, Wagner WD. 1988. Urinary thioether biological monitoring in the interaction between 1,2-dichloroethane and disulfiram in Sprague-Dawley rats. Am Ind Hyg Assoc J 49(1):10-16. 10.1080/15298668891379297.

Inskeep PB, Koga N, Cmarik JL, et al. 1986. Covalent binding of 1,2-dihaloalkanes to DNA and stability of the major DNA adduct, S-[2-(N7-guanyl)ethyl]glutathione. Cancer Res 46(6):2839-2844.

Isacson P, Bean JA, Splinter R, et al. 1985. Drinking water and cancer incidence in Iowa. III. Association of cancer with indices of contamination. Am J Epidemiol 121(6):856-869. 10.1093/oxfordjournals.aje.a114056.

Jafvert CT, Wolfe LN. 1987. Degradation of selected halogenated ethanes in anoxic sediment-water systems. Environmental Toxicology and Chemistry 6(11):827-837. 10.1002/etc.5620061102.

Jakobson I, Wahlberg JE, Holmberg B, et al. 1982. Uptake via the blood and elimination of 10 organic solvents following epicutaneous exposure of anesthetized guinea pigs. Toxicol Appl Pharmacol 63(2):181-187. 10.1016/0041-008x(82)90039-4.

Janssen D, Scheper A, Witholt B. 1984. Biodegradation of 2-chloroethanol and 1,2-dichloroethane by pure bacterial culture. In: Houwink E & van der Meer R, ed. Innovations in biotechnology. Amsterdam, The Netherlands: Elsevier Science Publishers, 169-178.

Jean PA, Reed DJ. 1989. In vitro dipeptide, nucleoside, and glutathione alkylation by S-(2-chloroethyl)glutathione and S-(2-chloroethyl)-L-cysteine. Chem Res Toxicol 2(6):455-460.

Jeffers PM, Ward LM, Woytowitch LM, et al. 1989. Homogeneous hydrolysis rate constants for selected chlorinated methanes, ethanes, ethenes, and propanes. Environ Sci Technol 23(8):965-969. 10.1021/es00066a006.

Jenssen D, Ramel C. 1980. The micronucleus test as part of a short-term mutagenicity test program for the prediction of carcinogenicity evaluated by 143 agents tested. Mutation Research 75:191-202.

Jin X, Liao Y, Tan X, et al. 2018a. Involvement of CYP2E1 in the Course of Brain Edema Induced by Subacute Poisoning With 1,2-Dichloroethane in Mice. Front Pharmacol 9:1317. 10.3389/fphar.2018.01317.

Jin X, Liao Y, Tan X, et al. 2018b. Involvement of the p38 MAPK signaling pathway in overexpression of matrix metalloproteinase-9 during the course of brain edema in 1,2-dichloroethane-intoxicated mice. Neurotoxicology 69:296-306. 10.1016/j.neuro.2018.07.022.

Johansson I, Ekstrom G, Scholte B, et al. 1988. Ethanol-fasting- and acetone-inducible cytochromes P450 in rat liver: Regulation and characteristics of enzymes belonging to the IIB and IIE gene subfamilies. Biochemistry 27:1925-1934.

Johnson MK. 1967. Metabolism of chloroethanol in the rat. Biochemical Pharmacology 16(1):185-199. 10.1016/0006-2952(67)90199-2.

Jury WA, Russo D, Streile G, et al. 1990. Evaluation of volatilization by organic chemicals residing below the soil surface. Water Resources Research 26(1):13-20. 10.1029/WR026i001p00013.

Jüttner F. 1986. Analysis of organic compounds (VOC) in the forest air of the Southern Black Forest. Chemosphere 15(8):985-992. 10.1016/0045-6535(86)90551-5.

Kanada T, Uyeta M. 1978. Mutagenicity screening of organic solvents in microbial systems. Mutat Res 54:215.

Kanada M, Miyagawa M, Sato M, et al. 1994. Neurochemical profile of effects of 28 neurotoxic chemicals on the central nervous system in rats (1). Effects of oral administration on brain contents of biogenic amines and metabolites. Ind Health 32(3):145-164. 10.2486/indhealth.32.145.

Kavlock R, Chernoff N, Carver B, et al. 1979. Teratology studies in mice exposed to municipal drinking-water concentrates during organogenesis. Food Cosmet Toxicol 17(4):343-347.

Kellam R, Dusetzina M. 1980. Human exposure to ethylene dichloride: Potential for regulation via EPA's proposed airborne carcinogen policy. In: Ames B, Infante P, & Reitz R, ed. Ethylene dichloride: A potential health risk? Banbury report No. 5. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 265-274.

Kelley M, Magar VS, Hoeppel R, et al. 1998. Intrinsic remediation of chlorinated hydrocarbons in cocontaminated groundwater plumes at the naval air station Fallon, Nevada. In: Wickramanayake GB & Hinchee RE, ed. Natural attenuation: Chlorinated and recalcitrant compounds. Columbus, OH: Battelle Press, 315-320.

Kelly TJ, Mukund R, Spicer CW, et al. 1994. Concentrations and transformations of hazardous air pollutants. Environ Sci Technol 28(8):378A-387A. 10.1021/es00057a003.

Kessels H, Hoogerwerf W, Lips J. 1992. The determination of volatile organic compounds from EPA method 524.2 using purge-and-trap capillary gas chromatography, ECD, and FID. Journal of Chromatographic Science 30(7):247-255. 10.1093/chromsci/30.7.247.

Kim DH, Guengerich FP. 1989. Excretion of the mercapturic acid S-[2-N7-guanyl) ethyl]-N-acetyl cysteine in urine following administration of ethylene dibromide to rats. Cancer Research 49:5843-5847.

Kim DH, Guengerich FP. 1990. Formation of the DNA adduct S-[2-(N7-guanyl)ethyl]glutathione from ethylene dibromide: effects of modulation of glutathione and glutathione S-transferase levels and lack of a role for sulfation. Carcinogenesis 11(3):419-424. 10.1093/carcin/11.3.419.

King MT, Beikirch H, Eckhardt K, et al. 1979. Mutagenicity studies with X-ray-contrast media, analgesics, antipyretics, antirheumatics and some other pharmaceutical drugs in bacterial, Drosophila and mammalian test systems. Mutation Research/Genetic Toxicology 66(1):33-43. 10.1016/0165-1218(79)90005-3.

Kitchin KT, Brown JL. 1994. Dose-response relationship for rat liver DNA damage caused by 49 rodent carcinogens. Toxicology 88(1-3):31-49. 10.1016/0300-483x(94)90109-0.

Klaunig JE, Ruch RJ, Pereira MA. 1986. Carcinogenicity of chlorinated methane and ethane compounds administered in drinking water to mice. Environ Health Perspect 69:89-95. 10.1289/ehp.866989.

Kramer R, Foureman G, Greene K, et al. 1987. Nephrotoxicity of S-(2-chloroethyl) glutathione in the Fischer rat: evidence for gamma-glutamyltranspeptidase-independent uptake by the kidney. J Pharmacol Exp Ther 242(2):741-748.

Kramers PG, Mout HC, Bissumbhar B, et al. 1991. Inhalation exposure in Drosophila mutagenesis assays: experiments with aliphatic halogenated hydrocarbons, with emphasis on the genetic activity profile of 1,2-dichloroethane. Mutat Res 252(1):17-33.

Krill RM, Sonzogni WC. 1986. Chemical monitoring of Wisconsin's groundwater. Journal AWWA 78(9):70-75. 10.1002/j.1551-8833.1986.tb05812.x.

Krishnan K, Andersen M, Clewell Hr, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang R, ed. Toxicology of chemical mixtures. New York, NY: Academic Press, 399-437.

Kronevi T, Wahlberg JE, Holmberg B. 1981. Skin pathology following epicutaneous exposure to seven organic solvents. Int J Tissue React 3(1):21-30.

Kurtz JP, Wolfe EM, Woodland AK, et al. 2010. Evidence for increasing indoor sources of 1, 2-dichloroethane since 2004 at two Colorado residential vapor intrusion sites. Groundwater Monitoring & Remediation 30(3):107-112.

Lam RHF, Brown JP, Fan AM. 1994b. Chemicals in California drinking water: Source of contamination, risk assessment, and drinking water standards. In: Wang R, ed. Water contamination and health: Integration of exposure assessment, toxicology, and risk assessment. New York, NY: Marcel Dekker, Inc., 15-44.

Lam RHF, Brown JP, Fan AM, et al. 1994a. Chemicals in California drinking water: source contaminants, risk assessment, risk management, and regulatory standards. Journal of Hazardous Materials 39(2):173-192. 10.1016/0304-3894(94)00053-0.

Lane RW, Riddle BL, Borzelleca JF. 1982. Effects of 1,2-dichloroethane and 1,1,1-trichloroethane in drinking water on reproduction and development in mice. Toxicology and Applied Pharmacology 63(3):409-421. 10.1016/0041-008x(82)90270-8.

Lanzarone NA, McCarty PL. 1990. Column studies on methanotrophic degradation of trichloroethene and 1,2-dichloroethane. Ground Water 28(6):910-919. 10.1111/j.1745-6584.1990.tb01727.x.

LaRegina J, Bozzelli JW, Harkov R, et al. 1986. Volatile organic compounds at hazardous waste sites and a sanitary landfill in New Jersey. Environmental Progress 5(1):18-27. 10.1002/ep.670050109.

Larranaga M, Lewis Sr R, Lewis R. 2016. Hawley's Condensed Chemical Dictionary 16th Edition. Hoboken, NJ: John Wiley & Sons, 584.

Lee M, Mazierski P, Buchanan R, et al. 1995. Intrinsic in situ anaerobic biodegradation of chlorinated solvents at an industrial landfill. In: Hinchee R, Wilson J, & Downey D, ed. Intrinsic bioremediation. Columbus, OH: Battelle Press, 205-222.

Leeder JS, Kearns GL. 1997. Pharmacogenetics in pediatrics. Implications for practice. Pediatr Clin North Am 44(1):55-77.

Lehtinen J, Veijanen A. 2011. Determination of odorous VOCs and the risk of occupational exposure to airborne compounds at the waste water treatment plants. Water Sci Technol 63(10):2183-2192.

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

Liu G, Niu J, Zhang C, et al. 2016. Characterization and assessment of contaminated soil and groundwater at an organic chemical plant site in Chongqing, Southwest China. Environ Geochem Health 38(2):607-618. 10.1007/s10653-015-9746-4.

Liu JR, Fang S, Ding MP, et al. 2010. Toxic encephalopathy caused by occupational exposure to 1, 2-Dichloroethane. J Neurol Sci 292(1-2):111-113. 10.1016/j.jns.2010.01.022.

Livesey JC, Anders MW. 1979. In vitro metabolism of 1,2-dihaloethanes to ethylene. Drug Metab Dispos 7(4):199-203.

Lochhead HB, Close HP. 1951. Ethylene dichloride plastic cement: a case of fatal poisoning. J Am Med Assoc 146(14):1323-1324.

Lock EA. 1989. Mechanism of nephrotoxic action due to organohalogenated compounds. Toxicol Lett 46(1-3):93-106. 10.1016/0378-4274(89)90120-3.

Loffler FE, Champine JE, Ritalahti KM, et al. 1997. Complete reductive dechlorination of 1,2-dichloropropane by anaerobic bacteria. Appl Environ Microbiol 63(7):2870-2875.

Lone MI, Nazam N, Hussain A, et al. 2016. Genotoxicity and immunotoxic effects of 1,2-dichloroethane in Wistar rats. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev 34(3):169-186. 10.1080/10590501.2016.1193924.

