

Toxicological Profile for 1,1-Dichloroethene

Draft for Public Comment

December 2019



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

DISCLAIMER

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

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

FOREWORD

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

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

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

Each profile includes the following:

- (A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, intermediate, and chronic health effects;
- (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine the levels of exposure that present a significant risk to human health due to acute, intermediate, and chronic duration exposures; and
- (C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

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

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

Written comments may also be sent to: Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
Environmental Toxicology Branch
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

VERSION HISTORY

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

CONTRIBUTORS & REVIEWERS

CHEMICAL MANAGER TEAM

Malcolm Williams, D.V.M., Ph.D. (Lead)	David W. Wohlers, Ph.D.
Mike Fay, Ph.D.	Christina Coley, B.S.
Susan Zells Ingber, A.B., M.S.P.P.	
ATSDR, Division of Toxicology and Human Health Sciences, Atlanta, GA	SRC, Inc., North Syracuse, NY

REVIEWERS

Interagency Minimal Risk Level Workgroup:

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

Additional reviews for science and/or policy:

ATSDR, Division of Community Health Investigations; ATSDR, Office of Science; NCEH, Division of Laboratory Science; NCEH, Division of Environmental Health Science and Practice.

PEER REVIEWERS

1. G.A. Shakeel Ansari, Ph.D., Professor, Department of Pathology, University of Texas Medical Branch, Galveston, Texas
2. James V. Bruckner, Ph.D., Professor Emeritus of Pharmacology & Toxicology, Department of Pharmaceutical & Biomedical Sciences, College of Pharmacy, University of Georgia, Athens, Georgia
3. F. Peter Guengerich, Ph.D., Professor of Biochemistry, Tadashi Inagami Chair in Biochemistry, Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, Tennessee

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

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

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

CONTENTS

DISCLAIMER	ii
FOREWORD	iii
VERSION HISTORY	v
CONTRIBUTORS & REVIEWERS	vi
CONTENTS	vii
LIST OF FIGURES	ix
LIST OF TABLES	x
CHAPTER 1. RELEVANCE TO PUBLIC HEALTH	1
1.1 OVERVIEW AND U.S. EXPOSURES	1
1.2 SUMMARY OF HEALTH EFFECTS	1
1.3 MINIMAL RISK LEVELS (MRLs)	7
CHAPTER 2. HEALTH EFFECTS	10
2.1 INTRODUCTION	10
2.2 DEATH	46
2.3 BODY WEIGHT	48
2.4 RESPIRATORY	49
2.5 CARDIOVASCULAR	50
2.6 GASTROINTESTINAL	50
2.7 HEMATOLOGICAL	51
2.8 MUSCULOSKELETAL	51
2.9 HEPATIC	52
2.10 RENAL	54
2.11 DERMAL	56
2.12 OCULAR	56
2.13 ENDOCRINE	56
2.14 IMMUNOLOGICAL	57
2.15 NEUROLOGICAL	57
2.16 REPRODUCTIVE	58
2.17 DEVELOPMENTAL	58
2.18 OTHER NONCANCER	60
2.19 CANCER	60
2.20 GENOTOXICITY	64
2.21 MECHANISMS OF ACTION	67
CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS	70
3.1 TOXICOKINETICS	70
3.1.1 Absorption	70
3.1.2 Distribution	71
3.1.3 Metabolism	72
3.1.4 Excretion	76
3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models	78
3.1.6 Animal-to-Human Extrapolations	79
3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE	80
3.3 BIOMARKERS OF EXPOSURE AND EFFECT	81

3.3.1	Biomarkers of Exposure.....	82
3.3.2	Biomarkers of Effect.....	83
3.4	INTERACTIONS WITH OTHER CHEMICALS.....	83
CHAPTER 4.	CHEMICAL AND PHYSICAL INFORMATION.....	86
4.1	CHEMICAL IDENTITY.....	86
4.2	PHYSICAL AND CHEMICAL PROPERTIES.....	86
CHAPTER 5.	POTENTIAL FOR HUMAN EXPOSURE.....	88
5.1	OVERVIEW.....	88
5.2	PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL.....	89
5.2.1	Production.....	89
5.2.2	Import/Export.....	91
5.2.3	Use.....	91
5.2.4	Disposal.....	92
5.3	RELEASES TO THE ENVIRONMENT.....	92
5.3.1	Air.....	93
5.3.2	Water.....	94
5.3.3	Soil.....	95
5.4	ENVIRONMENTAL FATE.....	96
5.4.1	Transport and Partitioning.....	96
5.4.2	Transformation and Degradation.....	97
5.5	LEVELS IN THE ENVIRONMENT.....	100
5.5.1	Air.....	101
5.5.2	Water.....	101
5.5.3	Sediment and Soil.....	110
5.5.4	Other Media.....	111
5.6	GENERAL POPULATION EXPOSURE.....	111
5.7	POPULATIONS WITH POTENTIALLY HIGH EXPOSURES.....	113
CHAPTER 6.	ADEQUACY OF THE DATABASE.....	114
6.1	INFORMATION ON HEALTH EFFECTS.....	114
6.2	IDENTIFICATION OF DATA NEEDS.....	116
6.3	ONGOING STUDIES.....	122
CHAPTER 7.	REGULATIONS AND GUIDELINES.....	123
CHAPTER 8.	REFERENCES.....	125
APPENDICES		
APPENDIX A.	ATSDR MINIMAL RISK LEVEL WORKSHEETS.....	A-1
APPENDIX B.	LITERATURE SEARCH FRAMEWORK FOR 1,1-DICHLOROETHENE.....	B-1
APPENDIX C.	FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR 1,1-DICHLOROETHENE.....	C-1
APPENDIX D.	USER'S GUIDE.....	D-1
APPENDIX E.	QUICK REFERENCE FOR HEALTH CARE PROVIDERS.....	E-1
APPENDIX F.	GLOSSARY.....	F-1
APPENDIX G.	ACRONYMS, ABBREVIATIONS, AND SYMBOLS.....	G-1

LIST OF FIGURES

1-1. Health Effects Found in Animals Following Inhalation Exposure to 1,1-Dichloroethene	2
1-2. Health Effects Found in Animals Following Oral Exposure to 1,1-Dichloroethene	3
1-3. Summary of Sensitive Targets of 1,1-Dichloroethene – Inhalation	7
1-4. Summary of Sensitive Targets of 1,1-Dichloroethene – Oral.....	8
2-1. Overview of the Number of Studies Examining 1,1-Dichloroethene Health Effects	13
2-2. Levels of Significant Exposure to 1,1-Dichloroethene – Inhalation.....	29
2-3. Levels of Significant Exposure to 1,1-Dichloroethene – Oral.....	42
3-1. Metabolic Scheme for 1,1-Dichloroethene.....	74
5-1. Number of NPL Sites with 1,1-Dichloroethene Contamination.....	88
6-1. Summary of Existing Health Effects Studies on 1,1-Dichloroethene By Route and Endpoint	115

LIST OF TABLES

1-1. Minimal Risk Levels (MRLs) for 1,1-Dichloroethene	9
2-1. Levels of Significant Exposure to 1,1-Dichloroethene – Inhalation.....	14
2-2. Levels of Significant Exposure to 1,1-Dichloroethene – Oral.....	35
2-3. Acute Lethality Results Among Laboratory Animals Exposed to 1,1-Dichloroethene Vapor.....	47
2-4. Genotoxicity of 1,1-Dichloroethene <i>In Vitro</i>	64
2-5. Genotoxicity of 1,1-Dichloroethene <i>In Vivo</i>	67
4-1. Chemical Identity of 1,1-Dichloroethene	86
4-2. Physical and Chemical Properties of 1,1-Dichloroethene	87
5-1. Facilities that Produce, Process, or Use 1,1-Dichloroethene	90
5-2. Releases to the Environment from Facilities that Produce, Process, or Use 1,1-Dichloroethene	94
5-3. Lowest Limit of Detection Based on Standards	100
5-4. Summary of Environmental Levels of 1,1-Dichloroethene.....	100
5-5. 1,1-Dichloroethene Levels in Water, Soil, and Air of National Priorities List (NPL) Sites.....	101
5-6. Air Monitoring Data for 1,1-Dichloroethene.....	102
5-7. Water Monitoring Data for 1,1-Dichloroethene	105
7-1. Regulations and Guidelines Applicable to 1,1-Dichloroethene.....	123

CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

1,1-Dichloroethene (Chemical Abstracts Service [CAS] Registry Number 75-35-4, synonyms include 1,1-dichloroethylene and vinylidene chloride) is a human-made chemical that does not occur naturally in the environment. The major use for 1,1-dichloroethene is as a chemical intermediate to make other products. 1,1-Dichloroethene is used to make various plastics, such as packaging materials and flexible films such as Saran™ plastic wrap, and as flame retardant coatings for fiber and carpet backing.

1,1-Dichloroethene is a colorless liquid that evaporates quickly at room temperature, has a mild, sweet smell, is flammable, and burns quickly.

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

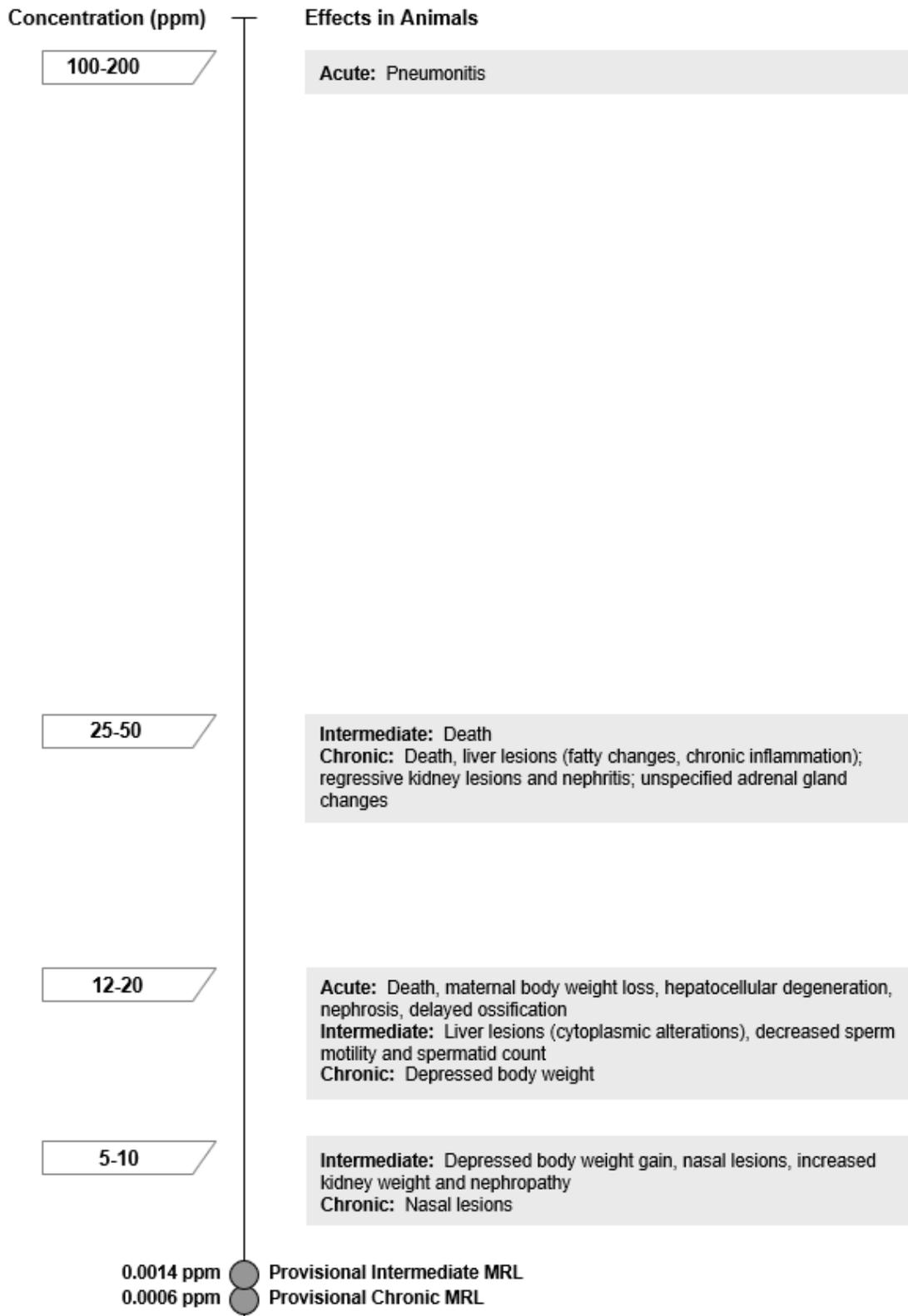
1.2 SUMMARY OF HEALTH EFFECTS

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

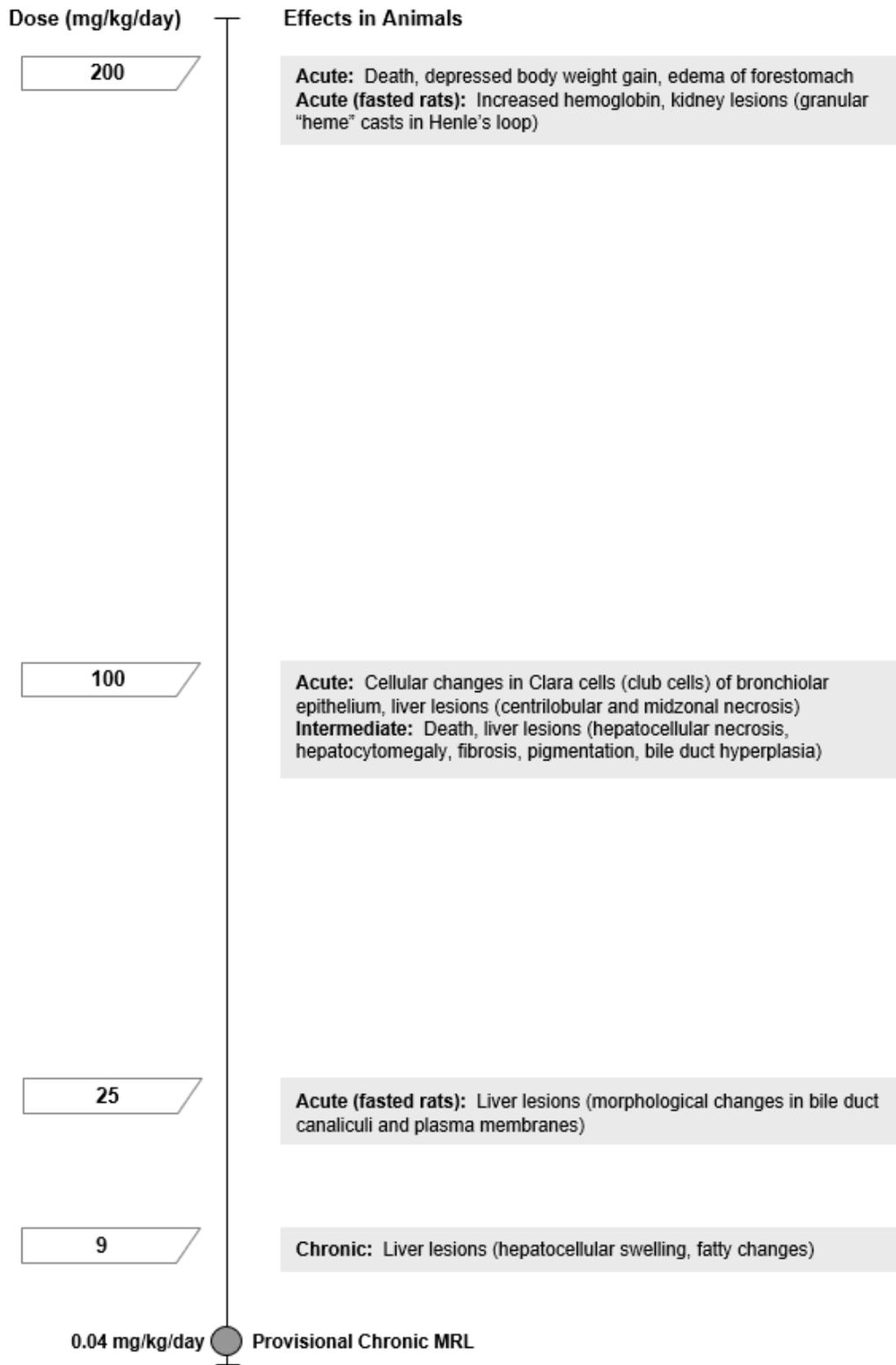
- Upper respiratory tract toxicity is a presumed health effect for humans
- Liver toxicity is a presumed health effect for humans
- Kidney toxicity is a presumed health effect for humans

1. RELEVANCE TO PUBLIC HEALTH

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



1. RELEVANCE TO PUBLIC HEALTH

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

1. RELEVANCE TO PUBLIC HEALTH

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

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

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

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

1. RELEVANCE TO PUBLIC HEALTH

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

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

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

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

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

1. RELEVANCE TO PUBLIC HEALTH

adenocarcinoma in males, pulmonary tumors in males and females, and mammary gland tumors in females Maltoni et al. (1985).

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

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

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

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

1. RELEVANCE TO PUBLIC HEALTH

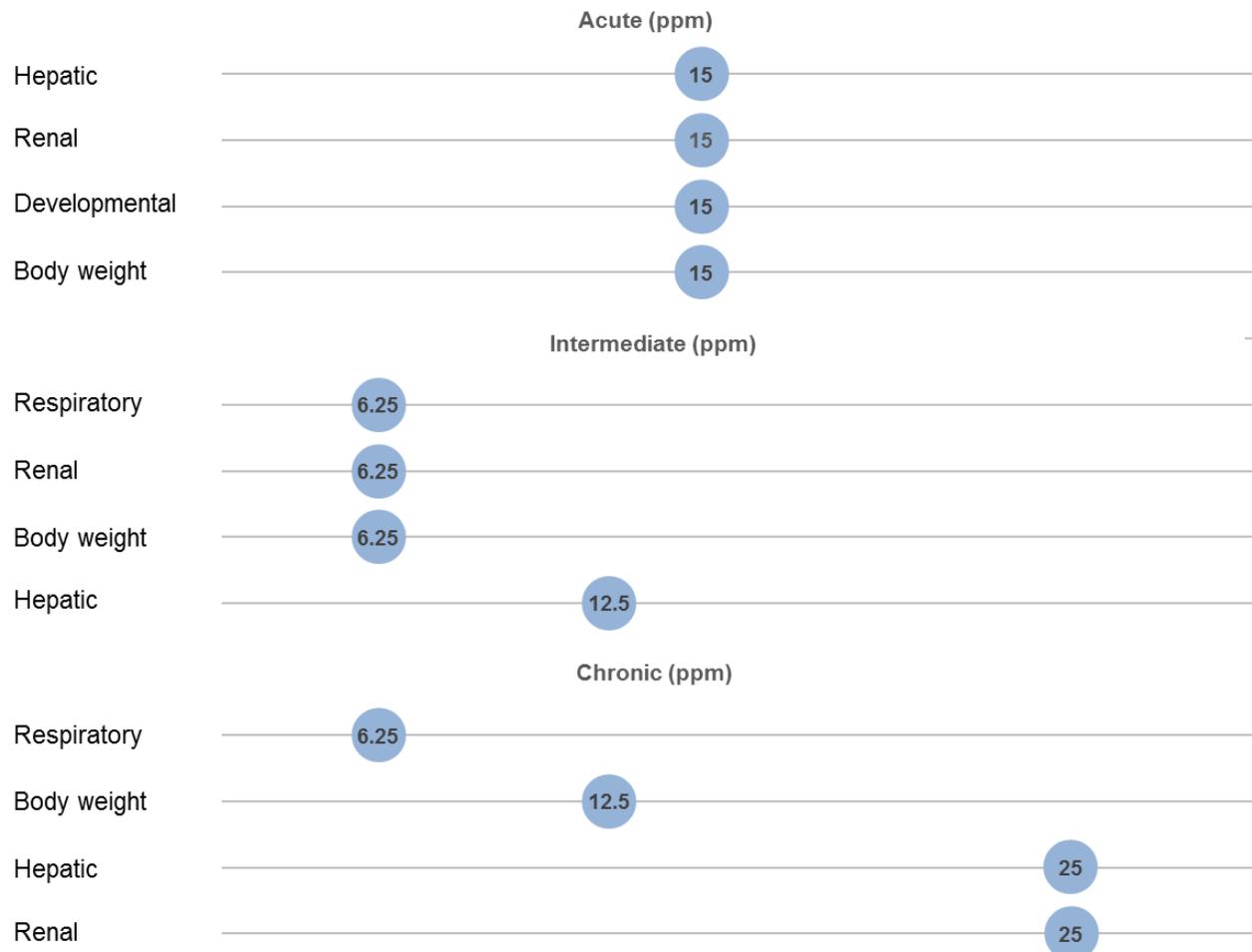
1.3 MINIMAL RISK LEVELS (MRLs)

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

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

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

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



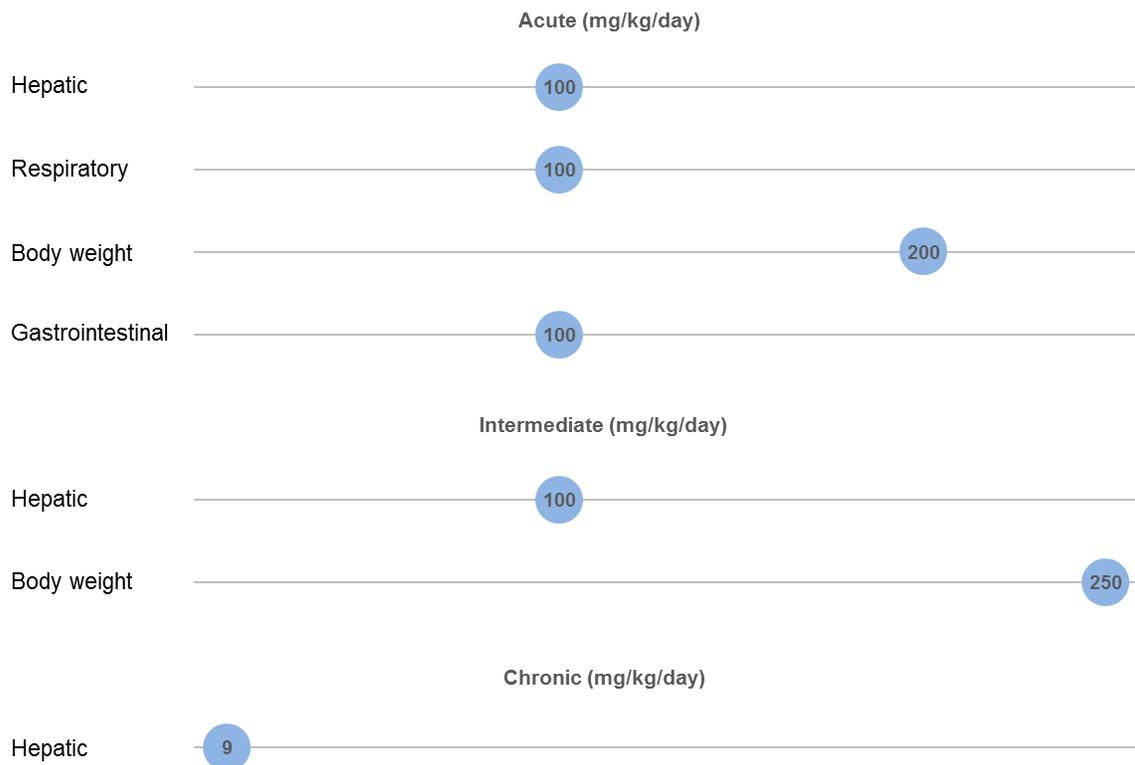
1. RELEVANCE TO PUBLIC HEALTH

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

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

The liver is the most sensitive target of 1,1-dichloroethene oral exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals; no reliable dose-response data were available for humans.



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

1. RELEVANCE TO PUBLIC HEALTH

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

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute	Insufficient data for MRL derivation				
Intermediate (provisional)	0.001	Nasal olfactory epithelium necrosis	BMCL _{10HEC} of 0.043 ppm	30	NTP 2015a
Chronic (provisional)	0.0006	Nasal olfactory epithelium metaplasia	BMCL _{10HEC} of 0.017 ppm	30	NTP 2015a
Oral exposure (mg/kg/day)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic (provisional)	0.05	Hepatic midzonal fatty change Hepatocellular hypertrophy	BMDL ₁₀ of 4.61 mg/kg/day BMDL ₁₀ of 4.89 mg/kg/day	100	Humiston et al. 1978; Quast et al. 1983

^aSee Appendix A for additional information.

BMCL₁₀ = upper 95% confidence limit on the benchmark concentration (BMC) associated with benchmark response rate of 10%; BMDL₁₀ = upper 95% confidence limit on the benchmark dose (BMD) associated with benchmark response rate of 10%; HEC = human equivalent concentration.

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of 1,1-dichloroethene. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

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

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to 1,1-dichloroethene, but may not be inclusive of the entire body of literature. A systematic review of the scientific evidence of the health effects associated with exposure to 1,1-dichloroethene was also conducted; the results of this review are presented in Appendix C.

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

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

2. HEALTH EFFECTS

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

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

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

- **Body weight:** Depressed body weight or depressed body weight gain and actual body weight loss have been reported following inhalation or oral exposure of laboratory animals.
- **Respiratory Endpoints:** Upper respiratory tract toxicity is a presumed health effect for humans based on strong evidence in animals. Increased lung weight, nasal lesions (e.g., hyperostosis, chronic active inflammation, metaplasia and atrophy in olfactory epithelium, hyperplasia in respiratory epithelium, turbinate atrophy), and laryngeal lesions (respiratory epithelial necrosis, metaplasia, and hyperplasia) have been associated with repeated inhalation exposure of rats and/or mice to 1,1-dichloroethene vapor. Clara cell (club cell) damage in the lungs was observed following oral exposure to 1,1-dichloroethene.
- **Hepatic Endpoints:** Liver toxicity is a presumed health effect for humans based on strong evidence in animals. 1,1-Dichloroethene-induced liver effects, evidenced by biochemical changes (e.g., increases in serum liver enzyme levels, induction of hepatic enzymes) and marked histological changes (e.g., hepatocellular swelling, degeneration and necrosis of hepatocytes), have been reported in rats and mice for both inhalation and oral exposure routes. Fasting increases the hepatotoxicity of 1,1-dichloroethene.

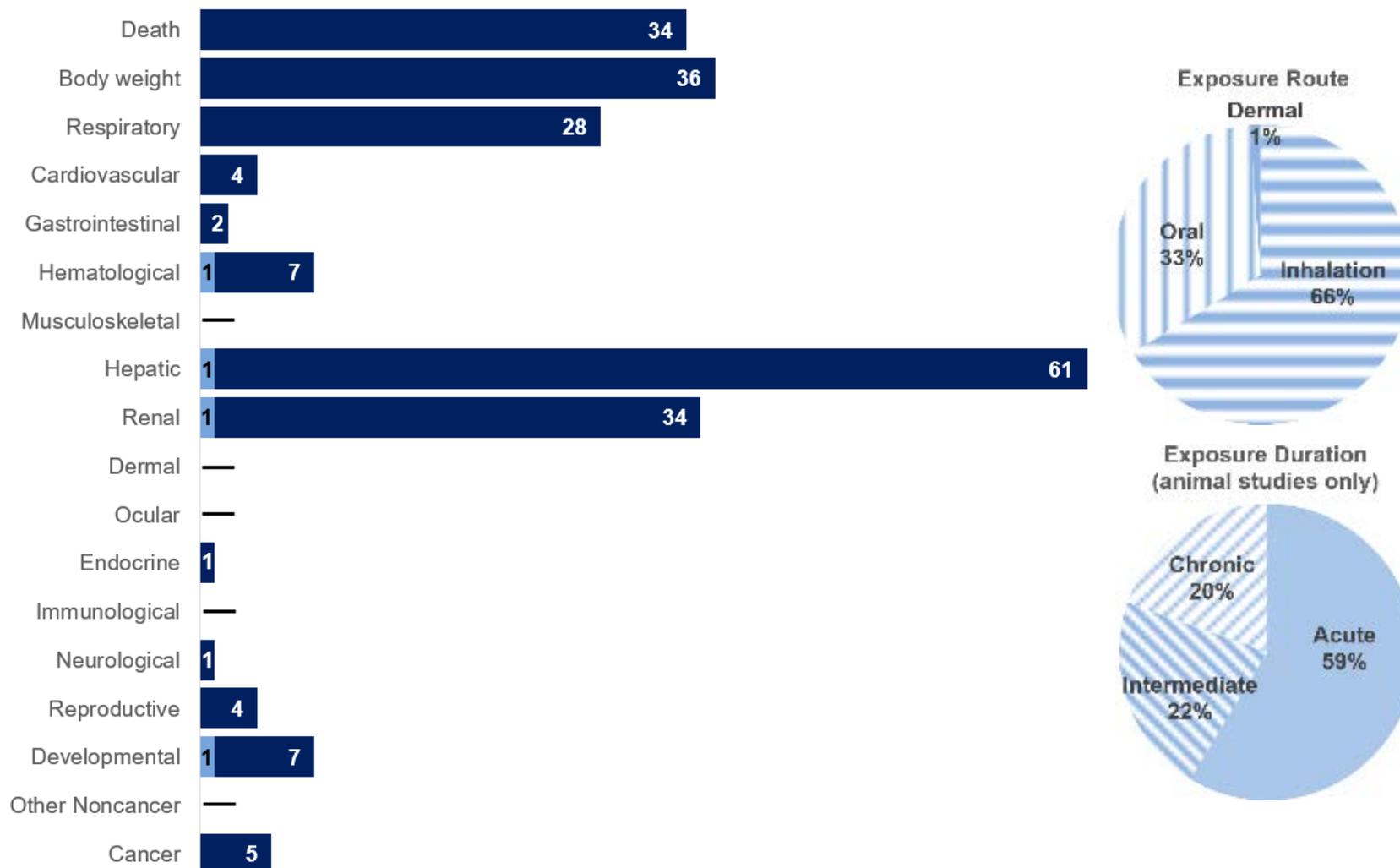
2. HEALTH EFFECTS

- **Renal Endpoints:** Kidney toxicity is a presumed health effect for humans based on strong evidence in animals. 1,1-Dichloroethene-induced kidney effects, evidenced by increased kidney weight, enzyme changes (decreases in kidney monooxygenase and epoxide hydrolase levels), and histological changes (nephropathy and tubular swelling, degeneration, necrosis, and granular casts) were observed following repeated inhalation exposure; male mice appear to be most susceptible to 1,1-dichloroethene renal toxicity. Fasting increases renal toxicity.
- **Developmental Endpoints:** Delayed ossification of selected bones was reported for fetuses from maternal mice exposed to 1,1-dichloroethene vapor during gestation.
- **Cancer:** Increased incidences of selected tumor types have been reported in some studies of rats or mice, most of which employed the inhalation exposure route. EPA (2002) considered available animal data to provide “*suggestive evidence* of carcinogenicity but not sufficient evidence to assess human carcinogenic potential following inhalation exposure” and “*inadequate* for an assessment of human carcinogenic potential by the oral route.” IARC recently assigned 1,1-dichloroethene to Group 2B, based on “sufficient evidence of carcinogenicity in experimental animals” and no data or “inadequate evidence” in humans (Gross et al. 2017).

2. HEALTH EFFECTS

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

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



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

2. HEALTH EFFECTS

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

Figure Key ^a	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
ACUTE EXPOSURE									
1	Rat (Sprague-Dawley) 4–22 M	Once 4 hours	0, 200, 250, 300, 375, 400	BC, BW, HP, LE, OW	Renal		250		At 250 ppm, swelling in renal cortex of fasted male rats At 300 ppm, cortical tubular necrosis of fasted male rats
Jackson and Conolly 1985									
2	Rat (Sprague-Dawley) 2–24 M	Once 4 hours	0, 250	BI	Hepatic		250		Decreased mitochondrial GSH
Jaeger 1977									
3	Rat (Holtzman) 5 M	Once 4 hours	0, 2,000	BI, CS, LE	Death Hepatic			2,000 2,000	Death of 2/5 rats exposed during period of low GSH activity Increased serum alanine α-ketoglutarate transaminase activity
Jaeger et al. 1973a									
4	Rat (Holtzman) 5-6 M	Once 4 hours	Up to 20,000	EA, LE	Death Hepatic	100	150	600	Fasted male rat LC ₅₀ Increased serum alanine α-ketoglutarate transaminase activity in fasted rats
Jaeger et al. 1974									
5	Rat (Holtzman) 5–6 M	Once 4 hours	Up to 20,000	EA, LE	Death Hepatic			15,000 2,000	Nonfasted male rat LC ₅₀ Increased serum alanine α-ketoglutarate transaminase activity in nonfasted rats
Jaeger et al. 1974									
6	Rat (Sprague-Dawley) 4 M	Once 6 hours	10, 200	BM, EX, HP, TM, UM	Hepatic Renal			200 200	Centrilobular degeneration and necrosis in fasted rats; no effect in nonfasted rats Hemoglobinuria; tubular degeneration in fasted rats; no effect in nonfasted rats
McKenna et al. 1978b									

2. HEALTH EFFECTS

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

Figure Key ^a	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
7	Rat (Sprague-Dawley) 30 F treated 21 F control	GDs 6–15 7 hours/day	0 or 80	BW, CS, DX, FI, MX, OW, WI	Bd wt Hepatic Develop	80 80	80		Increased incidence of wavy ribs and delayed ossification of the skull
Murray et al. 1979									
8	Rat (Sprague-Dawley) 30 F treated 18 F control	GDs 6–15 7 hours/day	0 or 160	BW, CS, DX, FI, MX, OW, WI	Bd wt Hepatic Develop	160 160	160		Wavy ribs and delayed ossification of skull and cervical vertebrae
Murray et al. 1979									
9	Rat (Sprague-Dawley) 44 F treated 47 F control	GDs 6–15 7 hours/day	0 or 20	BW, CS, DX, FI, MX, OW, WI	Bd wt Develop	20 20			
Murray et al. 1979									
10	Rat (CD) 19–24 F	GDs 8–20 22– 23 hours/day	0, 56, 283	BH, BW, FX, LE, MX	Bd wt			56	Maternal body weight loss
Short et al. 1977a									
11	Rat (CD) 18–58 F	GDs 6–16 22– 23 hours/day	0, 15, 57, 300, 449	BW, DX, FI, MX	Death Bd wt			15 15	2/18 maternal rats died Maternal body weight loss
Short et al. 1977a									
12	Rat (CD) 5 or 10 M	1–3 days 22– 23 hours/day	0, 60	BW, EA, HP, LE, OF	Hepatic Renal		60		Mild to moderate centrilobular degeneration and/or necrosis, mild bile duct hyperplasia
Short et al. 1977c, 1977d									

2. HEALTH EFFECTS

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

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

2. HEALTH EFFECTS

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

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

2. HEALTH EFFECTS

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

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

2. HEALTH EFFECTS

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

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

2. HEALTH EFFECTS

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

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

2. HEALTH EFFECTS

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

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

2. HEALTH EFFECTS

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

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

2. HEALTH EFFECTS

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

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

2. HEALTH EFFECTS

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

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

2. HEALTH EFFECTS

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

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

2. HEALTH EFFECTS

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

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

2. HEALTH EFFECTS

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

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

2. HEALTH EFFECTS

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

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

Maltoni et al. 1985

^aThe number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

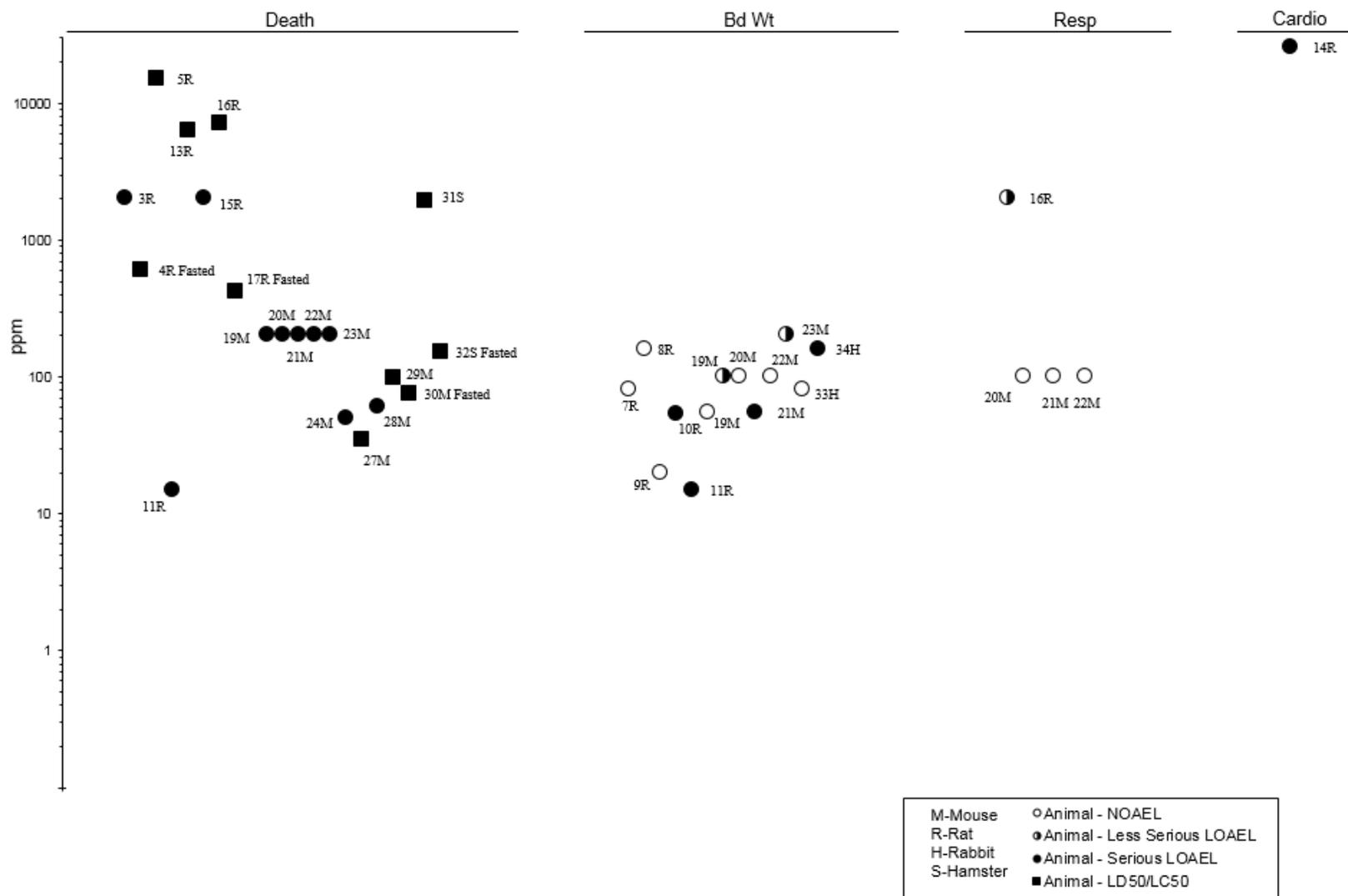
^bUsed to derive a provisional intermediate-duration inhalation minimal risk level (MRL) of 0.001 ppm for 1,1-dichloroethene; based on results from benchmark dose analysis (BMCL₁₀ of 1.84 ppm), adjustment for intermittent exposure, conversion to a human equivalent concentration, and an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability); see Appendix A for more detailed information regarding the provisional MRL.