Lorah MM, Olsen LD. 1999. Degradation of 1,1,2,2-tetrachloroethane in a freshwater tidal wetland: Field and laboratory evidence. Environ Sci Technol 33(2):227-234. 10.1021/es980503t.

Ma J, Li H, Spiese R, et al. 2016. Vapor intrusion risk of lead scavengers 1, 2-dibromoethane (EDB) and 1, 2-dichloroethane (DCA). Environmental pollution 213:825-832.

Maltoni C, Valgimigli L, Scarnato C. 1980. Long-term carcinogenic bioassays on ethylene dichloride administered by inhalation to rats and mice.

Martin G, Knorpp K, Huth K, et al. 1969. Clinical features, pathogenesis and management of dichloroethane poisoning. Ger Med Mon 14(2):62-64 passim.

McCann J, Simmon V, Streitwieser D, et al. 1975. Mutagenicity of chloroacetaldehyde, a possible metabolic product of 1, 2-dichloroethane (ethylene dichloride), chloroethanol (ethylene chlorohydrin), vinyl chloride, and cyclophosphamide. Proceedings of the National Academy of Sciences 72(8):3190-3193.

McCollister DD, Hollingsworth RL, Oyen F, et al. 1956. Comparative inhalation toxicity of fumigant mixtures: Individual and joint effect of ethylene dichloride, carbon tetrachloride, and ethylene dibromide. . Arch Ind Health 13:1-7.

McDonald TJ, Kennicutt MC, Brooks JM. 1988. Volatile organic compounds at a coastal Gulf of Mexico site. Chemosphere 17(1):123-136. 10.1016/0045-6535(88)90050-1.

McNally WD, Fostvedt G. 1941. Ethylene dichloride poisoning. Ind Med 10(9):373-374.

Milman H, Story D, Riccio E, et al. 1988. Rat liver foci and in-vitro assays to detect initiating and promoting effects of chlorinated ethanes and ethylenes. Ann N Y Acad Sci 534:521-530. https://doi.org/10.1111/j.1749-6632.1988.tb30143.x.

Mitoma C, Steeger T, Jackson SE, et al. 1985. Metabolic disposition study of chlorinated hydrocarbons in rats and mice. Drug Chem Toxicol 8(3):183-194. 10.3109/01480548508999169.

Miyahara M, Toyoda M, Saito Y. 1995. Volatile Halogenated Hydrocarbons in Foods. Journal of Agricultural and Food Chemistry 43(2):320-326. 10.1021/jf00050a011.

Miyamoto K, Urano K. 1996. Reaction rates and intermediates of chlorinated organic compounds in water and soil. Chemosphere 32(12):2399-2408. https://doi.org/10.1016/0045-6535(96)00142-7.

Monster AC. 1986. Biological monitoring of chlorinated hydrocarbon solvents. J Occup Med 28(8):583-588. 10.1097/00043764-198608000-00012.

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.

Morgan D, Cooper SW, Carlock DL, et al. 1991. Dermal absorption of neat and aqueous volatile organic chemicals in the Fischer 344 rat. Environ Res 55(1):51-63.

Moriya M, Ohta T, Watanabe K, et al. 1983. Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat Res 116(3-4):185-216.

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

Nachtomi E, Alumot E, Bondi A. 1966. The metabolism of ethylene dibromide in the rat: I. Identification of detoxification of products in urine. Israel Journal of Chemistry 4:239-246.

Nagano K, Umeda Y, Senoh H, et al. 2006. Carcinogenicity and chronic toxicity in rats and mice exposed by inhalation to 1,2-dichloroethane for two years. J Occup Health 48(6):424-436.

Nakajima T, Sato A. 1979. Enhanced activity of liver drug-metabolizing enzymes for aromatic and chlorinated hydrocarbons following food deprivation. Toxicol Appl Pharmacol 50(3):549-556.

NAS/NRC. 1989. Biological markers in reproductive toxicology. National Research Council. Board of Environmental Studies and Toxicology. Committee on Biological Markers.

NCI. 1978. Bioassay of 1,2-dichloroethane for possible carcinogenicity. Natl Cancer Inst Carcinog Tech Rep Ser 55:1-103.

NCI. 2021. Ethylene dichloride (Code C44383). NCI term browser. https://ncit.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary=NCI_Thesaurus&ns=NCI_Thesaurus&code=C44383. April 30, 2021.

Nestmann ER, Lee EG, Matula TI, et al. 1980. Mutagenicity of constituents identified in pulp and paper mill effluents using the Salmonella/mammalian-microsome assay. Mutat Res 79(3):203-212.

NIOSH. 1976. National occupational hazard survey (1972-74). Cincinnati, OH: U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health.

NIOSH. 1978. Revised recommended standard: Occupational exposure to ethylene dichloride (1,2-dichloroethane) Cincinnati, OH: U.S. Department of Health, Education, and Welfare, National

Institute for Occupational Safety and Health, Division of Criteria Documents and Standards Development.

NIOSH. 1984. National occupational exposure survey (1980-83). Cincinnati, OH U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health.

NIOSH. 1994. NIOSH manual of analytical methods. Method 1003 Cincinnati, OH: U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health

NIOSH. 2018. Ethylene dichloride. NIOSH pocket guide to chemical hazards. Centers for Disease Control and Prevention. https://www.cdc.gov/niosh/npg/npgd0271.html. May 14, 2019.

Niu QZ, Qinli; Li, Laiyu; Yang, Lijun; Guo, Xiaoli; Liang, Youxin; Huang, Jianxun. 2009. 1,2-dichloroethane induced toxic encephalopathy. Neuroscience Research 65:S249.

NOAA. 2019. Emergency Response Planning Guidelines (ERPGs). https://response.restoration.noaa.gov/oil-and-chemical-spills/chemical-spills/resources/emergency-response-planning-guidelines-erpgs.html

Nouchi T, Miura H, Kanayama M, et al. 1984. Fatal intoxication by 1,2-dichloroethane-a case report. International Archives of Occupational Environmental Health 54(2):111-113. 10.1007/bf00378513.

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). Toxic Rep Ser 4:1-54.

NTP. 2016. 1,2-Dichloroethane CAS No. 107-06-2. Report on Carcinogens, Fourteenth Edition. National Toxicology Program, Department of Health and Human Services. https://ntp.niehs.nih.gov/ntp/roc/content/profiles/dichloroethane.pdf

Nylander P-O OH, Rasmuson B, et al. . 1978. Mutagenic effects of petrol in Drosophila melanogaster: I. Effects of benzene and 1,2-dichloroethane. Mutation Research 57:163-167.

OECD. 2002. SIDS initial assessment report for 14th SIAM: 1,2-Dichloroethane. https://hpvchemicals.oecd.org/ui/handler.axd?id=95f8d194-732a-4cc9-b59b-839ed3b18732.

Oldenhuis R, Vink RL, Janssen DB, et al. 1989. Degradation of chlorinated aliphatic hydrocarbons by Methylosinus trichosporium OB3b expressing soluble methane monooxygenase. 55(11):2819-2826.

Oliver BG, Pugsley CW. 1986. Chlorinated contaminants in St. Clair River sediments. Water Quality Research Journal 21(3):368-379. 10.2166/wqrj.1986.032.

O'Neil M. 2013. The Merck Index - An encyclopedia of chemicals, drugs, and biologicals. Cambridge, UK: Royal Society of Chemistry, 702.

Ott M, Teta J, Greenberg H. 1989. Lymphatic and hematopoietic tissue cancer in a chemical manufacturing environment. American Journal of Industrial Medicine 16:631-644.

Parkinson A. 1996. Biotransformation of xenobiotics. In: Klaassen C, Amdur M, & Doull J, ed. Casarett and Doull's toxicology: The basic science of poisons. New York, NY: McGraw-Hill Companies, Inc., 113-114,172-175.

Payan JP, Beydon D, Fabry JP, et al. 1993. Urinary thiodiglycolic acid and thioether excretion in male rats dosed with 1,2-dichloroethane. J Appl Toxicol 13(6):417-422.

Payan JP, Saillenfait AM, Bonnet P, et al. 1995. Assessment of the developmental toxicity and placental transfer of 1,2-dichloroethane in rats. Fundam Appl Toxicol 28(2):187-198.

Pearson CR, McConnell G. 1975. Chlorinated C1 and C2 hydrocarbons in the marine environment. Proc R Soc Lond B Biol Sci 189(1096):305-332. 10.1098/rspb.1975.0059.

Peijnenburg W, Eriksson L, de Groot A, et al. 1998. The kinetics of reductive dehalogenation of a set of halogenated aliphatic hydrocarbons in anaerobic sediment slurries. Environ Sci Pollut Res Int 5(1):12-16. 10.1007/bf02986368.

Pellizzari ED, Hartwell TD, Perritt RL, et al. 1986. Comparison of indoor and outdoor residential levels of volatile organic chemicals in five U.S. geographical areas. Environment International 12(6):619-623. https://doi.org/10.1016/0160-4120(86)90104-2.

Perocco P, Prodi G. 1981. DNA damage by haloalkanes in human lymphocytes cultured in vitro. Cancer Lett 13(3):213-218.

Plumb Jr RH. 1987. A comparison of ground water monitoring data from CERCLA and RCRA sites. 7(4):94-100. 10.1111/j.1745-6592.1987.tb00968.x.

Pohl HR, Scinicariello F. 2011. The impact of CYP2E1 genetic variability on risk assessment of VOC mixtures. Regul Toxicol Pharmacol 59(3):364-374.

Pohl H, Luukinen B, Holler J. 2005. Health effects classification and its role in the derivation of minimal risk levels: Reproductive and endocrine effects. Regul Toxicol Pharmacol 42:209-217.

Pott WA, Benjamin SA, Yang RS. 1998. Antagonistic interactions of an arsenic-containing mixture in a multiple organ carcinogenicity bioassay. . Cancer Letters 133.

Prodi G, Arfellini G, Colacci A, et al. 1986. Interaction of halocompounds with nucleic acids. . Toxicologic Pathology 14:438-444.

Przezdziak J, Bakula S. 1975. Acute poisoning with 1,2-dichloroethane. Wiad Lek 28(11):983-987.

PubChem. 2021. Compound summary: 1,2-Dichloroethane. National Library of Medicine, National Center for Biotechnology Information. https://pubchem.ncbi.nlm.nih.gov/. April 30, 2021.

Raisbeck M, Brown E, Kanchanapangka S, et al. 1990. Ketonic potentiation of haloalkane-induced nephrotoxicity. In: Goldstein R, Hewitt W, & Hook J, ed. Toxic interactions. San Diego, CA: Academic Press, Inc., 321-366.

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

Rannug U, Beije B. 1979. The mutagenic effect of 1,2-dichloroethane on Salmonella typhimurium: II. Activation by the isolated perfused rat liver. Chem Biol Interaction 24:265-285.

Rao KS, Murray JS, Deacon MM, et al. 1980. Teratogenicity and reproduction studies in animals inhaling ethylene dichloride In: Ames B, Infante P, & Reitz R, ed. Ethylene dichloride: A potential health risk? . Cold Spring Harbor, NY Cold Spring Harbor Laboratory 149-166.

Reeve G, Bond G, Lloyd J, et al. 1983. An investigation of brain tumors among chemical plant employees using a sample-based cohort method. J Occup Med 25:387-393.

Regno V, Arulgnanendran J, Nirmalakhandan N. 1998. Microbial toxicity in soil medium. Ecotoxicology and Environmental Safety 39(1):48-56. https://doi.org/10.1006/eesa.1997.1609.

Reitz R, Fox T, Domoradzki J, et al. 1980. Pharmacokinetics and macromolecular interactions of ethylene dichloride: Comparison of oral and inhalation exposures. In: Ames B, Infante P, & Reitz R, ed. Ethylene dichloride: A potential health risk? Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 135-148.