^cUsed to derive a provisional chronic-duration inhalation MRL of 0.0006 for 1,1-dichloroethene; based on results from benchmark dose analysis (BMCL₁₀ of 0.45 ppm), adjustment for intermittent exposure, conversion to a human equivalent concentration, and an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability); see Appendix A for more detailed information regarding the provisional MRL.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BC = serum (blood) chemistry; Bd wt or BW = body weight; BI = biochemical changes; BM = blood metabolites; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; EA = enzyme activity; Endocr = endocrine; EX = excretion; F = female(s); FI = food intake; FX = fetal toxicity; GD = gestation day(s); GN = gross necropsy; GSH = glutathione; HE = hematology; Hemato = hematological; HP = histopathology; LC₅₀ = lethal concentration, 50% kill; LE = lethality; min = minute(s); LOAEL = lowest-observed-adverse-effect level; M = male(s); mo = month(s); MX = maternal toxicity; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OW = organ weight; Repro = reproductive; Resp = respiratory; TM = tissue metabolites; UM = urinary metabolites; UR = urinalysis; WI = water intake

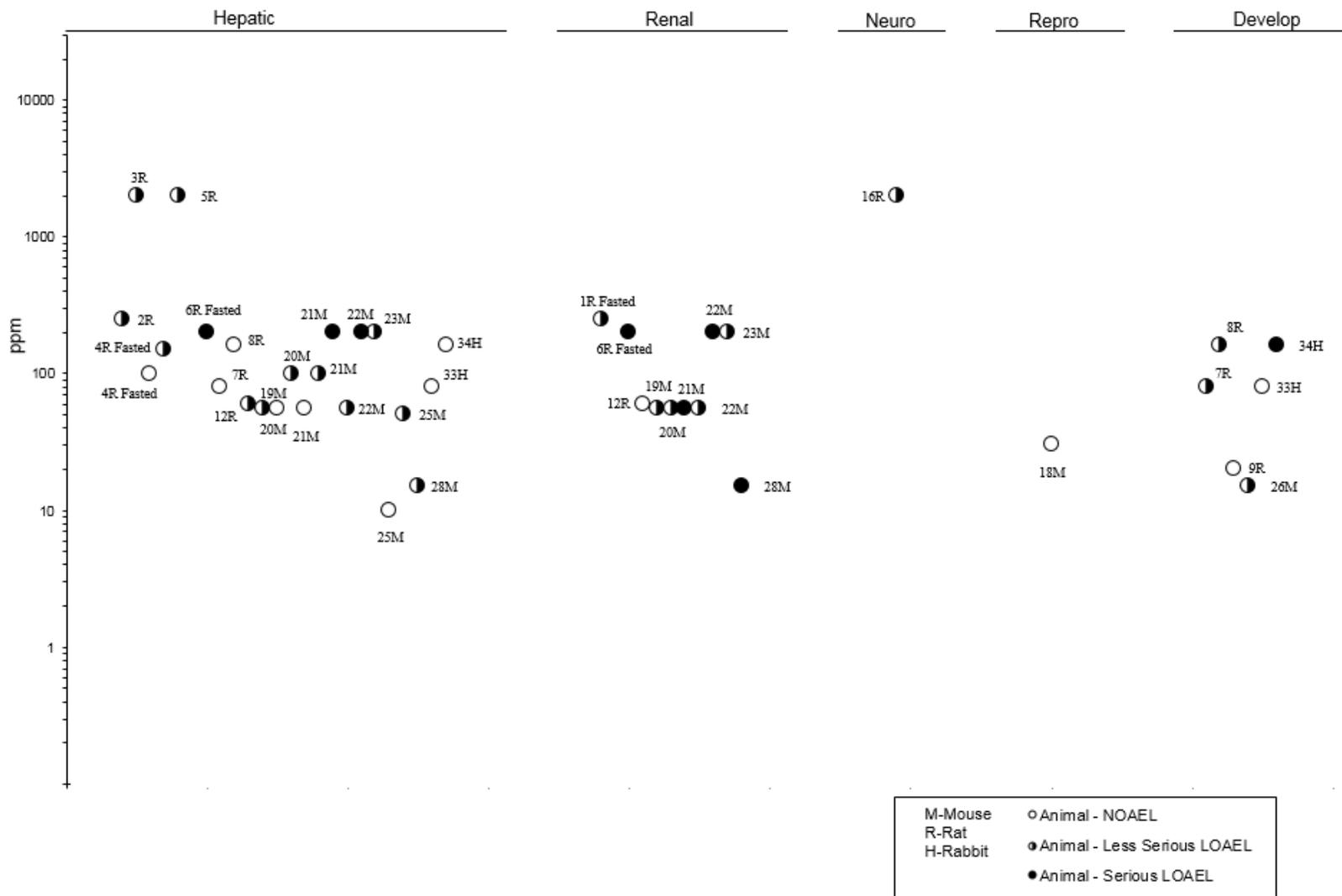
2. HEALTH EFFECTS

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



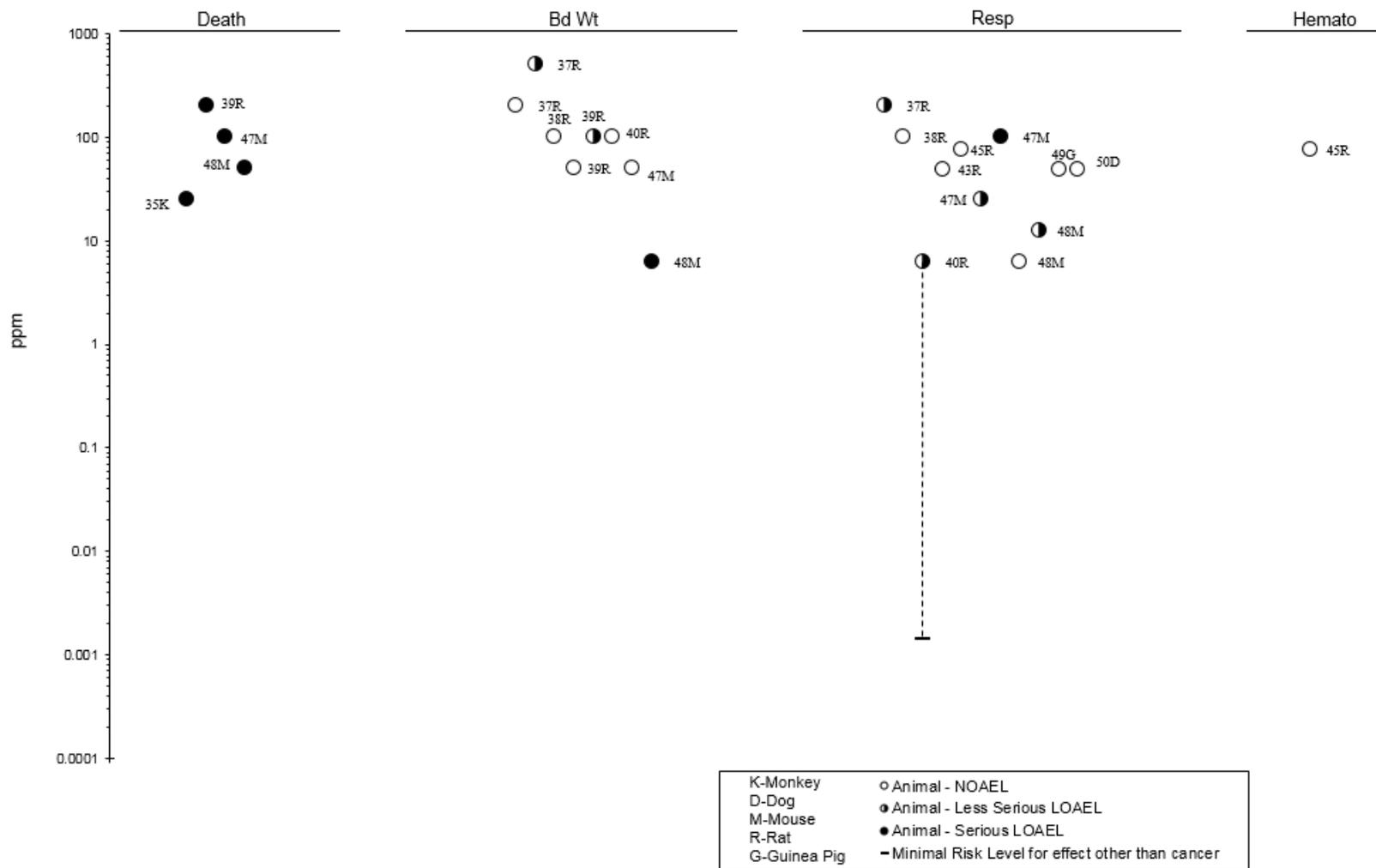
2. HEALTH EFFECTS

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



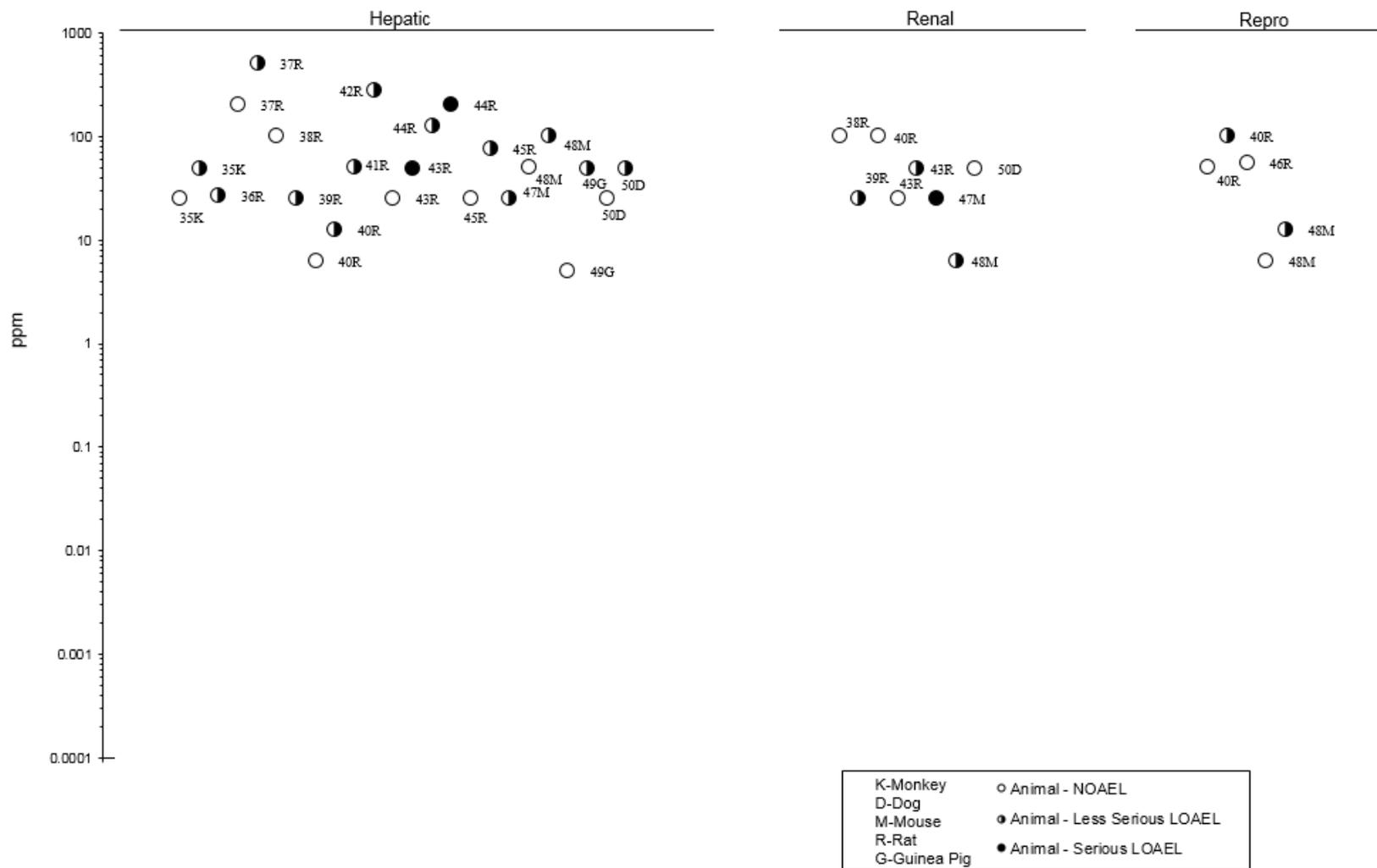
2. HEALTH EFFECTS

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



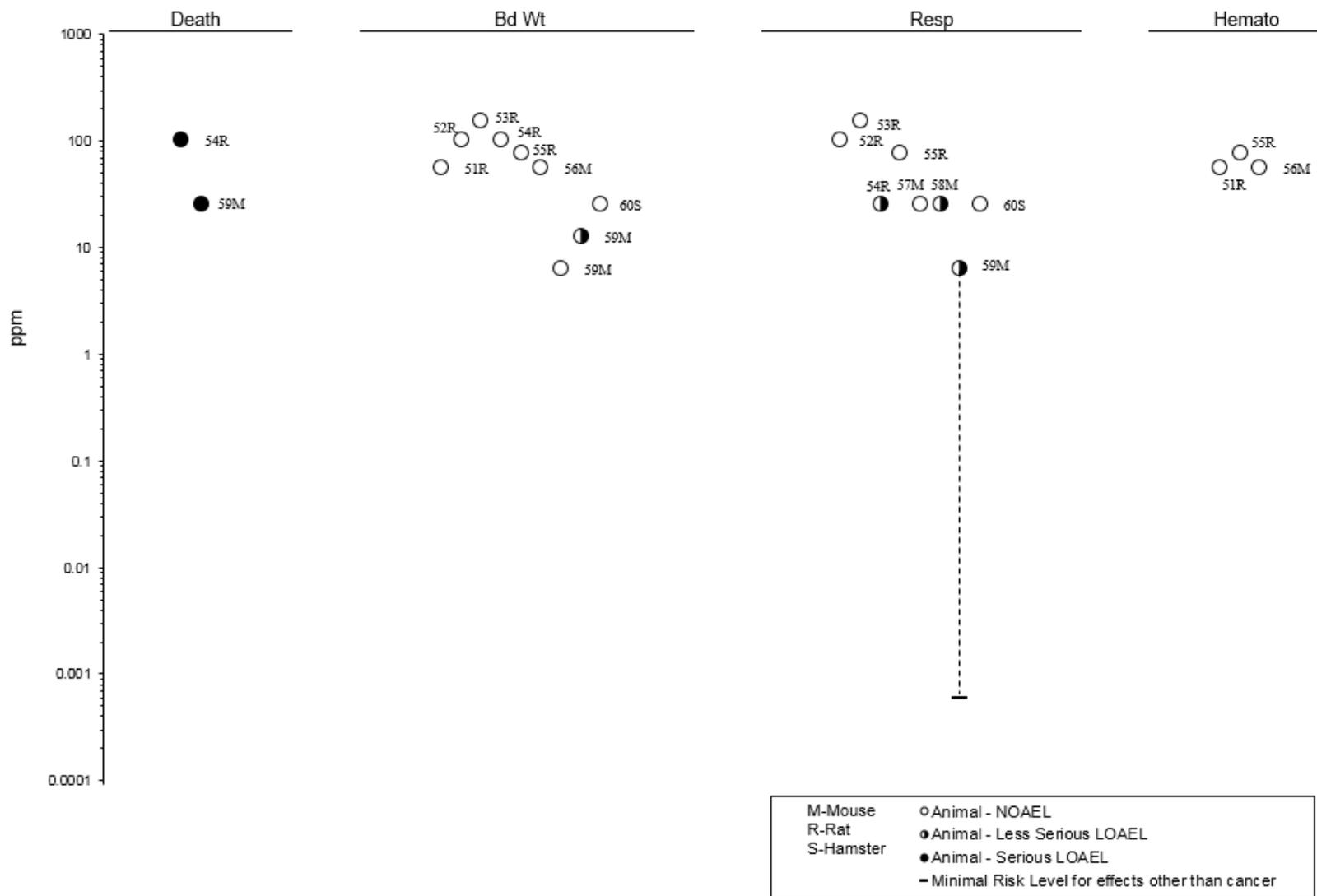
2. HEALTH EFFECTS

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



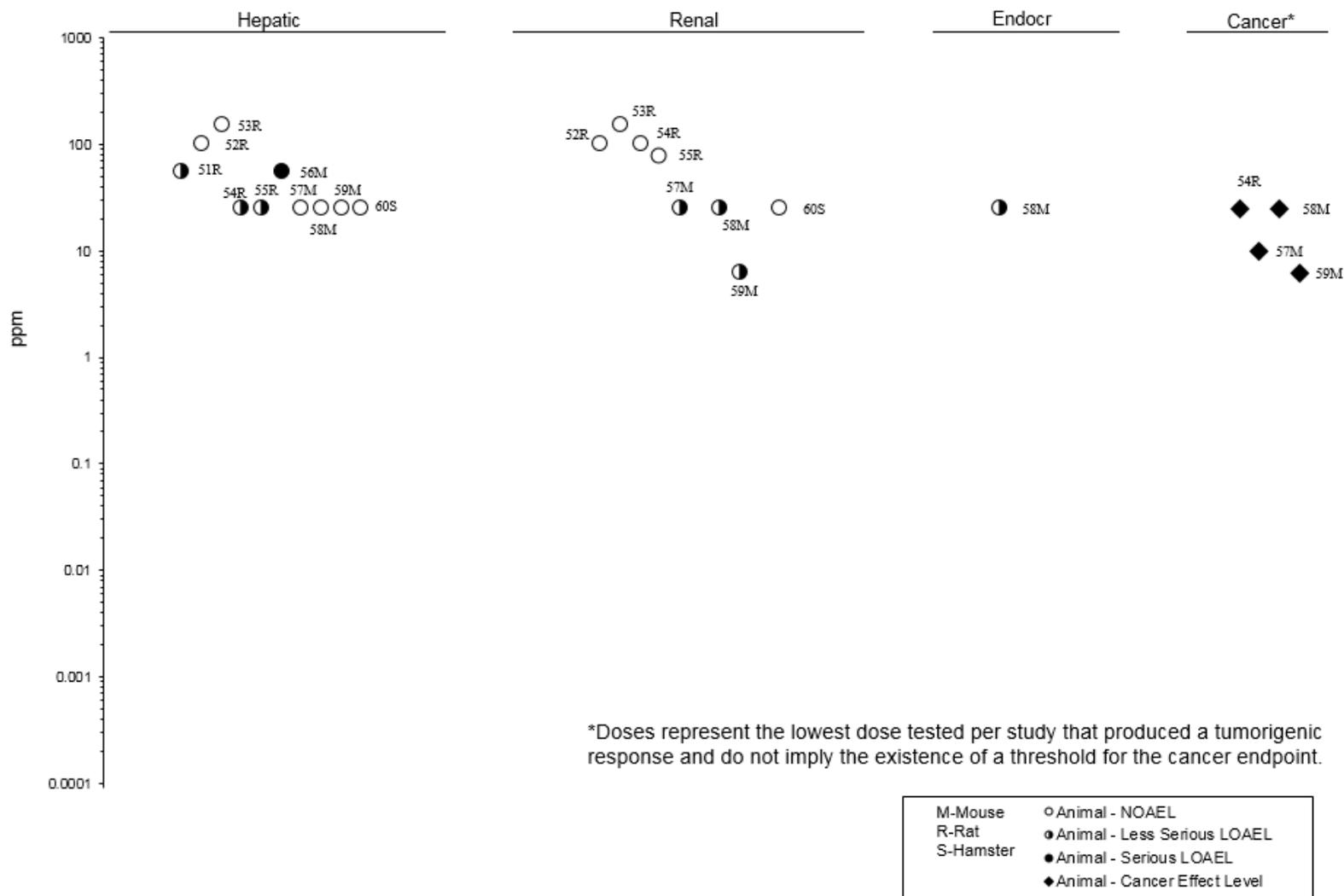
2. HEALTH EFFECTS

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



2. HEALTH EFFECTS

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



2. HEALTH EFFECTS

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

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

2. HEALTH EFFECTS

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

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

2. HEALTH EFFECTS

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

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

2. HEALTH EFFECTS

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

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

2. HEALTH EFFECTS

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

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

2. HEALTH EFFECTS

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

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

2. HEALTH EFFECTS

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

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

NTP 1982

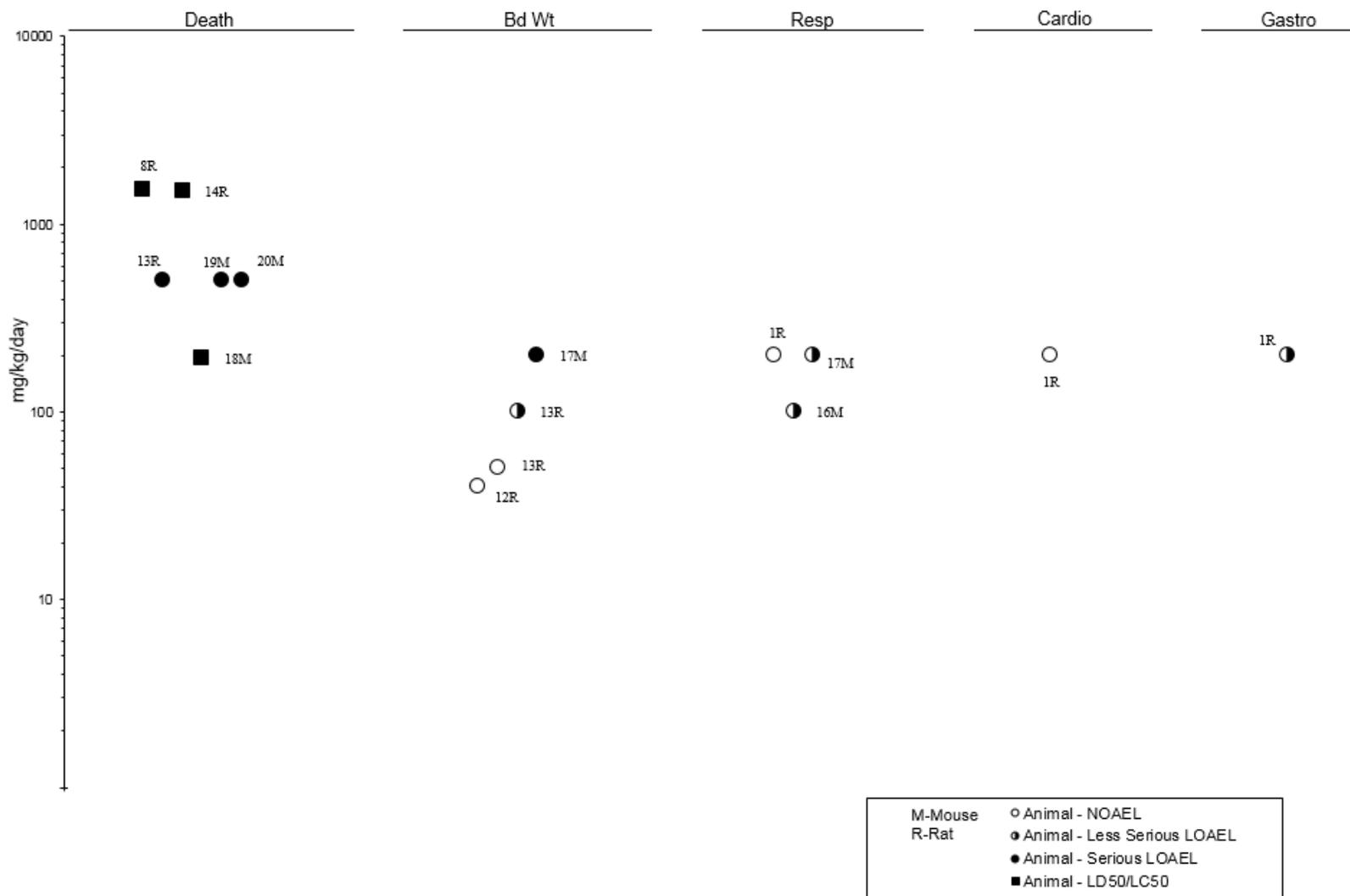
^aThe number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

^bUsed to derive a provisional chronic-duration oral minimal risk level (MRL) of 0.05 mg/kg/day for 1,1-dichloroethene; based on results from benchmark dose analysis (BMDL₁₀ values of 4.61 mg/kg/day for hepatic midzonal fatty change and 4.89 mg/kg/day for hepatocellular hypertrophy) and an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability); see Appendix A for more detailed information regarding the provisional MRL.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BC = serum (blood) chemistry; Bd wt or BW = body weight; BI = biochemical changes; Cardio = cardiovascular; CS = clinical signs; Develop = developmental; EA = enzyme activity; F = female(s); FI = food intake; FX = fetal toxicity; Gastro = gastrointestinal; GD = gestation day(s); GN = gross necropsy; GO = gavage in oil; Hemato = hematological; HP = histopathology; LD₅₀ = lethal dose, 50% kill; LDH = lactate dehydrogenase; LE = lethality; min = minute(s); LOAEL = lowest-observed-adverse-effect level; M = male(s); MX = maternal toxicity; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OW = organ weight; Repro = reproductive; Resp = respiratory; W = drinking water; WI = water intake

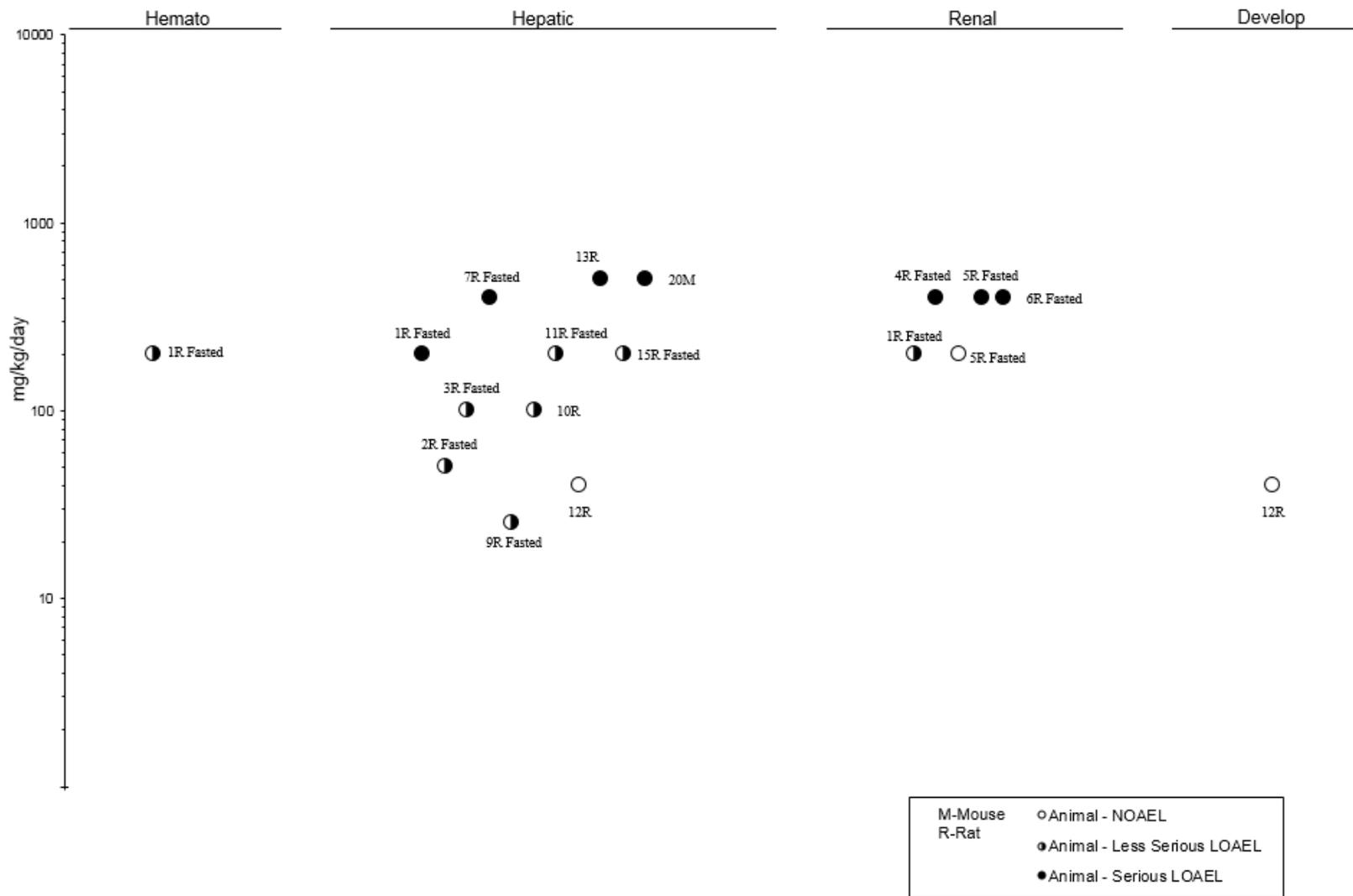
2. HEALTH EFFECTS

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



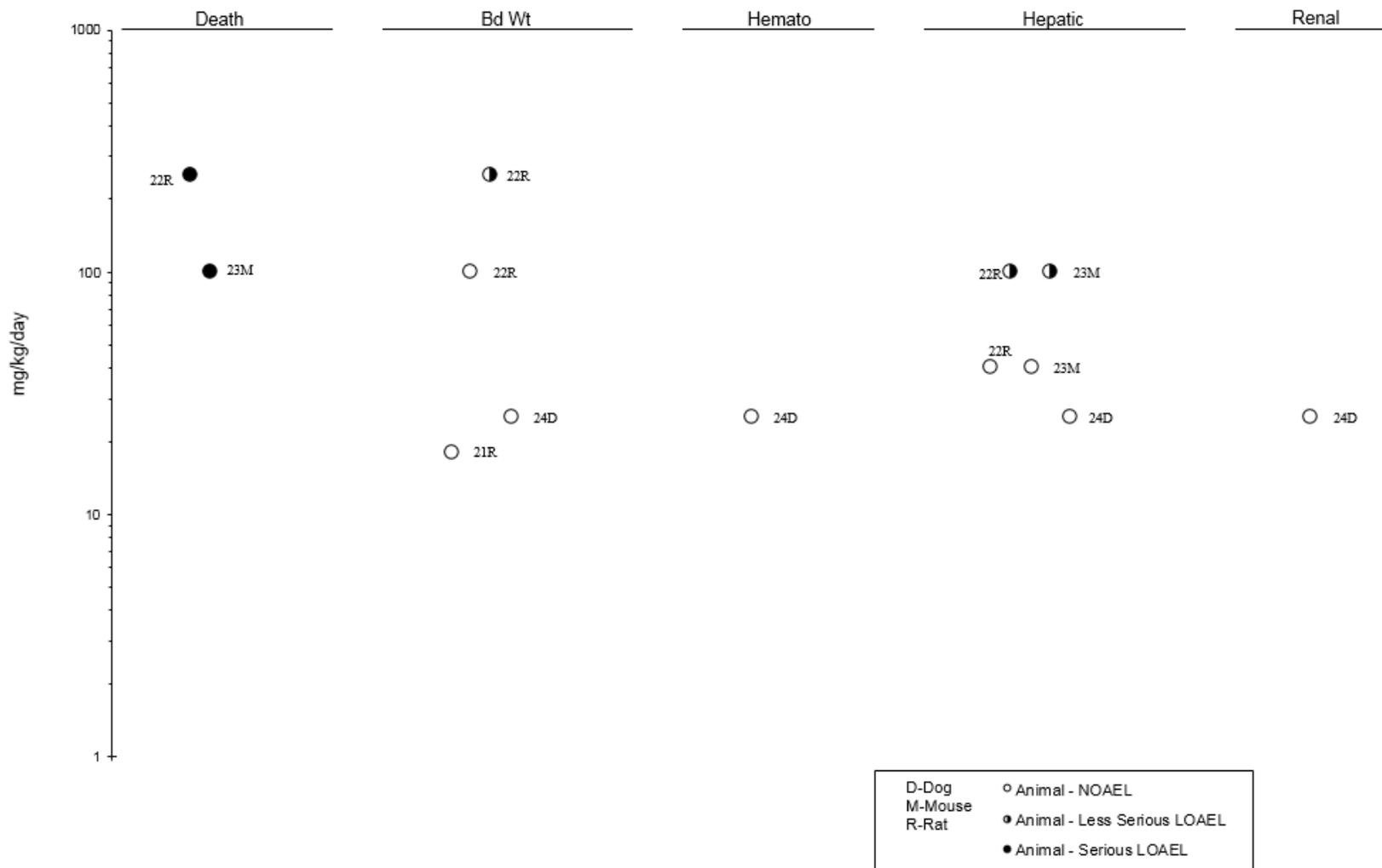
2. HEALTH EFFECTS

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



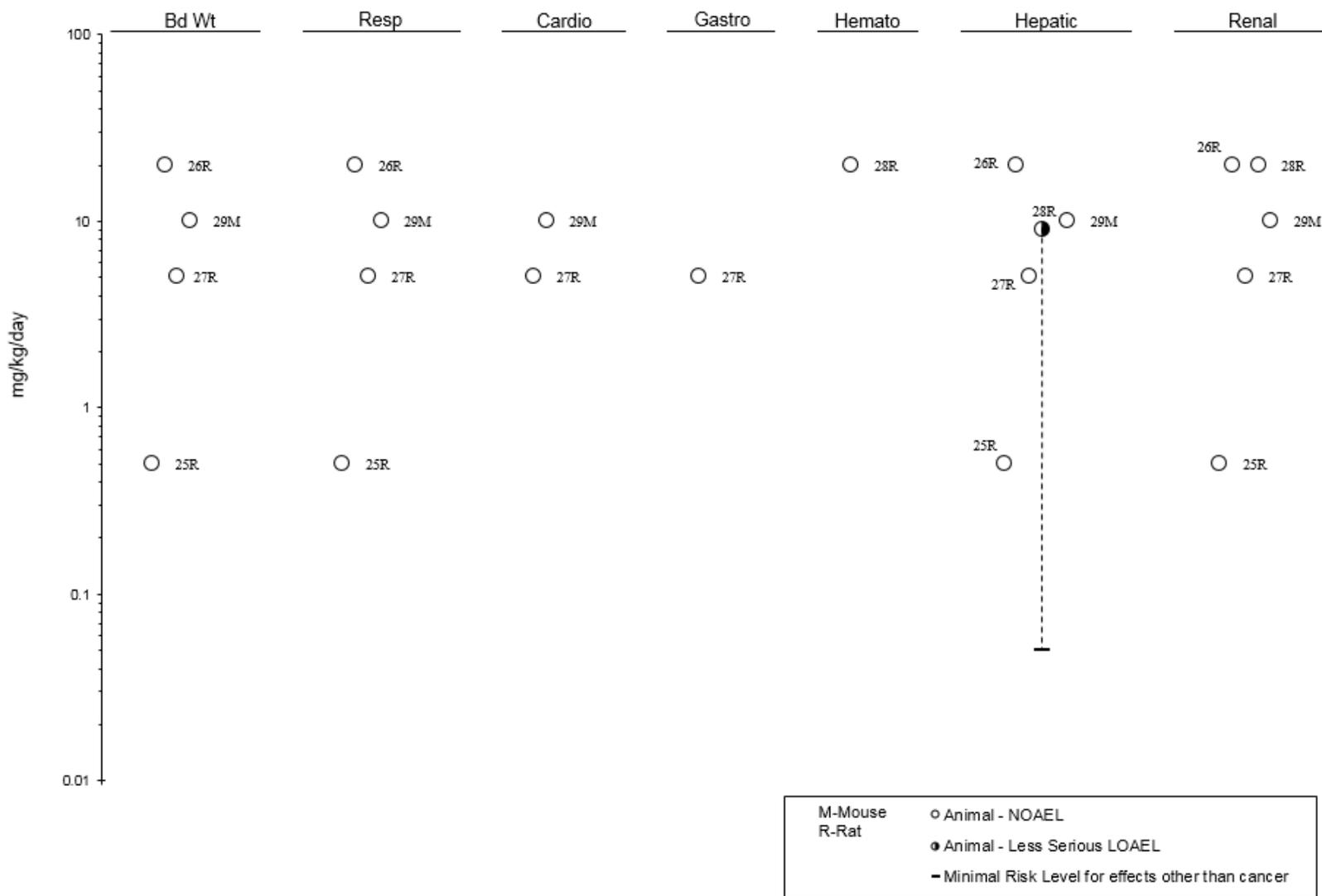
2. HEALTH EFFECTS

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



2. HEALTH EFFECTS

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



2. HEALTH EFFECTS

2.2 DEATH

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

The lethality of 1,1-dichloroethene in animals following inhalation exposure varies considerably and is influenced by such factors as species, strain, sex, and food intake. LC₅₀ values for laboratory animals acutely exposed to 1,1-dichloroethene vapor are presented in Table 2-3. Fasted laboratory animals were much more susceptible to the lethal effects of inhaled 1,1-dichloroethene than animals maintained on normal diet, mice were more susceptible than rats, and males were more susceptible than females. Single 4-hour exposure of Sprague-Dawley rats maintained on normal diet resulted in LC₅₀ values of 7,145 ppm for males and 10,275 ppm for females (Zeller et al. 1979a); among similarly-exposed Sprague-Dawley rats fasted for 16 hours prior to exposure, 4-hour LC₅₀ values were 415 ppm for males and 6,545 ppm for females. Jaeger et al. (1974) reported respective LC₅₀ values of 15,000 and 600 ppm for nonfasted and fasted male Holtzman rats exposed to 1,1-dichloroethene vapor for 4 hours. Similar exposures of fed and fasted Chinese hamsters resulted in 4-hour LC₅₀ values of 1,915 and 2,945 ppm for fed males and females, respectively, and 150 ppm and 455 ppm for fasted males and females, respectively (Klimisch and Freisberg 1979a, 1979b). Although the effects of fasting on the acute lethality of inhaled 1,1-dichloroethene among fed and fasted mice have not been compared in a single strain, available results indicate that mice are markedly more sensitive than rats. For example, 4-hour LC₅₀ values of 98 and 105 ppm were calculated for fed male and female CD-1 mice (Short et al. 1977c, 1977d). Fasting of mice does not appear to significantly affect acute lethality, as indicated by 4-hour LC₅₀ values of 75 and 125 ppm for fasted NMRI male and female mice, respectively (Zeller et al. 1979c). The proposed mechanism by which fasting increases the toxicity of 1,1-dichloroethene is discussed in Section 2.21.