Reitz RH, Fox TR, Ramsey JC, et al. 1982. Pharmacokinetics and macromolecular interactions of ethylene dichloride in rats after inhalation or gavage. Toxicology and Applied Pharmacology 62(2):190-204. https://doi.org/10.1016/0041-008X(82)90117-X.

Rembold H, Wallner P, Nitz S, et al. 1989. Volatile components of chickpea (Cicer arietinum L.) seed. Journal of Agricultural and Food Chemistry 37(3):659-662. 10.1021/jf00087a018.

Rodgman A, Perfetti T. 2013. The chemical components of tobacco smoke. Boca Raton: CRC Press

Rodriguez-Arnaiz, R. 1998. Biotransformation of several structurally related 2B compounds to reactive metabolites in the somatic w/w+ assay of Drosophila melanogaster. Environmental Molecular Mutagenesis 31.

Roldan-Arjona T, Garchia-Pedraja M, Luque-Romero F, et al. 1991. An association between mutagenicity of the Ara test of Salmonella typhimurium and carcinogenicity in rodents for 16 halogenated aliphatic hydrocarbons. Mutagenesis 6:199-205.

Romert L, Magnusson J, Ramel C. 1990. The importance of glutathione and glutathione transferase for somatic mutations in Drosophila melanogaster induced by in vivo by 1,2-dichloroethane. Carcinogenesis 11:1399-1402.

Roose P, Dewulf J, Brinkman UA, et al. 2001. Measurement of volatile organic compounds in sediments of the Scheldt estuary and the Southern North Sea. Water Res 35(6):1478-1488.

Ruffalo CA, Gouvier WD, Pinkston JB, et al. 2000. Ethylene dichloride: Neuropsychological effects of chronic exposure. Archives of Clinical Neuropsychology 15:653-850.

Sabljić A, Güsten H, Verhaar H, et al. 1995. QSAR modelling of soil sorption. Improvements and systematics of log KOC vs. log KOW correlations. Chemosphere 31(11):4489-4514. https://doi.org/10.1016/0045-6535(95)00327-5.

Salovsky P, Shopova V, Dancheva V, et al. 2002. Early pneumotoxic effects after oral administration of 1,2-dichloroethane. J Occup Environ Med 44(5):475-480.

Sano M, Tappel AL. 1990. Halogenated hydrocarbon and hydroperoxide-induced lipid peroxidation in rat tissue slices. Journal of Agricultural and Food Chemistry 38(2):437-441. 10.1021/jf00092a022.

Sasaki YF, Saga A, Akasaka M, et al. 1998. Detection of in vivo genotoxicity of haloalkanes and haloalkenes carcinogenic to rodents by the alkaline single cell gel electrophoresis (comet) assay in multiple mouse organs. Mutat Res 419(1-3):13-20.

Sato A, Nakajima T, Koyama Y. 1981. Dose-related effects of a single dose of ethanol on the metabolism in rat liver of some aromatic and chlorinated hydrocarbons. Toxicol Appl Pharmacol 60:8-15.

Schlacter MM, Crawford AA, John JA. 1979. Effects of inhaled ethylene dichloride on embryonal and fetal development in rats and rabbits. Midland, MI: Dow Chemical Co.

Schönborn H, Prellwitz W, Baum P. 1970. [Consumption coagulation pathology of 1,2-dichloroethane poisoning]. Klin Wochenschr 48:822-824.

Sherwood RL, O'Shea W, Thomas PT, et al. 1987. Effects of inhalation of ethylene dichloride on pulmonary defenses of mice and rats. Toxicol Appl Pharmacol 91(3):491-496.

Sigma-Aldrich. 2020. Safety data sheet: 1,2-Dichloroethane. Version 6.4. https://www.sigmaaldrich.com/MSDS/MSDS/DisplayMSDSPage.do?country=US&language=en&productNumber=284505&brand=SIAL&PageToGoToURL=%2Fsafety-center.html.

Simula T, Glancey M, Wolf C. 1993. Human glutathione S-transferase-expressing Salmonella typhimurium tester strains to study the activation/detoxification of mutagenic compounds: Studies with halogenated compounds, aromatic amines and aflatoxin B1. Carcinogenesis 14:1371-1376.

Singh HB, Salas LJ, Stiles RE. 1982. Distribution of selected gaseous organic mutagens and suspect carcinogens in ambient air. Environ Sci Technol 16(12):872-880. 10.1021/es00106a010.

Singh B, Salas L, Viezee W, et al. 1992. Measurement of volatile organic chemicals at selected sites in California (Vol. 26).

Sipes IG, Gandolfi AJ. 1980. In vitro comparative bioactivation of aliphatic halogenated hydrocarbons. In: Holmstedt B, Lauwerys R, Mercier M, et al., ed. Developments in toxicology and environmental science. Vol. 8: Mechanisms of toxicity and hazard evaluation. Proceedings of the Second Congress on Toxicology held in Brussels, Belgium, July 6-11, 1980. Amsterdam, The Netherlands: Elsevier/North Holland Biomedical Press, 501-506.

Snedecor G. 2004. Chloroethylenes. In: Kirk-Othmer Encyclopedia of Chemical Technology. John Wiley & Sons.

Speitel GE, Closmann FB. 1991. Chlorinated solvent biodegradation by methanotrophs in unsaturated soils. 117(5):541-558. doi:10.1061/(ASCE)0733-9372(1991)117:5(541).

Spencer HC, Rowe VK, Adams EM, et al. 1951. Vapor toxicity of ethylene dichloride determined by experiments on laboratory animals. AMA Arch Ind Hyg Occup Med 4(5):482-493.

Spreafico F, Zuccato E, Marcucci M, et al. 1980. Pharmacokinetics of ethylene dichloride in rats treated by different routes and its long-term inhalatory toxicity. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory.

Squillace PJ, Moran MJ, Price CV. 2004. VOCs in shallow groundwater in new residential/commercial areas of the United States. Environ Sci Technol 38(20):5327-5338.

Stangroom SJ, Collins CD, Lester JN. 1998. Sources of Organic Micropollutants to Lowland Rivers. Environmental Technology 19(7):643-666. 10.1080/09593331908616722.

Steichen J, Koelliker J, Grosh D, et al. 1988. Contamination of farmstead wells by pesticides, volatile organics, and inorganic chemicals in Kansas. GWMR 8(3):153-160. https://doi.org/10.1111/j.1745-6592.1988.tb01092.x.

Storer RD, Conolly RB. 1983. Comparative in vivo genotoxicity and acute hepatotoxicity of three 1,2-dihaloethanes. Carcinogenesis 4(11):1491-1494. 10.1093/carcin/4.11.1491.

Storer R, Conolly R. 1985. An investigation of the role of microsomal oxidative metabolism in the in vivo genotoxicity of 1,2-dichloroethane. Toxicol Appl Pharmacol 77:36-46.

Storer R, Jackson N, Conolly R. 1984. In vivo genotoxicity and acute hepatotoxicity of 1,2-dichloroethane in mice: Comparison of oral, intraperitoneal, and inhalation routes of exposure. Cancer Research 44:4267-4271.

Stucki G, Thuer M. 1994. Increased removal capacity for 1,2-dichloroethane by biological modification of the granular activated carbon process. Appl Microbiol Biotechnol 42(1):167-172.

Stucki G, Krebser U, Leisinger T. 1983. Bacterial growth on 1,2-dichloroethane. Experientia 39(11):1271-1273.

Suffet IH, Brenner L, Cairo PR. 1980. GC/MS identification of trace organics in Philadelphia drinking waters during a 2-year period. Water Research 14(7):853-867. https://doi.org/10.1016/0043-1354(80)90266-3.

Suguro M, Numano T, Kawabe M, et al. 2017. Lung tumor induction by 26-week dermal application of 1,2-dichloroethane in CB6F1-Tg rasH2 mice. Toxicol Pathol 45(3):427-434. 10.1177/0192623317701003.

Sun Q, Wang G, Gao L, et al. 2016. Roles of CYP2e1 in 1,2-dichloroethane-induced liver damage in mice. Environ Toxicol 31(11):1430-1438. 10.1002/tox.22148. Epub 2015 Apr 30.

Sweeney LM, Gargas ML. 2016. Route-to-route extrapolation of 1,2-dichloroethane studies from the oral route to inhalation using physiologically based pharmacokinetic models. Regul Toxicol Pharmacol 81:468-479. 10.1016/j.yrtph.2016.10.005.

Sweeney LM, Saghir SA, Gargas ML. 2008. Physiologically based pharmacokinetic model development and simulations for ethylene dichloride (1,2-dichloroethane) in rats. Regul Toxicol Pharmacol 51(3):311-323. 10.1016/j.yrtph.2008.05.002.

Tabak HH, Quave SA, Mashni CI, et al. 1981. Biodegradability studies with organic priority pollutant compounds. Journal (Water Pollution Control Federation) 53(10):1503-1518.

Tafazoli M, Baeten A, Geerlings P, et al. 1998. In vitro mutagenicity and genotoxicity study of a number of short-chain chlorinated hydrocarbons using the micronucleus test and the alkaline single cell gel electrophoresis technique (Comet assay) in human lymphocytes: a structure-activity relationship (QSAR) analysis of the genotoxic and cytotoxic potential. Mutagenesis 13(2):115-126. 10.1093/mutage/13.2.115.

Take M, Takanobu K, Takeuchi T, et al. 2013. Distribution of blood and tissue concentrations in rats by inhalation exposure to 1,2-dichloroethane. Journal of Environmental Science and Health, Part A 48(9):1031-1036. 10.1080/10934529.2014.928193.

Tan E, Hsie A. 1981. Mutagenicity and cytotoxicity of haloethanes as studied in the CHO/HGPRT system. Mutation Research 90:183-191.

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

Teta M, Ott M, Schnatter A. 1989. An update of mortality due to brain neoplasms and other causes among employees of petrochemical facility. Journal of Occupational Medicine 33:45-51.

Theiss J, Stoner G, Shimkin M, et al. 1977. Test for carcinogenicity of organic contaminants of United States drinking waters by pulmonary tumor response in strain A mice. Cancer Research 37:2717-2720.

Thier R, Taylor J, Pemble S, et al. 1993. Expression of mammalian glutathione S-transferase 5-5 in Salmonella typhimurium TA1535 leads to base-pair mutations upon exposure to dihalomethanes. Proc Natl Acad Sci U S A 90:8576-8580.

Tilley SK, Reif DM, Fry RC. 2017. Incorporating ToxCast and Tox21 datasets to rank biological activity of chemicals at Superfund sites in North Carolina. Environment International 101:19-26. https://doi.org/10.1016/j.envint.2016.10.006.

Torkelson T, Rowe VK. 1981. Halogenated aliphatic hydrocarbons. In:ed. Patty's industrial hygiene and toxicology Vol. 2B: Toxicology. New York, NY: John Wiley & Sons, 3491-3497.

TRI17. 2018. Toxic Chemical Release Inventory. National Toxicology Information Program: Bethesda, MD.

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

U.S. Census. 2018. Trade Definitions. https://www.census.gov/foreign-trade/reference/definitions/index.html#general_imports

Urusova T. 1953. [The possible presence of dichloroethane in human milk with exposure in industrial conditions.] Gig Sanit 18:36-37.

USITC. 2019. 1,2-Dichloroethane import and export data. United States International Trade Commission. https://dataweb.usitc.gov/. May 29, 2019.

Vamvakas S, Dekant W, Henschler D. 1989. Assessment of unscheduled DNA synthesis in a cultured line of renal epithelial cells exposed to cysteine-S-conjugates of haloalkenes and haloalkanes. Mutation Research 222:329-335.

Vamvakas S, Dekant W, Schiffmann D, et al. 1988. Induction of unscheduled DNA synthesis and micronucleus formation in Syrian hamster embryo fibroblasts treated with cysteine S-conjugates of chlorinated hydrocarbons. Cell Biol Toxicol 4:393-404.

Van Bladeren P. 1983. Metabolic activation of xenobiotics: Ethylene dibromide and structural analogs. J Am Coll Toxicol 2:73-83.

Van Bladeren P, Van der Gen A, Breimer D, et al. 1979. Stereoselective activation of vicinal dihalogen compounds to mutagens by glutathione conjugation. Biochemical Pharmacology 28(16):2521-2524.

van Bladeren PJ, Breimer DD, Rotteveel-Smijs GM, et al. 1981. The relation between the structure of vicinal dihalogen compounds and their mutagenic activation via conjugation to glutathione. Carcinogenesis 2(6):499-505. 10.1093/carcin/2.6.499.

Van Duuren B, Goldschmidt B, Loewengart G, et al. 1979. Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. J Natl Cancer Inst 63:1433-1439.

van Esch GJ, Kroes R, van Logten MJ, et al. 1977. Ninety-day toxicity study with 1,2dichloroethane (DCE) in rats. Bilthoven, Netherlands: National Institute of Public Health and Environmental Hygiene.

Vandenbergh PA, Kunka BS. 1988. Metabolism of volatile chlorinated aliphatic hydrocarbons by Pseudomonas fluorescens. Appl Environ Microbiol 54(10):2578-2579.

Ventura F, Romero J, Parés J. 1997. Determination of dicyclopentadiene and its derivatives as compounds causing odors in groundwater supplies. Environ Sci Technol 31(8):2368-2374. 10.1021/es960987y.

Verschueren K. 1996. Handbook of environmental data on organic chemicals. 3rd edition. New York, NY: Van Nostrand Reinhold Company, 963-965.

Vieira I, Pasanen M, Raunio H, et al. 1998. Expression of CYP2E1 in human lung and kidney during development and in full-term placenta: a differential methylation of the gene is involved in the regulation process. Pharmacol Toxicol 83(5):183-187.

Vogel E, Nivard M. 1993. Performance of 181 chemicals in a Drosophila assay predominantly monitoring interchromosomal mitotic recombination. Mutagenesis 8:57-81.

Vozovaya MA. 1974. [Development of the progeny of 2 generations obtained from females exposed to the effects of dichloroethane]. Gig Sanit(7):25-28.

Vozovaya MA. 1977. [The effect of dichloroethane on the sexual cycle and embryogensis of experimental animals]. Akusk Ginekol (Moscow) 2:57-59.

Vulcan Materials Company. 1989. Written communication. Public comment on toxicological profile for 1,2-dichloroethane. In: Vulcan Materials Company, Birmingham, AL.

Wallace LA. 1991. Comparison of risks from outdoor and indoor exposure to toxic chemicals. Environ Health Perspect 95:7-13.

Wallace LA, Pellizzari E, Leaderer B, et al. 1987. Emissions of volatile organic compounds from building materials and consumer products. Atmospheric Environment (1967) 21(2):385-393. https://doi.org/10.1016/0004-6981(87)90017-5.

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

Wallace L, Pellizzari E, Hartwell T, et al. 1986. Concentrations of 20 volatile organic compounds in the air and drinking water of 350 residents of New Jersey compared with concentrations in their exhaled breath. J Occup Med 28(8):603-608.

Wang G, Qi Y, Gao L, et al. 2013. Effects of subacute exposure to 1,2-dichloroethane on mouse behavior and the related mechanisms. Hum Exp Toxicol 32(9):983-991. 10.1177/0960327112470270. Epub 2012 Dec 21.

Wang G, Yuan Y, Gao L, et al. 2018. Disruption of intracellular ATP generation and tight junction protein expression during the course of brain edema induced by subacute poisoning of 1,2-dichloroethane. Front Neurosci 12:12. 10.3389/fnins.2018.00012. eCollection 2018.

Wang G, Yuan Y, Zhang J, et al. 2014. Roles of aquaporins and matrix metalloproteinases in mouse brain edema formation induced by subacute exposure to 1,2-dichloroethane. Neurotoxicology and Teratology 44:105-112.

Wang T, Xu D, Fan Q, et al. 2017. 1,2-Dichloroethane impairs glucose and lipid homeostasis in the livers of NIH Swiss mice. Toxicology 380:38-49.

Watanabe K, Liberman RG, Skipper PL, et al. 2007. Analysis of DNA adducts formed in vivo in rats and mice from 1,2-dibromoethane, 1,2-dichloroethane, dibromomethane, and dichloromethane using HPLC/accelerator mass spectrometry and relevance to risk estimates. Chem Res Toxicol 20(11):1594-1600. 10.1021/tx700125p. Epub 2007 Oct 2.

Watwood ME, White CS, Dahm CN. 1991. Methodological modifications for accurate and efficient determination of contaminant biodegradation in unsaturated calcareous soils. Appl Environ Microbiol 57(3):717-720.

Waxweiler R, Alexander V, Leffingwell S, et al. 1983. Mortality from brain tumor and other causes in a cohort of petrochemical workers. J Natl Cancer Inst 70:75-81.

Weiss G. 1980. Hazardous chemicals data book (Vol. 4). Park Ridge, NJ: Noyes Data Corporation, 433.

Westrick JJ, Mello JW, Thomas RF. 1984. The Groundwater Supply Survey. Journal (American Water Works Association) 76(5):52-59.

WHO. 1995. International program on chemical safety. Environmental health criteria 176. Geneva, Switzerland: World Health Organization.

WHO. 2000. Chapter 5.6: 1,2-Dichloroethane. In: Air quality guidelines - Second edition. Copenhagen, Denmark: WHO Regional Office for Europe.

WHO. 2003. 1,2-Dichloroethane in drinking-water. Background document for development of WHO guidelines for drinking-water quality. Geneva, Switzerand: World Health Organization. WHO/SDE/WSH/03.04/67.

Williams GM, Mori H, McQueen CA. 1989. Structure-activity relationships in the rat hepatocyte DNA-repair test for 300 chemicals. Mutat Res 221(3):263-286.

Wilson JT, McNabb JF, Balkwill DL, et al. 1983. Enumeration and characterization of bacteria indigenous to a shallow water-table aquifer. Groundwater 21(2):134-142. https://doi.org/10.1111/j.1745-6584.1983.tb00710.x.

Wilson JT, Enfield CG, Dunlap WJ, et al. 1981. Transport and fate of selected organic pollutants in a sandy soil. 10(4):501-506. 10.2134/jeq1981.00472425001000040016x.

Wirtschafter ZT, Schwartz ED. 1939. Acute ethylene dichloride poisoning. Journal of Industrial Hygiene and Toxicology 21:126-131.

Withey J, Collins B. 1980. Chlorinated aliphatic hydrocarbons used in the foods industry: The comparative pharmacokinetics of methylene chloride, 1,2-dichloroethane, chloroform and trichloroethylene after i.v. administration in the rat. J Environ Pathol Toxicol 3:313-332.

Withey JR, Karpinski K. 1985. The fetal distribution of some aliphatic chlorinated hydrocarbons in the rat after vapor phase exposure. Biol Res Pregnancy Perinatol 6(2):79-88.

Withey JR, Collins BT, Collins PG. 1983. Effect of vehicle on the pharmacokinetics and uptake of four halogenated hydrocarbons from the gastrointestinal tract of the rat. 3(5):249-253. 10.1002/jat.2550030506.

WQP. 2020. Water quality portal data: 1,2-Dichloroethane. Advisory Committee on Water Information (ACWI); Agricultural Research Service (ARS); Environmental Protection Agency (EPA); National Water Quality Monitoring Council (NWQMC); United States Geological Survey (USGS). . https://www.waterqualitydata.us/portal/. August 18, 2020.

Yamamoto K, Fukushima M, Kakutani N, et al. 1997. Volatile organic compounds in urban rivers and their estuaries in Osaka, Japan. Environ Pollut 95(1):135-143.

Yllner S. 1971. Metabolism of 1,2-dichloroethane-14C in the mouse. . Acta Pharmacol Toxicol 30:257-265.

Yodaiken RE, Babcock JR. 1973. 1, 2-Dichloroethane poisoning. Archives of Environmental Health: An International Journal 26(5):281-284. 10.1080/00039896.1973.10666277.

Zeng N, Zhang Z, Jiang H, et al. 2019. LncRNA-241 inhibits 1, 2-Dichloroethane-induced hepatic apoptosis. Toxicol In Vitro 61:104650.

Zeng N, Jiang H, Fan Q, et al. 2018. Aberrant expression of miR-451a contributes to 1,2-dichloroethane-induced hepatic glycerol gluconeogenesis disorder by inhibiting glycerol kinase expression in NIH Swiss mice. J Appl Toxicol 38(2):292-303. 10.1002/jat.3526. Epub 2017 Sep 28.

Zhan F, Zheng W, Liu L, et al. 2011. Diagnosis and prognosis evaluation of 1,2-dichloroethane encephalopathy--magnetic resonance imaging combined with diffusion tensor imaging and magnetic resonance spectroscopy study. Neurol India 59(1):108-110. 10.4103/0028-3886.76884.

Zhang Q, Niu Q, Li LY, et al. 2011. Establishment of a poisoned animal model of toxic encephalopathy induced by 1,2-dichloroethane. Int J Immunopathol Pharmacol 24(1 Suppl):79s-83s.

Zhang L, Jenssen D. 1994. Studies on intrachromosomal recombination in SP5/V79 Chinese hamster cells upon exposure to different agents related to carcinogenesis. Carcinogenesis 15:2303-2310.

Zhang Y, Li G, Zhong Y, et al. 2017. 1,2-Dichloroethane Induces Reproductive Toxicity Mediated by the CREM/CREB Signaling Pathway in Male NIH Swiss Mice. Toxicol Sci 160(2):299-314. 10.1093/toxsci/kfx182.

Zhao SF, Zhang XC, Bao YS. 1984. The study on the effects of 1,2-dichloroethane on the development of mice. Chinese J Ind Hyg Occup Dis 2:343-346.

Zhao SF, Zhang XC, Bao YS. 1989. The study on the effects of 1,2-dichloroethane on reproductive function. Chineses J Prevent Med 23:199-202.

Zhao SF, Zhang XC, Zhang LF, et al. 1997. The evaluation of developmental toxicity of chemicals exposed occupationally using whole embryo culture. Int J Dev Biol 41(2):275-282.

Zhou X, Zhou W, Zhou J, et al. 2015. 1,2-Dichloroethane-induced toxic leukoencephalopathy with a brain biopsy. Neurol Sci 36(5):817-819. 10.1007/s10072-014-1949-4. Epub 2014 Sep 13.

Zhou X, Cao Y, Leuze C, et al. 2016. Early non-invasive detection of acute 1,2-dichloroethane-induced toxic encephalopathy in rats. In Vivo 30(6):787-793.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND 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. Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in

the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,2-Dichloroethane
CAS Numbers: 107-06-2
Date: January 2022
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute
Provisional MRL: 0.3 ppm (1 mg 1,2 dichloroethane/m^3)
Critical Effect: Degeneration, with necrosis, olfactory epithelium
Reference: Hotchkiss 2010
Point of Departure: $BMCL_{10}$ of 57.42 ppm
($BMCL_{HEC}$ of 9.19 ppm)
Uncertainty Factor: 30
LSE Graph Key: 14R
Species: Rat

Provisional MRL Summary: A provisional acute-duration inhalation MRL of 0.3 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 57.42 ppm converted to human equivalent concentration ($BMCL_{HEC}$) of 9.19 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 inhalation exposure; these studies examine a wide range of endpoints including neurotoxicity (Heppel et al. 1945; Hotchkiss et al. 2010; Jin et al. 2018a; Jin et al. 2018b; Niu et al. 2009; Wang et al. 2013; Wang et al. 2014; Wang et al. 2018; Zhang et al. 2011; Zhou et al. 2016), liver and kidney effects (Hotchkiss et al. 2010; Spencer et al. 1951; Sun et al. 2016), respiratory effects (Chan et al. 2002; Hotchkiss 2010), immunotoxicity (Sherwood et al. 1987), developmental toxicity (Rao et al. 1980; Schlacter et al. 1979), reproductive toxicity (Zhang et al. 2017), gastrotoxicity (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 select LOAELs is presented in Table A-1.