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

2. HEALTH EFFECTS

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

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

^aDeaths occurred in rats exposed during a period of low glutathione (GSH) activity.

^bNo deaths in female mice similarly exposed for 3 or 8 days.

^cNo deaths in similarly-exposed female Swiss, Balb/c, or C57Bl mice.

F = female(s); GD = gestation day; LC₅₀ = lethal concentration, 50% kill; M = male(s)

2. HEALTH EFFECTS

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

Reported single-dose oral LD₅₀ values were 1,800 and 1,500 mg/kg in male and female rats, respectively (Ponomarkov and Tomatis 1980), and 217 and 194 mg/kg in male and female mice, respectively (Jones and Hathaway 1978a). In repeated-dose studies of rats and mice, high rates of mortality were observed at doses ≥ 500 mg/kg/day (rats) and ≥ 250 mg/kg/day (mice) (NTP 1982).

2.3 BODY WEIGHT

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

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

2. HEALTH EFFECTS

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

2.4 RESPIRATORY

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

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

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

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

2. HEALTH EFFECTS

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

2.5 CARDIOVASCULAR

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

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

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

2.6 GASTROINTESTINAL

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

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

2. HEALTH EFFECTS

2.7 HEMATOLOGICAL

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

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

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

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

2.8 MUSCULOSKELETAL

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

2. HEALTH EFFECTS

2.9 HEPATIC

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

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

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

2. HEALTH EFFECTS

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

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

1,1-Dichloroethene exposure-related hepatic effects such as cytoplasmic alterations, fatty changes, and/or focal necrosis were reported in other intermediate- and chronic-duration inhalation studies of laboratory animals exposed at 25–75 ppm (Balmer et al. 1976; Lee et al. 1977, 1978; Plummer et al. 1990; Prendergast et al. 1967; Quast et al. 1986).

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

2. HEALTH EFFECTS

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

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

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

2.10 RENAL

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

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

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

2. HEALTH EFFECTS

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

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

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

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

2. HEALTH EFFECTS

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

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

2.11 DERMAL

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

2.12 OCULAR

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

2.13 ENDOCRINE

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

2. HEALTH EFFECTS

2.14 IMMUNOLOGICAL

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

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

2.15 NEUROLOGICAL

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

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

2. HEALTH EFFECTS

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

2.16 REPRODUCTIVE

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

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

2.17 DEVELOPMENTAL

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

2. HEALTH EFFECTS

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

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

In a series of studies that employed gestational exposure of laboratory animals to 1,1-dichloroethene vapor for up to 23 hours/day (Short et al. 1977a, 1977b), most developmental effects (skeletal anomalies, soft tissue anomalies, decreased pup weight, fetal resorptions) occurred at exposure levels that induced maternal toxicity (e.g., decreased maternal body weight, death). However, increased incidences of unossified incus and incompletely ossified sternbrae were observed in fetuses from maternal mice exposed to 1,1-dichloroethene vapor at 15 ppm (a nonmaternally toxic exposure level) for up to 23 hours/day (Short et al. 1977a). No evidence of exposure-related developmental neurotoxicity was observed among surviving pups subjected to a battery of behavioral tasks when tested at various lactational days (postnatal days 1–21) following gestational exposure via their mothers exposed to 1,1-dichloroethene vapor at concentrations as high as 283 ppm during gestation (Short 1977a).

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

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

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

2. HEALTH EFFECTS

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

2.18 OTHER NONCANCER

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

2.19 CANCER

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

2. HEALTH EFFECTS

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

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

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

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

2. HEALTH EFFECTS

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

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

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

2. HEALTH EFFECTS

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

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

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

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

2. HEALTH EFFECTS

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

2.20 GENOTOXICITY

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

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

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

2. HEALTH EFFECTS

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

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

2. HEALTH EFFECTS

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

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

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

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

1,1-Dichloroethene has also been tested in several *in vivo* studies in animals; results are summarized in Table 2-5. In general, 1,1-dichloroethene did not demonstrate genotoxicity in mammalian studies *in vivo*. 1,1-Dichloroethene did not induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* exposed by feeding or injection (Foureman et al. 1994; also reported in NTP 2015a). 1,1-Dichloroethene did not induce chromosomal aberrations in rats intermittently exposed by inhalation at up to 75 ppm for up to 2 years (Rampy et al. 1977). 1,1-Dichloroethene did not induce micronuclei in bone marrow of mice following gavage administration or in fetal liver or blood following intraperitoneal administration to pregnant mice (Sawada et al. 1987). 1,1-Dichloroethene inhalation was associated with low rates of DNA alkylation in the livers and kidneys of mice and rats (Reitz et al. 1980). DNA repair mechanisms were induced in the kidney cells of mice in which normal replicative DNA synthesis had been inhibited, but apparently not in mouse liver nor kidneys or liver of rats (Reitz et al. 1980). Negative

2. HEALTH EFFECTS

results were reported in assays for dominant lethal mutations in mice (Andersen et al. 1977) and rats (Short et al. 1977b). In a mouse host-mediated assay system, 1,1-dichloroethene induced gene mutation and gene conversion in yeast (Bronzetti et al. 1981).

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

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

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

2.21 MECHANISMS OF ACTION

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

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

2. HEALTH EFFECTS

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

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

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

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

Possible mechanisms responsible for increased susceptibility to 1,1-dichloroethene toxicity in fasted animals have been studied. Jaeger et al. (1973a) demonstrated that fasted rats exhibited depleted hepatic

2. HEALTH EFFECTS

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

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

3.1 TOXICOKINETICS

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

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

3.1.1 Absorption

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

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

3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

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

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

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

3.1.2 Distribution

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

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

3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

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

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

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

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

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

3.1.3 Metabolism

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

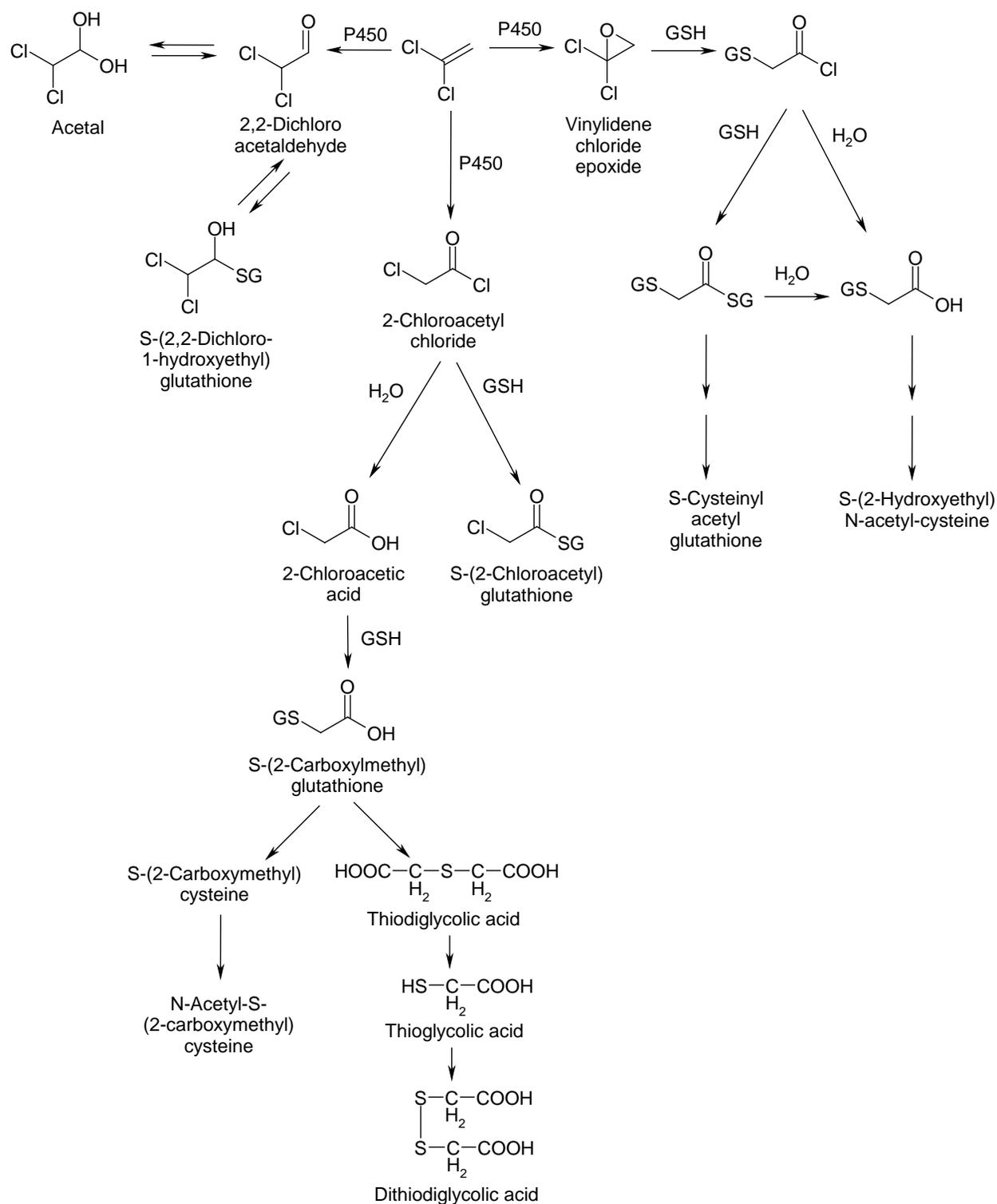
3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

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

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

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

3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

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

Source: NTP 2015a

3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

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

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

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

3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

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

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

3.1.4 Excretion

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

Following inhalation exposure of rats to low levels of 1,1-dichloroethene elimination is rapid, mostly as metabolites in the urine, and very little (1% of the administered dose) eliminated as the unchanged parent compound in the expired air (McKenna et al. 1973). After exposure to low levels (25–150 ppm) of 1,1-dichloroethene, steady-state levels of 1,1-dichloroethene in the expired air are achieved within 30–45 minutes, indicating that elimination is first-order at low levels of exposure (Dallas et al. 1983). Steady-state levels of 1,1-dichloroethene in expired air are never reached when exposure levels approach 200–300 ppm because metabolic processes are saturated. When metabolic processes become saturated,

3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

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

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

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

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

3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

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

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

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

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

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

3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

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

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

3.1.6 Animal-to-Human Extrapolations

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

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

3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

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

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

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

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

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

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

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

3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

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

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

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

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

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

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

3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to 1,1-dichloroethene are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see <http://www.cdc.gov/exposurereport/>). If available, biomonitoring data for 1,1-dichloroethene from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by 1,1-dichloroethene are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

No human data are available regarding biomarkers of exposure to 1,1-dichloroethene. Toxicokinetic studies in animals have identified 1,1-dichloroethene and a number of 1,1-dichloroethene metabolites in blood and urine and parent compound in expired air (see Section 3.1.3). The most reliable biomarker of exposure is parent compound in the blood, urine, or expired air; levels measured in these media might be useful to estimate levels of recent exposure to 1,1-dichloroethene. However, 1,1-dichloroethene

3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

metabolites are less reliable biomarkers because they are rapidly eliminated from the body; furthermore, some of them may be formed following exposure to other chlorinated substances as well.

3.3.2 Biomarkers of Effect

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

3.4 INTERACTIONS WITH OTHER CHEMICALS

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

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

3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

reduce the activity of metabolic enzymes and show some protective effects against the toxicity of 1,1-dichloroethene include pyrazole, 3-aminotriazol (Andersen et al. 1978).

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

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

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

Thyroidectomy protected rats from the hepatotoxic effects of 1,1-dichloroethene, probably by increasing the amount of hepatic GSH (Szabo et al. 1977). Thyroxine replacement in thyroidectomized rats exacerbated the liver damage seen upon subsequent exposure to 1,1-dichloroethene (Szabo et al. 1977).

Pretreatment of animals with compounds that deplete GSH levels (such as buthionine sulfoximine) increases the amount of liver damage caused by 1,1-dichloroethene exposure (Reichert et al. 1978). Conversely, pretreatment of animals with supplements containing high concentrations of the amino acids

3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

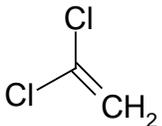
cysteine and/or methionine, both of which are metabolic contributors of the sulfhydryl group required for GSH biosynthesis, had a protective effect against the toxicity of 1,1-dichloroethene (Short et al. 1977d).

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

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

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

Characteristic	Information	Reference
Chemical name	1,1-Dichloroethene	ChemIDplus 2018
Synonym(s) and registered trade name(s)	1,1-DCE; 1,1-dichloroethylene; asym-dichloroethylene; VDC; vinylidene chloride; vinylidene chloride (II); vinylidene dichloride; vinylidine chloride	ChemIDplus 2018; EPA 2017a; NIOSH 2016
Chemical formula	C ₂ H ₂ Cl ₂	EPA 2017a
Chemical structure		ChemIDplus 2018
CAS Registry Number	75-35-4	EPA 2017a

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

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

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

4. CHEMICAL AND PHYSICAL INFORMATION

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

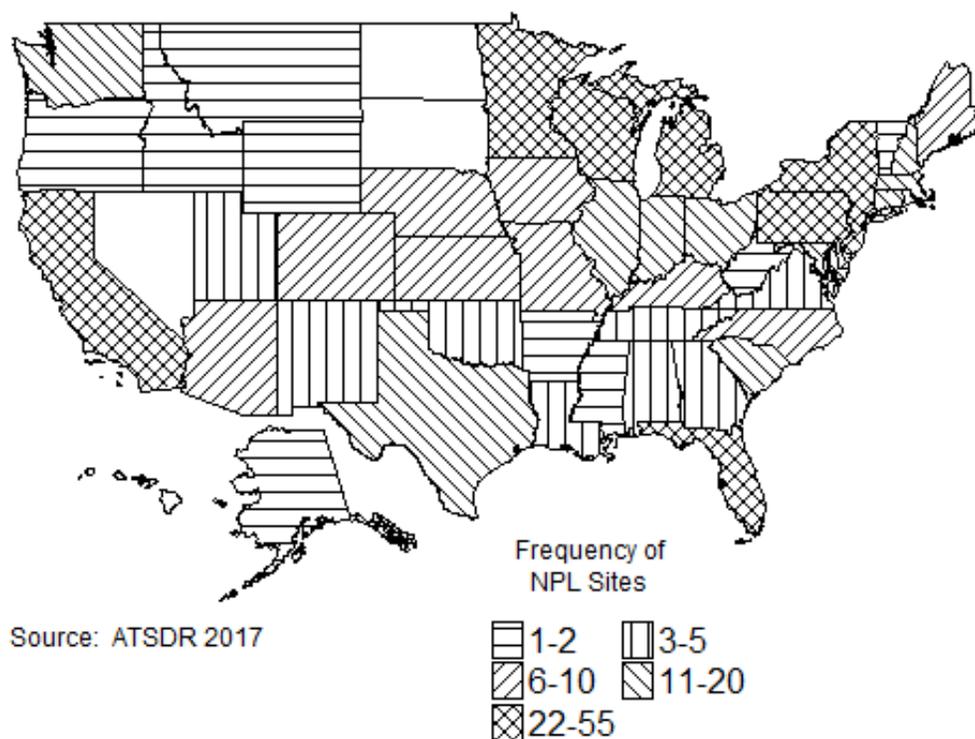
Property	Information	Reference
Molecular weight	96.94	EPA 2017a
Color	Colorless	Larranaga et al. 2016
Physical state	Liquid	Haynes 2014
Melting point	-122.5°C	Haynes 2014
Boiling point	31.7°C at 760 mmHg	O'Neil et al. 2013
Density at 20°C	1.213 g/cm ³	Haynes 2014
Odor	Mild sweet odor resembling that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

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

1,1-Dichloroethene has been identified in at least 610 of the 1,854 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2017). However, the number of sites in which 1,1-dichloroethene has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 608 are located within the United States and 2 are located in Puerto Rico (not shown).

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



- The potential for human exposure to 1,1-dichloroethene is greatest for individuals at its point of production, formulation, or transport. Occupational exposure to 1,1-dichloroethene may occur by inhalation and dermal contact. Workers involved in cleaning up hazardous waste or spill sites that contain 1,1-dichloroethene may potentially be exposed to this chemical.
- The general population may be exposed to 1,1-dichloroethene by inhalation of ambient air and ingestion of drinking water contaminated with this chemical. Those who live near hazardous waste sites contaminated with 1,1-dichloroethene, especially those who receive

5. POTENTIAL FOR HUMAN EXPOSURE

their drinking water from underground sources, may potentially be exposed to 1,1-dichloroethene, the levels of which will vary by location. Quantitative data that address levels of human exposure to 1,1-dichloroethene are limited.

- 1,1-Dichloroethene has been detected in air, surface water, groundwater, and soil, with the frequency of detection and the concentrations greatest near source areas (e.g., industrial areas, landfills, hazardous wastes sites).
- The primary sources of 1,1-dichloroethene in the environment are related to its synthesis, fabrication, and transport, and the manufacture of its polymer products. Smaller amounts of 1,1-dichloroethene may be released to surface water and soil primarily due to waste disposals. Most 1,1-dichloroethene in the environment evaporates quickly and enters the air. 1,1-Dichloroethene can enter soil, water, and air in large amounts during an accidental spill. It can also enter the environment as a degradation product of other chemicals in the environment.
- In the air, 1,1-dichloroethene undergoes rapid degradation with photochemically-produced hydroxyl radicals. 1,1-Dichloroethene has calculated atmospheric half-lives of 2–3 days. 1,1-Dichloroethene breaks down very slowly in water and the majority of this chemical will evaporate into air. 1,1-Dichloroethene is not readily transferred to fish or birds and only very small amounts enter the food chain. In soil, 1,1-dichloroethene either evaporates to the air or percolates down through soil with rainwater and enters groundwater. Small living organisms in soil and groundwater may transform it into other less harmful substances, although this is a slow process.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

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

5. POTENTIAL FOR HUMAN EXPOSURE

1,1-Dichloroethene is manufactured in chemical plants located in Texas and Louisiana. Two producers listed in the United States are Dow Chemical and Pittsburgh Paint and Glass (PPG) Industries (SRI 2011). In 1978, plant capacity at PPG Industries was estimated at 78 million pounds/year (EPA 1985a). Production capacity in 1985 was reported as 178 million pounds/year (EPA 1985a). This decreased from 1977, when production capacity was estimated at 270 million pounds (EPA 1977). Up-to-date data for the United States can be found using the Chemical Data Reporting (CDR) website, which reports information on the production and use of chemicals manufactured, imported, and exported. The CDR (EPA 2017d) lists two domestic manufacturers of 1,1-dichloroethene for 2016, Owensboro Specialty Polymers Inc. in Owensboro, Kentucky, using 1,1-dichloroethene as a reactant in the manufacture of adhesives and sealant chemicals, production volume withheld; and Olin Corporation's plant in Freeport, Texas, using 1,1-dichloroethene as a reactant in the manufacture of plastic material and resins; the volume used in site in 2016 was 9,088,728 pounds (EPA 2017d). The CDR lists two companies for 2012: The Dow Chemical Company's site in Freeport, Texas (manufacturing information is listed as confidential business information [CBI]) and Shin Etsu's Shintech Plaquemine Plant in Plaquemine, Louisiana, with a total production volume of approximately 108,000 pounds in 2011 and 63,000 pounds in 2010 (EPA 2014). National aggregate production volumes since 2011 have been withheld.

According to the Toxics Release Inventory (TRI), 26 facilities manufactured or processed 1,1-dichloroethene in 2015 (TRI15 2016). These data are listed in Table 5-1. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

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

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
GA	1	100,000	999,999	6
IL	1	1,000	9,999	12
KY	3	100	999,999	1, 3, 6
LA	8	0	999,999	1, 4, 5, 6, 12, 13
MI	1	1,000,000	9,999,999	1, 5, 6, 12, 14
MO	1	1,000	9,999	12
NC	1	100,000	999,999	6
NJ	1	100,000	999,999	6, 14
NV	1	10,000	99,999	12
OH	2	1,000	99,999	12

5. POTENTIAL FOR HUMAN EXPOSURE

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

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
TX	5	100	9,999,999	1, 2, 4, 5, 6, 12, 13, 14
WI	1	Not reported	Not reported	Not reported

^aPost office state abbreviations used.

^bAmounts on site reported by facilities in each state.

^cActivities/Uses:

- | | | |
|----------------------|-----------------------------|--------------------------|
| 1. Produce | 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: TRI15 2016 (Data are from 2015)

5.2.2 Import/Export

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

5.2.3 Use

1,1-Dichloroethene is used as a reactant for organic chemical synthesis, in the production of polyvinylidene chloride copolymers and sparingly as a chlorinated solvent (CDR 2018; Larranaga et al. 2016; O'Neil et al. 2013). Because of the instability of the polymer, 1,1-dichloroethene is usually used as a copolymer with acrylonitrile, vinyl chloride, methacrylonitrile, and methacrylate (Grayson 1985; Rossberg et al. 1986). 1,1-Dichloroethene can be copolymerized with vinyl chloride or acrylonitrile to produce flexible films for food packaging such as Saran™ plastic wrap and VELON wrap (vinyl taffeta), the major applications of polyvinylidene chloride copolymers (EPA 1977; Larranaga et al. 2016). These polymers, which have been commercially important since their introduction in the early 1940s, are used extensively in many types of flexible packing materials (including barrier, multilayer, and monolayer), as flame retardant coatings for fiber and carpet backing, and in piping, coating for steel pipes, and adhesive applications (EPA 1977). 1,1-Dichloroethene is found in many food and other packaging materials. At one time, Saran™ plastic wrap was found to contain up to 30 ppm 1,1-dichloroethene (Birkel et al. 1977). The plastic packaging films can contain no more than 10 ppm 1,1-dichloroethene (FDA 1988). If 1,1-dichloroethene is employed as an unavoidable solvent in the production of pharmaceuticals, the U.S.

5. POTENTIAL FOR HUMAN EXPOSURE

Food and Drug Administration (FDA) has set a concentration limit of 8 ppm in the final product (FDA 2018a).

5.2.4 Disposal

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

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥ 10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes $\geq 25,000$ pounds of any TRI chemical or otherwise uses $>10,000$ pounds of a TRI chemical in a calendar year (EPA 2005).

5. POTENTIAL FOR HUMAN EXPOSURE

5.3.1 Air

Estimated releases of 21,329 pounds (~9.67 metric tons) of 1,1-dichloroethene to the atmosphere from 26 domestic manufacturing and processing facilities in 2015, accounted for about 59% of the estimated total environmental releases from facilities required to report to the TRI (TRI15 2016). These releases are summarized in Table 5-2.

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

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

5. POTENTIAL FOR HUMAN EXPOSURE

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use 1,1-Dichloroethene^a

State ^c	RF ^d	Reported amounts released in pounds per year ^b							
		Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	Total release		
							On-site ^j	Off-site ^k	On- and off-site
GA	1	122	0	0	0	No data	122	No data	122
IL	1	1	0	0	2	No data	1	2	3
KY	3	6,617	0	0	21	No data	6,617	21	6,638
LA	8	5,761	0	0	1	0	5,761	1	5,762
MI	1	2,210	24	0	3	No data	2,234	3	2,237
MO	1	10	0	0	0	134	10	134	144
NC	1	2	0	0	0	No data	2	No data	2
NJ	1	93	1	0	0	No data	94	No data	94
NV	1	2	0	0	14,574	No data	14,576	No data	14,576
OH	2	5	0	0	0	No data	5	0	5
TX	5	6,507	2	0	2	No data	6,511	No data	6,511
WI	1	0	No data	No data	No data	No data	No data	No data	No data
Total	26	21,329	27	0	14,603	134	35,932	161	36,093

^aThe 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.

^bData in TRI are maximum amounts released by each facility.

^cPost office state abbreviations are used.

^dNumber of reporting facilities.

^eThe sum of fugitive and point source releases are included in releases to air by a given facility.

^fSurface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).

^gClass I wells, Class II-V wells, and underground injection.

^hResource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.

ⁱStorage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.

^jThe sum of all releases of the chemical to air, land, water, and underground injection wells.

^kTotal amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI15 2016 (Data are from 2015)

5.3.2 Water

Estimated releases of 27 pounds (~0.01 metric tons) of 1,1-dichloroethene to surface water from 26 domestic manufacturing and processing facilities in 2015, accounted for <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI15 2016). These releases are summarized in Table 5-2.

5. POTENTIAL FOR HUMAN EXPOSURE

Industrial releases of 1,1-dichloroethene to surface water contribute to the overall environmental loading of the chemical, but to a much lesser extent than atmospheric emissions. Liquid effluents produced during polymerization operations were estimated to contribute ≈ 2 tons of waste 1,1-dichloroethene each year (Neufeld et al. 1977). Other potential industrial sources of waste 1,1-dichloroethene in surface water are metal finishing and nonferrous metals manufacturing industries, soap and detergent manufacturers, electric coil coating and battery manufacturers, coal mines, laundries, and industries involving paint and ink formulation. 1,1-Dichloroethene has been measured in raw waste water from these industries at mean concentrations of 3–760 $\mu\text{g/L}$ (EPA 1981).

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

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

5.3.3 Soil

Estimated releases of 14,603 million pounds (~ 6.62 metric tons) of 1,1-dichloroethene to soils from 26 domestic manufacturing and processing facilities in 2015, accounted for about 40% of the estimated total environmental releases from facilities required to report to the TRI (TRI15 2016). These releases are summarized in Table 5-2.

5. POTENTIAL FOR HUMAN EXPOSURE

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

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

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

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

Water. The dominant removal process for 1,1-dichloroethene from surface waters is expected to be volatilization. As the magnitude of the Henry's law constant for 1,1-dichloroethene, 2.61×10^{-2} atm-m³/mole at 24°C (Gossett 1987) indicates, 1,1-dichloroethene is likely to volatilize rapidly into the atmosphere from water. Because of this, 1,1-dichloroethene is generally not found in surface water in high concentrations. Based on its Henry's Law constant, the volatilization half-life in a model lake 1 m deep with a 0.05 m/second current and a 0.5 m/second wind is estimated to be 3.9 days; the volatilization half-life of 1,1-dichloroethene in a model river 1 m deep flowing 1 m/second with a wind speed of 3 m/second is estimated to be 1 hour (EPA 2012).

5. POTENTIAL FOR HUMAN EXPOSURE

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

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

5.4.2 Transformation and Degradation

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

Air. Atmospheric degradation of 1,1-dichloroethene is expected to be dominated by gas-phase oxidation with photochemically produced hydroxyl radicals. An experimental rate constant for this process of 1.09×10^{-11} cm³/molecule-second at 25°C has been determined (Kwok and Atkinson 1995). Based on a 12-hour day of sunlight, using an average atmospheric hydroxyl radical concentration of 5×10^5 molecule/cm³, a half-life of 1.5 days can be calculated for this process. A higher atmospheric concentration of hydroxyl radicals (5×10^6 molecules/cm³) will reduce the half-life of 1,1-dichloroethene from 1.5 days to 3.5 hours (Grosjean 1990). The products expected from this reaction are phosgene, formaldehyde, and chloroacetyl chloride (Tuazon et al. 1988). Pearson and McConnell (1975) reported a tropospheric half-life for 1,1-dichloroethene of 8 weeks, resulting from an experiment with limitations such as non-ideal air characteristics and $\pm 50\%$ reproducibility due to climate parameters noted.

5. POTENTIAL FOR HUMAN EXPOSURE

Atmospheric degradation of 1,1-dichloroethene may also occur by a gas-phase reaction with other atmospheric oxidants, namely ozone and nitrate radicals, although these processes are slower than the reaction of 1,1-dichloroethene with hydroxyl radicals (Grosjean 1990). An experimental rate constant for the gas-phase reaction of ozone with 1,1-dichloroethene of 3.7×10^{-21} cm³/molecule-second at 25°C (Atkinson and Carter 1984) translates to an atmospheric half-life of >8 years for this process using an average atmospheric ozone concentration of 7×10^{11} molecule/cm³. Nitrate radicals are destroyed by sunlight, and the oxidation of organic compounds by this oxidant is only important at night. The rate constant for the oxidation of 1,1-dichloroethene by nitrate radicals, 1.78×10^{-15} cm³/molecule-second at 25°C (Sabljić and Gusten 1990), translates to a half-life of 19 days in a moderately polluted atmosphere, although at nitrate concentrations of 50 ppt the half-life may be reduced to 6 days (Grosjean 1990). Using Fourier transform infrared spectroscopy (FTIR) spectrometry, 1,1-dichloroethene reaction with hydroxyl radicals and nitrates was observed; reaction products of 1,1-dichloroethene with hydroxyl radicals and nitrates in air include chloroacetyl chloride, phosgene, formaldehyde, carbon monoxide, and nitric acid; a hydroxyl radical reaction rate constant of 12×10^{-12} cm³/molecule-second was calculated corresponding to an atmospheric half-life of approximately 16 hours (EPA 1983a). Lacking chromophores that absorb radiation at wavelengths >290 nm, direct vapor phase photolysis is not expected to be an important fate process for 1,1-dichloroethene (Lyman et al. 1982).

Water. Photolysis and hydrolysis of 1,1-dichloroethene in natural aquatic media are not significant environmental fate processes (EPA 1982). The estimated half-life for the hydrolysis of 1,1-dichloroethene at 25°C under neutral (or slightly basic) conditions is 1.2×10^8 years (Jeffers et al. 1989). Estimated hydrolysis half-lives of 6–9 months at pH values ranging from 4.5 to 8.5 have also been reported (Cline and Delfino 1987). Conflicting results have been obtained for the aerobic biotransformation of 1,1-dichloroethene. Biotransformation under anaerobic conditions is likely the dominant transformation process for 1,1-dichloroethene in groundwater; however, complete mineralization has not been confirmed. 1,1-Dichloroethene and its transformation products have been postulated as toxic to microbial populations. Transformation capacities were measured for chlorinated hydrocarbons using two mixed and two pure methane-oxidizing cultures; 1,1-dichloroethene exhibited the greatest toxicity with mean transformation values of 0.11, 0.25, 0.39, and 0.36 µmol/mg being an order of magnitude lower than other similar chlorinated hydrocarbons (Chang and Alvarez 1996). Oxidation of 1,1-dichloroethene by methane and aromatic monooxygenases has been demonstrated with removal rates greater than 95% in 24 hours (Chauhan et al. 1998; Dolan and McCarty 1995). In aqueous batch studies at 20°C using aquifer material from a Superfund site under aerobic conditions, 1,1-dichloroethene was not found to be toxic at concentrations up to 1 mg/L, yet its transformation products were highly toxic;

5. POTENTIAL FOR HUMAN EXPOSURE

biotransformation of 1,1-dichloroethene as a result of methyl monooxygenase activity was apparent, but ceased after the first few hours of incubation with the mixed methanotrophic culture in the presence and absence of formate with transformation rates of 0.063 and 0.045 μmol 1,1-dichloroethene/mg of total suspended solids, respectively (Dolan and McCarty 1995). Pearson and McConnel (1975) found no evidence for biotransformation of 1,1-dichloroethene under aerobic conditions in water. Additionally, 0% biodegradation was observed after 28 days in an aerobic closed bottle test using an activated sludge inoculum (OECD 301D) (CITI1992). In contrast, aerobic degradation may occur under certain conditions; Tabak et al. (1981) reported transformation of 54% of 5 mg/L and 30% of 10 mg/L test concentrations of 1,1-dichloroethene under aerobic conditions within 1 week after incubation with a domestic waste water seed; these removal figures were adjusted to account for volatilization losses from control flasks of 24% for the 5 mg/L and 15% for the 10 mg/L test concentrations. Under anaerobic conditions, Ensign et al. (1992) observed that 1,1-dichloroethene was not degraded efficiently by propylene-grown *Xanthobacter* cells (strain Py2); the environmental media was not reported. However, Wilson et al. (1986) studied the behavior of 1,1-dichloroethene in authentic aquifer material known to support methanogenesis. The disappearance of 1,1-dichloroethene was observed with an initial 16-day lag phase and vinyl chloride, the major degradation product, was found in trace amounts. Baek et al. (1990) observed the biodegradation and formation of vinyl chloride under anaerobic conditions when 1,1-dichloroethene was incubated with digested sludge under both fermentative and methanogenic conditions. In an anaerobic continuous-flow column study evaluating the reductive dechlorination of perchloroethylene, reduction of 1,1-dichloroethene also led to vinyl chloride (Vogel McCarty 1985). It is important to note that vinyl chloride has been classified as a possible human carcinogen by EPA (EPA 1985a); ATSDR has produced a toxicological profile on this compound, including an addendum to the profile (ATSDR 2006, 2016).

Sediment and Soil. In studies simulating anaerobic conditions in groundwater and landfills, vinyl chloride was produced from the reductive dechlorination of 1,1-dichloroethene by microorganisms in anoxic sediment microcosms after 1–3 weeks of incubation (Barrio-Lage et al. 1986; Hallen et al. 1986); reported first-order rate constants for the depletion of 1,1-dichloroethene in anoxic sediments were 3.57×10^{-4} and 1.67×10^{-4} hours^{-1} corresponding to half-lives of 81 and 173 days, respectively (Barrio-Lage et al. 1986). A methane-utilizing culture isolated from lake sediment degraded 600 ng/mL 1,1-dichloroethene to 200 ng/mL under aerobic conditions within 2 days; the degradation products were nonvolatile and did not include vinyl chloride, which is known to be formed under anaerobic conditions (Fogel et al. 1986). Under aerobic conditions in soil microcosms with aquifer material, no measurable

5. POTENTIAL FOR HUMAN EXPOSURE

biotransformation of 1,1-dichloroethene was observed and any loss was attributed to sorption (Dolan and McCarty 1995).

5.5 LEVELS IN THE ENVIRONMENT

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

Concentrations of 1,1-dichloroethene in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on 1,1-dichloroethene levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-3 shows the lowest limit of detections that are achieved by analytical analysis of environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-4.

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

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

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

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

5. POTENTIAL FOR HUMAN EXPOSURE

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

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

Medium	Median ^a	Geometric mean ^a	Geometric standard deviation ^a	Number of quantitative measurements	NPL sites
Water (ppb)	24	33.8	15,000	484	257
Soil (ppb)	360	279	34,800	79	57
Air (ppbv)	1.31	4.42	11,500	39	30

^aConcentrations found in ATSDR site documents from 1981 to 2017 for 1,854 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

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

The EPA TEAM (Total Exposure Assessment Measurement) studies measured 1,1-dichloroethene concentrations in 1,085 personal air samples collected from 350 New Jersey residents (discrepancy in the actual number of residents sampled) over three seasons. Only 77 (7%) of the samples had measurable concentrations of 1,1-dichloroethene and 107 (10%) of the samples had trace levels. The detection limit ranged from 3 to 14 $\mu\text{g}/\text{m}^3$ (Wallace 1991).