The available data suggest that toxic effects to the nasal epithelium is the most sensitive endpoint following acute-duration inhalation exposure. In rats, olfactory epithelium degeneration with necrosis was seen at concentrations of 100 ppm to 2000 ppm, and a NOAEL of 50 ppm was observed (Hotchkiss et al. 2010).

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

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Respiratory Effects					
Rat/ Fischer 344	8 hrs (100, 150 ppm); 4 hrs (50 ppm)	50	100	Olfactory epithelium degeneration/necrosis	Hotchkiss et al. 2010

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

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Hepatic Effects					
Mouse/ Albino	3.5 hr/day 10 days	56	111	Increased CYP2E1 activity	Sun et al. 2016
Neurological Effects					
Mouse/ Albino	3.5 hr/day 10 days		56	Increased neurotransmitters and oxidative markers	Wang et al. 2013

The lowest NOAEL for an acute-duration study was 50 ppm.

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 NOAEL reported by Hotchkiss et al. (2010) was the lowest among the studies evaluating acute exposure. Additionally, changes in neurotransmitters and oxidative stress as studied in Wang et al. (2013) are of uncertain toxicological significance. Although findings from Sun et al. (2016) demonstrate roughly similar potential point of departure values, the large differences in the dose adjustment factor value for a category 1 respiratory endpoint like the one from Hotchkiss et al. (2010) versus the dose adjustment factor for a category 3 systemic endpoint like the one in Sun et al. (2016) would lead to an approximately 6.4-fold lower human equivalent concentration for the category 1 respiratory endpoint (EPA, 2012). Thus, no benchmark dose modeling was attempted using the Sun et al. (2016) study data.

Summary of the Principal Study:

J.A. Hotchkiss, A.K. Andrus, K.A. Johnson, S.M. Krieger, M.R. Woolhiser, J.P. Maurissen, Acute toxicologic and neurotoxic effects of inhaled 1,2-dichloroethane in adult Fischer 344 rats, Food and Chemical Toxicology, Volume 48, Issue 2, 2010, 470-481.

Fischer 344 rats were exposed to 0, 200, 600, or 2000 ppm (or 0.0, 196.4, 607.8, and 2029.0 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 (BAL) and histopathology of the respiratory tract and selected target organs. Neurobehavioral effects consistent with CNS depression were observed on day one, but not at subsequent times (day 8 or day 15). No neuropathological changes were reported. Degeneration/necrosis of the olfactory epithelium was reported at an exposure of 100 ppm. Nasal regeneration occurred at 200 ppm. A decrease in adrenals, kidney, and liver weights occurred at a dose of 2000 ppm.

Selection of the Point of Departure for the Provisional MRL: Benchmark dose (BMD) modeling was conducted to identify a point of departure using the analytically measured data for degeneration/necrosis of nasal epithelium in rats administered 1,2-dichloroethane via inhalation. 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 3.1.2) using a BMR of 10%

extra risk and the default settings for the application of restrictions. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, BMCL <10 times the lowest non-zero dose, and scaled residual at the data point (except the control) closest to the predefined benchmark response (BMR). Among all of the models providing adequate fit to the data, the BMCL from the model with the lowest Akaike's Information Criterion (AIC) was chosen, since all BMCLs from the viable estimated models were within a 3-fold range. BMDS recommended the frequentist restricted log-logistic model for nasal epithelium degeneration/necrosis, and after verifying the model fit by the four criteria listed above, this 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. Hotchkiss et al. (2010) results from 4 hour exposures to 1,2-dichloroethane via inhalation and subsequent incidence of nasal epithelium degeneration/necrosis

Analytically Measured Mean Concentration Delivered (ppm)	N (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

Table A-3. Selected Results from BMC Analysis of Incidences of Nasal Degeneration/Necrosis in Female Rats Administered 1,2-Dichloroethane by Inhalation (Hotchkiss et al. 2010)

Model	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)	P Value[a]	AIC	Scaled residuals[b]	
					Dose below BMC	Dose above BMC
Dichotomous Hill	96.97	57.89	1.00	25.96	0.00	0.00
Gamma[c]	83.06	55.73	0.86	26.01	0.07	0.00
Log-Logistic[d,e]	**84.68**	**57.42**	**0.98**	**24.04**	**0.07**	**0.00**
Multistage (3-degree)[f]	60.32	36.28	0.57	25.80	-0.86	0.00
Multistage (2-degree)[f]	42.87	25.40	0.20	28.87	-1.32	0.00
Weibull[c]	78.45	50.57	0.61	26.39	-0.42	0.00
Logistic	81.81	53.84	0.85	24.46	0.26	-0.08
Log-Probit	84.32	57.62	0.93	25.97	0.02	0.00
Probit	81.49	52.26	0.91	24.26	0.24	-0.01

[a]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.

[b]Scaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.

[c]Power restricted to ≥1.

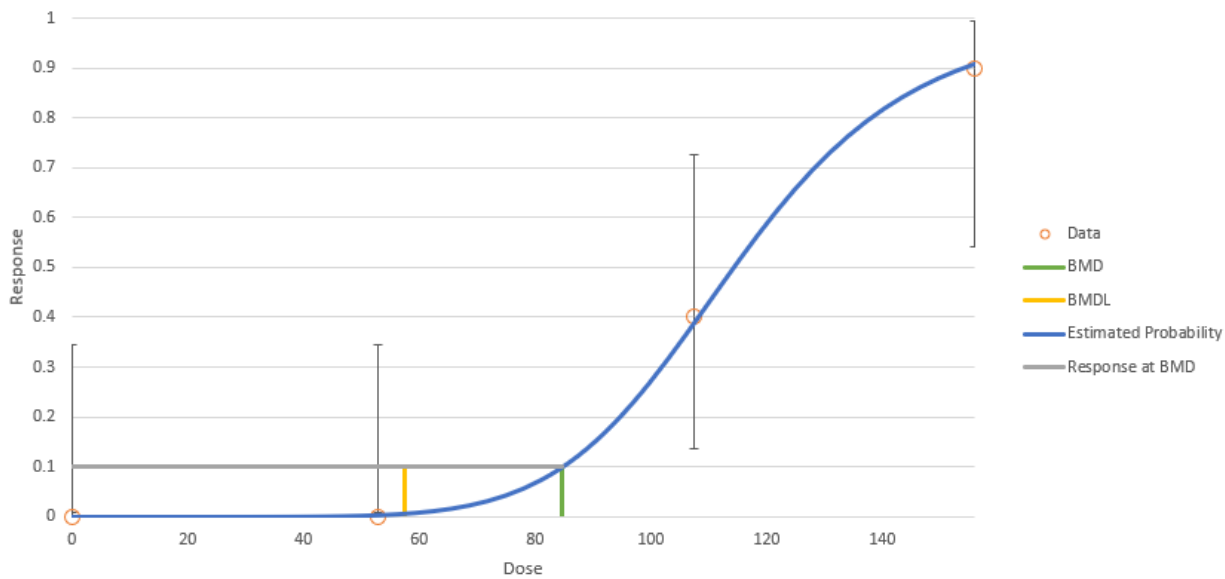
[d]Selected model. All models provided adequate fit to the data except for the Multistage (1-degree). BMCLs for models providing adequate fit were within a 3-fold range; therefore, the model with the lowest AIC was selected (Log-Logistic).

[e]Slope restricted to ≥1.

[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = benchmark concentration (maximum likelihood estimate of the concentration associated with the selected benchmark response); BMCL10 = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk); DF = degree of freedom

Figure A-1. Fit of Log-Logistic Model to Data on Incidence of Nasal Degeneration/Necrosis in Combined Male and Female Rats administered 1,2-Dichloroethane via Inhalation (ppm)



***Adjustment for Intermittent Exposure**:* Doses were not adjusted from an intermittent exposure to a continuous exposure as blood levels of 1,2-dichloroethane reached equilibrium within 2 to 3 hours of the onset of inhalation exposure and this endpoint is considered a local instead of a systemic effect.

Human Equivalent Concentration: The $BMCL_{10}$ was converted to a Human Equivalent Concentration (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, 2012). This $RGDR_{ET}$ is calculated using the following equation as defined by EPA (1994a):

$$RGDR_{ET} = \frac{\left(\frac{V_E}{SA_{ET}}\right)_A}{\left(\frac{V_E}{SA_{ET}}\right)_H}$$

Where:

V_E = Ventilation rate (L/min)

SA_{ET} = Surface area of the extrathoracic region (cm^2)

A = Laboratory animal

H = Human

The default ventilation rate for female F344 rats is defined by EPA (1994a) as 0.167 L/min. The default ventilation rate for humans is defined by EPA (1994a) as 13.8 L/min. Default extrathoracic surface areas are defined by EPA (1994a) to be 15 cm^2 for rats and 200 cm^2 for humans. Thus, the $RGDR_{ET}$ is calculated as the following:

$$RGDR_{ET} = \frac{\left(\frac{0.167\ L/min}{15\ cm^2}\right)}{\left(\frac{13.8\ L/min}{200\ cm^2}\right)}$$

$$RGDR_{ET} = 0.16$$

Multiplying the $BMCL_{10}$ of 57.42 ppm by the $RGDR_{ET}$ of 0.16 yields a $BMCL_{HEC}$ of 9.19 ppm.

Use of the benchmark dose modeling results was selected over the NOAEL given it uses the full dose-response data as opposed to the NOAEL, which is based on a single data point.

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

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

Provisional MRL = $BMCL_{HEC}$ ÷ UFs
9.19 ppm ÷ (10 × 3) = 0.30 ppm

Other Additional Studies or Pertinent Information that Lend Support to this MRL: A chronic study on rats intermittently exposed to 50 ppm of 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 of rats.

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

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,2-Dichloroethane
CAS Numbers: 107-06-2
Date: January 2022
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate

Provisional MRL Summary: There are insufficient data for derivation of an intermediate duration inhalation MRL as the most sensitive endpoint is represented by a serious effect.

Rationale for Not Deriving an MRL: An MRL has not been derived for intermediate inhalation exposure to 1,2-dichloroethane. The most sensitive endpoint for deriving an intermediate inhalation MRL is related to morphological abnormalities in sperm in mice (Zhang et al. 2017). Since such large effects on sperm abnormalities are considered serious effects, this precludes the derivation of an intermediate inhalation MRL (Pohl et al. 2005; ATSDR 2018). Several studies have evaluated the toxicity of 1,2-dichloroethane following intermediate inhalation exposure; these studies examined hepatotoxicity (Heppel et al. 1946; Spencer et al. 1951; Wang et al. 2017), reproductive toxicity (Rao et al. 1980; Vozovaya 1977; Zhang et al. 2017; Zhao et al. 1997), and neurotoxicity (Dang et al. 2019; Zhan et al. 2011; Zhou et al. 2015). The LOAELs for the relevant studies ranged from 24.7 ppm to 700 ppm; a summary of select NOAELs/LOAELs is presented in Table A-4, excluding those LOAELs deemed to be serious. $NOAEL_{ADJ}$ and $LOAEL_{ADJ}$ represent values that have been duration adjusted to estimate continuous exposure when exposures were delivered intermittently.