5.5.2 Water

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

5. POTENTIAL FOR HUMAN EXPOSURE

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

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
Palermo Wellfield Superfund Site, Washington	Ambient air monitoring sites	March and December 2017; May 19, 2016; September 2015; February and September 2014; April and October 2013	0.12–0.17 µg/m ³	Not Detected: Material analyzed for, but not detected above the method LOD	Detection/quantitation limits of the methods used: 0.12, 0.16, and 0.17 µg/m ³ ; multiple samples collected at Superfund site	WQP 2018
USGS New Mexico Water Science Center	Ambient air monitoring sites	September 2016		Not detected: material analyzed for, but not detected above the method LOD	Two samples	WQP 2018
Pennsylvania, Texas, Rhode Island, Ohio, Kentucky, Arizona, Colorado, Florida, Georgia, Illinois, Indiana, Massachusetts, Michigan, Missouri, New Jersey, New York, North Carolina, Oklahoma, Utah, Vermont, Virginia, Washington	Ambient air monitoring sites	2017		0.059 ppbv	Detected in 11 out of 124 samples; Philadelphia, Pennsylvania; Deer Park, Texas; Pawtucket, Rhode Island; Cincinnati, Ohio; Calvert, Kentucky; Laredo, Texas; Denton, Texas; Dallas, Texas	EPA 2017b

5. POTENTIAL FOR HUMAN EXPOSURE

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

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
Arizona, Colorado, Florida, Georgia, Illinois, Indiana, Iowa, Kentucky, Massachusetts, Michigan, Missouri, New Jersey, New York, North Carolina, Ohio, Oklahoma, Pennsylvania, Rhode Island, Texas, Utah, Virginia, Washington	Ambient air monitoring sites	2016		0.0013–0.056 ppbv	Detected in 12 out of 124 samples; Pawtucket, Rhode Island; Deer Park, Texas; Candor, North Carolina; Philadelphia, Pennsylvania; Raleigh, North Carolina; Davie, Florida; Fort Lauderdale, Florida; Coconut Creek, Florida; Dania, Florida	EPA 2016b
New Jersey	Ambient air	1983–1984	Maximum: 97 ppb	0.39–38.9 ppb, measured at waste sites, and an arithmetic mean concentration of 2.6 ppb measured at the sanitary landfill		Harkov et al. 1985; LaRegina et al. 1986
New Jersey	Ambient air	July–August 1981		0.35–0.38 ppb	Newark, Elizabeth, and Camden New Jersey	Harkov et al. 1987
Kanawha Valley, West Virginia; Los Angeles, California; and Houston, Texas	Ambient air	1986–1987		0.84 ppb	Detected in 24 of 79 ambient air samples	Pleil et al. 1988
U.S. cities	Ambient air	Prior to 1981	0.005–0.03 ppb			Singh et al. 1981, 1982

5. POTENTIAL FOR HUMAN EXPOSURE

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

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
Research Triangle Park, North Carolina	Indoor air	Prior to 1985		47.3 ppb (summer); 7.1 ppb (winter)	26 homes and apartments	EPA 1985a
United States	Ambient and indoor air	1988		4.6 ppb	Daily average concentration from rural, suburban, urban, and source-dominated sites	EPA 1988b
United States	Ambient and indoor air	1988	Median 0.0 ppbv (ambient and indoor)	4.612 ppbv ambient; 19.665 ppbv indoor	Daily average ambient concentration from rural, suburban, urban, and source-dominated sites (1,275 data points); daily average indoor concentration from residential, offices, and personal (2,120 data points)	EPA 1988b
Palermo Wellfield Superfund Site, Washington	Indoor air	April and October 2013; February 2014	0.16–0.17 µg/m ³	Not detected: the analyte was analyzed for, but was not detected, at a level greater than or equal to the level of the adjusted contract required quantitation limit for sample and method	Detection/quantitation limits of the methods used: 0.12 and 0.16 µg/m ³	WQP 2018

LOD = limit of detection; USGS = U.S. Geological Survey

5. POTENTIAL FOR HUMAN EXPOSURE

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

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
Grenada, Mississippi	Industrial related site	January 2016	Not detected		Not detected at or above the detection limit of 0.50 ppb	Grenada 2016
Virginia, Washington	Surface water	2016, 2017, 2018	Not detected		Material analyzed for, but not detected above the method LOD of 0.5 µg/L	WQP 2018
Virginia, Washington, Oregon	Surface water	2015	Not detected		Material analyzed for, but not detected above the method LOD of 0.600 µg/L	WQP 2018
Palermo Wellfield Superfund Site, Washington	Groundwater	February 2018	Not detected		Activity depth: 28–105 feet; material analyzed for, but not detected; LOD: 0.2–0.4 µg/L	WQP 2018
USGS Georgia Water Science Center; USGS Massachusetts Water Science Center; USGS New Jersey Water Science Center; Boomsnub/Airco Superfund Site EPA Region 10; USGS California Water Science Center; USGS Tennessee Water Science Center; USGS Idaho Water Science Center; Palermo Wellfield Superfund Site by Geengineers Inc.; State of Oregon Department of Environmental Quality; Blackfeet Nation (Montana); Minnesota Pollution Control Agency, Ambient Groundwater; USGS Pennsylvania Water Science Center; USGS Texas Water Science Center; USGS Iowa Water Science Center; USGS New Hampshire Water Science	Groundwater; Superfund Sites; USGS monitoring sites	2017	Not detected–13.8 µg/L		Activity depth: 4–1,414 feet	WQP 2018

5. POTENTIAL FOR HUMAN EXPOSURE

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

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
Center; USGS Puerto Rico Water Science Center; USGS Connecticut Water Science Center; USGS Colorado Water Science Center; USGS Utah Water Science Center; USGS Missouri Water Science Center; USGS New Mexico Water Science Center; USGS Maryland Water Science Center; USGS Oregon Water Science Center; USGS Arizona Water Science Center; USGS Illinois Water Science Center; USGS Arkansas Water Science Center; USGS New York Water Science Center						
Palermo Wellfield Superfund Site by Geoengineers Inc.; Arizona Department of Environmental Quality; Minnesota Pollution Control Agency, Ambient Groundwater; Boomsnub/Airco Superfund Site EPA Region 10; State of Oregon Department of Environmental Quality; USGS Pennsylvania Water Science Center; USGS Missouri Water Science Center; USGS Washington Water Science Center; USGS New Jersey Water Science Center; USGS Kansas Water Science Center; USGS Massachusetts Water Science Center; USGS Connecticut Water	Groundwater; Superfund sites; USGS monitoring sites	2016	Not detected–690 µg/L		Activity depth: 4–158.8 feet	WQP 2018

5. POTENTIAL FOR HUMAN EXPOSURE

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

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
Science Center; USGS Maine Water Science Center; USGS Tennessee Water Science Center; USGS Idaho Water Science Center; USGS West Virginia Water Science Center; USGS California Water Science Center; USGS Georgia Water Science Center; USGS Maryland Water Science Center; USGS New York Water Science Center; USGS South Carolina Water Science Center; USGS Texas Water Science Center; USGS New Mexico Water Science Center; USGS Oregon Water Science Center; USGS Michigan Water Science Center; USGS Minnesota Water Science Center; USGS New Hampshire Water Science Center; USGS Arkansas Water Science Center; USGS Oklahoma Water Science Center; USGS Colorado Water Science Center; USGS Nevada Water Science Center; USGS Florida Water Science Center; USGS Ohio Water Science Center; USGS Wyoming Water Science Center; USGS Wisconsin Water Science Center						
United States	Domestic well water	1985–2002	Not reported	Not reported	Detected in 19 of 1,207 water samples; 1 of 2,400 samples above the EPA MCL	Rowe et al. 2007

5. POTENTIAL FOR HUMAN EXPOSURE

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

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
South Carolina	Surface water at a VOC-contaminated site	2000–2006	<0.14–48,000 µg/L	Not reported	Solid Waste Management Unit 12, Naval Weapons Station Charleston, North Charleston, South Carolina	USGS 2006
South Carolina	Groundwater at a VOC-contaminated site	2000–2006	<0.13–<16 µg/L	Not reported	Solid Waste Management Unit 12, Naval Weapons Station Charleston, North Charleston, South Carolina	USGS 2006
United States	Domestic well water	2000–2001	Not reported	Not reported	Detected in two wells, one above the EPAs MCL	Aelion and Conte
United States	Groundwater wells	1985–1995	Not reported	Not reported	Detected in 3% of urban wells, and 0.3% of rural wells	Squillace et al. 1999
United States	Domestic well water	1982	Not reported	Median concentration of 0.3 µg/L	Detected in 9 of 466 water samples	Cotruvo 1985
United States		Prior to 1984	Maximum: 6.3 µg/L	Subset median values: 0.28–1.2 µg/L	Detected in 2.3% of 945 samples of finished drinking water taken from community-based groundwater sources in a nationwide survey; quantification limit of 0.2 ppb	Rajagopal and Li 1991; Westrick et al. 1984
United States	Finished water	Prior to 1985	0.2–0.5 µg/L (estimated mean 0.3 µg/L)	Not reported	About 3% of the drinking water supplies in the United States	EPA 1985a
United States	Urban storm water runoff	Prior to 1984	1.5–4 µg/L	Not reported	Nationwide Urban Runoff Program (NURP)	Cole et al. 1984
U.S. cities	Groundwater	Prior to 1980			Detected in 7.1% of samples	EPA 1980b
U.S. cities	Raw and finished surface water	Prior to 1980	0.2–0.51 µg/L	0.36 µg/L	Not detected in a survey of 105 raw water samples; detected in 1.9% of 103 finished water samples	EPA 1980b

5. POTENTIAL FOR HUMAN EXPOSURE

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

Location(s)	Geographic type	Date(s)	Range	Mean concentration	Notes	Reference
United States		Prior to 1985			Detected in 6% of 8,714 surface water samples monitored nationwide	Staples et al. 1985
United States	Surface waters near industrial sites	Prior to 1977	<1–550 µg/L			Going and Spigarelli 1977
United States		Prior to 1985			Detected in 3.3% of 1,350 effluent samples monitored nationwide	Staples et al. 1985
United States	Raw and treated waste waters from industrial related site	Prior to 1981	<1–>5 mg/L		Raw and treated waste waters: from industries involving paint and ink formulation, soap and detergent manufacturing, coil coating, battery manufacturing, coal mining, and laundries (minimum), and from the metal finishing and nonferrous metals manufacturing industries (maximum)	EPA 1981

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

5. POTENTIAL FOR HUMAN EXPOSURE

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

5.5.3 Sediment and Soil

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

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

1,1-Dichloroethene was analyzed for, but was not detected, at a concentrations greater than or equal to the method quantitation/detection limits ranging from 0.00072 to 0.021 mg/kg in monitoring samples of subsurface soil and sediment at depths between 105 and 111 feet at the Palermo Wellfield Superfund Site in Washington in January 2014 (WQP 2018).

5. POTENTIAL FOR HUMAN EXPOSURE

5.5.4 Other Media

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

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

5.6 GENERAL POPULATION EXPOSURE

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

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

The FDA estimated the cumulative daily intake of five polymeric materials produced with 1,1-dichloroethene used in food contact applications at 0.00035 mg/kg body weight/day (FDA 2018b).

The Fourth National Report on Human Exposures to Environmental Chemicals, published and updated by the Centers for Disease Control and Prevention reporting biomonitoring data from the National Health and Nutrition Examination Survey (NHANES) shows that concentrations of 1,1-dichloroethene in whole blood were below the detection limit of 0.009 ng/mL in samples from 1,364, 3,163, and 2,810 members

5. POTENTIAL FOR HUMAN EXPOSURE

of the U.S. general population for the survey years 2003–2004, 2005–2006, and 2007–2008, respectively (CDC 2017).

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

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

Neither the NOHS nor the NOES databases contain information on the frequency, concentration, or duration of exposure of workers to any of the chemicals listed therein. Rather, they only provide estimates of workers potentially exposed to the chemicals. Varying occupational exposure levels can be found in the literature. Reported ranges of concentrations associated with the monomer and polymer plants are ≈ 23 –25 and 6–12 ppb, respectively (Walling 1984). Exposure concentrations $\leq 1,900$ ppm have been reported in a copolymer monofilament fiber production plant (Ott et al. 1976). However, in polymer manufacturing plants, worker exposure has been reported as < 5 ppm (Jaeger 1975). Wallace (1991) reported an exposure concentration of 120 ppm for a cabinet maker; however, the concentration decreased to 14 ppm when measured during a different season (the seasons were not reported).

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

5. POTENTIAL FOR HUMAN EXPOSURE

The Occupational Safety and Health Administration (OSHA) has set the 8-hour TWA permissible exposure level (PEL) to 5 ppm (OSHA 2018).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

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

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

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

CHAPTER 6. ADEQUACY OF THE DATABASE

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

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

6.1 INFORMATION ON HEALTH EFFECTS

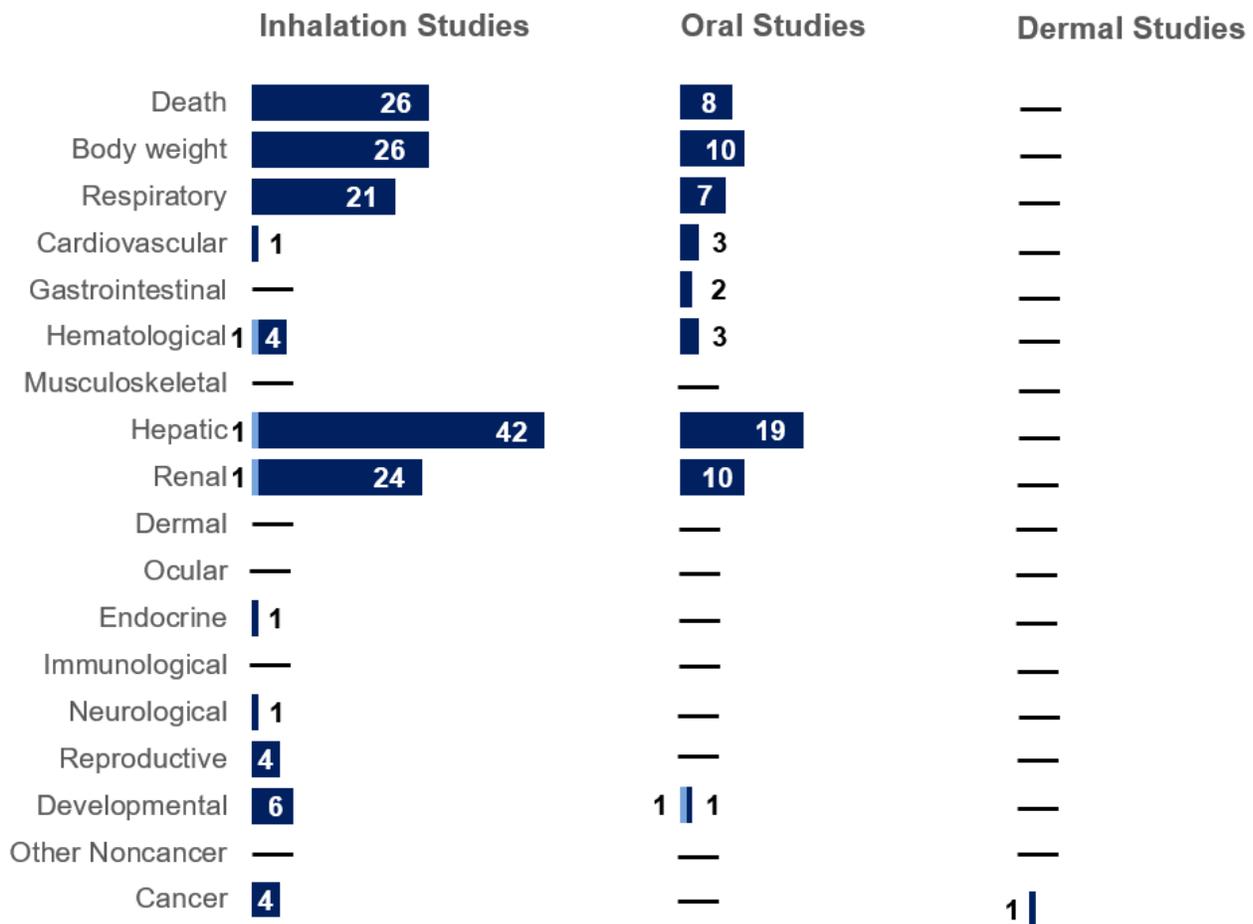
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to 1,1-dichloroethene that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of 1,1-dichloroethene. The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

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

6. ADEQUACY OF THE DATABASE

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

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



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

6. ADEQUACY OF THE DATABASE

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

6.2 IDENTIFICATION OF DATA NEEDS

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

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

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

6. ADEQUACY OF THE DATABASE

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

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

Health Effects.

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

6. ADEQUACY OF THE DATABASE

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

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

Biomarkers of Exposure and Effect.

Exposure. Information regarding populations exposed specifically to 1,1-dichloroethene is not available; therefore, no known biomarker of exposure to 1,1-dichloroethene has been identified in humans.

However, if 1,1-dichloroethene is metabolically disposed of by humans in a way similar to that observed in animals, 1,1-dichloroethene in expired air could be a biomarker of recent exposure to relatively high concentrations of 1,1-dichloroethene. Similarly, urinary excretion of metabolites such as thioglycolic acid could also be considered a biomarker of recent exposure. Such urinary metabolites would not be specific biomarkers for 1,1-dichloroethene exposure because other chemicals produce similar urinary

6. ADEQUACY OF THE DATABASE

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

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

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

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

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

6. ADEQUACY OF THE DATABASE

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

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

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

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

Environmental Fate. Sufficient data exist to show that hydrolysis is not significant in determining the half-life in aqueous media. The available data suggest that 1,1-dichloroethene can undergo transformation by reaction with radical species in the atmosphere and biodegradation under certain conditions in water and soil/sediments as discussed in Section 5.4.2. The atmospheric half-life of 1,1-dichloroethene in air following hydroxyl radical reaction is estimated to be 4–20 hours, and the products of this reaction are highly toxic phosgene, formaldehyde, and chloroacetyl chloride (Tuazon et al. 1988). The estimated half-life for hydrolysis of 1,1-dichloroethene at 25°C under neutral conditions is 1.2×10^8 years (Jeffers et al. 1989). 1,1-Dichloroethene is reduced to vinyl chloride under various conditions in groundwater and sediment. In a methane-utilizing culture from lake sediment, 1,1-dichloroethene was degraded under aerobic conditions within 2 days; the end products, although unspecified, did not include vinyl chloride. Additional studies are needed to characterize aerobic and

6. ADEQUACY OF THE DATABASE

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

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

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

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

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

6. ADEQUACY OF THE DATABASE

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

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

6.3 ONGOING STUDIES

Lawrence M. Schell, Ph.D., of the State University of New York at Albany is evaluating the effects of specific toxicants (including dichloroethylene) on menstrual cycle characteristics impacting fertility within an Akwesasne Mohawk population (RePORTER 2017).

CHAPTER 7. REGULATIONS AND GUIDELINES

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

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

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

Agency	Description	Information	Reference
Air			
EPA	RfC	2×10^{-1} mg/m ³ ^a	IRIS 2002
WHO	Air quality guidelines	No data	WHO 2010
Water & Food			
EPA	Drinking water health advisories		EPA 2018
	1-Day (10 kg child)	2 mg/L	
	10-Day (10 kg child)	1 mg/L	
	DWEL	2 mg/L	
	Lifetime (70 kg adult)	0.4 mg/L	
	10 ⁻⁴ Cancer risk	0.006 mg/L	
	National primary drinking water regulations		EPA 2009a
	MCL	0.007 mg/L	
	Potential health effects from long-term exposure above the MCL	Liver problems	
	Public health goal	0.007 mg/L	
	RfD	5×10^{-2} mg/kg/day ^b	IRIS 2002
WHO	Drinking water quality guidelines	Not established ^c	WHO 2017
FDA	EAFUS ^d	No data	FDA 2013
Cancer			
ACGIH	Carcinogenicity classification	A4 ^{e,f}	ACGIH 2001, 2016
HHS	Carcinogenicity classification	No data	NTP 2016
EPA	Carcinogenicity classification	Group C ^{g,h}	IRIS 2002
IARC	Carcinogenicity classification	Group 2B ^{i,j}	IARC 2018 , Grosse et al. 2017

7. REGULATIONS AND GUIDELINES

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

Agency	Description	Information	Reference
Occupational			
ACGIH	TLV	5 ppm (20 mg/m ³) ^k	ACGIH 2001, 2016
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction	No data	OSHA 2016a , 2016b , 2016c
NIOSH	REL (up to 10-hour TWA)	Ca ^l	NIOSH 2016
	IDLH	Ca ^l	
Emergency Criteria			
EPA	AEGLs-air	No data	EPA 2016a
DOE	PACs-air		DOE 2016b
	PAC-1 ^m	45 ppm	
	PAC-2 ^m	500 ppm	
	PAC-3 ^m	1,000 ppm	

^aBased on liver toxicity (fatty change); point of departure = BMCL₁₀: 6.9 mg/m³; composite uncertainty factor = 30; confidence = medium.

^bBased on liver toxicity (fatty change); point of departure = BMDL₁₀: 4.6 mg/kg/day; composite uncertainty factor = 100; confidence = medium.

^cOccurs in drinking water at concentrations well below those of health concern.

^dThe EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.

^eA4: Not classifiable as a human carcinogen.

^fBased on equivocal animal bioassays that indicate very limited evidence of carcinogenicity.

^gGroup C: Possible human carcinogen.

^hSuggestive evidence of carcinogenicity via the inhalation route, but not sufficient evidence to assess human carcinogenic potential following inhalation exposure. Data are inadequate for an assessment of human carcinogenic potential via the oral route.

ⁱGroup 2B: Possibly carcinogenic to humans.

^jBased on sufficient evidence of carcinogenicity in laboratory animals and no data in human beings.

^kTLV is recommended for occupational exposure to minimize the potential for liver necrosis and kidney toxicity seen in animal studies. This value also provides protection against central nervous system depression, symptoms of inebriation, and possible unconsciousness reported in humans acutely exposed at 4,000 ppm.

^lPotential occupational carcinogen.

^mDefinitions of PAC terminology are available from U.S. Department of Energy ([DOE 2016a](#)).

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health concentration; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

- *ACGIH. 2001. Documentation of the TLVs and BEIs for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists. May 3, 2017.
- *ACGIH. 2016. TLVs and BEIs based on the documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists. May 3, 2017.
- Adeniji SA, Kerr JA, Williams MR. 1981. Rate constants for ozone-alkene reactions under atmospheric conditions. *Int J Chem Kinet* 13:209-217.
- *Aelion CM, Conte BC. 2004. Susceptibility of residential wells to VOC and nitrate contamination. *Environ Sci Technol* 38(6):1648-1653.
- *Andersen ME, Jenkins J. 1977. Oral toxicity of 1,1-dichloroethylene in the rat: Effects of sex, age, and fasting. *Environ Health Perspect* 21:157-163.
- *Andersen ME, Jones RA, Jenkins LJ. 1978. The acute toxicity of single, oral doses of 1,1-dichloroethylene in the fasted male rat: Effect of induction and inhibition of microsomal enzyme activities on mortality. *Toxicol Appl Pharmacol* 46:227-234.
- Andersen ME, Thomas OE, Gargas ML, et al. 1980. The significance of multiple detoxification pathways for reactive metabolites in the toxicity of 1,1-dichloroethylene. *Toxicol Appl Pharmacol* 52:422-432.
- +*Anderson D, Hodge MCE, Purchase IFH. 1977. Dominant lethal studies with the halogenated olefins vinyl chloride and vinylidene dichloride in male CD-1 mice. *Environ Health Perspect* 21:71-78.
- Apfeldorf R, Infante PF. 1981. Review of epidemiologic study results of vinyl chloride-related compounds. *Environ Health Perspect* 41:221-226.
- Ashby J, Tennant RW. 1991. Definitive relationships among chemical structure, carcinogenicity and mutagenicity for 301 chemicals tested by the U.S. National Toxicology Program. *Mutat Res* 257:229-306.
- *Ashley DL, Bonin MA, Cardinali FL, et al. 1992. Determining volatile organic compounds in human blood from a large sample population by using purge and trap gas chromatography/mass spectrometry. *Anal Chem* 64:1021-1029.
- Atkinson R. 1989. Kinetics and mechanisms of the gas-phase reactions of the hydroxyl radical with organic compounds. *J Phys Chem Ref Data Monograph* No. 1.
- *Atkinson R, Carter WPL. 1984. Kinetics and mechanisms of gas-phase reactions of ozone with organic compounds under atmospheric conditions. *Chem Rev* 84:437-470.
- *ATSDR. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles; Notice. Agency for Toxic Substances and Disease Registry. *Fed Regist* 54(174):37618-37634.
- *ATSDR. 1990. Health assessment for Waite Park ground water contamination site, Waite Park, Minnesota, Region 5. Atlanta, GA: Agency for Toxic Substances and Disease Registry. CERCLIS No. MND981002249, Report 1989. PB90107475.
- *ATSDR. 1994. Toxicological profile for 1,1-dichloroethene. Atlanta, GA: Agency for Toxic Substances and Disease Registry. <https://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=722&tid=130>. May 31, 2018.
- *ATSDR. 2006. Toxicological profile for vinyl chloride. Agency for Toxic Substances and Disease Registry. <https://www.atsdr.cdc.gov/toxprofiles/tp20.pdf>. June 27, 2018.

* Cited in text

+ Cited in supplemental document

8. REFERENCES

- *ATSDR. 2017. 1,1-Dichloroethene. 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/index.html>. May 22, 2018.
- *Baden JM, Kelley M, Wharton RS, et al. 1977. Mutagenicity of halogenated ether anesthetics. *Anesthesiology* 46(5):346-350.
- *Baek NH, Jaffe PR, Shingal N. 1990. Simulating the degradation of TCE under methanogenesis. *J Environ Sci Health A25*:987-1005.
- 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* 65:169-176.
- +*Balmer MF, Rampy LW, Quast JF. 1976. 90-Day repeated inhalation toxicity study of vinylidene chloride in rats. Toxicology Research Laboratory, Health and Environmental Research, Dow Chemical U.S.A., Midland, MI.
- *Ban M, Hettich D, Bonnet P. 2003. Effect of inhaled industrial chemicals on systemic and local immune response. *Toxicology* 184(1):41-50.
- *Ban M, Langonne I, Huguet N, et al. 2006. Inhaled chemicals may enhance allergic airway inflammation in ovalbumin-sensitized mice. *Toxicology* 226(2-3):161-171. <http://doi.org/10.1016/j.tox.2006.06.012>.
- Barber LB II, Thurman EM, Takahashi Y, et al. 1992. Comparison of purge and trap GC/MS and purgeable organic chloride analysis for monitoring volatile chlorinated hydrocarbons. *Ground Water* 30:836-842.
- *Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. *Regul Toxicol Pharmacol* 8:471-486.
- *Barrio-Lage G, Parsons FZ, Nassar RS, et al. 1986. Sequential dehalogenation of chlorinated ethenes. *Environ Sci Technol* 20:96-99.
- Barrio-Lage G, Parsons FZ, Nassar RS, et al. 1987. Biotransformation of trichloroethene in a variety of subsurface materials. *Environ Toxicol Chem* 6:571-578.
- *Bartsch H, Malaveille C, Barbin A, et al. 1979. Mutagenic and alkylating metabolites of haloethylenes, chlorobutadienes and dichlorobutenes produced by rodent and human liver tissues. *Arch Toxicol* 41:249-277.
- Bartsch H, Malaveille C, Montesano R, et al. 1975. Tissue-mediated mutagenicity of vinylidene chloride and 2-chlorobutadiene in *Salmonella typhimurium*. *Nature* 255:641-643.
- *Birkel TJ, Roach JAG, Sphon JA. 1977. Determination of vinylidene chloride in Saran films by electron capture gas-solid chromatography and confirmation by mass spectrometry. *J Assoc Off Anal Chem* 60(5):1210-1213.
- *Boublik T, Fried V, Hala E. 1984. 1,1-Dichloroethylene. In: *The vapour pressures of pure substances*. 2nd ed. Amsterdam: Elsevier, 96.
- Bouwer EJ, Rittman BE, McCarthy PL. 1981. Anaerobic degradation of halogenated 1- and 2-carbon organic compounds. *Environ Sci Technol* 15:596-599.
- *Bronzetti G, Bauer C, Corsi C, et al. 1981. Genetic activity of vinylidene chloride in yeast. *Mutat Res* 89:179-185.
- 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* 74:479-484.
- *Bruckner JV, Ramanathan R, Lee KM, et al. 2002. Mechanisms of circadian rhythmicity of carbon tetrachloride hepatotoxicity. *J Pharmacol Exp Ther* 300(1):273-281. <http://doi.org/10.1124/jpet.300.1.273>.
- *Bruckner JV, White CA, Muralidhara S, et al. 2010. Influence of exposure route and oral dosage regimen on 1, 1-dichloroethylene toxicokinetics and target organ toxicity. *J Pharmacol Exp Ther* 333(2):519-527. <http://doi.org/10.1124/jpet.109.162479>.
- *Busch JT. 1985. Final report on the safety assessment of p-hydroxyanisole. *J Am Coll Toxicol* 4(5):31-63.

8. REFERENCES

- Cain D, Helsel DR, Ragone SE. 1989. Preliminary evaluations of regional ground-water quality in relation to land use. *Ground Water* 27(2):230-244.
- *Carlson GP, Fuller GC. 1972. Interaction of modifiers of hepatic microsomal drug metabolism and inhalation toxicity of 1,1-dichloroethylene. *Res Commun Chem Pathol Pharmacol* 4(3):553-560.
- Carpenter CP, Smith HPJ, Pozzani UC. 1949. The assay of acute vapor toxicity, and the grading and interpretation of results on 96 chemical compounds. *J Ind Hyg Toxicol* 31:343-340.
- *CDC. 2017. Fourth national report on human exposure to environmental chemicals. Updated tables, January 2017, volume 1. Atlanta, GA: Centers for Disease Control and Prevention, Department of Health and Human Services. https://www.cdc.gov/biomonitoring/pdf/FourthReport_UpdatedTables_Volume1_Jan2017.pdf. February 23, 2017.
- *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.
- *Charbonneau M, Greselin E, Brodeur J, et al. 1991. Influence of acetone on the severity of the liver injury induced by haloalkane mixtures. *Can J Physiol Pharmacol* 69:1901-1907.
- *Chauhan S, Barbieri P, Wood TK. 1998. Oxidation of trichloroethylene, 1,1-dichloroethylene, and chloroform by toluene/o-xylene monooxygenase from *Pseudomonas stutzeri* OX1. *Appl Environ Microbiol* 64(8):3023-3024.
- *ChemIDplus. 2018. 1,1-Dichloroethylene. ChemIDplus: A Toxnet database. Bethesda, MD: U.S. National Library of Medicine. <https://chem.nlm.nih.gov/chemidplus/name/1%2C1dichloroethene>. May 19, 2017.
- +*Chieco P, Moslen MT, Reynolds ES. 1981. Effect of administrative vehicle on oral 1,1-dichloroethylene toxicity. *Toxicol Appl Pharmacol* 57:146-155.
- *Chieco P, Moslen MT, Reynolds ES. 1982. Histochemical evidence that plasma and mitochondrial membranes are primary foci of hepatocellular injury caused by 1,1-dichloroethylene. *Lab Invest* 46(4):413-421.
- *Chopra NM, Campbell BS, Hurley JC. 1978. Systematic studies on the breakdown of endosulfan in tobacco smokes: Isolation and identification of the degradation products from the pyrolysis of endosulfan I in a nitrogen atmosphere. *J Agric Food Chem* 26(1):255-258.
- *Chu W, Chan KH. 1999. The prediction of partitioning coefficients for chemicals causing environmental concern. *Sci Total Environ* 248:1-10.
- *CITI. 1992. In: Biodegradation and bioaccumulation data of existing chemicals based on the CSCL Japan. Chemicals Inspection & Testing Institute, Japan, 23.
- Clair P, Tua M, Simian H. 1991. Capillary columns in series for GC analysis of volatile organic pollutants in atmospheric and alveolar air. *J High Resolut Chromatogr* 14:383-391.
- Clark RM, Goodrich JA, Deininger RA. 1986. Drinking water and cancer mortality. *Sci Total Environ* 53:153-172.
- Clayton GD, Clayton PB, eds. 1981. *Patty's industrial hygiene and toxicology*. Vol. 2B, 3rd ed. New York, NY: John Wiley & Sons, 3545-3550.
- *Clewell HJ, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. *Toxicol Ind Health* 1(4):111-131.
- *Cline PV, Viste DR. 1985. Migration and degradation patterns of volatile organic compounds. *Waste Manag Res* 3(1):351-360.
- *Cole RH, Frederick RE, Healy RP, et al. 1984. Preliminary findings of the priority pollutant monitoring project of the nationwide urban runoff program. *J Water Pollut Control Fed* 56:898-908.
- Conkle JP, Camp BJ, Welch BE. 1975. Trace composition of human respiratory gas. *Arch Environ Health* 30:290-295.
- Contant RW, Lewis RG, Mulik JD. 1984. Passive sampling device with reversible adsorption mechanics of sampling. In: *Proceedings of National Symposium on Recent Advances in Pollutant Monitoring of Ambient Air and Stationary Sources*. PB8514405X, 67-73.

8. REFERENCES

- *Costa AK, Ivanetich KM. 1982. Vinylidene chloride: Its metabolism by hepatic microsomal cytochrome p-450 *in vitro*. *Biochem Pharmacol* 31(11):2083-2092.
- *Cotruvo JA. 1985. Organic micropollutants in drinking water: An overview. *Sci Total Environ* 47:7-26.
- *Cotti G, Maltoni C, Lefemine G. 1988. Long-term carcinogenicity bioassay on vinylidene chloride administered by inhalation to Sprague-Dawley rats. *Ann NY Acad Sci* 534:160-168.
- *Crebelli R, Andreoli C, Carera A, et al. 1992. The induction of mitotic chromosome malsegregation in *Aspergillus nidulans*: Quantitative structure activity relationship (QSAR) analysis with chlorinated aliphatic hydrocarbons. *Mutat Res* 266:117-134.
- *Crume RV. 1991. The comparison of health risks between different environmental media at Superfund hazardous waste sites. *Air Waste Manage Assoc* 15A:1-14.
- *Dallas CE, Weir FW, Feldman S, et al. 1983. The uptake and disposition of 1,1-dichloroethylene in rats during inhalation exposure. *Toxicol Appl Pharmacol* 68:140-151.
- *Dawson BV, Johnson PD, Goldberg SJ, et al. 1990. Cardiac teratogenesis of trichloroethylene and dichloroethylene in a mammalian model. *J Am Coll Cardiol* 16:1304-1309.
- +*Dawson BV, Johnson PD, Goldberg SJ, et al. 1993. Cardiac teratogenesis of halogenated hydrocarbon-contaminated drinking water. *J Am Coll Cardiol* 21(6):1466-1472.
- *Dekant W, Vamvakas S, Anders MW. 1989. Bioactivation of nephrotoxic haloalkenes by glutathione conjugation: Formation of toxic and mutagenic intermediates by cysteine β -lyase. *Drug Metab Rev* 20:43-83.
- *DeLeon IR, Maberry MA, Overton EB, et al. 1980. Rapid gas chromatographic method for the determination of volatile and semivolatile organochlorine compounds in soil and chemical waste disposal site samples. *J Chromatogr Sci* 18:85-88.
- Denenberg BA, Miller RW. 1974. A continuous monitor for vinyl chloride monomers based upon an impregnated paper tape: Technical papers, regional technical conference. New York. Society of Plastics Engineers, Palisades Section, 146-162.
- Dilling WL, Bredeweg CJ, Tefertiller NB. 1976. Organic photochemistry: Simulated atmospheric photodecomposition rates of methylene chloride, 1,1,1-trichloroethane, trichloroethylene, tetrachloroethylene, and other compounds. *Environ Sci Technol* 10(4):351-356.
- 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* 9:833-837.
- *DOE. 2016a. Protective Action Criteria (PAC) with AEGLs, ERPGs, & TEELs: Rev. 29 for Chemicals of Concern - May 2016. Oak Ridge, TN: U.S. Department of Energy. <https://energy.gov/ehts/protective-action-criteria-pac-aegls-erpgs-teels-rev-29-chemicals-concern-may-2016>. February 28, 2017.
- *DOE. 2016b. Table 3: Protective Action Criteria (PAC) Rev. 29 based on applicable 60-minute AEGLs, ERPGs, or TEELs. Chemicals listed by CASRN. May 2016. Oak Ridge, TN: U.S. Department of Energy. https://sp.eota.energy.gov/pac/docs/Revision_29_Table3.pdf. February 28, 2017.
- *Dolan ME, McCarty PL. 1995. Methanotrophic chloroethene transformation capacities and 1,1-dichloroethene transformation product toxicity. *Environ Sci Technol* 29(11):2741-2747. <http://doi.org/10.1021/es00011a007>.
- *Dowsley TF, Reid K, Petsikas D, et al. 1999. Cytochrome P-450-dependent bioactivation of 1,1-dichloroethylene to a reactive epoxide in human lung and liver microsomes. *J Pharmacol Exp Ther* 289(2):641-648.
- *Dowsley TF, Ulreich JB, Bolton JL, et al. 1996. CYP2E1-dependent bioactivation of 1,1-dichloroethylene in murine lung: Formation of reactive intermediates and glutathione conjugates. *Toxicol Appl Pharmacol* 139(1):42-48. <http://doi.org/10.1006/taap.1996.0141>.
- *Drevon C, Kuroki T. 1979. Mutagenicity of vinyl chloride, vinylidene chloride and chloroprene in V79 Chinese hamster cells. *Mutat Res* 67:173-182.