Table A-4. Summary of Relevant NOAEL and LOAEL Values Following Intermediate Duration Inhalation Exposure to 1,2-Dichloroethane

Species	Duration	NOAEL ($NOAEL_{ADJ}$) (ppm)	LOAEL ($LOAEL_{ADJ}$) (ppm)	Effect	Reference
Hepatic effects					
Gn pig	7 hr/day 5 d/wk 246 days		100 (20.8)	Increased liver weight and fatty degeneration	Spencer et al. 1951
Mouse/ Swiss-Webster	6 hr/day 28 days		86 (21.5)	~20% increase in serum AST; ~10% increase in liver/bodyweight ratio; ~40% increase in glycogen contents in liver; ~50% increase in free fatty acid contents in liver	Wang et al. 2017
Monkey	7 hr/day 5 d/wk 25 wks		200 (41.7)	Fatty degeneration of liver	Heppel et al. 1946
Cardiovascular effects					
Monkey	7 hr/day 5 d/wk 25 wks		200 (41.7)	Fatty degeneration of myocardium	Heppel et al. 1946

Table A-4. Summary of Relevant NOAEL and LOAEL Values Following Intermediate Duration Inhalation Exposure to 1,2-Dichloroethane

Species	Duration	NOAEL ($NOAEL_{ADJ}$) (ppm)	LOAEL ($LOAEL_{ADJ}$) (ppm)	Effect	Reference
Endocrine effects					
Monkey	7 hr/day 5 d/wk 25 wks		200 (41.7)	Adrenal calcification	Heppel et al. 1946
Body weight effects					
Mouse/ Swiss-Webster	6 hr/day 28 days	86 (21.5)	173 (43.3)	25% decrease in body weight gain after 28 days	Wang et al. 2017
Mouse/ Swiss-Webster	6 hr/day 4 wks	86 (21.5)	173 (43.3)	15% decrease in body weight	Zhang et al. 2017
Reproductive effects					
Mouse/ Swiss-Webster	6 hr/day 4 wks	86 (21.5)	173 (43.3)*	29% decrease in sperm concentration	Zhang et al. 2017
Mouse/ Swiss-Webster	6 hr/day 4 wks		25 (6.3)*	570% increase in total sperm abnormalities	Zhang et al. 2017
Mouse/ Swiss-Webster	6 hr/day 4 wks	25 (6.3)	86 (21.5)*	160% increase in sperm head abnormalities	Zhang et al. 2017
Mouse/ Swiss-Webster	6 hr/day 4 wks	25 (6.3)	86 (21.5)*	230% increase in sperm body abnormalities	Zhang et al. 2017
Mouse/ Swiss-Webster	6 hr/day 4 wks	25 (6.3)	86 (21.5)*	470% increase in sperm tail abnormalities	Zhang et al. 2017

* indicates that the LOAEL represents a serious LOAEL, and thus an intermediate inhalation MRL cannot be derived

Adjusted Daily Dose = $Intermittent\ dose \times \frac{Exposure\ hours}{24\ hours} \times \frac{Exposure\ days}{7\ days}$

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

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dichloroethane
CAS Numbers: 107-06-2
Date: January 2022
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

Provisional MRL Summary: There are insufficient data for derivation of a chronic duration inhalation MRL. All studies identified either exhibited no effect, or only exhibited effects deemed to represent serious LOAELs, which cannot be used for the derivation of an MRL.

Rationale for Not Deriving an MRL: An MRL has not been derived for chronic inhalation exposure to 1,2-dichloroethane, because the two chronic studies either produced no health effect or cancer effects. As summarized in Table A-5, there are only two studies that investigate the effects of chronic inhalation exposure to 1,2-dichloroethane. Cheever et al. (1990) monitored for a number of health effects after treating rats to 50 ppm of 1,2-dichloroethane for 7 hours per day, 5 days per week, for 2 years, but found no effect. Nagano et al. (2006) found significant cancer effects in male mice after exposing them to 30 ppm of 1,2-dichloroethane for 6 hours per day, 5 days per week, for 104 weeks. MRLs are based on non-cancer health effects.

Table A-5. Summary of Relevant NOAEL and LOAEL Values Following Chronic Duration Inhalation Exposure to 1,2-Dichloroethane

Species	Duration	NOAEL ($NOAEL_{ADJ}$) (ppm)	LOAEL ($LOAEL_{ADJ}$) (ppm)	Effect	Reference
Respiratory					
Rat Sprague-Dawley	7 hr/day 5 d/wk 2 yrs	50 (10.4)		NOAEL without any LOAEL	Cheever et al. 1990
Cardiovascular					
Rat Sprague-Dawley	7 hr/day 5 d/wk 2 yrs	50 (10.4)		NOAEL without LOAEL	Cheever et al. 1990
Gastrointestinal					
Rat Sprague-Dawley	7 hr/day 5 d/wk 2 yrs	50 (10.4)		NOAEL without LOAEL	Cheever et al. 1990
Hematological					
Rat Sprague-Dawley	7 hr/day 5 d/wk 2 yrs	50 (10.4)		NOAEL without LOAEL	Cheever et al. 1990
Musculoskeletal					
Rat Sprague-Dawley	7 hr/day 5 d/wk 2 yrs	50 (10.4)		NOAEL without LOAEL	Cheever et al. 1990

Table A-5. Summary of Relevant NOAEL and LOAEL Values Following Chronic Duration Inhalation Exposure to 1,2-Dichloroethane

Species	Duration	NOAEL ($NOAEL_{ADJ}$) (ppm)	LOAEL ($LOAEL_{ADJ}$) (ppm)	Effect	Reference
Hepatic					
Rat Sprague-Dawley	7 hr/day 5 d/wk 2 yrs	50 (10.4)		NOAEL without LOAEL	Cheever et al. 1990
Renal					
Rat Sprague-Dawley	7 hr/day 5 d/wk 2 yrs	50 (10.4)		NOAEL without LOAEL	Cheever et al. 1990
Dermal					
Rat Sprague-Dawley	7 hr/day 5 d/wk 2 yrs	50 (10.4)		NOAEL without LOAEL	Cheever et al. 1990
Ocular					
Rat Sprague-Dawley	7 hr/day 5 d/wk 2 yrs	50 (10.4)		NOAEL without LOAEL	Cheever et al. 1990
Endocrine					
Rat Sprague-Dawley	7 hr/day 5 d/wk 2 yrs	50 (10.4)		NOAEL without LOAEL	Cheever et al. 1990
Bodyweight					
Rat Sprague-Dawley	7 hr/day 5 d/wk 2 yrs	50 (10.4)		NOAEL without LOAEL	Cheever et al. 1990
Rat Fischer 344	6 hr/day 5 d/wk 104 wks	160 (28.6)		NOAEL without LOAEL	Nagano et al. 2006
Mouse B6D2F1	6 hr/day 5 d/wk 104 wks	90 (16.1)		NOAEL without LOAEL	Nagano et al. 2006
Cancer					
Mouse B6D2F1	6 hr/day 5 d/wk 104 wks	10 (1.8)	30 (5.4)	Liver hemangiosarcoma	Nagano et al. 2006
Rat Fischer 344	6 hr/day 5 d/wk 104 wks	40 (7.1)	160 (28.6)	Mammary cancers	Nagano et al. 2006

Adjusted Daily Dose = $Intermittent\ dose \times \frac{Exposure\ hours}{24\ hours} \times \frac{Exposure\ days}{7\ days}$

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

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,2-Dichloroethane
CAS Numbers: 107-06-2
Date: January 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

Provisional MRL Summary: There are insufficient data for derivation of an acute duration provisional oral MRL.

Rationale for not deriving an MRL: An MRL has not been derived for acute-duration oral exposure (≤14 days) to 1,2-dichloroethane. The lowest effect level that can be identified for acute oral toxicity is a lowest-observed-adverse-effect level (LOAEL) of 4.9 mg/kg/day via oral gavage for immunosuppression from a mouse study (Munson et al. 1982). Doses lower than 4.9 mg/kg/day were not tested, precluding identification of a NOAEL. Male mice that were treated with 4.9 or 49 mg/kg/day by gavage for 14 days showed a significant dose-related reduction in humoral immune response (IgM response to sheep erythrocytes). The number of antibody-forming cells (AFCs) was dose-related and statistically significantly reduced at both dose levels; when adjusted to AFC/10^6 cells, there was an apparent negative trend with dose, but a significant reduction occurred only in the high-dose group. The cell-mediated immune response (delayed-type hypersensitivity response to sheep erythrocytes) was significantly reduced in both dose groups, but not in a dose-related manner. There was also a depression in leukocytes in the high dose group. However, administration of 1,2-dichloroethane in the drinking water at doses as high as 189 mg/kg/day for 90 days failed to induce immunosuppressive effects in mice in the Munson et al. (1982) study. Because of this lack of dose-response, it was determined that it may not be appropriate to base an MRL on an effect level from this gavage oil study due to toxicokinetic considerations of administration of the chemical by gavage as opposed to drinking water (e.g., possible bolus saturation of the detoxification/excretion mechanism can occur which may exacerbate toxicity at lower concentrations).

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

MINIMAL RISK LEVEL (MRL) WORKSHEETS

Chemical Name: 1,2-Dichloroethane
CAS Numbers: 107-06-2
Date: January 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate
Provisional MRL: 0.2 mg 1,2 dichloroethane/kg/day
Critical Effect: Renal
Reference: NTP 1991
Point of Departure: LOAEL 58 mg/kg/day
Uncertainty Factor: 300
LSE Graph Key: 14R
Species: Rat

Provisional MRL Summary: A provisional intermediate-duration oral MRL of 0.2 mg/kg/day was derived for 1,2-dichloroethane based on an increase in kidney weight in rats administered 1,2-dichloroethane via drinking water (NTP 1991). The increased kidney weight is considered to be an early-stage adverse effect because dose-related renal histopathology (tubular regeneration, indicative of previous tubular injury with subsequent repair) developed at higher doses in the same strain of rats.

The MRL is based on a LOAEL of 58 mg/kg/day and a total uncertainty factor of 300 (3 for use of a minimal LOAEL, 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; the potential endpoints examined include kidney and liver effects (Alumot et al. 1976; Cottalasso et al. 2002; Daniel et al. 1994; Munson et al. 1982; NTP 1991; van Esch et al. 1977), neurotoxicity (Daniel et al. 1994; NTP 1991; van Esch et al. 1977), gastrotoxicity (NTP 1991; van Esch et al. 1977); hematotoxicity (Daniel et al. 1994; Munson et al. 1982; NTP 1991; van Esch et al. 1977), and reproductive toxicity (Daniel et al. 1994; Lane et al. 1982; NTP 1991; van Esch et al. 1977). The LOAELs for these studies range from 58 mg/kg/day to 249 mg/kg/day. Table A-6 has a summary of effect levels.