8. REFERENCES

- Driss MR, Bouguerra ML. 1991. Analysis of volatile organic compounds in water by purge-and trap and gas chromatography techniques. *Int J Environ Anal Chem* 45:193-204.
- *D'Souza RW, Andersen ME. 1988. Physiologically based pharmacokinetic model for vinylidene chloride. *Toxicol Appl Pharmacol* 95:230-240.
- Dyksen JE, Hess AF. 1982. Alternatives for controlling organics in groundwater supplies. *J Am Water Works Assoc* 74:394-403.
- *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.
- Edney EO, Kleindienst TE, Corse EW. 1986. Room temperature rate constants for the reaction of OH with selected chlorinated and oxygenated hydrocarbons. *Int J Chem Kinet* 18:1355-1371.
- *Eichelberger JW, Bellar TA, Donnelly JP, et al. 1990. Determination of volatile organics in drinking water with US EPA method 524.2 and the ion trap detector. *J Chromatogr Sci* 28(9):460-467.
- *el-Masri HA, Constan AA, Ramsdell HS, et al. 1996. Physiologically based pharmacodynamic modeling of an interaction threshold between trichloroethylene and 1,1-dichloroethylene in Fischer 344 rats. *Toxicol Appl Pharmacol* 141(1):124-132. <http://doi.org/10.1006/taap.1996.0268>.
- *el-Masri HA, Tessari JD, Yang RS. 1996. Exploration of an interaction threshold for the joint toxicity of trichloroethylene and 1,1-dichloroethylene: Utilization of a PBPK model. *Arch Toxicol* 70(9):527-539.
- *Ensign SA, Hyman MR, Arp DJ. 1992. Cometabolic degradation of chlorinated alkenes by alkene monooxygenase in propylene-grown xanthobacter strain. *Appl Environ Microbiol* 53:3038-3046.
- EPA. 1975. National interim primary drinking water regulations. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.
- EPA. 1976. Summary characteristics of selected chemicals of near-term interest. Washington, DC: U.S. Environmental Protection Agency. EPA5601476004.
- *EPA. 1977. Market input/output studies task 1: Vinylidene chloride. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. PB273205.
- EPA. 1979a. Criteria and standards for the national pollutant discharge elimination system. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 125.
- *EPA. 1979b. Status assessment of toxic chemicals: Vinylidene chloride. Cincinnati, OH: U.S. Environmental Protection Agency. EPA6002792100. PB80146442.
- *EPA. 1980a. Fate of toxic and hazardous materials in the air environment. Research Triangle Park, NC: U.S. Environmental Protection Agency, Environmental Sciences Research Laboratory, Office of Research and Development. PB80221948
- *EPA. 1980b. Occurrence of volatile organics in drinking water. U.S. Environmental Protection Agency. EPA950R80033. <https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=94000GWC.txt>. May 30, 2018.
- *EPA. 1981. Treatability manual: Treatability data. Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development. EPA600282001a.
- *EPA. 1982. Aquatic fate process data for organic priority pollutants. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards. EPA4404S1014.
- *EPA. 1983a. Atmospheric chemistry of several toxic compounds. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development. EPA600S382092.
- EPA. 1983b. Administered permit programs: The national pollutant discharge elimination system. General permits. U.S. Environmental Protection Agency. *Fed Regist* 48:14153-14178.
- *EPA. 1984a. Appendix A to part 136-methods for organic chemical analysis of municipal and industrial wastewater. Method 601-purgeable halocarbons. U.S. Environmental Protection Agency. *Fed Regist* 49(209):43261-43271. <https://www.gpo.gov/fdsys/search/submitcitation.action?publication=FR> June 8, 2018.
- EPA. 1984b. Method 608 guidelines establishing test procedures for the analysis of pollutants under the Clean Water Act (40 CFR 136) purgeables. U.S. Environmental Protection Agency. *Fed Regist* 4914337-43383. June 27, 2018.

8. REFERENCES

- *EPA. 1984c. Method 1624 revision B - volatile organic compounds by isotope dilution GC/MS. Washington, DC: U.S. Environmental Protection Agency. Fed Regist 49(109):43407-43415. <https://www.gpo.gov/fdsys/search/submitcitation.action?publication=FR> June 8, 2018.
- *EPA. 1985a. Health assessment documents for vinylidene chloride: Final report. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA60088303IF.
- EPA. 1985b. National primary drinking water regulations: Volatile synthetic organic chemicals: Final rule and proposed rule. U.S. Environmental Protection Agency. Fed Regist 50:46900.
- EPA. 1985c. Designation, reportable quantities, and notification: Designation of hazardous substances. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4.
- *EPA. 1986a. Halogenated volatile organics - method 8010. Test methods for evaluating solid waste. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response SW-846. June 8, 2018.
- *EPA. 1986b. Method 8240 test methods for evaluating solid wastes: Laboratory manual physical/chemical methods. U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response. SW-846. June 8, 2018.
- EPA. 1986c. General pretreatment regulations for existing and new sources of pollution. U.S. Environmental Protection Agency. Fed Regist 43(123):27736-27773.
- EPA. 1986d. National human adipose tissue survey. National human monitoring program. Washington, DC: U.S. Environmental Protection Agency.
- *EPA. 1986e. Guidelines for carcinogen risk assessment. U.S. Environmental Protection Agency. Fed Regist 51(185):33992-34003.
- EPA. 1986f. Toxic substances, 1,1-dichloroethylene; proposed test rule. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR Part 799. Fed Regist 51(155):28840.
- *EPA. 1987a. Health advisory for 1,1-dichloroethylene. Washington, DC: U.S. Environmental Protection Agency, Office of Drinking Water.
- *EPA. 1987b. Health advisories for 25 organics. Washington, DC: U.S. Environmental Protection Agency. PB87235578. <https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB87235578.xhtml>. May 29, 2018.
- *EPA. 1988a. Recommendations for and documentation of biological values for use in risk assessment. Cincinnati, OH: U.S. Environmental Protection Agency. PB88179874. EPA600687008. <https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=34855>. June 27, 2018.
- *EPA. 1988b. National ambient volatile organic compounds (VOCs) data base update. Research Triangle Park, NC: U.S. Environmental Protection Agency. <https://nepis.epa.gov/Exe/ZyPDF.cgi/2000Tswa.PDF?Dockey=2000Tswa.PDF>. June 11, 2018.
- EPA. 1989. Designation of hazardous substances. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4.
- EPA. 1990. Interim methods for development of inhalation reference concentrations. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Office of Research and Development, Environmental Criteria and Assessment Office. PB90238890. EPA600890066A.
- EPA. 1991. Hazardous constituents. Appendix VIII. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.
- *EPA. 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Washington, DC: U.S. Environmental Protection Agency. EPA600890066F. https://www.epa.gov/sites/production/files/2014-11/documents/rfc_methodology.pdf. June 27, 2018.
- *EPA. 1996. Method 8260B: Volatile organic compounds by gas chromatography/mass spectrometry (GC/MS). U.S. Environmental Protection Agency. 8260B8261-8260B8286. <https://www.epa.gov/hw-sw846/sw-846-test-method-8260b-volatile-organic-compounds-gas-chromatography-mass-spectrometry>. June 27, 2018.

8. REFERENCES

- *EPA. 2002. Toxicological Review of 1,1-dichloroethylene (CAS no. 75-35-4): In support of summary information on the integrated risk information system (IRIS). Washington, DC: U.S. Environmental Protection Agency. EPA635R02002.
https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0039tr.pdf. June 11, 2018.
- *EPA. 2005. Toxic chemical release inventory reporting forms and instructions: Revised 2004 version. Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986). U.S. Environmental Protection Agency, Office of Environmental Information. EPA260B05001.
- *EPA. 2009a. National primary drinking water regulations. Washington, DC: U.S. Environmental Protection Agency, Office of Ground Water and Drinking Water. EPA816F090004.
- *EPA. 2009b. Hazardous waste characteristics: A user-friendly reference document. U.S. Environmental Protection Agency. <https://archive.epa.gov/epawaste/hazard/web/pdf/hw-char.pdf>. June 22, 2018.
- *EPA. 2012. Estimation Programs Interface Suite™ for Microsoft® Windows, v 4.11: 1,1-dichloroethene. Washington, DC: U.S. Environmental Protection Agency.
<https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface>. June 25, 2018.
- *EPA. 2015. ACToR: 1,1-dichloroethene (CASRN 75-35-4). Washington, DC: U.S. Environmental Protection Agency. June 25, 2018.
- *EPA. 2016a. Acute Exposure Guideline Levels (AEGLs) values. U.S. Environmental Protection Agency. <https://www.epa.gov/aegl/access-acute-exposure-guideline-levels-aegls-values#chemicals>. February 28, 2017.
- *EPA. 2016b. Air data: Air quality data collected at outdoor monitors across the U.S. Environmental Protection Agency. U.S. Environmental Protection Agency.
https://aqs.epa.gov/aqsweb/airdata/download_files.html. June 25, 2018.
- *EPA. 2017a. 1,1-Dichloroethylene: Substance registry services (SRS). U.S. Environmental Protection Agency.
https://ofmpub.epa.gov/sor_internet/registry/substreg/searchandretrieve/substancesearch/search.do?details=displayDetails&selectedSubstanceId=48931. April 20, 2017.
- *EPA. 2017b. Air data: Air quality data collected at outdoor monitors across the U.S. Environmental Protection Agency. U.S. Environmental Protection Agency.
https://aqs.epa.gov/aqsweb/airdata/download_files.html. June 25, 2018.
- *EPA. 2017c. Duke energy coal ash spill in Eden, NC: History and response timeline. Environmental Protection Agency. <https://www.epa.gov/dukeenergy-coalash/history-and-response-timeline>.
- *EPA. 2018. Drinking water standards and health advisories. Washington, DC: U.S. Environmental Protection Agency, Office of Water. EPA822S12001.
<https://www.epa.gov/sites/production/files/2018-03/documents/dwtable2018.pdf>. May 22, 2018.
- FDA. 1982. U.S. Food and Drug Administration. 21 Code of Federal Regulations Part 1172.210.
- FDA. 1983. Indirect food additives: Polymers. U.S. Food and Drug Administration. Fed Regist 48:38604-38606.
- FDA. 1986. Proposed uses of vinyl chloride polymers. U.S. Food and Drug Administration. Fed Regist 51:4177-4185.
- *FDA. 1988. Indirect food additives: Polymers. U.S. Food and Drug Administration. Fed Regist 53:47184-47185.
- *FDA. 2013. Everything added to food in the United States (EAFUS). Washington, DC: U.S. Food and Drug Administration. <http://www.accessdata.fda.gov/scripts/fcn/fcnavigation.cfm?rpt=eafuslisting>. February 28, 2017.

8. REFERENCES

- *FDA. 2018a. Q3C - Tables and list guidance for industry. 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).
<https://www.fda.gov/downloads/Drugs/Guidances/ucm073395.pdf>. May 14, 2018.
- *FDA. 2018b. Cumulative estimated daily intake. U.S. Food and Drug Administration:
<https://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=edisrev&displayAll=false&page=20>. May 16, 2018.
- *Ferrario JB, Lawler GC, Deleon IR, et al. 1985. Volatile organic pollutants in biota and sediments of Lake Pontchartrain. *Bull Environ Contam Toxicol* 34:246-255.
- *Fisher JW, Whittaker TA, Taylor DH, et al. 1989. Physiologically based pharmacokinetic modeling of the pregnant rat: A multiroute exposure model for trichloroethylene and its metabolite, trichloroacetic acid. *Toxicol Appl Pharmacol* 99(3):395-414. [http://doi.org/10.1016/0041-008x\(89\)90149-x](http://doi.org/10.1016/0041-008x(89)90149-x).
- Fielder RJ, Dale EA, Williams SD. 1985. Toxicity review 13: Vinylidene chloride. Her Majesty's Stationary Office, London, England.
- Fishbein L. 1979. Potential halogenated industrial carcinogenic and mutagenic chemicals: I. Halogenated unsaturated hydrocarbons. *Sci Total Environ* 11(2):111-161.
- *Foerst D. 1979. A sampling and analytical method for vinylidene chloride in air. *Am Ind Hyg Assoc J* 40:888-893.
- *Fogel MM, Taddeo AR, Fogel S. 1986. Biodegradation of chlorinated ethenes by a methane-utilizing mixed culture. *Appl Environ Microbiol* 51:720-724.
- *Forkert PG. 1999a. 1,1-Dichloroethylene-induced Clara cell damage is associated with *in situ* formation of the reactive epoxide. Immunohistochemical detection of its glutathione conjugate. *Am J Respir Cell Mol Biol* 20(6):1310-1318. <http://doi.org/10.1165/ajrcmb.20.6.3525>.
- *Forkert PG. 1999b. *In vivo* formation and localization of 1,1-dichloroethylene epoxide in murine liver: Identification of its glutathione conjugate 2-S-glutathionyl acetate. *J Pharmacol Exp Ther* 290(3):1299-1306.
- *Forkert PG. 2001. Mechanisms of 1,1-dichloroethylene-induced cytotoxicity in lung and liver. *Drug Metab Rev* 33(1):49-80. <http://doi.org/10.1081/dmr-100000140>.
- *Forkert PG, Boyd SM. 2001. Differential metabolism of 1,1-dichloroethylene in livers of A/J, CD-1, and C57BL/6 mice. *Drug Metab Dispos* 29(11):1396-1402.
- Forkert PG, Moussa M. 1991. 1,1-Dichloroethylene elicits dose-dependent alterations in covalent binding and glutathione in murine liver. *Drug Metab Dispos* 19:580-586.
- +*Forkert PG, Reynolds ES. 1982. 1,1-Dichloroethylene-induced pulmonary injury. *Exp Lung Res* 3:57-68.
- +*Forkert PG, Forkert L, Farooqui M, et al. 1985. Lung injury and repair: DNA synthesis following 1,1-dichloroethylene. *Toxicology* 36:199-214.
- Forkert PG, Geddes BA, Birch DW, et al. 1990. Morphologic changes and covalent binding of 1,1-dichloroethylene in Clara and alveolar type II cells isolated from lungs of mice following *in vivo* administration. *Drug Metab Dispos* 18(4):534-539.
- Forkert PG, Honey M, Racz WJ. 1987. Metabolic activation of 1,1-dichloroethylene by mouse lung and liver chromosomes. *Can J Physiol Pharmacol* 65(7):1496-1499.
- Forkert PG, Stringer V, Troughton KM. 1986. Pulmonary toxicity of 1,1-dichloroethylene: Correlation of early changes with covalent binding. *Can J Physiol Pharmacol* 64:112-121.
- *Fouremant P, Mason JM, Valencia R, et al. 1994. Chemical mutagenesis testing in *Drosophila*. IX. Results of 50 coded compounds tested for the National Toxicology Program. *Environ Mol Mutagen* 23(1):51-63.
- Fusillo TV, Hochreiter JJ, Lord DG. 1985. Distribution of volatile organic compounds in a New Jersey coastal plain aquifer system. *Ground Water* 23:354-360.
- +*Gage JC. 1970. The subacute inhalation toxicity of 109 industrial chemicals. *Br J Ind Med* 27:1-18.

8. REFERENCES

- Gay BWJ, Hanst PL, Bufalini JJ, et al. 1976. Atmospheric oxidation of chlorinated ethylenes. *Environ Sci Technol* 10(1):58-67.
- *Gilbert J, Shepherd MJ, Startin JR, et al. 1980. Gas chromatographic determination of vinylidene chloride monomer in packaging films and in foods. *J Chromatogr* 197:71-78.
- *Glende EA, Recknagel RO. 1992. Phospholipase A, activation and cell injury in isolated rat hepatocytes exposed to bromotrichloromethane, chloroform and 1,1-dichloroethylene as compared to effects of carbon tetrachloride. *Toxicol Appl Pharmacol* 113:159-162.
- *Glisson BT, Craft BF, Nelson JH, et al. 1986. Production of vinylidene chloride from the thermal decomposition of methyl chloroform. *Am Ind Assoc J* 47:427-435.
- *Going JE, Spigarelli JL. 1977. Environmental monitoring near industrial sites: Vinylidene chloride. Washington, D.C: U.S. Environmental Protection Agency, Office of Toxic Substances. EPA560677X26.
- *Goldberg SJ, Lebowitz MD, Graver EJ, et al. 1990. An association of human congenital cardiac malformations and drinking water contaminants. *J Am Coll Cardiol* 16:155-164.
- Goodman LS, Gilman A. 1990. The pharmacological basis of therapeutics. 8th Ed. Elmsford, NY: Pergamon Press.
- Goodman G, Wilson R. 1991. Quantitative prediction of human cancer risk from rodent carcinogenic potencies: A closer look at the epidemiological evidences for some chemicals not definitively carcinogenic in humans. *Regul Toxicol Pharmacol* 14:118-146.
- Gosselin RE, Smith RP, Hodge HC. 1984. Clinical toxicology of commercial products. 6th ed. Baltimore, MD: William and Wilkins.
- *Gossett JM. 1987. Measurement of Henry's Law constant for C₁ and C₂ chlorinated hydrocarbon. *Environ Sci Technol* 21:202-208.
- Grayson M, ed. 1983. Kirk-Othmer concise encyclopedia of chemical technology. Vol. 23, 3rd ed. New York, NY: John Wiley & Sons, 764-794.
- *Grayson M, ed. 1985. Vinylidene chloride and poly(vinylidene chloride). In: Kirk-Othmer concise encyclopedia of chemical technology. New York, NY: John Wiley & Sons, 1223-1224.
- *Greim H, Bonse G, Radwan Z, et al. 1975. Mutagenicity *in vitro* and potential carcinogenicity of chlorinated ethylenes as a function of metabolic oxirane formation. *Biochem Pharmacol* 24:2013-2017.
- Grimsrud EP, Rasmussen RA. 1975. Survey and analysis of halocarbons in the atmosphere by gas chromatography-mass spectrometry. *Atmos Environ* 9:1014-1017.
- *Grosjean D. 1990. Atmospheric chemistry of toxic contaminants: 1. Reaction rates and atmospheric persistence. *J Air Waste Manage Assoc* 40(10):1397-1402.
- Grosjean D. 1991. Atmospheric chemistry of toxic contaminants: 5. Unsaturated halogenated aliphatics: Allyl chloride, chloroprene, hexachlorocyclopentadiene, vinylidene chloride. *J Air Waste Manager Assoc* 41:182-189.
- *Grosse Y, Loomis D, Guyton KZ, et al. 2017. Some chemicals that cause tumours of the urinary tract in rodents. *Lancet Oncol* 18(8):1003-1004. [http://doi.org/10.1016/S1470-2045\(17\)30505-3](http://doi.org/10.1016/S1470-2045(17)30505-3).
- *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. <http://doi.org/10.1021/tx00020a008>.
- *Haag WR, Mill T. 1988. Effect of a subsurface sediment on hydrolysis of haloalkanes and epoxides. *Environ Sci Technol* 22:658-663.
- Haddad LM, Winchester JF. 1990. Clinical management of poisoning and drug overdose. 2nd ed. Philadelphia, PA: W.B. Saunders Co., 1220.
- Hall LW, Hall WS, Bushong SJ, et al. 1987. *In situ* striped bass (*Morone saxatilis*) contaminant and water quality studies in the Potomac River. *Aquatic Toxicol* 10:73-99.
- *Hallbourg RR, Delfino JJ, Miller WL. 1992. Organic priority pollutants in groundwater and surface water at three landfills in north central Florida. *Water Air Soil Pollut* 65(3-4):307-322.

8. REFERENCES

- *Hallen RT, Pyne JW, Molton PM. 1986. Transformation of chlorinated ethenes and ethanes by anaerobic microorganisms. *Abstr Pap Am Chem Soc* 26(2):344-346.
- Hannah SA, Austern BM, Eralp AE, et al. 1986. Comparative removal of toxic pollutants by six wastewater treatment processes. *J WPCF* 58:27-34.
- *Hansch C, Leo A, Hoekman D. 1995. Octanol logP. In: *Exploring QSAR: Hydrophobic, electronic, and steric constants*. Washington, DC: American Chemical Society, 4.
- *Harkov R, Gianti SJ, Bozzelli JW, et al. 1985. Monitoring volatile organic compounds at hazardous and sanitary landfills in New Jersey. *J Environ Sci Health* 20:491-501.
- *Harkov R, Kebbekus B, Bozzelli JW. 1987. Volatile organic compounds at urban sites in New Jersey. In: Lioy PJ, Daisey JM, eds. *Toxic air pollution*. Chelsea, MI: Lewis Publishers, Inc., 69-88.
- *Hayes AS, Pandiri AR, Ton TT, et al. 2016. Renal cell carcinomas in vinylidene chloride-exposed male B6C3FI mice are characterized by oxidative stress and TP53 pathway dysregulation. *Toxicol Pathol* 44(1):71-87.
- *Haynes WM. 2014. Physical constants of organic compounds: 1,1-Dichloroethene. In: *CRC handbook of chemistry and physics*. 95th ed. Boca Raton, FL: Taylor & Francis Group, 3-162.
- +*Henck JW, Quast JF, Rampy LW. 1979. A comparison of four mouse strains exposed to subchronically inhaled vinylidene chloride (VDC). Toxicology Research Laboratory, Health and Environmental Science, Dow Chemical U.S.A., Midland, MI.
- *Henschler D. 1979. [Vinylidene chloride: Hazardous substances compiled by establishment of MAK values and fixing of limit values for dusts working groups. In: Commission for the testing of hazardous substances of the Deutsche Forschungsgemeinschaft.] *Vet-lag Chemie GmbH 3 U-Z:l-19*. (German and English translation).
- Henschler D, Broser F, Hopf HC. 1970. Polyneuritis cranialis following poisoning with chlorinated acetylene while handling vinylidene chloride copolymers. *Arch Toxicol* 26:62-75.
- Hertz CD, Hudson CW, Bardsley AR, et al. 1992. Verification of method detection limits for organic compounds in drinking water. *Proceedings of the Water Quality Technology Conference ISS 1:647-665*.
- *Hewitt WR, Plaa GL. 1983. Dose dependent modification of 1,1-dichloroethylene toxicity by acetone. *Toxicol Lett* 16:145-152.
- Hiatt MH. 1983. Determination of volatile organic compounds in fish samples by vacuum distillation and fused silica capillary gas chromatography/mass spectrometry. *Anal Chem* 55:506-515.
- Hoar SK, Santodonato J, Cameron TP, et al. 1985. Monographs on human exposures to chemicals in the workplace. *J Occup Med* 27:585-588.
- *Hong CB, Winston JM, Thornburg LP, et al. 1981. Follow-up study on the carcinogenicity of vinyl chloride and vinylidene chloride in rats and mice: Tumor incidence and mortality subsequent to exposure. *J Toxicol Environ Health* 7:909-924.
- +*Humiston CG, Quast JF, Wade CE, et al. 1978. Results of a two-year toxicity and oncogenicity study with vinylidene chloride incorporated in the drinking water of rats. Dow Chemical Company. Chem Mfg Assn. Submitted to the U.S. EPA under TSCA section FYI. OTS0000007-0. FYI-AX-0978-0007. [unpublished study to be peer reviewed]
- Hurt ME, Valentine R, Alvarez L. 1993. Developmental toxicity of inhaled trans-1,2-dichloroethylene in the rat. *Fundam Appl Toxicol* 20:225-230.
- *IARC. 1987. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Supplement 7: Update of IARC monographs volumes 1-42. Lyon, France: World Health Organization, International Agency for Research on Cancer.
- *IARC. 2018. Agents classified by the IARC Monographs, Volumes 1-118. Lyon, France: International Agency for Research on Cancer. http://monographs.iarc.fr/ENG/Classification/List_of_Classifications.pdf. May 22, 2018.
- *ILO, WHO. 2018. International Chemical Safety Card. Vinylidene chloride. International Labour Organization and World Health Organization. <http://incem.org/documents/icsc/icsc/eics0083.htm>. June 22, 2018.

8. REFERENCES

- Insel PA. 1990. Analgesic--antipyretic and antiinflammatory agents: Drugs employed in the treatment of rheumatoid arthritis and gout. In: Gilman AG, Rall TW, Nies AS, et al., eds. Goodman and Gilman's the pharmacological basis of therapeutics. 8th ed. New York, NY: Pergamon Press, 656-659.
- *IRIS. 2002. 1,1-Dichloroethylene (1,1-DCE); CASRN 75-35-4. Integrated Risk Information System. Chemical assessment summary. Washington, DC: U.S. Environmental Protection Agency. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0039_summary.pdf. May 3, 2017.
- Iwan GR. 1987. Drinking water quality concerns of New York City, past and present. *Ann NY Acad Sci* 502:183-204.
- +*Jackson NM, Conolly RB. 1985. Acute nephrotoxicity of 1,1-dichloroethylene in the rat after inhalation exposure. *Toxicol Lett* 29:191-199.
- *Jaeger RJ. 1975. Vinyl chloride monomer: Comments on its hepatotoxicity and interaction with 1,1-dichloroethylene. *Ann NY Acad Sci* 246:150-151.
- +*Jaeger RJ. 1977. Effect of 1,1-dichloroethylene exposure on hepatic mitochondria. *Res Commun Chem Pathol Pharmacol* 18(1):83-94.
- *Jaeger RJ, Conolly RB, Murphy SD. 1973a. Diurnal variation of hepatic glutathione concentration and its correlation with 1,1-dichloroethylene inhalation toxicity in rats. *Res Commun Chem Pathol Pharmacol* 6:465-471.
- +*Jaeger RJ, Conolly RB, Murphy SD. 1974. Effect of 18 hour fast and glutathione depletion on 1,1-dichloroethylene-induced hepatotoxicity and lethality in rats. *Exp Mol Pathol* 20:187-198.
- Jaeger RJ, Conolly RB, Murphy SD. 1975a. Short term inhalation toxicity of halogenated hydrocarbons effects on fasting rats. *Arch Environ Health* 30:26-31.
- *Jaeger RJ, Conolly RB, Reynolds ES, et al. 1975b. Biochemical toxicology of unsaturated halogenated monomers. *Environ Health Perspect* 11:121-128.
- *Jaeger RJ, Shoner LG, Coffman LJ. 1977a. 1,1-Dichloroethylene hepatotoxicity: Proposed mechanism of action and distribution and binding of [¹⁴C] radioactivity following inhalation exposure in rats. *Environ Health Perspect* 21:113-119.
- *Jaeger RJ Szabo S, Coffman LJ. 1977b. 1,1-Dichloroethylene hepatotoxicity: Effect of altered thyroid function and evidence for the subcellular site of injury. *J Toxicol Environ Health* 3:545-555.
- +*Jaeger RJ, Trabulus MJ, Murphy SD. 1973b. Biochemical effects of 1,1-dichloroethylene in rats: Dissociation of its hepatotoxicity from a lipoperoxidative mechanism. *Toxicol Appl Pharmacol* 24:457-467.
- *Jaeger RJ, Trabulus MJ, Murphy SD. 1973c. The interaction of adrenalectomy, partial adrenal replacement therapy, and starvation with hepatotoxicity and lethality after 1,1-dichloroethylene intoxication. *Toxicol Appl Pharmacol* 25:491.
- Jatirert CT, Wolfe NL. 1987. Degradation of selected halogenated ethanes in anoxic sediment-water systems. *Environ Toxicol Chem* 6(11):327-837.
- *Jeffers PM, Ward LM, Woytowitch LM, et al. 1989. Homogenous hydrolysis rate constants for selected chlorinated methanes, ethanes, ethenes, and propanes. *Environ Sci Technol* 23:965-969.
- +*Jenkins J, Trabulus MJ, Murphy SD. 1972. Biochemical effects of 1,1-dichloroethylene in rats: Comparison with carbon tetrachloride and 1,2-dichloroethylene. *Toxicol Appl Pharmacol* 23:501-510.
- +*Jenkins LJ, Andersen ME. 1978. 1,1-Dichloroethylene nephrotoxicity in the rat. *Toxicol Appl Pharmacol* 46(1):131-141.
- John JA, Murray FJ, Smith FA, et al. 1978. Teratogenic evaluation of vinyl chloride, vinylidene chloride, and styrene in laboratory animals. *Teratology* 17:48A.
- +*Jones BK, Hathway DE. 1978a. Differences in metabolism of vinylidene chloride between mice and rats. *Br J Cancer* 37:411-417.
- *Jones BK, Hathway DE. 1978b. The biological fate of vinylidene chloride in rats. *Chem Biol Interact* 20:27-41.

8. REFERENCES

- *Jones BK, Hathway DE. 1978c. Tissue-mediated mutagenicity of vinylidene chloride in *Salmonella typhimurium* TA1535. *Cancer Lett* 5:1-6.
- *Kainz A, Cross H, Freeman S, et al. 1993. Effects of 1,1-dichloroethene and of some of its metabolites on the functional viability of mouse hepatocytes. *Fundam Appl Toxicol* 21:140-148.
- +*Kanz MF, Reynolds ES. 1986. Early effects of 1,1-dichloroethylene on canalicular and plasma membranes: Ultrastructure and stereology. *Exp Mol Pathol* 44:93-110.
- +*Kanz MF, Taj Z, Moslen MT. 1991. 1,1-Dichloroethylene hepatotoxicity: Hypothyroidism decreases metabolism and covalent binding but not injury in the rat. *Toxicology* 70:213-229.
- Keisel L, Liszka M, Rutkowski M. 1975. [Gas chromatographic determination of trace impurities in distillates of vinyl chloride monomer.] *Chem Anal (Warsaw)* 20:555-562. (Polish)
- Kennedy GL, Graepel GJ. 1991. Acute toxicity in the rat following either oral or inhalation exposure. *Toxicol Lett* 56:317-326.
- Kirshen N. 1984. Analysis of trace volatile organic chemicals in water. *Am Lab* 16:62-67.
- Kitchin KT, Brown JL, Kulkarni AP. 1992. Predictive assay for rodent carcinogenicity using *in vivo* biochemical parameters: Operational characteristics and complementarity. *Mutat Res* 266:253-272.
- Kleopfer RD, Easley DM, Haas BB, et al. 1985. Anaerobic degradation of trichloroethylene in soil. *Environ Sci Technol* 19:277-280.
- +*Klimisch HJ, Freisberg KO. 1979a. [Report on the determination of acute toxicity (LC50) by inhalation of vinylidene chloride in Chinese striped hamsters (fed) during a 4-hour exposure period.] BASF Aktiengesellschaft, Ludwigshafen (German). HSE Translation No. 9M
- +*Klimisch HJ, Freisberg KO. 1979b. [Report on the determination of acute toxicity (LC50) by inhalation of vinylidene chloride in Chinese striped hamsters (fasting) during a 4-hour exposure period.] BASF Aktiengesellschaft, Ludwigshafen. (German). HSE Translation No. 9M
- Klimisch HJ, Deckardt K, Mitea D. 1979. [Subchronic toxicity of vinylidene chloride in rats after 6 weeks exposure.] BASF Aktiengesellschaft, Ludwigshafen 3 1. (German). HSE Translation No. 9Q.
- *Koch R, Schlegelmilch R, Wolf HU. 1988. Genetic effects of chlorinated ethylenes in the yeast *Saccharomyces cerevisiae*. *Mutat Res* 206:209-216.
- Kramer CG, Mutchler JE. 1972. The correlation of clinical and environmental measurements for workers exposed to vinyl chloride. *Am Ind Hyg Assoc J* 33:19-30.
- Krijgsheld KR, Gram TE. 1984. Selective induction of renal microsomal cytochrome P-450-linked monooxygenases by 1,1-dichloroethylene in mice. *Biochem Pharmacol* 33:1951-1956.
- *Krijgsheld KR, Lowe MC, Mimnaugh EG, et al. 1984. Selective damage to nonciliated bronchiolar epithelial cells in relation to impairment of pulmonary monooxygenase activities by 1,1-dichloroethylene in mice. *Toxicol Appl Pharmacol* 74:201-213.
- Krill RM, Sonzogni WC. 1986. Chemical monitoring of Wisconsin's groundwater. *J Am Water Works Assoc (September)*:70-75.
- *Krishnan K, Anderson ME, Clewell HJ, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang RSH, ed. *Toxicology of chemical mixtures. Case studies, mechanisms, and novel approaches*. San Diego, CA: Academic Press, 399-437.
- Kurginyan KA, Shirinyan VT. 1969. [Identification and quantitative determination of some impurities in chloropyrene.] *Arm Khim Zh (USSR)* 22:61-65. (Russian)
- *Kwok ES, Atkinson R. 1995. Estimation of hydroxyl radical reaction rate constants for gas-phase organic compounds using a structure-reactivity relationship: An update. *Atmos Environ* 29(14):1685-1695.
- *LaRegina J, Bozzelli JW, Harkov R, et al. 1986. Volatile organic compounds at hazardous waste sites and a sanitary landfill in New Jersey. *Environ Prog* 5:18-27.
- *Larranaga MD, Lewis RJ, Lewis RA. 2016. Vinylidene chloride. In: *Hawley's condensed chemical dictionary*. Hoboken, NJ: John Wiley & Sons, Inc., 1417.
- *Lash LH, Fisher JW, Lipscomb JC, et al. 2000. Metabolism of Trichloroethylene. *Environ Health Perspect* 108(Suppl 2):177-200.

8. REFERENCES

- +*Lee CC, Bhandari JC, Winston JM, et al. 1977. Inhalation toxicity of vinyl chloride and vinylidene chloride. *Environ Health Perspect* 21:25-32.
- +*Lee CC, Bhandari JC, Winston JM, et al. 1978. Carcinogenicity of vinyl chloride and vinylidene chloride. *J Toxicol Environ Health* 4:15-30.
- *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.
- Liebler DC. 1984. Formation and disposition of reactive metabolites in the biotransformation of vinylidene chloride. *Diss Abstr Int* 45(5):1445-1448.
- *Liebler DC, Guengerich FP. 1983. Olefin oxidation by cytochrome P-450: Evidence for group migration in catalytic intermediates formed with vinylidene chloride and trans-1-phenyl-1-butene. *Biochemistry* 22:5482-5489.
- *Liebler DC, Latwesen DG, Reeder TC. 1988. S-(2-Chloroacetyl)glutathione, a reactive glutathione thiol ester and a putative metabolite of 1,1-dichloroethylene. *Biochemistry* 27:3652-3657.
- *Liebler DC, Meredith MJ, Guengerich FP. 1985. Formation of glutathione conjugates by reactive metabolites of vinylidene chloride in microsomes and isolated hepatocytes. *Cancer Res* 45:186-193.
- *Lin SN, Fu FW, Bruckner JV, et al. 1982. Quantitation of 1,1- and 1,2-dichloroethylene in body tissues by purge-and-trap gas chromatography. *J Chromatogr* 244(2):311-320.
- Linenberg A, Davis R, Robinson D. 1991. Hazardous waste site measurements of low levels of chlorinated hydrocarbons using a portable gas chromatograph. *Hazard Mater Control* 4:42-46.
- *Luthra R, Kyle GM, Mehta PS, et al. 1984. Effects of carbon tetrachloride and 1,1-dichloroethylene on rat hepatic microsomal calcium- and/or magnesium-stimulated ATPase. *Biochem Pharmacol* 33:3295-3298.
- *Lyman WJ, Reehl WF, Rosenblatt DH. 1990. Rate of hydrolysis. In: *Handbook of chemical property estimation methods*. Washington, DC: American Chemical Society, 7-4.
- *Mackay D, Paterson S. 1981. Calculating fugacity. *Environ Sci Technol* 15:1006-1014.
- *Malaveille C, Planche G, Bartsch H. 1977. Factors for efficiency of the Salmonella/microsome mutagenicity assay. *Chem Biol Interact* 17(2):129-136.
- Maltoni C. 1977. Recent findings on the carcinogenicity of chlorinated olefins. *Environ Health Perspect* 21:1-5.
- *Maltoni C, Ciliberti A, Carretti D. 1982. Experimental contributions in identifying brain potential carcinogens in the petrochemical industry. *Ann NY Acad Sci* 381:216-249.
- Maltoni C, Cotti G, Morisi L, et al. 1977. Carcinogenicity bioassays of vinylidene chloride: Research plan and early results. *Med Lav* 68 (4):241-262.
- +*Maltoni C, Lefemine P, Cotti G, et al., eds. 1985. *Experimental research on vinylidene chloride carcinogenesis: Archives of research on industrial carcinogenesis*. Vol. 3. Princeton, NJ: Princeton Scientific Publishers.
- *Masuda Y, Nakayama N. 1983. Protective action of diethyldithiocarbamate and carbon disulfide against acute toxicities induced by 1,1-dichloroethylene in mice. *Toxicol Appl Pharmacol* 71:42-45.
- Maziasz TJ, Liu J, Madhu C, et al. 1991. The differential effects of hepatotoxicants on the sulfation pathway in rats. *Toxicol Appl Pharmacol* 110:365-373.
- McCarty PL, Siegrist H, Vogel TM, et al. 1986. *Biotransformation of groundwater contaminants: Final report*. Department of Civil Engineering, Stanford University, Stanford, CA.
- *McDougal JN, Jepson GW, Clewell HJ, et al. 1990. Dermal absorption of organic chemical vapors in rats and humans. *Fundam Appl Toxicol* 14(2):299-308. [http://doi.org/10.1016/0272-0590\(90\)90209-3](http://doi.org/10.1016/0272-0590(90)90209-3).
- McGeorge LJ, Krietzman SJ, Dupuy CJ, et al. 1992. National survey of drinking water standards and guidelines for chemical contaminants. *Am Water Works Assoc J* 84:72-76.
- *McGregor D, Brown AG, Cattanaach P, et al. 1991. Responses of the L5178Y mouse lymphoma forward mutation assay: V. Gases and vapors. *Environ Mol Mutagen* 17:122-129.
- *McKenna MJ, Watanabe PG, Gehring PG. 1977. Pharmacokinetics of vinylidene chloride in the rat. *Environ Health Perspect* 21:99-105.

8. REFERENCES

- *McKenna MJ, Zempel JA, Madrid EO, et al. 1978a. Metabolism and pharmacokinetic profile of vinylidene chloride in rats following oral administration. *Toxicol Appl Pharmacol* 45(3):821-835.
- +*McKenna MJ, Zempel JA, Madrid EO, et al. 1978b. The pharmacokinetics of [¹⁴C] vinylidene chloride in rats following inhalation exposure. *Toxicol Appl Pharmacol* 45(2):599-610.
- *McNab WW, Narasimhan TN. 1994. Degradation of chlorinated hydrocarbons and groundwater geochemistry: A field study. *Environ Sci Technol* 28(5):769-775.
<http://doi.org/10.1021/es00054a005>.
- Mendelsohn ML, Moore DH II, Lohman PHM. 1992. A method for comparing and combining short-term genotoxicity test data: Results and interpretation. *Mutat Res* 266:43-60.
- Moore L. 1980. Inhibition of liver microsome calcium pump by *in vivo* administration of CCl₄, CHCl₃, and 1,1-dichloroethylene (vinylidene chloride). *Biochem Pharmacol* 29:2505-2511.
- *Mortelmans K, Haworth S, Lawlor T, et al. 1986. Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. *Environ Mutagen* 8(suppl 7):1-119.
- Moslen MT, Reynolds ES. 1985. Rapid, substrate-specific, and dose-dependent deactivation of liver cytosolic glutathione S-transferase *in vivo* by 1,1-dichloroethylene. *Res Commun Chem Pathol Pharmacol* 47(1):59-72.
- *Moslen MT, Dunsford HA, Karnasuta C, et al. 1989a. Histochemical and immunocytochemical evidence of early, selective bile canaliculi injury after 1,1-dichloroethylene in rats. *Am J Pathol* 134:1099-1112.
- +*Moslen MT, Poisson LR, Reynolds ES. 1985. Cholestasis and increased biliary excretion of insulin in rats given 1,1-dichloroethylene. *Toxicology* 34:201-209.
- *Moslen MT, Whitehead RF, Ferguson AE, et al. 1989b. Protection by L-2-Oxothiazolidine-4-carboxylate, a cysteine prodrug, against 1,1-dichloroethylene hepatotoxicity in rats is associated with decreases in toxin metabolism and cytochrome P-450. *J Pharmacol Exp Ther* 248(1):157-163.
- *Moussa M, Forkert PG. 1992. 1,1-Dichloroethylene-induced alterations in glutathione and covalent binding in murine lung: Morphological, histochemical, and biochemical studies. *J Pathol* 166:199-207.
- +*Murray FJ, Nitschke KD, Rampy LW, et al. 1979. Embryotoxicity and fetotoxicity of inhaled or ingested vinylidene chloride in rats and rabbits. *Toxicol Appl Pharmacol* 49:189-202.
- Nakaguma H, Tajima K, Sato I, et al. 1992. Simultaneous determinations of 11 volatile chlorinated hydrocarbons in soil. *Jpn J Toxicol Environ Health* 38:240-246.
- *Nakahama T, Mizuno M, Otsuka Y, et al. 2001. Comparative study on the mode of action of chlorinated ethylenes on the expression of rat CYP forms. *J Health Sci* 47(3):278-287.
- *Nakajima T, Koyama Y, Sato A. 1982. Dietary modification of metabolism and toxicity of chemical substances-with special reference to carbohydrate. *Biochem Pharmacol* 31(6):1005-1011.
- *NAS/NRC. 1989. Report of the oversight committee. In: *Biologic markers in reproductive toxicology*. Washington, DC: National Academy of Sciences, National Research Council, National Academy Press, 15-35.
- *Neufeld ML, Sittenfield M, Wolk KF, et al. 1977. Market input/output studies--task I: Vinyl chloride. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances. EPA560677403.
- *NIOSH. 1976. National occupational hazard survey. Cincinnati, OH: U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health.
- NIOSH. 1978. Vinyl halides carcinogenicity: Current intelligence bulletin. Washington, DC: U.S. Department of Health, Education, and Welfare, National Institute for Occupational Safety and Health, 79-102.
- *NIOSH. 1984. 1,1-Dichloroethylene. National occupational exposure survey (1981-1983). Cincinnati, OH: National Institute for Occupational Safety and Health.
<https://web.archive.org/web/20111026175554/http://www.cdc.gov/noes/noes1/83011sic.html>. June 26, 2018.

8. REFERENCES

- NIOSH. 1992. NIOSH recommendations for occupational safety and health: Compendium of policy documents and statements. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service Center for Disease Control, National Institute for Occupational Safety and Health. PB92162536.
- *NIOSH. 1994. NIOSH manual of analytical methods. Method 1015. Vol. 2, 3rd ed. Cincinnati, OH: National Institute for Occupational Safety and Health. <https://www.cdc.gov/niosh/docs/2003-154/pdfs/1015.pdf>. June 28, 2018.
- *NIOSH. 2016. Vinylidene chloride: NIOSH pocket guide to chemical hazards. National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. <https://www.cdc.gov/niosh/npg/npgd0661.html>. May 29, 2019.
- Nirmalakhandan NN, Speece RE. 1988. Prediction of aqueous solubility of organic chemicals based on molecular structure. *Environ Sci Technol* 22:328-338.
- +*Nitschke KD, Smith FA, Quast JM, et al. 1983. A three-generation rat reproductive toxicity study of vinylidene chloride in the drinking water. *Fundam Appl Toxicol* 3:75-79.
- NJDH. 1992a. Population-based surveillance and etiological research of adverse reproductive outcomes and toxic wastes; Report on Phase IV-A: Public drinking water contamination and birthweight, fetal deaths, and birth defects: A cross-sectional study. Trenton, NJ: New Jersey Department of Health, jointly published with the Agency for Toxic Substances and Disease Registry. April 1992.
- NJDH. 1992b. Population-based surveillance and etiological research of adverse reproductive outcomes and toxic wastes; Report on Phase IV-B: Public drinking water contamination and birthweight, fetal deaths, and birth defects: A cross-sectional study. Trenton, NJ: New Jersey Department of Health, jointly published with the Agency for Toxic Substances and Disease Registry. April 1992.
- +*NTP. 1982. NTP technical report on the carcinogenesis bioassay of vinylidene chloride (CAS No. 75-35-4) in F344 rats and B6C3F1 mice (gavage study). Research Triangle Park, NC: National Toxicology Program, U.S. Department of Health and Human Services, Public Health Services, National Institutes of Health. Technical report series No. 228. NIH Publication No. 82-1784. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr228.pdf. February 2, 2017.
- *NTP. 2013. Draft OHAT approach for systematic review and evidence integration for literature-based health assessments- February 2013. National Toxicology Program, U.S. Department of Health and Human Services, Office of Health Assessment and Translation. https://ntp.niehs.nih.gov/ntp/ohat/evaluationprocess/draftohatapproach_february2013.pdf. April 13, 2016.
- +*NTP. 2015a. NTP technical report on the toxicology and carcinogenesis studies of vinylidene chloride (CAS No. 75-35-4) in F344/N rats and B6C3F1/N mice (Inhalation studies). Research Triangle Park, NC: National Toxicology Program. U.S. Department of Health and Human Services, National Institutes of Health. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr582_508.pdf. May 8, 2018.
- *NTP. 2015b. Handbook for conducting a literature-based health assessment using OHAT approach for systematic review and evidence integration. National Toxicology Program, U.S. Department of Health and Human Services, Office of Health Assessment and Translation.
- *NTP. 2016. Report on carcinogens, Fourteenth Edition. CASRN Index in MS Excel. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. <https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html#P>. February 28, 2017.
- +*Oesch F, Protic-Sabljić M, Friedberg T, et al. 1983. Vinylidene chloride: Changes in drug metabolizing enzymes, mutagenicity and relation to its targets for carcinogenesis. *Carcinogenesis* 4(8):1031-1038.
- *Oki N, Nakano T, Okuno T, et al. 1990. Emission of volatile chlorinated organic compounds by combustion of waste water organochlorine material. *Chemosphere* 21:761-770.
- *Okine LK, Gram TE. 1986. *In vitro* studies on the metabolism and covalent binding of [¹⁴C]1,1-dichloroethylene by mouse liver, kidney and lung. *Biochem Pharmacol* 35(16):2789-2795.

8. REFERENCES

- *Okine LK, Goochee JM, Gran TE. 1985. Studies on the distribution and covalent binding of 1,1-dichloroethylene in the mouse: Effects of various pretreatments on covalent binding *in vivo*. *Biochem Pharmacol* 34(22):4051-4057.
- *O'Neil MJ, Heckelman PE, Dobbelaar PH, et al. 2013. Vinylidene chloride. In: *The Merck Index: An encyclopedia of chemicals, drugs, and biologicals*. 15th ed. Whitehouse Station, NJ: The Royal Society of Chemistry, 1858.
- OSHA. 1982. Access to employee exposure and medical records; proposed modification; request for comments and notice of public hearing. Occupational Safety and Health Administration. *Fed Regist* 47:30420-30438.
- *OSHA. 2016a. Subpart D - Occupational health and environment controls. Section 1926.55 - Gases, vapors, fumes, dusts, and mists. Appendix A to Part 1926.55 - threshold limit values of airborne contaminants for construction. Code of Federal Regulations. 29 CFR 1926.55. <https://www.gpo.gov/fdsys/pkg/CFR-2016-title29-vol8/pdf/CFR-2016-title29-vol8-sec1926-55.pdf>. March 6, 2017.
- *OSHA. 2016b. Subpart Z - Toxic and hazardous substances. Air contaminants. Code of Federal Regulations. 29 CFR 1910.1000. <https://www.gpo.gov/fdsys/pkg/CFR-2016-title29-vol6/pdf/CFR-2016-title29-vol6-sec1910-1000.pdf>. March 6, 2017.
- *OSHA. 2016c. Subpart Z - Toxic and hazardous substances. Air contaminants. Table Z - Shipyards. Code of Federal Regulations. 29 CFR 1915.1000. <https://www.gpo.gov/fdsys/pkg/CFR-2016-title29-vol7/pdf/CFR-2016-title29-vol7-sec1915-1000.pdf>. March 6, 2017.
- *Ott MG, Fishbeck WA, Townsend JC, et al. 1976. A health study of employees exposed to vinylidene chloride. *J Occup Med* 18:735-738.
- Ott MG, Langner RR, Holder BB. 1975. Vinyl chloride exposure in a controlled industrial environment: A long-term mortality experience in 594 employees. *Arch Environ Health* 30(7):333-339.
- Pankow JF, Rosen ME. 1988. Determination of volatile compounds in water by purging directly to a capillary column with whole column cryotrapping. *Environ Sci Technol* 22(4):398-405.
- Parsons F, Lage GB. 1985. Chlorinated organics in simulated groundwater environments. *JAWWA* 77(5):52-59.
- Patterson JW, Kodukala PS. 1981. Emission and effluent control: Biodegradation of hazardous organic pollutants. *Chem Eng Progress* April:48-55.
- *Pearson CR, McConnel G. 1975. Chlorinated C₁ and C₂ hydrocarbons in the marine environment. *Proc R Soc Lond* 189:305-332.
- *Pellizzari ED, Zweidinger RA, Sheldon LS. 1985. GC/MS determination of volatile hydrocarbons in breath samples. In: Fishbein L, O'Neill IK, eds. *Environmental carcinogens selected methods of analysis*. Vol. 7. Lyon, France: World Health Organization, International Agency for Research on Cancer, 413-431.
- Pleil JD, Oliver K, McClenny WA. 1985. Volatile organic compounds in indoor air: A survey of various structures. Research Triangle Park, NC: U.S. Environmental Protection Agency, Environmental Monitoring Systems Lab. PB85198356. EPA600D85100.
- *Pleil JD, Oliver KD, McClenny WA. 1988. Ambient air analyses using nonspecific flame ionization and electron capture detection compared to specific detection by mass spectroscopy. *J Air Pollut Control Assoc* 38:1006-1010.
- *Plumb RH Jr. 1987. A comparison of ground water monitoring data from CERCLA and RCRA sites. *Ground Water Monit Rev* 7:94-100.
- +*Plummer JL, Hall PM, Ilsley AH, et al. 1990. Influence of enzyme induction and exposure profile on liver injury due to chlorinated hydrocarbon inhalation. *Pharmacol Toxicol* 67:329-335.
- Politziki GR, Beiniek D, Lahaniatis ES, et al. 1982. Determination of vapor pressures of nine organic chemicals adsorbed on silica gel. *Chemosphere* 11:1217-1229.
- +*Ponomarkov V, Tomatis L. 1980. Long-term testing of vinylidene chloride and chloroprene for carcinogenicity in rats. *Oncology* 37:136-141.

8. REFERENCES

- +*Prendergast JA, Jones RA, Jenkins LJ, et al. 1967. Effects on experimental animals of long-term inhalation of trichloroethylene, carbon tetrachloride, 1,1,1-trichloroethane, dichlorodifluoromethane, and 1,1-dichloroethylene. *Toxicol Appl Pharmacol* 10:270-289.
- *Putchá L, Bruckner JV, D'Souza R, et al. 1986. Toxicokinetics and bioavailability of oral and intravenous 1,1-dichloroethylene. *Fundam Appl Toxicol* 6:240-250.
- +*Quast JF. 1976. Pathology report on male and female rats exposed to vinylidene chloride vapors for 6 hours per day, 5 days per week during a 30-day period. Toxicology Research Laboratory, Health and Environmental Sciences, Dow Chemical U.S.A., Midland, MI.
- +*Quast JF, Humiston CG, Wade CE, et al. 1983. A chronic toxicity and oncogenicity study in rats and subchronic toxicity study in dogs on ingested vinylidene chloride. *Fundam Appl Toxicol* 3(1):55-62.
- +*Quast JF, McKenna MJ, Rampy LW, et al. 1986. Chronic toxicity and oncogenicity study on inhaled vinylidene chloride in rats. *Fund Appl Toxicol* 6:105-144.
- *Rajagopal R, Li P-C. 1991. Comparison of two screening methods for the detection of volatile organic compounds in ground water. *J Chemometrics* 5:321-333.
- *Rampy LW, Quast JF, Humiston CG, et al. 1977. Interim results of two-year toxicological studies in rats of vinylidene chloride incorporated in the drinking water or administered by repeated inhalation. *Environ Health Perspect* 21:33-43.
- Raymer JH, Pellizzari ED, Thomas KW, et al. 1991. Elimination of volatile organic compounds in breath after exposure to occupational and environmental microenvironments. *J Expo Anal Environ Epidemiol* 1:439-452.
- *Raymer JH, Thomas KW, Cooper SD, et al. 1990. A device for sampling of human alveolar breath for the measurement of expired volatile organic compounds. *J Anal Toxicol* 14(6):337-344.
- Reichert D, Henschler D. 1978. Uptake and hepatotoxicity of 1,1-dichloroethylene by the isolated blood-perfused rat liver. *Int Arch Occup Environ Health* 41:169-178.
- *Reichert D, Werner HW, Henschler D. 1978. Role of liver glutathione in 1,1-dichloroethylene metabolism and hepatotoxicity in intact rats and isolated perfused rat liver. *Arch Toxicol* 41:169-179.
- *Reichert D, Werner HE, Metzler M, et al. 1979. Molecular mechanism of 1,1-dichloroethylene toxicity: Excreted metabolites reveal different pathways of reactive intermediates. *Arch Toxicol* 42:159-169.
- +*Reitz RH, Watanabe PG, McKenna MJ, et al. 1980. Effects of vinylidene chloride on DNA synthesis and DNA repair in the rat and mouse: A comparative study with dimethylnitrosamine. *Toxicol Appl Pharmacol* 52(3):357-370.
- *RePORTER. 2017. 1,1-Dichloroethene. National Institutes of Health, Research Portfolio Online Reporting Tools. <http://projectreporter.nih.gov/reporter.cfm>. May 30, 2018.
- *Reynolds E, Moslen M. 1977. Damage to hepatic cellular membranes by chlorinated olefins with emphasis on synergism and antagonism. *Environ Health Perspect* 21:137-147.
- +*Reynolds ES, Kanz MF, Chieco P, et al. 1984. 1,1-Dichloroethylene: An apoptotic hepatotoxin? *Environ Health Perspect* 57:313-320.
- *Reynolds ES, Moslen MT, Boor PJ, et al. 1980. 1,1-Dichloroethylene hepatotoxicity. Time course of GSH changes and biochemical aberrations. *Am J Pathol* 101(2):331-344.
- Reynolds ES, Moslen MT, Szabo S, et al. 1975. Hepatotoxicity of vinyl chloride and 1,1-dichloroethylene. *Am J Pathol* 81:219-236.
- *Roldan-Arjona T, Garcia-Predrajas MD, Luque-Romero FL, 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.
- *Rooney AA, Boyles AL, Wolfe MS, et al. 2014. Systematic review and evidence integration for literature-based environmental health science assessments. *Environ Health Perspect* 122(7):711-718. 10.1289/ehp.1307972. *Rossberg M, Lendle W, Tegel A, et al. 1986. Chlorinated hydrocarbons. In: Gerhartz W, Yamamoto YS, Campbell FT, et al., eds. *Ullman's encyclopedia of industrial chemistry*. Fifth edition, Vol. A6. New York, NY: UCH Publishers, 294-297.

8. REFERENCES

- *Rowe BL, Toccalino PL, Moran MJ, et al. 2007. Occurrence and potential human-health relevance of volatile organic compounds in drinking water from domestic wells in the United States. *Environ Health Perspect* 115(11):1539-1546.
- *Sabljic A, Gusten H. 1990. Predicting the night-time nitrate radical reactivity in the troposphere. *Atmos Environ Part A Gen Top* 24(1):73-78.
- *Sabljic A, Gusten H, Verhaar H, et al. 1995. QSAR modelling of soil sorption. Improvements and systematics of log K_{oc} vs. log K_{ow} correlations. *Chemosphere* 31(11/12):4489-4514.
- Sapigni E, Paolini M, Mesirca R, et al. 1991. Short-chain aliphatic halocompounds *in vivo* effects on microsomal monooxygenase P450-dependent system. *Pharmacol Res* 25:77-78.
- *Sasaki M, Sugimura K, Yoshida MA, et al. 1980. Cytogenetic effects of 60 chemicals on cultured human and Chinese hamster cells. *La Kromosomo II* 20:574-584.
- *Sato A, Nakajima T, Koyama Y. 1983. Interaction between ethanol and carbohydrate on the metabolism in rat liver of aromatic and chlorinated hydrocarbons. *Toxicol Appl Pharmacol* 68:242-249.
- *Sawada M, Sofuni T, Ishidate M. 1987. Cytogenetic studies on 1,1-dichloroethylene and its two isomers in mammalian cells *in vitro* and in *in vivo*. *Mutat Res* 187:157-163.
- Sax NI, Lewis RJ Jr. 1987. Vinylidene chloride. In: *Hawley's condensed chemical dictionary*. 11th ed. New York, NY: Van Nostrand Reinhold Co, 1224.
- Schuetzle D, Cronn D, Crittenden AL, et al. 1975. Molecular composition of secondary aerosol and its possible origin. *Environ Sci Technol* 9:838.
- Shamat NA, Maier WJ. 1980. Kinetics of biodegradation of chlorinated organics. *J Water Poll Control Fed* 52:2158-2166.
- +*Short RD, Minor JL, Winston JM, et al. 1977a. Toxicity studies of selected chemicals: Task II. The development of vinylidene chloride inhaled by rats and mice during gestation. Washington, DC: U.S. Environmental Protection Agency. EPA560677022.
- +*Short RD, Minor JL, Winston JM, et al. 1977b. A dominant lethal study in male rats after repeated exposures to vinyl chloride or vinylidene chloride. *J Toxicol Environ Health* 3:965-968.
- +*Short RD, Winston JM, Minor JL, et al. 1977c. Effect of various treatments on toxicity of inhaled vinylidene chloride. *Environ Health Perspect* 21:125-129.
- +*Short RD, Winston JM, Minor JL, et al. 1977d. Toxicity of vinylidene chloride in mice and rats and its alteration by various treatments. *J Toxicol Environ Health* 3:913-921.
- Sidhu KS. 1991. Standard setting processes and regulations for environmental contaminants in drinking water: State versus federal needs and viewpoints. *Regul Toxicol Pharmacol* 13:293-308.
- +*Siegel J, Jones RA, Coon A, et al. 1971. Effects on experimental animals of acute, repeated and continuous inhalation exposures to dichloroacetylene mixtures. *Toxicol Appl Pharmacol* 18:168-174.
- Siegers CP, Steffen B, Younes M. 1988. Antidotal effects of deferoxamine in experimental liver injury - role of lipid peroxidation. *Pharmacol Res Comm* 20(4):337-343.
- *Siletnik LM, Carlson GP. 1974. Cardiac sensitizing effects of 1,1-dichloroethylene: Enhancement by phenobarbital pretreatment. *Arch Int Pharmacodyn* 210:359-364.
- *Simmonds AC, Reilly CA, Baldwin RM, et al. 2004. Bioactivation of 1,1-dichloroethylene to its epoxide by CYP2E1 and CYP2F enzymes. *Drug Metab Dispos* 32(9):1032-1039.
- *Singh HB, Salas LJ, Smith AL, et al. 1981. Measurements of some potentially hazardous organic chemicals in urban environments. *Atmos Environ* 15:601-612.
- *Singh HB, Salas LJ, Stiles RE. 1982. Distribution of selected gaseous organic mutagens and suspect carcinogens in ambient air. *Environ Sci Technol* 16:872-880.
- Slivon LE, Ho JS, Budde WL. 1992. Real-time measurement of volatile organic compounds in water using mass spectrometry with a helium-purged hollow fiber membrane. *ACS Symp Ser* 508:169-177.
- Spain MA, Middleditch BS, Bafus DA, et al. 1985. Dehydrohalogenation of atmospheric contaminants in the space cabin. *Aviation Space Environ Med* 56:262-264.

8. REFERENCES

- *Squillace PJ, Moran MJ, Lapman WW, et al. 1999. Volatile organic compounds in untreated groundwater of the United States, 1985-1995. *Environ Sci Technol* 33(23):4176-4187.
- *Staples CA, Werner A, Hoogheem T. 1985. Assessment of priority pollutant concentrations in the United States using STORET database. *Environ Toxicol Chem* 4:131-142.
- +*Szabo S, Jaeger RJ, Moslen MT, et al. 1977. Modification of 1,1-dichloroethylene hepatotoxicity by hypothyroidism. *Toxicol Appl Pharmacol* 42:367-376.
- *Tabak HH, Quave SA, Mashni CI, et al. 1981. Biodegradability studies with organic priority pollutant compounds. *J Water Poll Control Fed* 53:1503-1518.
- Thiess AM, Frentzel-Beyme R, Penning E. 1979. Mortality study of vinylidene chloride exposed persons. In: Hien C, Kilian DJ, eds. *Proceedings of the 5th Medichem Congress*. San Francisco, CA: University of California at San Francisco, 270-278.
- *Torkelson TR, Rowe VK. 1981. Halogenated aliphatic hydrocarbons containing chlorine, bromine, and iodine: Vinylidene chloride. In: Clayton GD, Clayton FE, eds. *Patty's industrial hygiene and toxicology*. Volume 2B, 3rd ed. New York, NY: John Wiley and Sons, 3545-3550.
- *Tornqvist M, Osterman-Golkar S, Kautiainen A, et al. 1986. Tissue doses of ethylene oxide in cigarette smokers determined from adduct levels in hemoglobin. *Carcinogenesis* 7(9):1519-1521.
- *TRI15. 2016. TRI explorer: Providing access to EPA's toxics release inventory data. Washington, DC: U.S. Environmental Protection Agency, Office of Information Analysis and Access. Office of Environmental Information. Toxics Release Inventory. <http://www.epa.gov/triexplorer/>. October 4, 2018.
- *Tuazon EC, Atkinson R, Aschmann SM, et al. 1988. Atmospheric reactions of chloroethenes with the OH radical. *Int J Chem Kinet* 20(3):241-266.
- *USGS. 2006. Investigation of contaminated ground-water contamination at solid waste management Unit 12, Naval Weapons Station Charleston, North Charleston, South Carolina. <https://pubs.usgs.gov/sir/2009/5166/pdf/sir20095166.pdf>. April 20, 2017.
- *Vamvakas S, Anders MW. 1990. Formation of reactive intermediates by phase II enzymes: Glutathione-dependent bioactivation reactions. In: Witmer CM, ed. *Advances in experimental medicine and biology*. New York, NY: Plenum Publishing Co., 13-24.
- *Van Duuren BL, Goldschmidt BM, Loewengart G, et al. 1979. Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. *J Natl Cancer Inst* 63(6):1433-1439.
- *Van't Hof J, Schairer LA. 1982. Tradescantia assay system for gaseous mutagens: A report of the U.S. Environmental Protection Agency Gene-Tox Program. *Mutat Res* 99:303-315.
- Varma MM. 1985. A case study of Moyer Landfill site, Collegetown, PA. *Proceedings of the Pennsylvania Academy of Sciences* 59:67-73.
- *Veith GD, DeFoe D, Knuth M. 1985. Structure-activity relationships for screening organic chemicals for potential ecotoxicity effects. *Drug Metab Rev* 15:1295-1303.
- *Verschuere K. 1983. *Handbook of environmental data of organic chemicals*. 2nd ed. New York, NY: Van Nostrand Reinhold Co., 487-488.
- Victorin K, Stahlberg M. 1991. Mutagenic activity of photoreaction products formed from chlorinated ethenes and nitrogen dioxide. *Environ Res* 55:178-187.
- *Viola PL, Caputo A. 1977. Carcinogenicity studies on vinylidene chloride. *Environ Health Perspect* 21:45-47.
- *Vogel TM, McCarty PL. 1985. Biotransformation of tetrachloroethylene to trichloroethylene, dichloroethylene, vinyl chloride, and carbon dioxide under methanogenic conditions. *Appl Environ Microbiol* 49(5):1080-1083.
- *Wallace LA. 1991. Comparison of risks from outdoor and indoor exposure to toxic chemicals. *Environ Health Perspect* 95:7-13.
- *Wallace L, Pellizzari E, Hartwell T, et al. 1984. Personal exposure to volatile organic compounds: I. Direct measurements in breathing-zone air, water, food, and exhaled breath. *Environ Res* 35:293-319.

8. REFERENCES

- 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* 28:603-608.
- Wallace L, Pellizzari E, Hartwell T, et al. 1987. The TEAM study: Personal exposures to toxic substances in air, drinking water, and breath of 400 residents of New Jersey, North Carolina, and North Dakota. *Environ Res* 43:290-307.
- Wallace L, Zweidinger R, Erickson MCS, et al. 1982. Monitoring individual exposure: Measurements of volatile organic compounds in breathing-zone air, drinking water, and exhaled breath. *Environ Int* 8:269-282.
- *Walling JF. 1984. The utility of distributed air volume sets when sampling ambient air using solid absorbents. *Atmos Environ* 18(4):855-859.
- *Wang T, Lenahan R, Kanik M. 1985a. Impact of trichloroethylene contaminated groundwater discharged to the Main Canal and Indian River Lagoon, Vero Beach, Florida. *Bull Environ Contam Toxicol* 34:578-586.
- *Wang TC, Lenahan R, Kanik M, et al. 1985b. The removal of trichloroethylene contaminated groundwater at Vero Beach, Florida. *Arch Environ Contam Toxicol* 14(60):719-723.
- *Warbrick EV, Dearman RJ, Ashby J, et al. 2001. Preliminary assessment of the skin sensitizing activity of selected rodent carcinogens using the local lymph node assay. *Toxicology* 163(1):63-69.
- *Waskell L. 1978. A study of the mutagenicity of anesthetics and their metabolites. *Mutat Res Lett* 57:141-153.
- *Watanabe PG, Reitz RH, Schumann AM, et al. 1980. Implications of the mechanisms of tumorigenicity for risk assessment. *The Scientific Basis of Toxicity Assessment* 6:69-81.
- *Waxweiler R. 1981. Epidemiologic problems associated with exposure to several agents. *Environ Health Perspect* 42:51-56.
- *Weiss G, cd. 1986. Vinyl chloride. Hazardous chemicals data book. 2nd ed. Park Ridge, NJ: Noyes Data Corporation, 1014.
- *Westrick JJ, Mello JW, Thomas RF. 1984. The groundwater supply survey. *J Am Water Works Assoc* 1:52-59.
- WHO. 1984. Guidelines for drinking-water quality. Recommendations. Geneva, Switzerland: World Health Organization.
- *WHO. 2003. 1,1-Dichloroethene (vinylidene chloride). Concise international chemical assessment document. World Health Organization, United Nations Environment Programme. Document 51. <http://www.who.int/ipcs/publications/cicad/en/cicad51.pdf>. April 20, 2017.
- *WHO. 2010. Guidelines for indoor air quality: Selected pollutants. Geneva, Switzerland: World Health Organization. http://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf. January 08, 2014.
- *WHO. 2017. Guidelines for drinking-water quality. Fourth edition incorporating the first addendum. Geneva, Switzerland: World Health Organization. <http://apps.who.int/iris/bitstream/10665/254637/1/9789241549950-eng.pdf?ua=1>. February 28, 2017.
- *Wilson BH, Smith GB, Rees JF. 1986. Biotransformations of selected alkylbenzenes and halogenated aliphatic hydrocarbons in methanogenic aquifer material: A microcosm study. *Environ Sci Technol* 20:997-1002.
- Wilson JT, McNabb JF. 1983. Biological transformation of organic pollutants in groundwater, EOS August:501-505.
- Wilson JT, Enfield CG, Dunlap WJ, et al. 1981. Transport and fate of selected organic pollutants in a sandy soil. *J Environ Qual* 10:501-506.
- Woodward KN, McDonald A, Joshi S. 1991. Ranking of chemicals for carcinogenic potency—a comparative study of 13 carcinogenic chemicals and an examination of some of the issues involved. *Carcinogenesis* 12:1061-1066.

8. REFERENCES

- *WQP. 2017. 1,1-Dichloroethene. Water quality portal. 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). May 15, 2017.
- *WQP. 2018. 1,1-Dichloroethene. Water quality portal. 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/>. May 14, 2018.
- *Wright PB, Moore L. 1991. Potentiation of the toxicity of model hepatotoxicants by acetaminophen. *Toxicol Appl Pharmacol* 109:327-335.
- Yamaguchi K, Nishi S. 1991. [GC-MS determination of dichloroethylene isomers in water. *Bunseki Kagaku* 40:T131-T136. (Japanese)]
- *Yamazaki H, Oda Y, Funae Y, et al. 1992. Participation of rat liver cytochrome P450 2E1 in the activation of N-nitrosodimethylamine and N-nitrosodiethylamine to products genotoxic in an acetyltransferase-overexpressing *Salmonella typhimurium* strain (NM2009). *Carcinogenesis* 13(6):979-985. <http://doi.org/10.1093/carcin/13.6.979>.
- *Yasuhara A, Morita M. 1988. Formation of chlorinated aromatic hydrocarbons by thermal decomposition of vinylidene chloride polymer. *Environ Sci Technol* 22:646-650.
- +*Zeller H, Klimisch HJ, Freisberg KO. 1979a. [Report on the determination of acute toxicity (LC50) of vinylidene chloride in Sprague-Dawley rats (fed) during a 4-hour exposure]. BASF Aktiengesellschaft, Ludwigshafen FRG. HSE Translation No. 9K. (German)
- +*Zeller H, Klimisch HJ, Freisberg KO. 1979b. [Report on the determination of acute toxicity (LC50) by inhalation of vinylidene chloride in vapour form in Sprague Dawley rats (fasting) during a 4 hour exposure.] BASF Aktiengesellschaft, Ludwigshafen. HSE Translation No. 9L. (German)
- +*Zeller H, Klimisch HJ, Freisberg KO. 1979c. [Report on the determination of acute toxicity (LC50) by inhalation of vinylidene chloride in NMRI mice (fasting) during a 4-hour exposure.] BASF Aktiengesellschaft, Ludwigshafen. HSE Translation No. 9P. (German)
- *Zhang J, Joslyn AP, Chiu PC. 2006. 1,1-Dichloroethene as a predominant intermediate of microbial trichloroethene reduction. *Environ Sci Technol* 40(6):1830-1836.

APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥ 365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, 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 Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,1-Dichloroethene
CAS Numbers: 75-35-4
Date: December 2019
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute

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

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

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,1-Dichloroethene
CAS Numbers: 75-35-4
Date: December 2019
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate
MRL 0.001 ppm (provisional)
Critical Effect: Atrophy in nasal olfactory epithelium
Reference: NTP 2015a
Point of Departure: BMCL_{10HEC} of 0.043 ppm
Uncertainty Factor: 30
LSE Graph Key: 40
Species: Rat

MRL Summary: A provisional intermediate-duration inhalation MRL of 0.001 ppm has been derived for 1,1-dichloroethene based on combined incidences of atrophy in nasal olfactory epithelium of F344/N male and female rats exposed to 1,1-dichloroethene vapor for 6 hours/day, 5 days/week for 14 weeks (NTP 2015a). The MRL is based on a BMCL_{10HEC} of 0.043 ppm and a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

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

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

APPENDIX A

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

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

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

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

Summary of the Principal Study:

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

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

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

APPENDIX A

- **Hepatic:** Hepatic centrilobular cytoplasmic alterations were observed in males at 12.5 ppm (6/10 rats) and all males at higher exposure levels. Exposure-related liver lesions in female rats were limited to hepatocellular cytoplasmic vacuolization in all females exposed at 50 and 100 ppm.
- **Renal:** Slightly increased relative kidney weights were noted in males at 6.25, 12.5, and 100 ppm (3–7% greater than controls), but not at 25 or 50 ppm. Females exhibited exposure concentration-related significantly increased relative kidney weights at exposure levels ≥ 12.5 -ppm (6–16% greater than controls). There was no evidence of exposure-related increased incidences of renal lesions in males or females (NOAEL of 100 ppm).
- **Reproductive:** At the highest exposure level (100 ppm), males exhibited 5% decreased sperm motility and 15–16% decreased spermatid count.

APPENDIX A

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

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

^aIncidence (severity; 1 = minimal, 2 = mild, 3 = moderate, 4 = marked).

^bSignificantly different from chamber control incidence by the Poly-3 test ($p < 0.05$).

^cSignificantly different from chamber control incidence by the Poly-3 test ($p < 0.01$).

^dMineralization was described as "deposits of greyish-blue material in the basement membrane, often underlying an atrophic epithelium or disrupting the epithelium, and most often affecting the lateral walls and turbinates." The deposits were not actually within the olfactory epithelium.

^eSignificantly different from chamber control incidence by Fisher's exact test ($p < 0.05$) performed by SRC, Inc.

^fSignificantly different from chamber control incidence by Fisher's exact test ($p < 0.01$) performed by SRC, Inc.

Source: NTP 2015a

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

APPENDIX A

candidate critical effect because this lesion was not observed at the lowest exposure level (6.25 ppm) resulting in atrophy and necrosis in olfactory epithelium.

The incidence data for atrophy and for necrosis in the olfactory epithelium of the male and the female rats were fit to all standard dichotomous models in the EPA Benchmark Dose Software (BMDS, version 2.7.0.1) using a benchmark response (BMR) of 10% change in incidence from controls. Based on relatively similar male and female exposure concentration-response data for atrophy and for necrosis in olfactory epithelium, incidence data for both sexes were also combined to increase the statistical power of the benchmark result. Analysis of the data for necrosis in males and females using EPA's Categorical Regression Analysis (Cater 3.1) software confirmed the acceptability of combining male and female incidence data. Adequate model fit was judged by three criteria: goodness-of-fit statistics (p -value >0.1), scaled residuals (within ± 2 units) at the data points (except the control) closest to the predefined BMR, and visual inspection of the proximity of the predicted dose-response curve to the observed data points closest to the BMR. For each dataset, among all models providing adequate fit to the data, the lowest BMCL was selected as the point of departure (POD) when the difference between the BMCLs estimated from these models was >3 -fold; otherwise, the BMCL from the model with the lowest Akaike Information Criterion (AIC) was chosen. A BMR of 10% over the control incidence was used.

Model predictions for nasal olfactory epithelium atrophy in the male rats are presented in Table A-3. All models provided adequate fit to the data as judged by goodness-of-fit p -value and scaled residual criteria. The $BMCL_{10}$ values varied by >3 -fold; therefore, the lowest $BMCL_{10}$ (0.42 ppm from the 1-degree Multistage model) was initially considered as a potential POD. However, visual inspection of the 1-degree Multistage fit (Figure A-1) revealed relatively poor correlation between predicted incidence and observed incidence in the region corresponding to the two experimental data points closest to the control value; therefore, the model fit was considered inadequate. All other models provided adequate fit; among these models, the lowest $BMCL_{10}$ (0.72 ppm) from the 4-degree Multistage model was selected as a potential POD because the $BMCL_{10}$ values varied by >3 -fold. The 4-degree Multistage model fit is presented in Figure A-2.

APPENDIX A

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

Model	DF	χ^2	χ^2 Goodness- of-fit p-value ^a	Scaled residuals ^b			AIC	BMC ₁₀ (ppm)	BMCL ₁₀ (ppm)
				Dose below BMC	Dose above BMC	Overall largest			
Gamma ^c	5	0.01	1	0	-0.02	0.12	15.49	4.81	2.17
Logistic	4	0	1	0	0	0	17.46	5.67	2.29
LogLogistic ^d	5	0	1	0	0	0.008	15.46	5.66	3.01
LogProbit ^d	4	0	1	0	0	0	17.46	5.54	2.85
Multistage (1-degree) ^{e,f}	5	4.14	0.53	-1.57	1.23	-1.57	20.95	0.65	0.42
Multistage (2-degree) ^e	5	1.13	0.95	0	-0.75	0.76	17.13	2.37	0.74
Multistage (3-degree) ^e	5	0.16	1	0	-0.23	0.32	15.72	3.55	0.83
Multistage (4-degree)^{e,g}	4	0.15	1	0	-0.22	0.31	17.71	3.57	0.72
Multistage (5-degree) ^e	3	0.05	1	0	-0.12	0.19	19.54	3.78	0.74
Probit	4	0	1	-0.001	0	0.003	17.46	4.97	2.00
Weibull ^c	4	0	1	0	0	0.002	17.46	4.52	1.72

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMC; also the largest residual at any concentration.