Table A-6. Summary of Relevant NOAEL and LOAEL Values Considered for Derivation of an Intermediate Duration Oral Provisional MRL for 1,2-Dichloroethane

Species	Duration/ route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Hepatic Effects					
Rat NS	2 x/d 5-7 wk (F)	30	80	Fatty liver	Alumot et al. 1976
Rat F344/N	1 x/day 5 days/wk 13 wks (GO)		18 F	Increase in absolute and relative liver weight	NTP 1991

Table A-6. Summary of Relevant NOAEL and LOAEL Values Considered for Derivation of an Intermediate Duration Oral Provisional MRL for 1,2-Dichloroethane

Species	Duration/ route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Renal Effects					
Rat F344/N	13 wks (W)		58 F	Increase in absolute and relative kidney weight, renal tubular regeneration	NTP 1991
Rat F344/N	1 x/day 5 days/wk 13 wks (GO)	37 F	75 F	Increase in absolute and relative kidney weight	NTP 1991
Rat Sprague-Dawley	90 days 1x/day (GO)	37.5	75	Increase in relative kidney weight	Daniel et al. 1994
Rat Wistar	1x /day 5 d/wk 90 days (GO)	30	90	Increase in relative kidney weight	Van Esch et al. 1977
Mouse B6C3F1	13 wks (W)		249 M	Tubular regeneration	NTP 1991
Body weight					
Rat Sprague-Dawley	90 days 1x/day (GO)	75	150	17% reduced body weight gain	Daniel et al. 1994

G = gavage; GD = gestation day; GO = gavage in oil vehicle; GW = gavage in water vehicle; LOAEL = lowest observed adverse effect level; M= Male; NOAEL = no-observed-adverse-effect level;

* Serious LOAELs are not considered for MRL derivation. Lowest serious LOAEL provided for reference.

The available data suggest nephrotoxicity, specifically increased kidney weight, is the most sensitive endpoint following intermediate-duration oral exposure. In female rats, increased kidney weight was observed at 58 mg/kg/day (NTP 1991). Increased relative kidney weight was seen in rats treated with 75 or 90 mg/kg/day by gavage for 90 days (Daniel et al. 1994; van Esch et al. 1977). Renal effects (e.g., increased kidney weight and tubular epithelial degeneration) were also found in animals following high-level acute- and intermediate-duration inhalation exposure (Heppel et al. 1946; NTP 1991; Spencer et al. 1951) and intermediate-duration dermal exposure (Suguro et al. 2017). A similar LOAEL was identified for increased liver weight, at 60 mg/kg/day in rats (van Esch et al. 1977).

It is worth noting, however, that there were lower doses administered in the NTP 1991 study that yielded changes in relative organ weight. Specifically, in female F344/N rats, increased absolute and relative liver weight were observed following intermediate-duration exposure to 18 mg/kg/day via gavage oil. However, it may not be appropriate, in this case, to base an MRL on an effect level from a gavage oil study due to toxicokinetic considerations (e.g., possible bolus saturation of the detoxification/excretion mechanism). No other intermediate-duration oral study exhibited these hepatic effects at concentrations this low, including the Alumot et al. 1976 study, which tested organ weights of rats after doses of 0, 15, 30, and 80 mg/kg/day, and resulted in a hepatic LOAEL of 80 mg/kg/day.

Selection of the Principal Study: NTP (1991) conducted a study on effects of 1,2-dichloroethane oral exposure in rats and mice. There was a dose-related increase in the incidence of renal tubular regeneration (minimal to mild) in F344/N females at 58 mg/kg/day; incidences progressively increased from 1/10 at 102 mg/kg/day to 9/10 at 601 mg/kg/day.

Summary of the Principal Study:

NTP. 1991a. Toxicity studies of 1,2-dichloroethane (ethylene dichloride) (CAS No. 107-06-2) in F344/N rats, Sprague Dawley rats, Osborne-Mendel rats and B6C3F1 mice (drinking water and gavage studies). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institute of Health, National Toxicology Program. NIH Publication No. 91-3123.

Groups of F344/N rats, Sprague-Dawley rats, Osborne-Mendel rats, and B6C3F1 mice (10 animals/sex/strain) 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, 49-60, 86-99, 146-165, 259-276, and 492-518 mg/kg/day in the male rats and 0, 58-82, 102-126, 172-213, 311-428, and 531-727 mg/kg/day in the female rats. Intake estimates in the mice were 0, 249, 448, 781, 2,710, and 4,207 mg/kg/day in males and 0, 244, 647, 1,182, 2,478, and 4,926 mg/kg/day in females. Additional groups of F344/N rats (10/sex) were administered 1,2-dichloroethane by gavage on 5 days/week for 13 weeks to compare toxicity resulting from bolus administration with that of the continuous exposure in drinking water. Gavage doses were 0, 30, 60, 120, 240, and 480 mg/kg in the male rats and 0, 18, 37, 75, 150, and 300 mg/kg in the 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.

Rat drinking water studies: Dose-related decreased water consumption occurred in all strains and both sexes. There was >10% reduction in body weight gain at 259 mg/kg in male F344/N rats, 518 mg/kg in male Sprague-Dawley rats, and 492 mg/kg in male Osborne-Mendel rats. There were no significant reductions in body weight gain in female rats of any strain. Liver weight and/or liver:body weight ratio significantly increased at 147 mg/kg in F344/N males and 102, 320, and 601 mg/kg in females; at 60 mg/kg in Sprague-Dawley males and 531 mg/kg in females; and at 88 mg/kg in Osborne-Mendel males. Kidney weight and/or kidney:body weight ratio significantly increased at 58 and 86 mg/kg in F344/N females and males, respectively; at 60 and 76 mg/kg in Sprague-Dawley males and females, respectively; and at 82 and 88 mg/kg in Osborne-Mendel females and males, respectively. There was a dose-related increase in the incidence of renal tubular regeneration (minimal to mild) in F344/N females; incidences progressively increased from 1/10 at 102 mg/kg/day to 9/10 at 601 mg/kg/day.

Mouse drinking water study: No mortality except in 90% of high-dose females. Body weight gain significantly reduced in high-dose males. Increased liver weight/liver:body weight ratio, significant at 249 mg/kg/day in males and 647 mg/kg/day in females. Increased kidney weight and kidney:body weight ratio, significant at 448 mg/kg/day in males and 244 mg/kg/day in females. Increased tubular regeneration (minimal to moderate) in males, increasing in incidence from 1/10 at 249 mg/kg/day to 9/10 at 4,207 mg/kg/day. Karyomegaly, dilatation, protein casts, and mineralization in kidneys also occurred in males at 4,207 mg/kg/day.

Rat gavage study: Deaths occurred in all males at 240 mg/kg and 90% of females at 300 mg/kg; clinical signs preceding death included tremors, salivation, and emaciation. Pathology in moribund/dead animals included necrosis in the thymus and cerebellum. Small but significant changes in various hematological parameters occurred in higher dose groups and were considered to be indicative of dehydration and attributed to significantly reduced water consumption (60% compared to controls). No effects on growth at

sublethal doses. Other effects included minimal to mild hyperplasia and inflammation of the forestomach epithelium (sometimes with foci of necrosis and mineralization) in 5/10 males at 240 mg/kg, 3/10 males at 480 mg/kg, and 3/10 females at 300 mg/kg. Liver weight and liver:body weight ratio significantly increased in males at 120 mg/kg (no data from higher doses due to mortality) and females at all doses (appears dose-related). Kidney weight and/or kidney:body weight ratio significantly increased in males at 30 mg/kg and 75 mg/kg in females. Kidney weight changes appeared to be dose-related, but no renal histopathological changes were observed.

Selection of the Point of Departure for the MRL: The lowest dose in female rats not administered by gavage, 58 mg/kg/day, is a LOAEL for kidney effects. The increased kidney weight is considered to be an early-stage minimal adverse effect because dose-related renal histopathology (tubular regeneration, indicative of previous tubular injury with subsequent repair) developed at higher doses in the same strain of rats. Benchmark dose modeling was attempted using the F344/N female rat data for increased absolute and relative kidney weight, but no models adequately fit the data.

Uncertainty Factor: The LOAEL of 58 mg/kg/day was divided by a total uncertainty factor of 300 (10 for human variability, 10 for extrapolation from animals to humans, and 3 for use of a minimal LOAEL), resulting in a provisional MRL of 0.2 mg/kg/day.

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

Provisional MRL = NOAEL ÷ UFs

58 mg/kg/day ÷ (10 × 10 × 3) = 0.2 mg/kg/day

Other Additional Studies or Pertinent Information: Renal effects (e.g., increased kidney weight and tubular epithelial degeneration) were also found in animals following high-level acute- and intermediate-duration inhalation exposure (Heppel et al. 1946; NTP 1991; Spencer et al. 1951). Reports of increased relative kidney weight in rats that were treated with 75 or 90 mg/kg/day by gavage for 90 days (Daniel et al. 1994; van Esch et al. 1977) are supportive of the 58 mg/kg/day LOAEL used to derive the MRL.

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

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,2-Dichloroethane
CAS Numbers: 107-06-2
Date: January 2022
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

Provisional MRL Summary: There are insufficient data for derivation of a chronic duration provisional oral MRL and no studies were identified that could be used for an MRL.

Rationale for not deriving an MRL: An MRL has not been derived for chronic oral exposure to 1,2-dichloroethane, because the two chronic studies located either observed no health effect or only observed death and cancer endpoints for which MRLs are not derived. The only chronic oral study that observed health effects tested rats and mice that were treated by gavage 5 days/week for up to 78 weeks (NCI 1978). This study had several limitations such as dosage adjustments, possible contamination by other chemicals tested in the same laboratory, poor survival, and small numbers of control animals. Additionally, it may not be appropriate, in this case, to base an MRL on an effect level from a gavage oil study due to toxicokinetic considerations (e.g., possible bolus saturation of the detoxification/excretion mechanism can occur which may exacerbate toxicity at lower concentrations).

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 was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for 1,2-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
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 2001. The following main databases were searched in March 2019:

The current literature search was intended to update the existing toxicological profile for 1,2-dichloroethane (ATSDR 2001), thus, the literature search was restricted to studies published between 1999 and 2019. The following main databases were searched in March 2019:

- MEDLINE
- PubMed
- Science Direct
- TOXLINE

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
MEDLINE 03/2019	(MH "Ethylene Dichlorides") OR AB "Dichlorides" OR "Ethylene Dichloroethanes" OR "1,2 dichloroethane" OR "dichloroethanes" OR "EDC" OR "Dutch Liquid" OR "1,2-Bichloroethane" OR "1,2-Dichloorethaan" OR "1,2-Dicloroetano" OR "1,2-Ethylene dichloride" OR "Aethylenchlorid" OR "alpha,beta-Dichloroethane" OR "Bichlorure d'ethylene" OR "Borer sol" OR "Brocide" OR "Chlorure d'ethylene" OR "Cloruro di ethene" OR "Destruxol borer-sol" OR "Di-chlor-mulsion" OR "Dichlor-Mulsion" OR "Dichloremulsion" OR "Dichloro-1,2-ethane" OR "Dichlorodiphenyl Dichloroethylene"OR "Dichlorure d'ethylene" OR "Dutch Oil" OR "EPA Pesticide Chemical Code 042003" OR "Ethane dichloride" OR "Ethyleendichloride" OR "Ethylene chloride" OR "Glycol dichloride" OR "sym-Dichloroethane" OR "Ethane, 1,2-dichloro-"" OR "Dichloroethane, 1,2-" OR "AI3-01656" OR "Caswell No. 440" OR "CCRIS 225" OR "Dicloruro de etileno" OR "ENT 1,656" OR "HSDB 65" OR "NCI-C00511" OR "RCRA WASTE NUMBER U077" OR "1,2-DCA" OR RN “107-06-2" Limited 1999-present
PubMed 03/2019	((("ethylene dichlorides"[MeSH Terms]) OR ("1,2-dichloroethane"[Supplementary Concept] OR "Dichloroethanes"[Supplementary Concept] OR "Dichlorides, Ethylene"[Supplementary Concept])) OR ("dichloroethane"[Text Word] OR "EDC"[Text Word] OR "dutch liquid"[Text Word] OR "1,2-Bichloroethane"[Text Word] OR "1,2-Dichloorethaan"[Text Word] OR "1,2-Dichlor-aethan"[Text Word] OR "1,2-Dicloroetano"[Text Word] OR "1,2-Ethylene dichloride"[Text Word] OR “Aethylenchlorid”[Text Word] OR “alpha,beta-Dichloroethane”[Text Word] OR “Bichlorure d'ethylene”[Text Word] OR “Borer sol”[Text Word] OR “Brocide”[Text Word] OR “Chlorure d'ethylene”[Text Word] OR “Cloruro di ethane”[Text Word] OR “Destruxol borer-sol”[Text Word] OR “Di-chlor-mulsion”[Text Word] OR “Dichlor-Mulsion”[Text Word] OR “Dichloremulsion”[Text Word] OR “Dichloro-1,2-ethane”[Text Word] OR “Dichloroethylene”[Text Word] OR “Dichlorure d'ethylene”[Text Word] OR “Dutch oil”[Text Word] OR “EPA Pesticide Chemical Code 042003”[Text Word] OR “Ethane dichloride”[Text Word] OR “Ethyleendichloride”[Text Word] OR “Ethylene chloride”[Text Word] OR “Glycol dichloride”[Text Word] OR “symdichloroethane”[Text Word] OR “Ethane, 1,2-dichloro-“[Text Word] OR “Dichloroethane, 1,2-“[Text Word] OR “AI3-01656”[Text Word] OR “Caswell No. 440”[Text Word] OR “CCRIS 225”[Text Word] OR “Dicloruro de etileno”[Text Word] OR “ENT 1,656”[Text Word] OR “HSDB 65”[Text Word] OR “NCI-C00511”[Text Word] OR “RCRA WASTE NUMBER U077”[Text Word] OR “1,2-DCA”[Text Word])) OR "107-06-2"[EC/RN Number]
Science Direct 03/2019	"1,2 Dichloroethane" OR "ethylene dichloride" OR "107-06-2" Limited 1999 - present
TOXLINE 03/2019	“1,2-dichloroethane” OR “Ethylene dichloride” OR “dichloroethane” OR “EDC” OR “Dutch liquid” OR “1,2-Bichloroethane” OR “1,2-Dichloorethaan” OR “1,2-Dichlor-aethan” OR “1,2-Dicloroetano” OR “1,2-Ethylene dichloride” OR “Aethylenchlorid” OR “alpha,beta-Dichloroethane” OR “Bichlorure d'ethylene” OR “Borer sol” OR “Brocide” OR “Chlorure d'ethylene” OR “Cloruro di ethene” OR “Destruxol borer-sol” OR “Di-chlor-mulsion” OR “Dichlor-Mulsion” OR “Dichloremulsion” OR “Dichloro-1,2-ethane” OR “Dichloroethylene” OR “Dichlorure d'ethylene” OR “Dutch oil” OR “EPA Pesticide Chemical Code 042003” OR “Ethane dichloride” OR “Ethyleendichloride” OR “Ethylene chloride” OR “Glycol dichloride” OR “sym-

Table B-2. Database Query Strings

Database search date	Query string
	Dichloroethane" OR "Ethane, 1,2-dichloro-" OR "Dichloroethane, 1,2-" OR "AI3-01656" OR "Caswell No. 440" OR "CCRIS 225" OR "Dicloruro de etileno" OR "ENT 1,656" OR "HSDB 65" OR "NCI-C00511" OR "RCRA WASTE NUMBER U077" OR "1,2-DCA" OR "107-06-2" Limited 1999-present

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
ChemView[a] 03/2019	Compounds searched: 107-06-2
Office of Pesticide Programs Chemical Search	Compounds searched: 107-06-2
Other	Identified throughout the assessment process

ChemView was searched for any TSCA submissions submitted to EPA.

The 2019 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 7,025
- Number of records identified from other strategies: 13
- Total number of records to undergo literature screening: 7,038

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

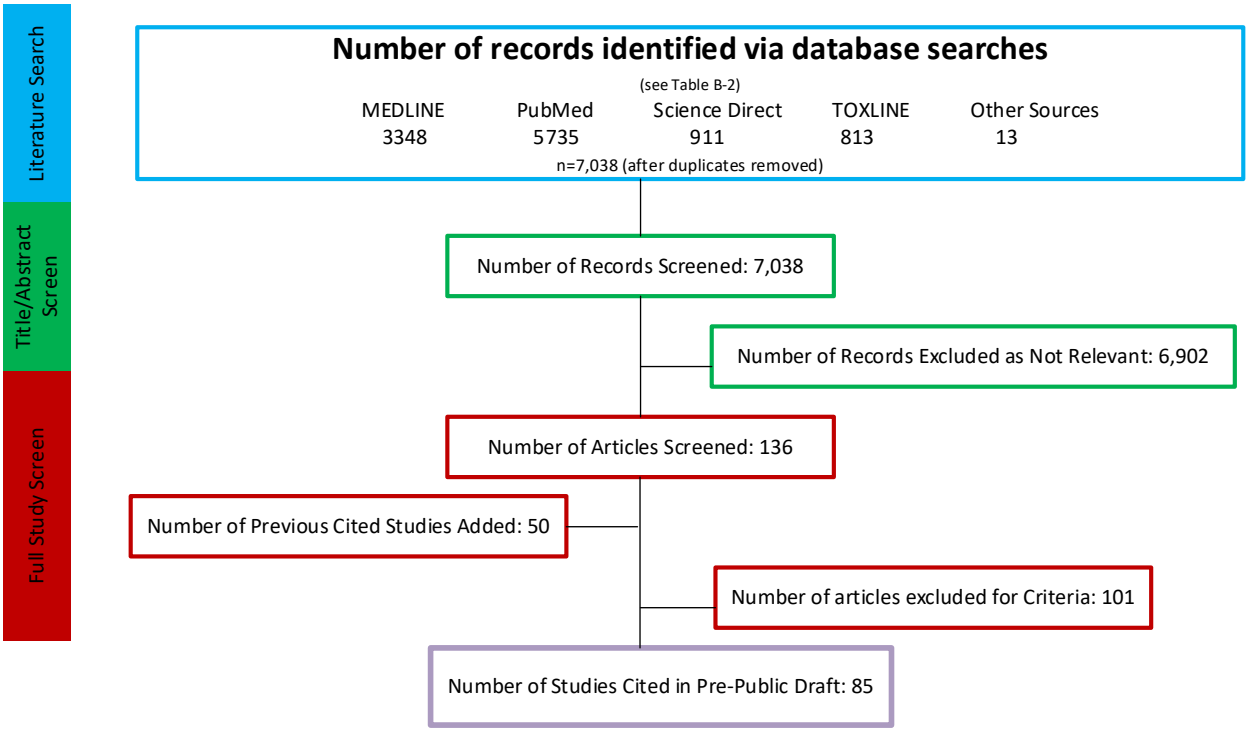
Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

- Number of titles and abstracts screened: 7,038
- Number of studies considered relevant and moved to the next step: 136

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: 136
- Number of studies cited in the pre-public draft of the toxicological profile: 35
- Total number of studies cited in the profile: 85

Figure B-1. March 2019 Literature Search Results and Screen for 1,2-Dichloroethane



APPENDIX C. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible

Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)

Internet: http://www.atsdr.cdc.gov

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.asp). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

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

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the

workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

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

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

Minimal Risk Levels (MRLs)

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

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

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

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

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

(LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

TABLE LEGEND

See Sample LSE Table (page D-5)

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

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

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

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

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for two years. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

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

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

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

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

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

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

FIGURE LEGEND

See Sample LSE Figure (page D-6)

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

(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.

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

Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

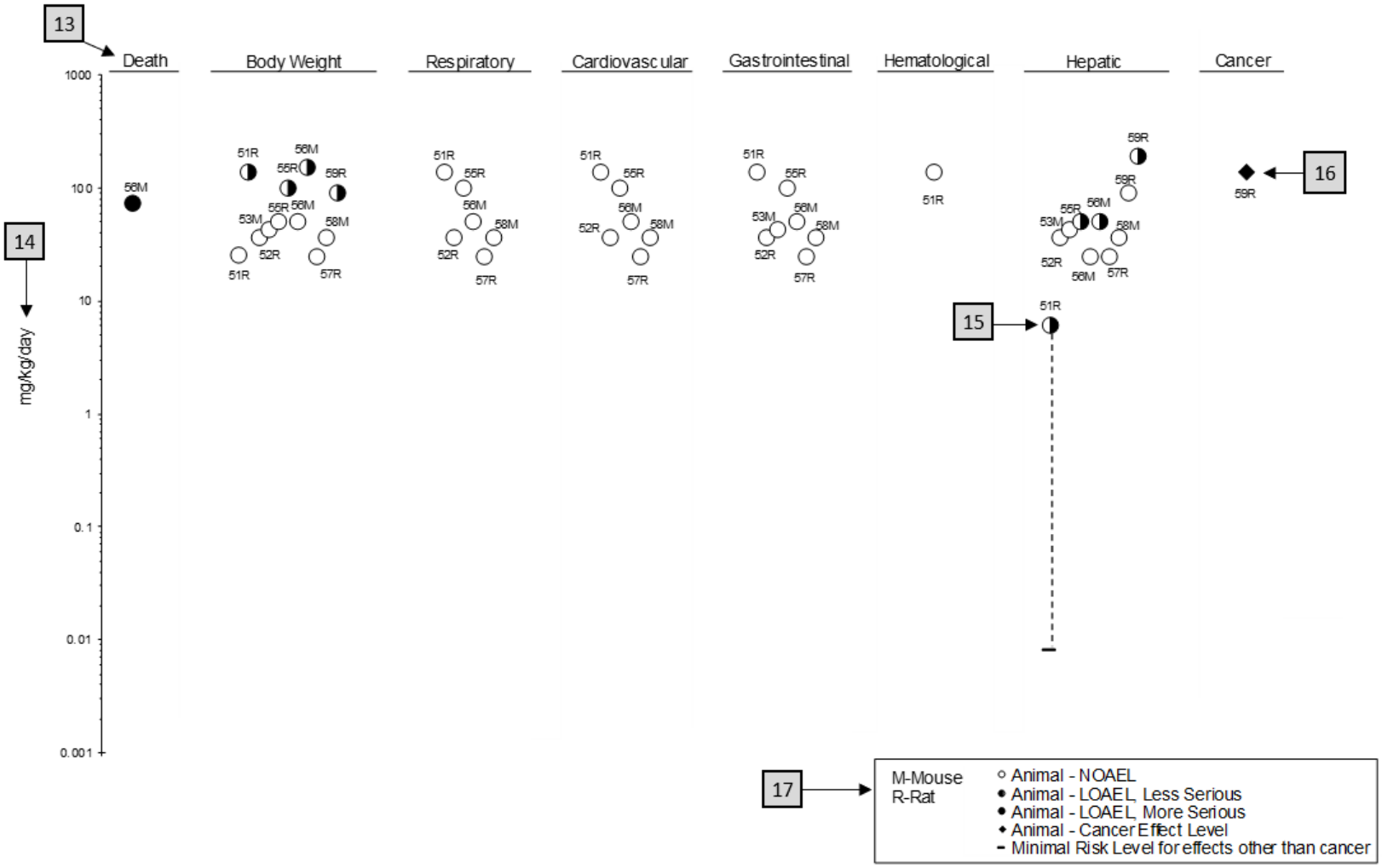
[a]The number corresponds to entries in Figure 2-x.

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

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

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

12 → Chronic (≥365 days)



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.

Ceiling Value—A concentration that must not be exceeded.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m3 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
BMDx	dose that produces a X% change in response rate of an adverse effect
BMDLx	95% lower confidence limit on the BMDx
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
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act

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

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

USGS	United States Geological Survey
USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q1*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result