^cPower restricted to ≥ 1 .

^dSlope restricted to ≥ 1 .

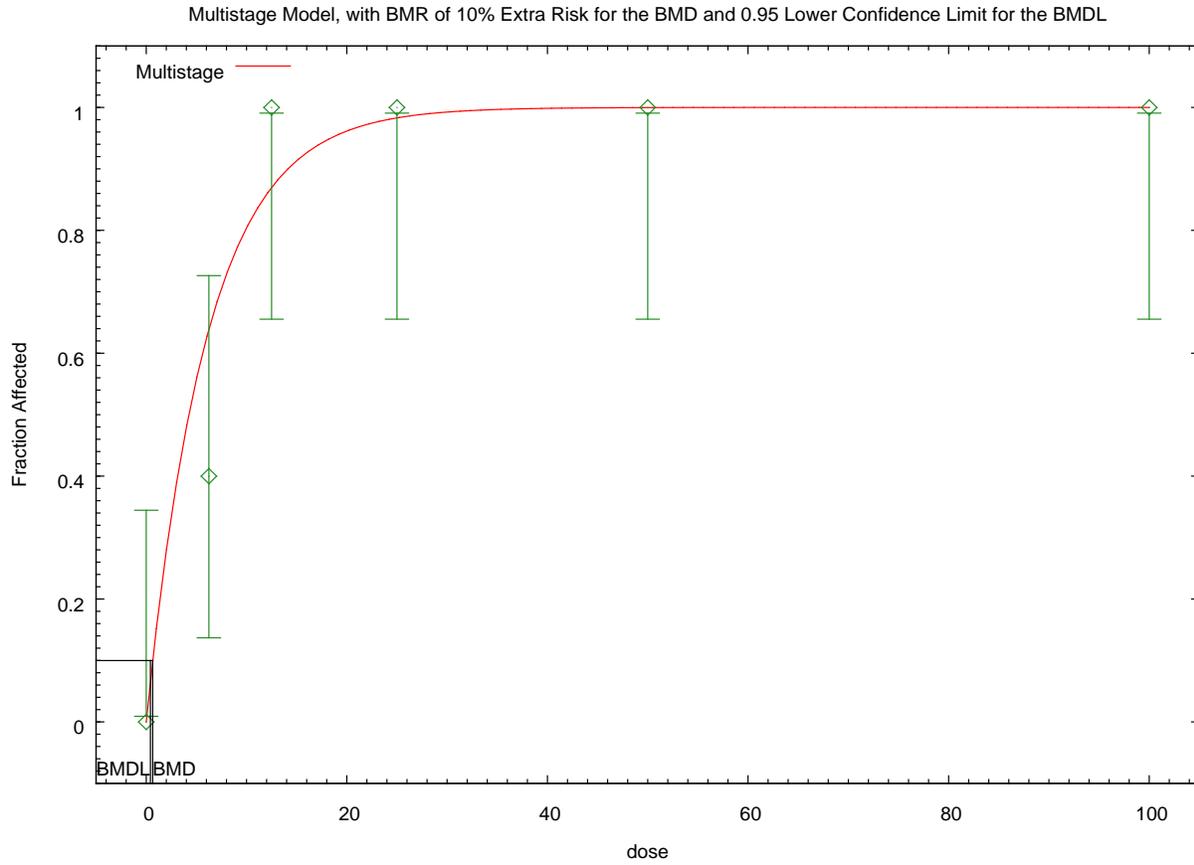
^eBetas restricted to ≥ 0 .

^fThe 1-degree Multistage model was judged to provide inadequate fit to the data based on visual inspection of the predicted dose-response curve (Figure A-1).

^gAmong models providing adequate fit to the data, BMCL₁₀ values varied by >3-fold; therefore, the model with the lowest BMCL₁₀ was selected as the best-fitting model (4-degree Multistage).

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

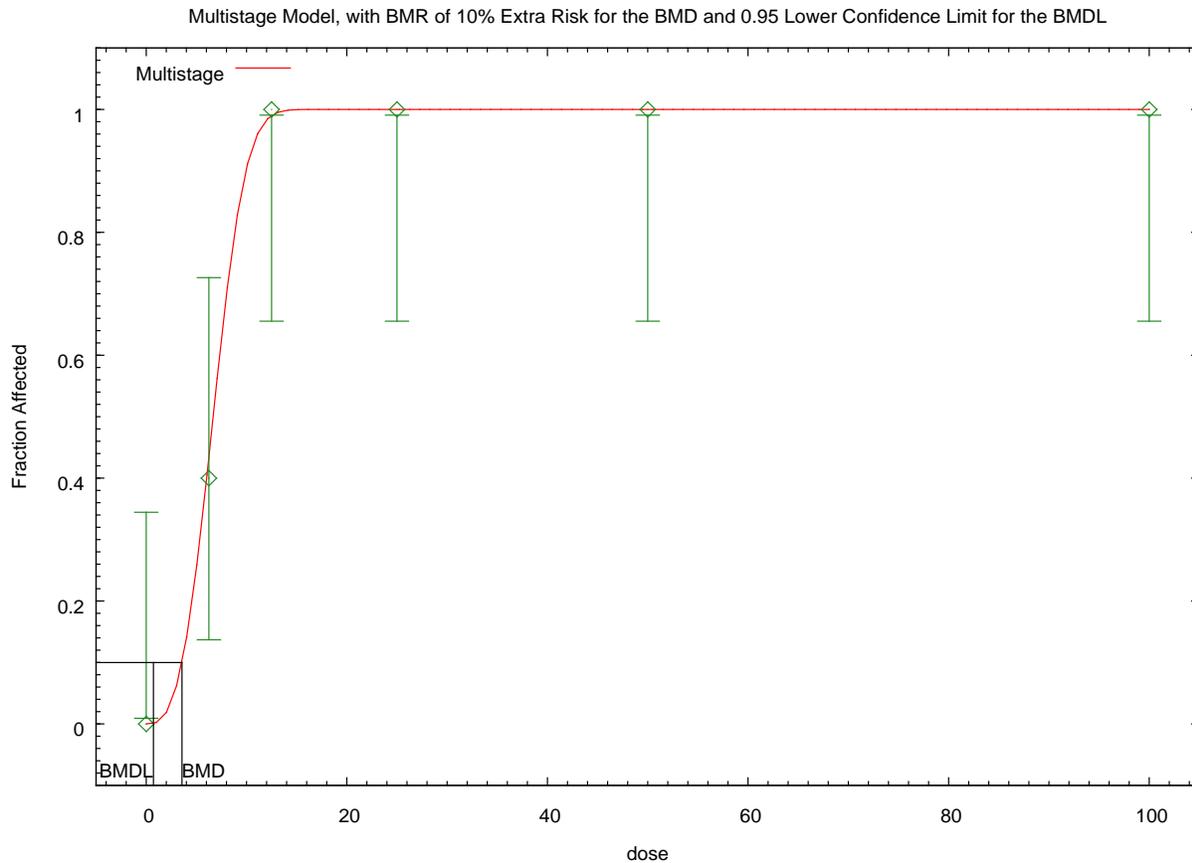
Figure A-1. Fit of 1-Degree Multistage Model for Nasal Olfactory Epithelium Atrophy in Male F344/N Rats Exposed to 1,1-Dichloroethene Vapor 6 Hours/Day, 5 Days/Week for 14 Weeks (Dose in ppm)



08:43 05/09 2018

APPENDIX A

Figure A-2. Fit of 4-Degree Multistage Model for Nasal Olfactory Epithelium Atrophy in Male F344/N Rats Exposed to 1,1-Dichloroethene Vapor 6 Hours/Day, 5 Days/Week for 14 Weeks (Dose in ppm)



08:43 05/09 2018

Model predictions for nasal olfactory epithelium atrophy in the female rats are presented in Table A-4. The 1-degree Multistage model provided inadequate fit to the data (scaled residual -2.30 at an exposure concentration near the BMC). All other models provided adequate fit to the data as judged by goodness-of-fit p-value and scaled residual criteria. The lowest $BMCL_{10}$ of 1.23 ppm (from the 4-degree Multistage model) was selected as a potential POD based on nasal olfactory epithelium atrophy in the female rats because the $BMCL_{10}$ values varied by >3-fold. The 4-degree Multistage model fit is presented in Figure A-3.

APPENDIX A

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

Model	DF	χ^2	χ^2 Goodness- of-fit p-value ^a	Scaled residuals ^b			AIC	BMC ₁₀ (ppm)	BMCL ₁₀ (ppm)
				Dose below BMC	Dose above BMC	Overall largest			
Gamma ^c	5	0.13	1	0	-0.15	0.32	12.24	5.48	3.93
Logistic	4	0	1	0	0	0	14.01	6.00	3.56
LogLogistic ^d	5	0	1	0	0	0.01	12.01	5.97	4.37
LogProbit ^d	4	0	1	0	0	0	14.01	5.97	4.35
Multistage (1-degree) ^{e,f}	5	8.08	0.15	0	-2.30	-2.30	22.55		
Multistage (2-degree) ^e	5	3.25	0.66	0	-1.40	-1.40	16.59	2.76	1.26
Multistage (3-degree) ^e	5	1.18	0.95	0	-0.87	-0.87	13.67	4.01	1.68
Multistage (4-degree)^{e,g}	4	1.15	0.89	0	-0.82	-0.82	15.66	4.05	1.23
Multistage (5-degree) ^e	3	0.38	0.95	0	-0.36	0.50	16.63	4.71	1.50
Probit	4	0	1	0	0	0	14.01	5.83	3.31
Weibull ^c	4	0	1	0	0	0.002	14.01	5.52	3.42

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMC; also the largest residual at any concentration.

^cPower restricted to ≥ 1 .

^dSlope restricted to ≥ 1 .

^eBetas restricted to ≥ 0 .

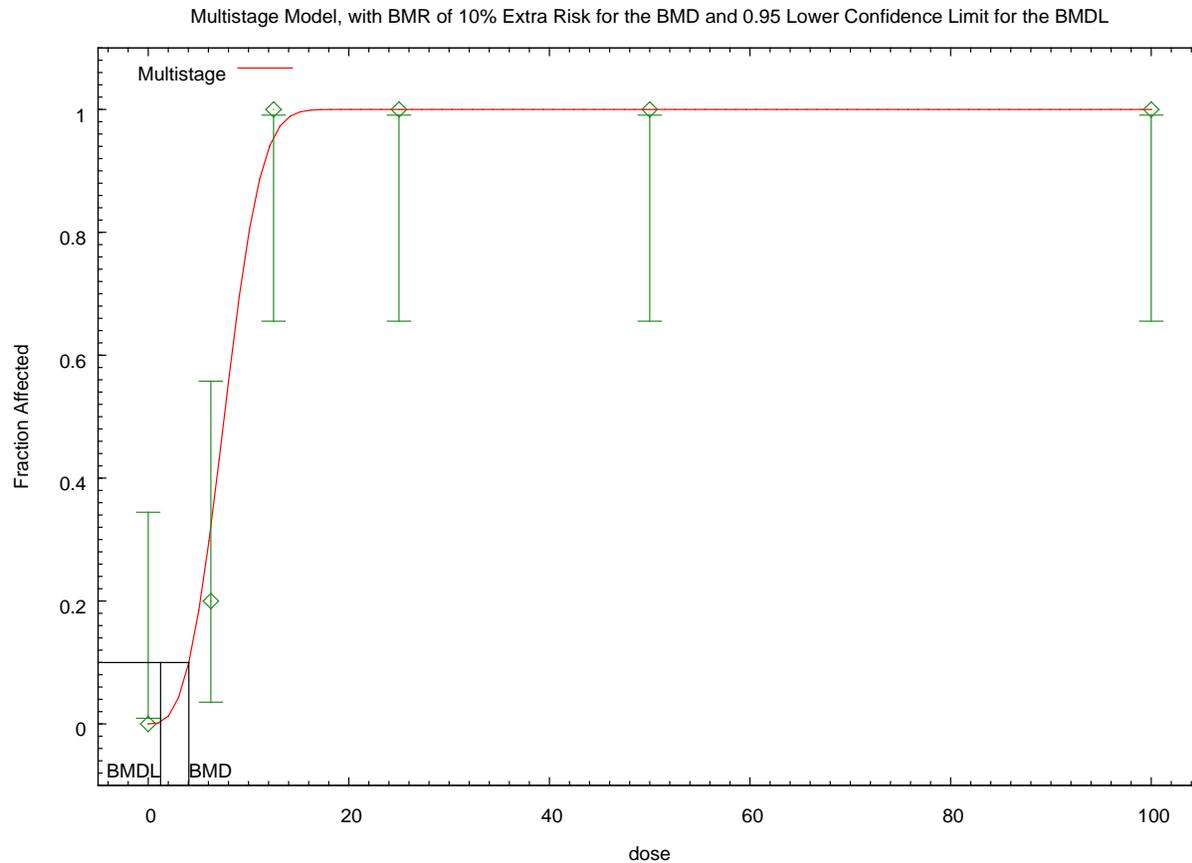
^fThe 1-degree Multistage model was judged to provide inadequate fit to the data (scaled residual -2.30 at an exposure concentration near the BMC).

^gAmong models providing adequate fit to the data, BMCL₁₀ values varied by >3-fold; therefore, the model with the lowest BMCL₁₀ was selected as the best-fitting model (4-degree Multistage).

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

APPENDIX A

Figure A-3. Fit of 4-Degree Multistage Model for Nasal Olfactory Epithelium Atrophy in Female F344/N Rats Exposed to 1,1-Dichloroethene Vapor 6 Hours/Day, 5 Days/Week for 14 Weeks (Dose in ppm)



Model predictions for combined incidences of nasal olfactory epithelium atrophy in the male and female rats are presented in Table A-5. The 1-degree Multistage model provided inadequate fit to the dataset (goodness-of-fit p-value <0.1). All other models provided adequate fit to the data. The 4-degree Multistage model BMCL₁₀ of 1.52 ppm (lowest BMCL₁₀) was selected as a potential POD based on combined incidences of nasal olfactory epithelium atrophy in the male and female rats because the BMCL₁₀ values varied by nearly 3-fold. The 4-degree Multistage model fit is presented in Figure A-4.

APPENDIX A

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

Model	DF	χ^2	χ^2 Goodness- of-fit p-value ^a	Scaled residuals ^b			AIC	BMC ₁₀ (ppm)	BMCL ₁₀ (ppm)
				Dose below BMC	Dose above BMC	Overall largest			
Gamma ^c	5	0.09	1	0	-0.086	0.28	26.60	5.12	3.91
Logistic	4	0	1	0	0	0	28.43	5.82	3.53
LogLogistic ^d	5	0	1	0	0	0.013	26.43	5.80	4.37
LogProbit ^d	4	0	1	0	0	0	28.43	5.75	4.29
Multistage (1-degree) ^{e,f}	5	11.79	0.038	0	-2.72	-2.72	41.82		
Multistage (2-degree) ^e	5	3.98	0.55	0	-1.49	-1.49	32.12	2.56	1.49
Multistage (3-degree) ^e	5	0.95	0.97	0	-0.68	0.70	27.87	3.81	1.89
Multistage (4-degree)^{e,g}	4	0.18	1	0	-0.18	0.38	28.75	4.35	1.52
Multistage (5-degree) ^e	3	0.07	1	0	-0.12	0.23	30.55	4.55	1.58
Probit	4	0	1	0	0	0	28.43	5.49	3.22
Weibull ^c	4	0	1	0	0	0.003	28.43	5.00	3.29

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMC; also the largest residual at any concentration.

^cPower restricted to ≥ 1 .

^dSlope restricted to ≥ 1 .

^eBetas restricted to ≥ 0 .

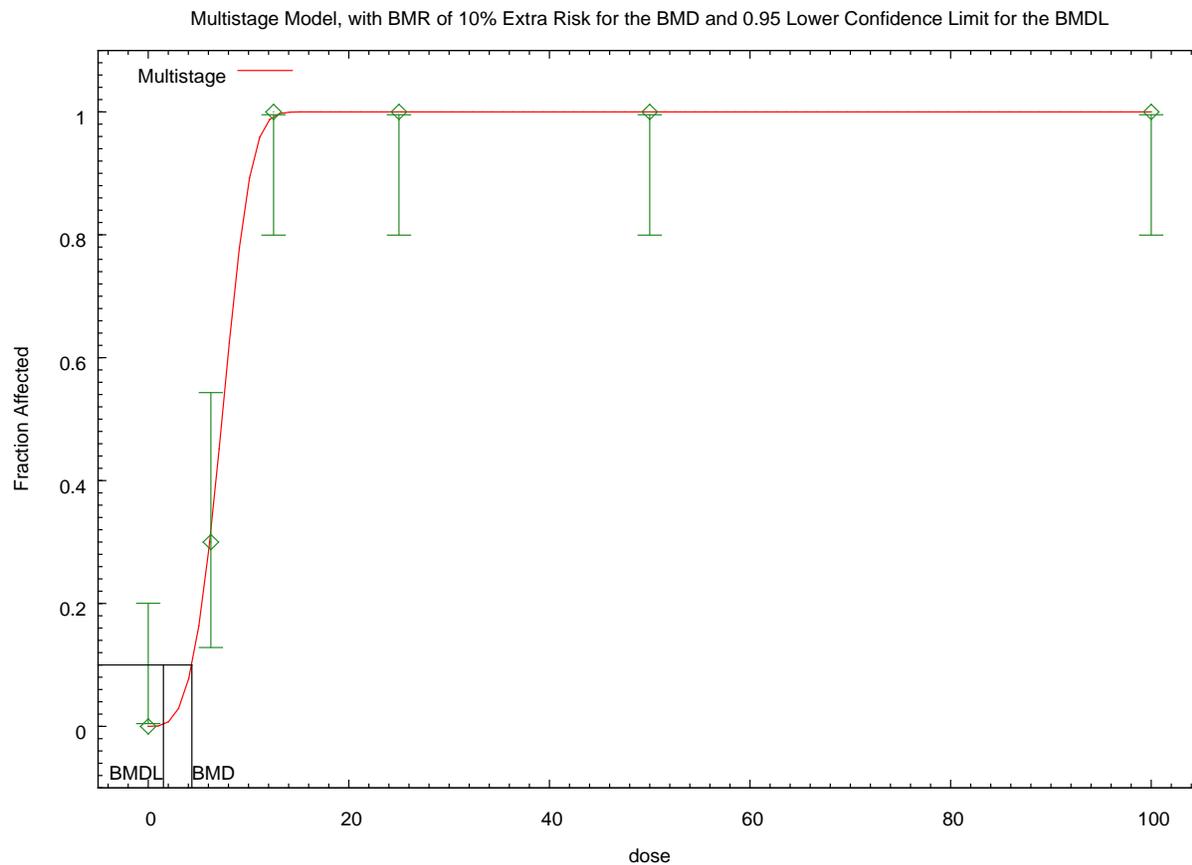
^fThe 1-degree Multistage model was judged to provide inadequate fit to the data (goodness-of-fit p-value <0.1).

^gAmong models providing adequate fit to the data, BMCL₁₀ values varied by nearly 3-fold; therefore, the model with the lowest BMCL₁₀ was selected as the best-fitting model (4-degree Multistage).

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

APPENDIX A

Figure A-4. Fit of 4-Degree Multistage Model for Combined Incidences of Nasal Olfactory Epithelium Atrophy in Male and Female F344/N Rats Exposed to 1,1-Dichloroethene Vapor 6 Hours/Day, 5 Days/Week for 14 Weeks (Dose in ppm)



17:44 09/13 2018

Model predictions for nasal olfactory epithelium necrosis in the male rats are presented in Table A-6. The Logistic, 5-degree Multistage, and Probit models provided inadequate fit to the dataset (i.e., goodness-of-fit p-value <0.1). Among the models providing adequate fit to the data, the lowest $BMCL_{10}$ of 0.72 ppm (from the LogLogistic model) was selected as a potential POD because the $BMCL_{10}$ values varied by >3-fold. The LogLogistic model fit is presented in Figure A-5.

APPENDIX A

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

Model	DF	χ^2	χ^2 Goodness- of-fit p-value ^a	Scaled residuals ^b			AIC	BMC ₁₀ (ppm)	BMCL ₁₀ (ppm)
				Dose below BMC	Dose above BMC	Overall largest			
Gamma ^c	5	8.18	0.1467	0	-0.40	-2.22	51.29	2.23	1.59
Logistic ^d	4	12.72	0.01	-1.66	-0.67	-2.01	60.60		
LogLogistic^{e,f}	4	5.89	0.21	0	-0.62	-1.89	51.85	2.53	0.72
LogProbit ^e	5	7.71	0.17	0	-0.27	-2.39	50.36	3.57	2.50
Multistage (1-degree) ^g	5	8.18	0.15	0	-0.40	-2.22	51.29	2.23	1.59
Multistage (2-degree) ^g	5	8.18	0.15	0	-0.40	-2.22	51.29	2.23	1.59
Multistage (3-degree) ^g	5	8.18	0.15	0	-0.40	-2.22	51.29	2.23	1.59
Multistage (4-degree) ^g	5	8.18	0.15	0	-0.40	-2.223	51.29	2.23	1.59
Multistage (5-degree) ^g	4	8.17	0.09	0	-0.39	-2.21	53.29		
Probit ^d	4	12.41	0.01	-0.67	1.40	2.08	60.84		
Weibull ^{c,d}	5	8.18	0.15	0	-0.402	-2.223	51.29	2.23	1.59

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMC; also the largest residual at any concentration.

^cPower restricted to ≥ 1 .

^dThe Logistic, 5-degree Multistage, and Probit models provided inadequate fit to the dataset (i.e., goodness-of-fit p-value <0.1).

^eSlope restricted to ≥ 1 .

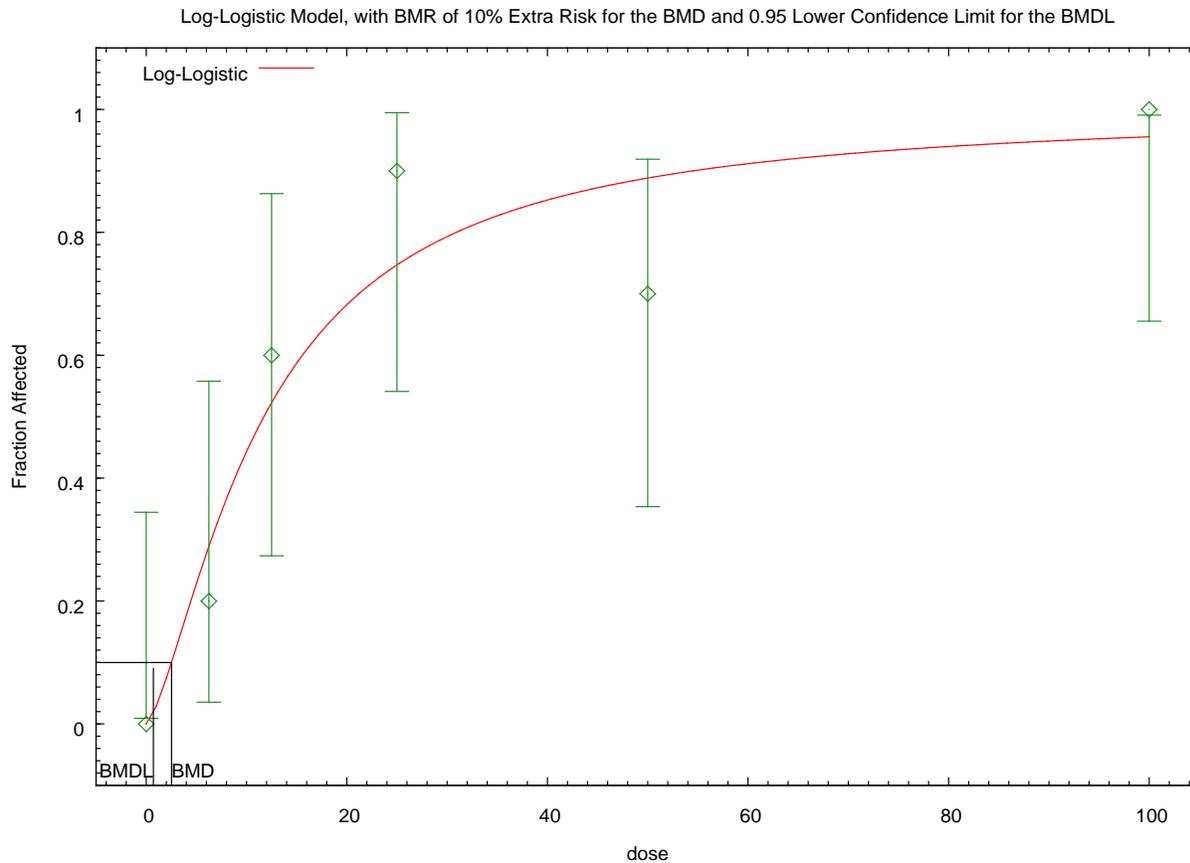
^fAmong models providing adequate fit to the data, BMCL₁₀ values varied by >3-fold; therefore, the model with the lowest BMCL₁₀ was selected as the best-fitting model (LogLogistic).

^gBetas restricted to ≥ 0 .

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

APPENDIX A

Figure A-5. Fit of LogLogistic Model for Nasal Olfactory Epithelium Necrosis in Male F344/N Rats Exposed to 1,1-Dichloroethene Vapor 6 Hours/Day, 5 Days/Week for 14 Weeks (Dose in ppm)



Model predictions for nasal olfactory epithelium necrosis in the female rats are presented in Table A-7. All models provided adequate fit to the data as judged by goodness-of-fit p-value and scaled residual criteria. However, visual inspection of the 1-degree Multistage fit (Figure A-6) revealed relatively poor correlation between predicted incidence and observed incidence in the region corresponding to the two experimental data points closest to the control value; therefore, the model fit was considered inadequate. All other models provided adequate fit. The 3-degree Multistage model $BMCL_{10}$ of 2.49 ppm (corresponding to the lowest AIC) was selected as a potential POD based on nasal olfactory epithelium necrosis in the female rats because the $BMCL_{10}$ values varied by <3-fold. The 3-degree Multistage model fit is presented in Figure A-7.

APPENDIX A

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

Model	DF	χ^2	χ^2 Goodness- of-fit p-value ^a	Scaled residuals ^b			AIC	BMC ₁₀ (ppm)	BMCL ₁₀ (ppm)
				Dose below BMC	Dose above BMC	Overall largest			
Gamma ^c	4	0.79	0.94	0.25	0.09	-0.61	37.29	7.03	2.97
Logistic	4	1.09	0.90	0.07	0.65	0.65	37.70	8.80	5.74
LogLogistic ^d	4	1.65	0.80	0.48	0.06	-0.82	38.47	7.57	4.05
LogProbit ^d	4	1.48	0.83	0.50	-0.09	-0.78	38.16	7.40	4.16
Multistage (1-degree) ^{e,f}	5	3.09	0.69	0.00	-0.98	1.19	38.86	2.52	1.75
Multistage (2-degree) ^e	4	0.42	0.98	0.05	0.20	-0.45	36.76	6.45	2.66
Multistage (3-degree)^{e,g}	4	0.22	0.99	0.00	-0.16	0.30	36.45	5.44	2.49
Multistage (4-degree) ^e	3	0.16	0.98	0.00	-0.22	0.28	38.35	5.14	2.37
Multistage (5-degree) ^e	3	0.12	0.99	0.00	-0.19	0.25	38.30	5.31	2.31
Probit	4	0.79	0.94	0.09	0.57	0.57	37.26	8.23	5.41
Weibull ^c	4	0.52	0.97	0.19	0.23	-0.51	36.87	6.94	3.07

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMC; also the largest residual at any concentration.

^cPower restricted to ≥ 1 .

^dSlope restricted to ≥ 1 .

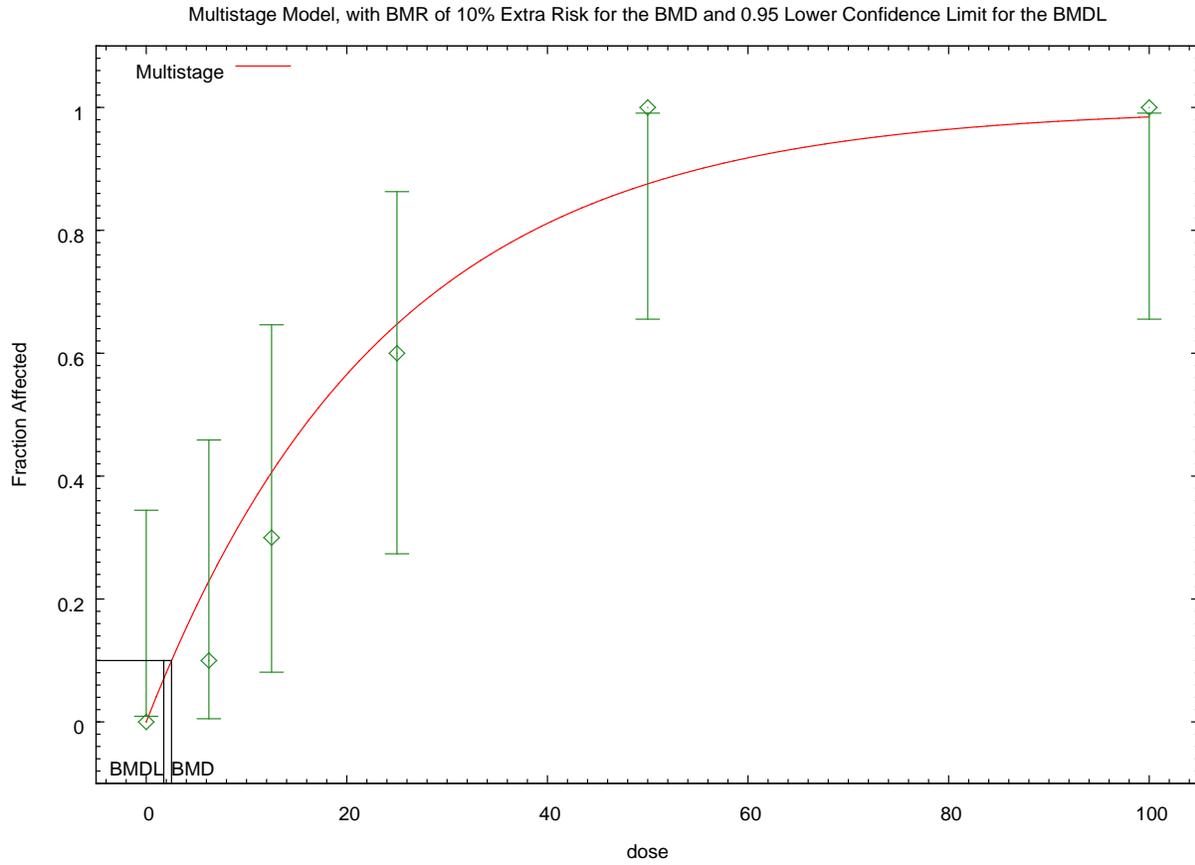
^eBetas restricted to ≥ 0 .

^fThe 1-degree Multistage model was judged to provide inadequate fit to the data based on visual inspection of the predicted dose-response curve (Figure A-6).

^gAmong models providing adequate fit to the data, BMCL₁₀ values varied by <3-fold; therefore, the model with the lowest AIC was selected as the best-fitting model (3-degree Multistage).

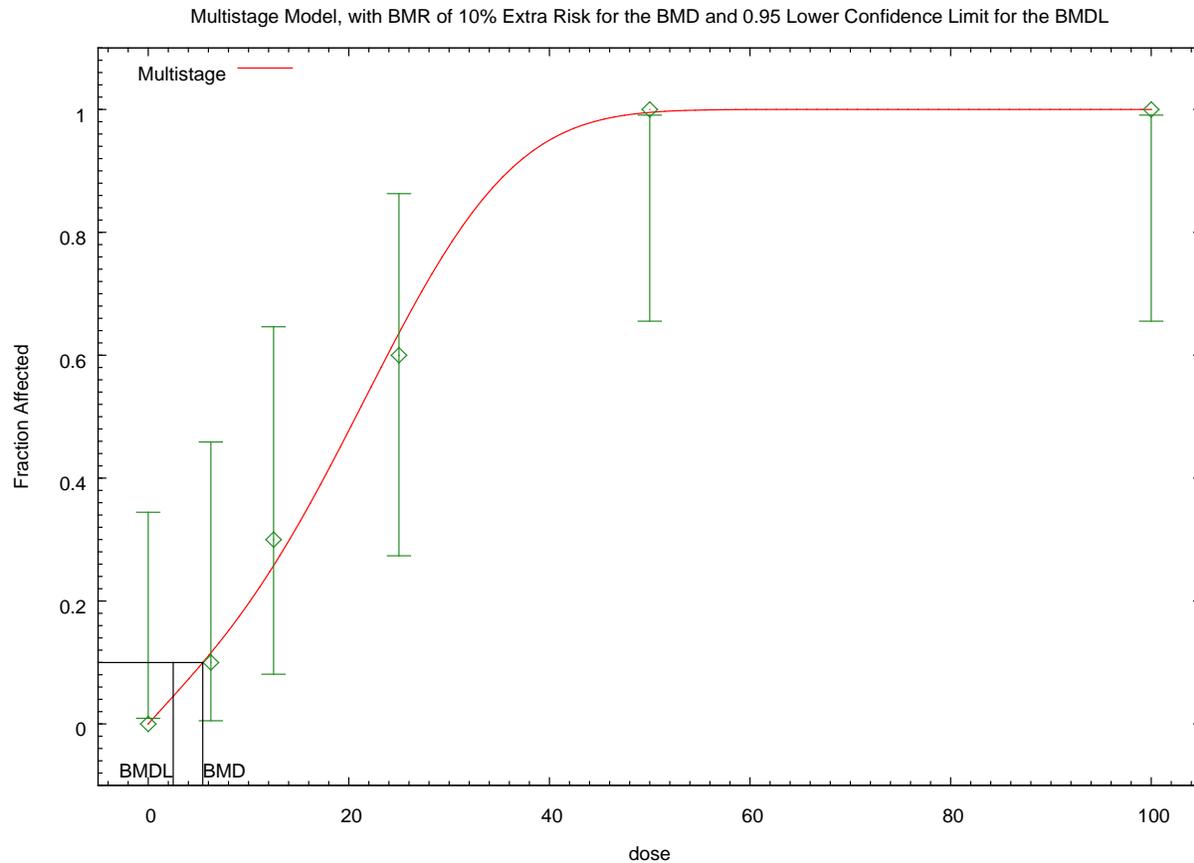
AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., ₁₀ = exposure concentration associated with 10% extra risk); DF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

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



APPENDIX A

Figure A-7. Fit of 3-Degree Multistage Model for Nasal Olfactory Epithelium Necrosis in Female F344/N Rats Exposed to 1,1-Dichloroethene Vapor 6 Hours/Day, 5 Days/Week for 14 Weeks (Dose in ppm)



Model predictions for combined incidences of nasal olfactory epithelium necrosis in the male and female rats are presented in Table A-8. The Logistic and Probit models provided inadequate fit to the dataset (goodness-of-fit p-value <0.1). All other models provided adequate fit to the data as judged by goodness-of-fit p-value and scaled residual criteria. The 1-degree Multistage model BMCL₁₀ of 2.36 ppm (corresponding to the lowest AIC) was selected as a potential POD based on combined incidences of nasal olfactory epithelium necrosis in the male and female rats because the BMCL₁₀ values varied by <3-fold. The 1-degree Multistage model fit is presented in Figure A-8.

APPENDIX A

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

Model	DF	χ^2	χ^2 Goodness- of-fit p-value ^a	Scaled residuals ^b			AIC	BMC ₁₀ (ppm)	BMCL ₁₀ (ppm)
				Dose below BMC	Dose above BMC	Overall largest			
Gamma ^c	4	2.10	0.72	0	-0.62	-0.93	89.98	3.21	1.87
Logistic ^d	4	10.07	0.040	-0.59	1.27	-1.93	99.21		
LogLogistic ^e	4	1.51	0.83	0	-0.19	-0.91	89.76	4.58	2.46
LogProbit ^e	4	1.42	0.84	0	-0.23	-0.90	89.51	4.66	3.20
Multistage (1-degree)^{f,g}	5	2.15	0.83	0	-0.97	-0.97	88.31	2.36	1.84
Multistage (2-degree) ^f	4	2.20	0.70	0	-0.85	-0.85	90.19	2.55	1.85
Multistage (3-degree) ^f	4	2.17	0.71	0	-0.89	-0.89	90.15	2.47	1.85
Multistage (4-degree) ^f	4	2.10	0.72	0	-0.90	-0.90	90.07	2.46	1.86
Multistage (5-degree) ^f	4	2.03	0.73	0	-0.90	-0.90	89.98	2.45	1.87
Probit ^d	4	10.13	0.038	-0.60	1.33	-1.65	99.73		
Weibull ^c	4	2.15	0.71	0	-0.70	-0.88	90.06	2.94	1.86

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMC; also the largest residual at any concentration.

^cPower restricted to ≥ 1 .

^dThe Logistic and Probit models provided inadequate fit to the data (goodness-of-fit p-value <0.1).

^eSlope restricted to ≥ 1 .

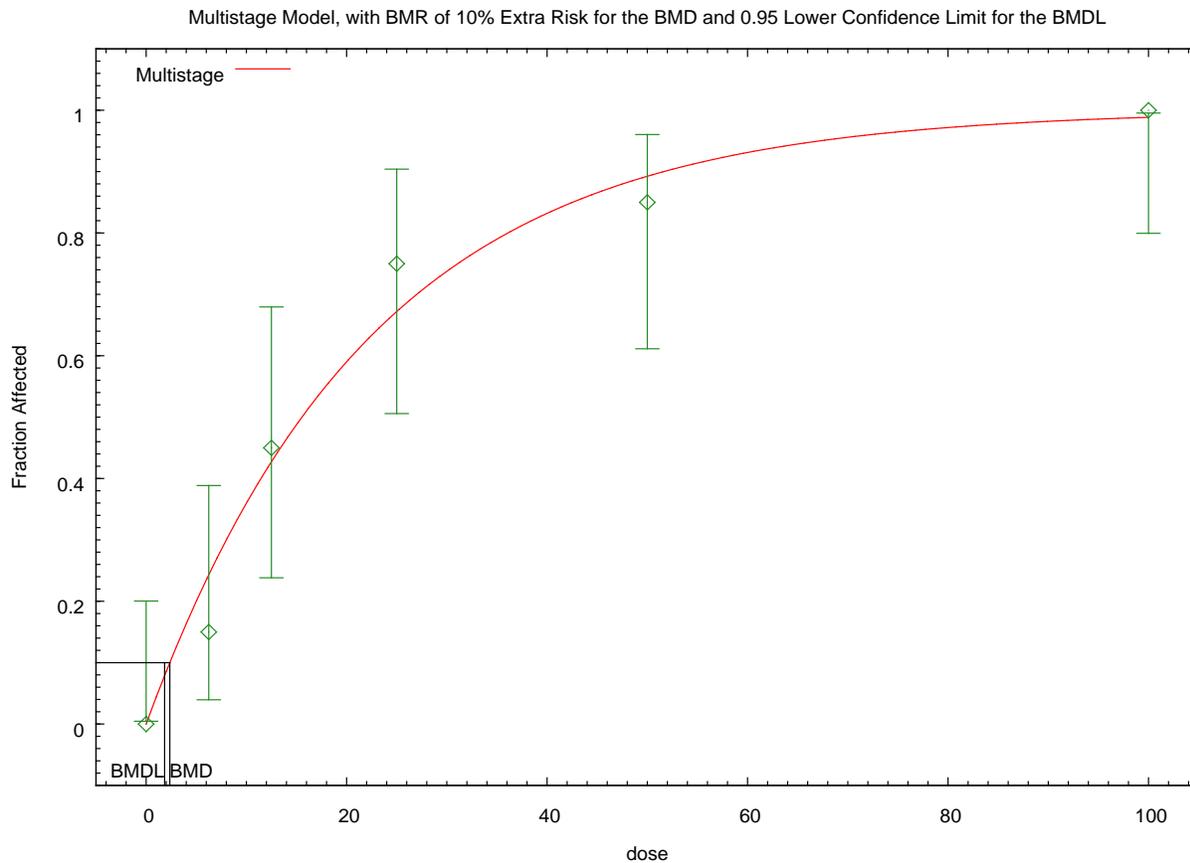
^fBetas restricted to ≥ 0 .

^gAmong models providing adequate fit to the data, BMCL₁₀ values varied by <3-fold; therefore, the model with the lowest AIC was selected as the best-fitting model (1-degree Multistage).

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

APPENDIX A

Figure A-8. Fit of 1-Degree Multistage Model for Combined Incidences of Nasal Olfactory Epithelium Necrosis in Male and Female F344/N Rats Exposed to 1,1-Dichloroethene Vapor 6 Hours/Day, 5 Days/Week for 14 Weeks (Dose in ppm)



11:42 09/10 2018

Best-fitting model predictions for atrophy and for necrosis in nasal olfactory epithelium of the male and female rats are presented in Table A-9. Among the best-fitting models, the lowest predicted BMC_{10} was 2.36 ppm for combined incidences of olfactory epithelium necrosis in the male and female rats; the corresponding $BMCL_{10}$ of 1.84 ppm was selected as the most conservative POD.

APPENDIX A

Table A-9. BMC₁₀ and BMCL₁₀ Values from the Best-Fitting Models for Selected Nonneoplastic Lesions in Nasal Olfactory Epithelium of Male and Female F344/N Rats Exposed to 1,1-Dichloroethene Vapor 6 Hours/Day, 5 Days/Week for 14 Weeks

Lesion type	Sex	Model	BMC ₁₀ (ppm)	BMCL ₁₀ (ppm)
Necrosis	Male	LogLogistic	2.53	0.72
	Female	Multistage 3-degree	5.44	2.49
	Combined	Multistage 1-degree	2.36^a	1.84
Atrophy	Male	Multistage 4-degree	3.57	0.72
	Female	Multistage 4-degree	4.05	1.23
	Combined	Multistage 4-degree	4.35	1.52

^aThe BMCL₁₀ of 1.84 ppm for necrosis in the male rats was selected as the preferred POD for deriving an intermediate-duration inhalation MRL for 1,1-dichloroethene because it corresponds to the lowest BMC₁₀ (2.36 ppm) among the group of best-fitting models for nasal olfactory epithelium lesions.

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

Intermittent Exposure: The BMCL₁₀ of 1.84 ppm was adjusted from intermittent exposure to a continuous exposure scenario according to the following equation:

$$\text{BMCL}_{10\text{ADJ}} = \text{BMCL}_{10} (0.72 \text{ ppm}) \times 6 \text{ hours}/24 \text{ hours} \times 5 \text{ days}/7 \text{ days} = 0.33 \text{ ppm}$$

Human Equivalent Concentration: To calculate a HEC, the BMCL_{10ADJ} was multiplied by the regional gas dose ratio (rat:human) for the extrathoracic region of the respiratory tract (RGDR_{ET}). The RGDR_{ET} was calculated according to the EPA (1994) equation 4-18:

$$\text{RGDR}_{\text{ET}} = \frac{\left(\frac{V_E}{SA_{\text{ET}}}\right)_A}{\left(\frac{V_E}{SA_{\text{ET}}}\right)_H}$$

where:

ET = extrathoracic region

V_E = minute volume (mL/minute)

SA = surface area (cm²)

A = animal (rat)

H = human

SA_{ET} values for rats (15 cm²) and humans (200 cm²) were taken from Table 4-4 of EPA (1994). The subchronic minute volume (V_E) for the male F344 rat was taken from Table 1-4 of EPA (1988a) in which it was presented as 0.019 m³/day (131.9 mL/minute). According to EPA (1994), the default minute volume for humans is 13,800 cm³/minute. Therefore:

$$\text{RGDR}_{\text{ET}} = \frac{\left(\frac{V_E}{SA_{\text{ET}}}\right)_A}{\left(\frac{V_E}{SA_{\text{ET}}}\right)_H} = \frac{\frac{131.9 \text{ mL}/\text{min}}{15 \text{ cm}^2}}{\frac{13,800 \text{ mL}/\text{min}}{200 \text{ cm}^2}} = 0.13$$

APPENDIX A

The $BMCL_{10HEC} = BMCL_{10ADJ} \times RGDR_{ET} = 0.33 \text{ ppm} \times 0.13 = 0.043 \text{ ppm}$

Uncertainty Factor: The $BMCL_{10HEC}$ of 0.043 ppm was divided by a total uncertainty factor of 30:

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

$$\begin{aligned} MRL &= BMCL_{10HEC} \div UFs \\ 0.043 \text{ ppm} &\div (3 \times 10) = 0.001 \text{ ppm} \end{aligned}$$

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

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,1-Dichloroethene
CAS Numbers: 75-35-4
Date: December 2019
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic
MRL: 0.0006 ppm (provisional)
Critical Effect: Metaplasia in nasal olfactory epithelium
Reference: NTP 2015a
Point of Departure: BMCL_{10HEC} of 0.017 ppm
Uncertainty Factor: 30
LSE Graph Key: 59
Species: Mouse

MRL Summary: A provisional chronic-duration inhalation MRL of 0.0006 ppm was derived for 1,1-dichloroethene based on metaplasia in nasal olfactory epithelium of male B6C3F1/N mice exposed to 1,1-dichloroethene vapor for 6 hours/day, 5 days/week for 105 weeks (NTP 2015a). The MRL is based on a BMCL_{10HEC} of 0.017 ppm and a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

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

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

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

APPENDIX A

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

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

^aLowest exposure concentration tested in the rats of the NTP (2015a) 2-year study.

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

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

Summary of the Principal Study:

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

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

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

APPENDIX A

- **Respiratory:** There were no indications of exposure-related increased incidences of nonneoplastic lesions in the lungs. Significantly increased incidences of selected nasal lesions were observed in both males and females at all exposure levels tested (6.25, 12.5, and 25 ppm). Incidence data are presented in Table A-11.
- **Renal:** Significantly increased incidences of renal tubule hyperplasia were observed in 6.25, 12.5, and 25 ppm groups of male mice (8/50, 22/50, and 16/50, respectively; no incidences in controls). This lesion was not considered for MRL derivation because it was considered a preneoplastic lesion. At 25 ppm, increased incidence of renal casts was observed in males.
- **Cancer:** At all 1,1-dichloroethene exposure levels (6.25, 12.5, and 25 ppm), male mice exhibited significantly increased incidences of renal tubule adenoma, carcinoma, and adenoma or carcinoma combined. Female mice exhibited significantly increased incidences of alveolar/bronchiolar carcinoma at 12.5 ppm (but not at 25 ppm), hepatocellular carcinoma at 25 ppm, hepatocellular adenoma or carcinoma combined at 12.5 and 25 ppm, hemangiosarcoma in the liver at 25 ppm, and hemangioma or hemangiosarcoma (combined) in all organs (combined) at 25 ppm.

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

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

^aIncidence (severity; 1 = minimal, 2 = mild, 3 = moderate, 4 = marked).

^bSignificantly different from chamber control incidence by the Poly-3 test (p<0.01).

^cSignificantly different from chamber control incidence by Fisher's exact test (p<0.01) performed by SRC, Inc.

BMD = benchmark dose

Source: NTP 2015a

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

APPENDIX A

female mice were fit to all standard dichotomous models in EPA's BMDS (version 2.7.0.1) using a BMR of 10% change in incidence from controls. Based on relatively similar male and female exposure concentration-response data, incidences were combined to increase the statistical power of the benchmark result; this procedure was employed for incidences of hyperostosis as well as olfactory epithelium metaplasia. Turbinate atrophy in the male and female mice was not fit to the models because 92% incidence occurred at the lowest exposure level tested. Adequate model fit was judged by three criteria: goodness-of-fit statistics (p-value >0.1), scaled residuals (within ± 2 units) at the data points (except the control) closest to the predefined BMR, and visual inspection of the proximity of the predicted dose-response curve to the observed data points closest to the BMR. For each dataset, among all models providing adequate fit to the data, the lowest BMCL was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest AIC was chosen.

Model predictions for hyperostosis in the nasal cavity of the male mice are presented in Table A-12. The Logistic and Probit models provided inadequate fit to the data (goodness-of-fit p-value <0.1). BMCLs for models providing adequate fit differed by nearly 3-fold. Therefore, the lowest BMCL₁₀ (0.56 ppm) was selected as a potential POD. The 1-degree Multistage model fit is presented in Figure A-9.

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

Model	DF	χ^2	χ^2 Goodness- of-fit p-value ^a	Scaled residuals ^b			AIC	BMC ₁₀ (ppm)	BMCL ₁₀ (ppm)
				Dose below BMC	Dose above BMC	Overall largest			
Gamma ^c	1	2.03	0.15	0.013	-0.40	-1.02	124.08	1.57	0.60
Logistic ^d	2	29.57	0.00	-1.43	0.93	-5.16	128.75		
LogLogistic ^e	1	0.32	0.57	0.005	-0.10	-0.44	122.57	2.84	1.66
LogProbit ^e	1	0.96	0.33	0.009	-0.24	-0.70	123.15	2.57	1.42
Multistage (1-degree)^{f,g}	2	3.08	0.21	0.068	-1.27	-1.27	123.53	0.68	0.56
Multistage (2-degree) ^f	1	2.62	0.11	0.033	-0.75	1.17	124.91	0.83	0.57
Multistage (3-degree) ^f	1	2.62	0.11	0.033	-0.75	1.17	124.91	0.83	0.57
Probit ^d	2	127.7	0.00	-1.75	1.15	-11.06	134.74		
Weibull ^c	1	2.25	0.13	0.023	-0.56	1.04	124.41	1.17	0.59

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.

^cPower restricted to ≥ 1 .

^dThe Logistic and Probit models provided inadequate fit to the data (goodness-of-fit p-value <0.1).

^eSlope restricted to ≥ 1 .

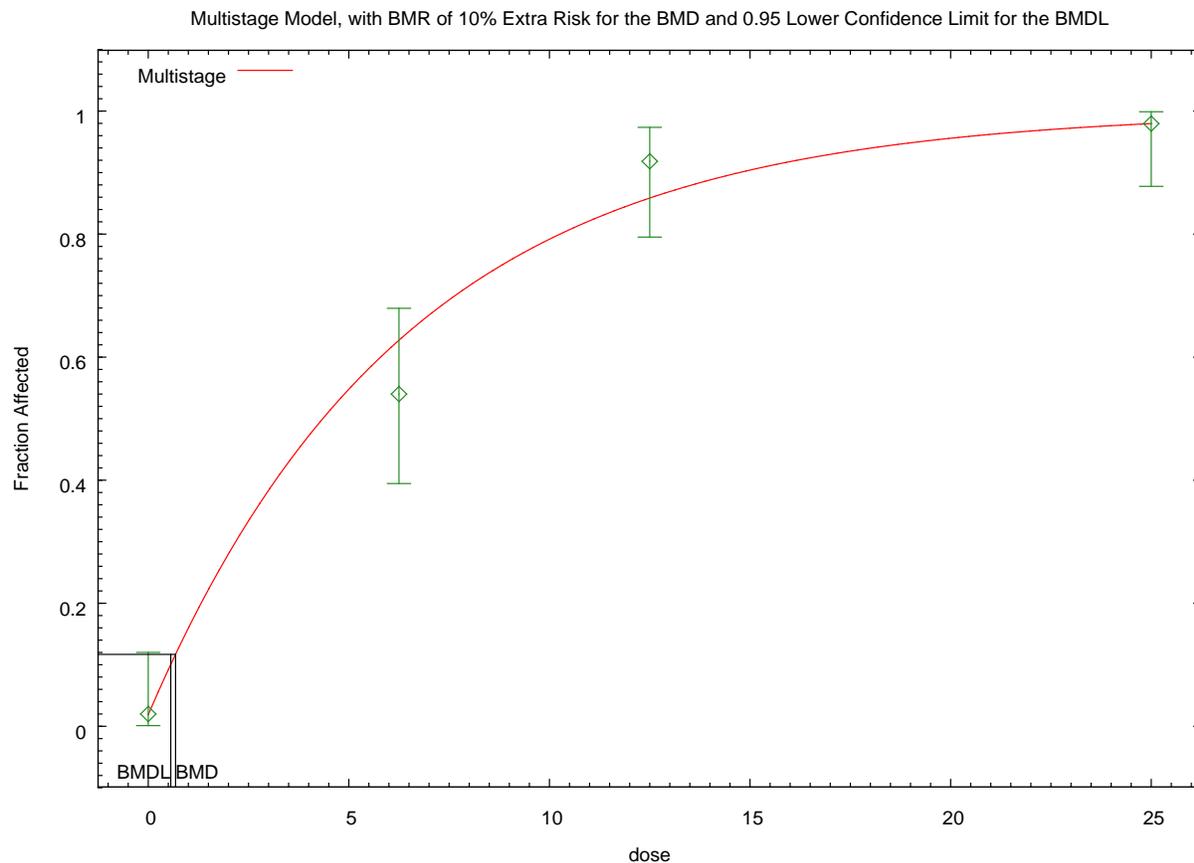
^fBetas restricted to ≥ 0 .

^gAmong models providing adequate fit to the data, BMCL₁₀ values varied by nearly 3-fold; therefore, the model with the lowest BMCL₁₀ was selected as the best-fitting model (1-degree Multistage).

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

APPENDIX A

Figure A-9. Fit of 1-Degree Multistage Model for Hyperostosis in the Nasal Cavity of Male B6C3F1/N Mice Exposed to 1,1-Dichloroethene Vapor 6 Hours/Day, 5 Days/Week for 105 Weeks (Dose in ppm)



Model predictions for hyperostosis in the nasal cavity of the female mice are presented in Table A-13. The LogLogistic model was the only model to provide adequate fit to the data (goodness-of-fit p-value <0.1 for all other models); the corresponding $BMCL_{10}$ of 3.46 ppm was selected as a potential POD. The LogLogistic model fit is presented in Figure A-10.

APPENDIX A

Table A-13. Model Predictions for Hyperostosis in the Nasal Cavity of Female B6C3F1/N Mice Exposed to 1,1-Dichloroethene Vapor for 6 Hours/Day, 5 Days/Week for 105 Weeks (NTP 2015a)

Model	DF	χ^2	χ^2 Goodness- of-fit p-value ^a	Scaled residuals ^b			AIC	BMC ₁₀ (ppm)	BMCL ₁₀ (ppm)
				Dose below BMC	Dose above BMC	Overall largest			
Gamma ^c	2	10.57	0.0051	0.00	-1.0	-2.39	119.25		
Logistic	2	49.16	0.00	-1.27	-0.23	-6.72	125.58		
LogLogistic^{d,e}	2	4.08	0.13	0.00	-0.42	-1.67	113.84	4.44	3.46
LogProbit ^d	2	6.77	0.03	0.00	-0.71	-1.94	116.28		
Multistage (1-degree) ^f	3	18.00	0.0004	0.00	-3.43	-3.43	128.35		
Multistage (2-degree) ^f	2	14.84	0.0006	0.00	-1.37	-2.67	123.15		
Multistage (3-degree) ^f	2	14.84	0.0006	0.00	-1.37	-2.67	123.15		
Probit	2	57.96	0.00	-1.51	-0.53	-6.95	133.18		
Weibull ^c	2	11.49	0.0032	0.00	-1.55	2.31	121.81		

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.

^cPower restricted to ≥ 1 .

^dSlope restricted to ≥ 1 .

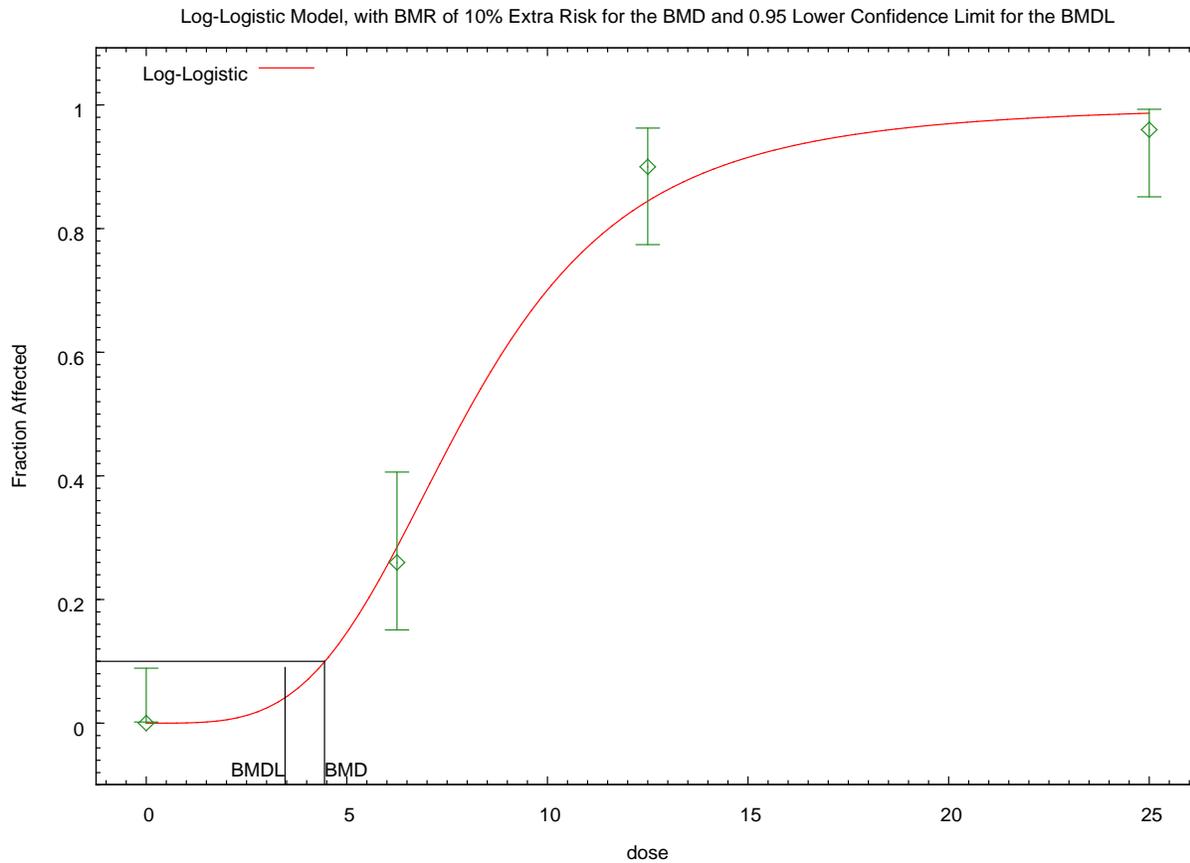
^eThe only model to provide adequate goodness-of fit.

^fBetas restricted to ≥ 0 .

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

APPENDIX A

Figure A-10. Fit of LogLogistic Model for Hyperostosis in the Nasal Cavity of Female B6C3F1/N Mice Exposed to 1,1-Dichloroethene Vapor 6 Hours/Day, 5 Days/Week for 105 Weeks (Dose in ppm)



17:29 05/04 2018

Model predictions for combined incidences of hyperostosis in the nasal cavity of the male and female mice are presented in Table A-14. None of the models provided adequate fit to the combined incidence data (i.e., goodness-of-fit p-values <0.1 for all models).

APPENDIX A

Table A-14. Model Predictions for Combined Incidence of Hyperostosis in Male and Female B6C3F1 Mice Exposed to 1,1-Dichloroethene Vapor 6 Hours/Day, 5 Days/Week for 105 Weeks (NTP 2015a)

Model	DF	χ^2	χ^2 Goodness- of-fit p-value ^a	Scaled residuals ^b			AIC	BMC ₁₀ (ppm)	BMCL ₁₀ (ppm)
				Dose below BMC	Dose above BMC	Overall largest			
Gamma ^c	1	10.46	0.00	0.036	-0.95	-2.33	248.00		
Logistic	2	67.43	0.00	-1.90	0.56	-7.87	257.54		
LogLogistic ^d	1	3.05	0.08	0.019	-0.33	-1.40	241.65		
LogProbit ^d	1	6.09	0.01	0.028	-0.64	-1.80	244.39		
Multistage (1-degree) ^e	2	17.48	0.00	0.14	-3.24	-3.24	255.71		
Multistage (2-degree) ^e	1	13.83	0.00	0.061	-1.61	2.57	252.42		
Multistage (3-degree) ^e	1	13.83	0.00	0.061	-1.61	2.57	252.42		
Probit	2	136	0.00	-2.32	0.50	-11.13	270.67		
Weibull ^c	1	5.94	0.01	0.08	-0.74	-1.81	274.34		

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMC; also the largest residual at any concentration.

^cPower restricted to ≥ 1 .

^dSlope restricted to ≥ 1 .

^eBetas restricted to ≥ 0 .

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

Model predictions for olfactory epithelium metaplasia in the nasal cavity of the male mice are presented in Table A-15. The Logistic and Probit models provided inadequate fit to the data (goodness-of-fit p-value <0.1). BMCL₁₀ values for models providing adequate fit differed by <3-fold. Therefore, the models with the lowest AIC (Gamma, Multistage, Weibull models) were selected as best-fitting models; the corresponding BMCL₁₀ of 0.45 ppm was selected as a potential POD. The representative Gamma model fit is presented in Figure A-11.

APPENDIX A

Table A-15. Model Predictions for Olfactory Epithelium Metaplasia in Male B6C3F1/N Mice Exposed to 1,1-Dichloroethene Vapor for 6 Hours/Day, 5 Days/Week for 105 Weeks (NTP 2015a)

Model	DF	χ^2	χ^2 Goodness- of-fit p-value ^a	Scaled residuals ^b			AIC	BMC ₁₀ (ppm)	BMCL ₁₀ (ppm)
				Dose below BMC	Dose above BMC	Overall largest			
Gamma^{c,d}	2	1.79	0.41	-0.045	0.11	-1.08	148.78	0.59	0.45
Logistic ^e	2	6.99	0.03	-0.47	0.48	-2.49	150.58		
LogLogistic ^f	1	0.52	0.47	0.012	-0.16	0.51	149.78	1.74	0.33
LogProbit ^f	1	0.83	0.36	0.017	-0.26	-0.57	150.10	1.35	0.73
Multistage (1-degree)^{d,g}	2	1.79	0.41	-0.045	0.11	-1.08	148.78	0.59	0.45
Multistage (2-degree)^{d,g}	2	1.79	0.41	-0.045	0.11	-1.08	148.78	0.59	0.45
Multistage (3-degree)^{d,g}	2	1.79	0.41	-0.045	0.11	-1.08	148.78	0.59	0.45
Probit	2	18.39	0.00	-1.0	0.92	-3.94	154.23		
Weibull^{c,d}	2	1.79	0.41	-0.045	0.11	-1.08	148.78	0.59	0.45

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.

^cPower restricted to ≥ 1 .

^dBMCLs for models providing adequate fit differed by <3-fold. Therefore, the models with the lowest AIC (Gamma, Multistage, and Weibull models) were selected as best-fitting models.

^eThe Logistic and Probit models provided inadequate fit to the data (goodness-of-fit p-value <0.1).

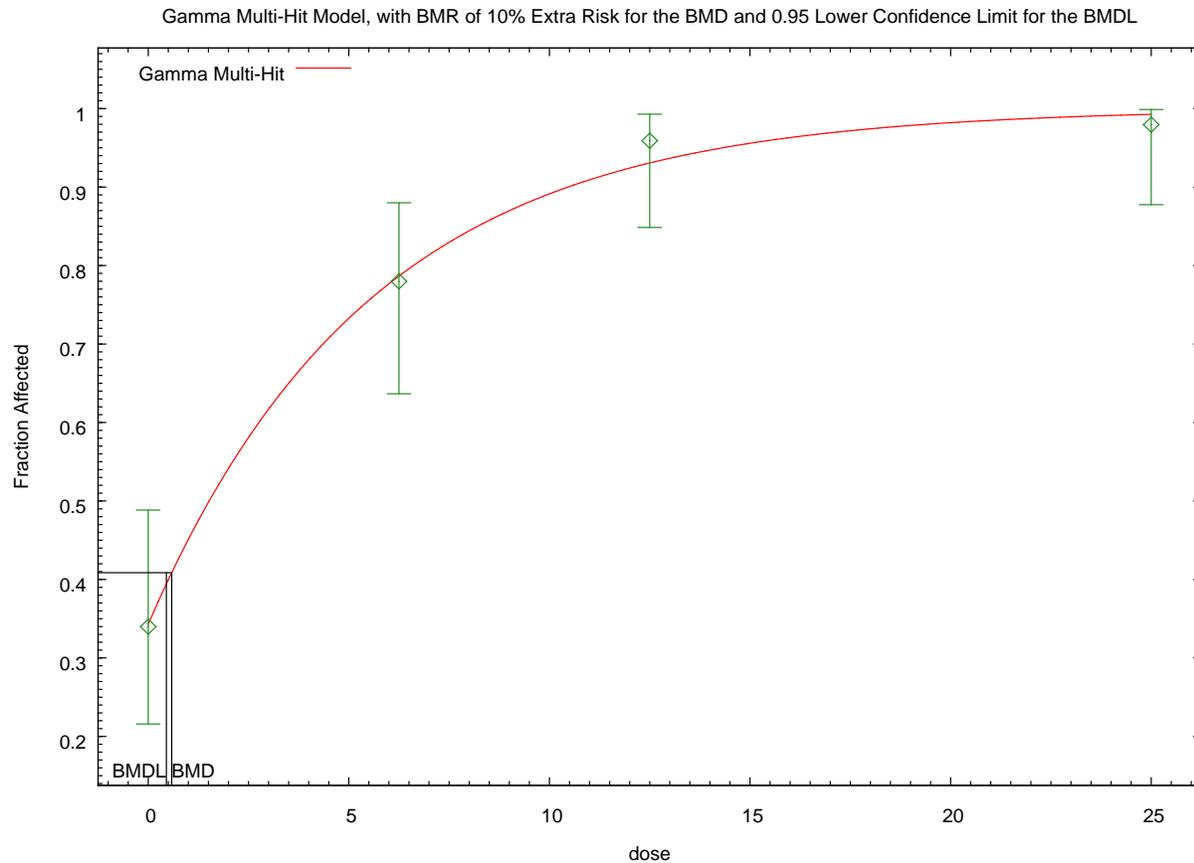
^fSlope restricted to ≥ 1 .

^gBetas restricted to ≥ 0 .

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

APPENDIX A

Figure A-11. Fit of Gamma Model for Olfactory Epithelium Metaplasia in the Nasal Cavity of Male B6C3F1/N Mice Exposed to 1,1-Dichloroethene Vapor 6 Hours/Day, 5 Days/Week for 105 Weeks (Dose in ppm)



Model predictions for olfactory epithelium metaplasia in the nasal cavity of the female mice are presented in Table A-16. The 1-degree and 3-degree Multistage model provided inadequate fit to the data (goodness-of-fit p-value <0.1). BMCLs for models providing adequate fit differed by <3-fold. Therefore, the BMCL₁₀ of 1.46 ppm was selected as a potential POD because the Probit model provided the lowest AIC among models with adequate fit to the data. The Probit model fit is presented in Figure A-12.

APPENDIX A

Table A-16. Model Predictions for Olfactory Epithelium Metaplasia in Female B6C3F1/N Mice Exposed to 1,1-Dichloroethene Vapor for 6 Hours/Day, 5 Days/Week for 105 Weeks (NTP 2015a)

Model	DF	χ^2	χ^2 Goodness- of-fit p-value ^a	Scaled residuals ^b			AIC	BMC ₁₀ (ppm)	BMCL ₁₀ (ppm)
				Dose below BMC	Dose above BMC	Overall largest			
Gamma ^c	1	0.00	0.99	-0.00	0.00	0.013	106.53	3.27	1.81
Logistic	2	0.15	0.93	0.20	-0.18	0.27	104.68	2.16	1.61
LogLogistic ^d	1	0.03	0.87	-0.001	0.007	0.16	106.58	3.97	2.81
LogProbit ^d	1	0.00	0.96	-0.00	0.002	0.045	106.53	3.73	2.56
Multistage (1-degree) ^{e,f}	2	7.51	0.02	0.17	-2.04	-2.04	113.39		
Multistage (2-degree) ^e	2	0.28	0.87	0.052	-0.34	0.40	104.83	2.18	0.94
Multistage (3-degree) ^{e,g}	0	0.00	NA						
Probit^h	2	0.02	0.99	0.073	-0.092	0.10	104.55	1.91	1.46
Weibull ^c	1	0.00	1.0	0.00	0.00	0.001	106.53	2.54	1.39

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.

^cPower restricted to ≥ 1 .

^dSlope restricted to ≥ 1 .

^eBetas restricted to ≥ 0 .

^fThe 1-degree Multistage model provided inadequate fit to the data (goodness-of-fit p-value <0.1).

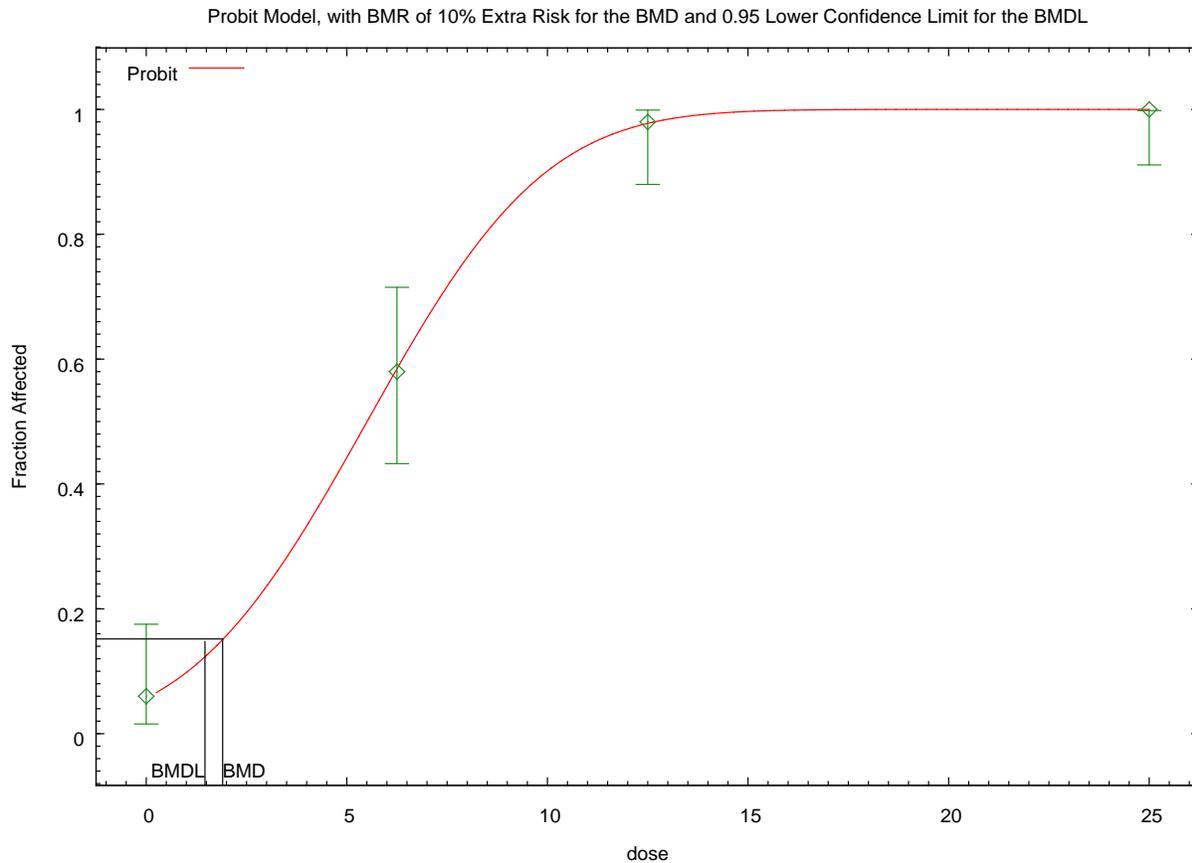
^gThe 3-degree Multistage model is inadequate because a goodness-of-fit p-value was not calculated.

^hBMCLs for models providing adequate fit differed by <3-fold. Therefore, the model with the lowest AIC was selected as the best-fitting model (Probit).

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

APPENDIX A

Figure A-12. Fit of Probit Model for Olfactory Epithelium Metaplasia in the Nasal Cavity of Female B6C3F1/N Mice Exposed to 1,1-Dichloroethene Vapor 6 Hours/Day, 5 Days/Week for 105 Weeks (Dose in ppm)



Model predictions for combined incidences of olfactory epithelium metaplasia in the male and female mice are presented in Table A-17. The LogLogistic model was the only model to provide adequate fit to the data (e.g., goodness-of-fit p-value >0.1). The corresponding $BMCL_{10}$ of 1.96 ppm was selected as a potential POD. The LogLogistic model fit is presented in Figure A-13.

APPENDIX A

Table A-17. Model Predictions for Combined Incidence of Olfactory Epithelium Metaplasia in Male and Female B6C3F1 Mice Exposed to 1,1-Dichloroethene Vapor 6 Hours/Day, 5 Days/Week for 105 Weeks (NTP 2015a)

Model	DF	χ^2	χ^2 Goodness- of-fit p-value ^a	Scaled residuals ^b			AIC	BMC ₁₀ (ppm)	BMCL ₁₀ (ppm)
				Dose below BMC	Dose above BMC	Overall largest			
Gamma ^c	1	6.05	0.01	0.04	-0.50	-2.04	273.66		
Logistic	2	12.07	0.00	-0.16	-0.12	-3.33	271.95		
LogLogistic^{d,e}	1	1.35	0.25	0.016	-0.15	-0.98	270.62	2.95	1.96
LogProbit ^d	1	3.19	0.07	0.034	-0.34	-1.45	271.99		
Multistage (1-degree) ^f	2	5.79	0.06	0.21	-1.59	1.77	274.05		
Multistage (2-degree) ^f	1	6.13	0.01	0.11	-0.99	1.64	275.24		
Multistage (3-degree) ^f	1	6.13	0.01	0.11	-0.99	1.64	275.24		
Probit	2	154	0.00	-0.79	0.44	-12.31	278.41		
Weibull ^c	1	5.94	0.01	0.08	-0.74	-1.81	274.34		

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMC; also the largest residual at any concentration.

^cPower restricted to ≥ 1 .

^dSlope restricted to ≥ 1 .

^eThe only model to provide adequate goodness-of-fit p-value ($p > 0.1$).

^fBetas restricted to ≥ 0 .

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

APPENDIX A

Figure A-13. Fit of LogLogistic Model for Combined Incidences of Olfactory Epithelium Metaplasia in the Nasal Cavity of Male and Female B6C3F1/N Mice Exposed to 1,1-Dichloroethene Vapor 6 Hours/Day, 5 Days/Week for 105 Weeks (Dose in ppm)

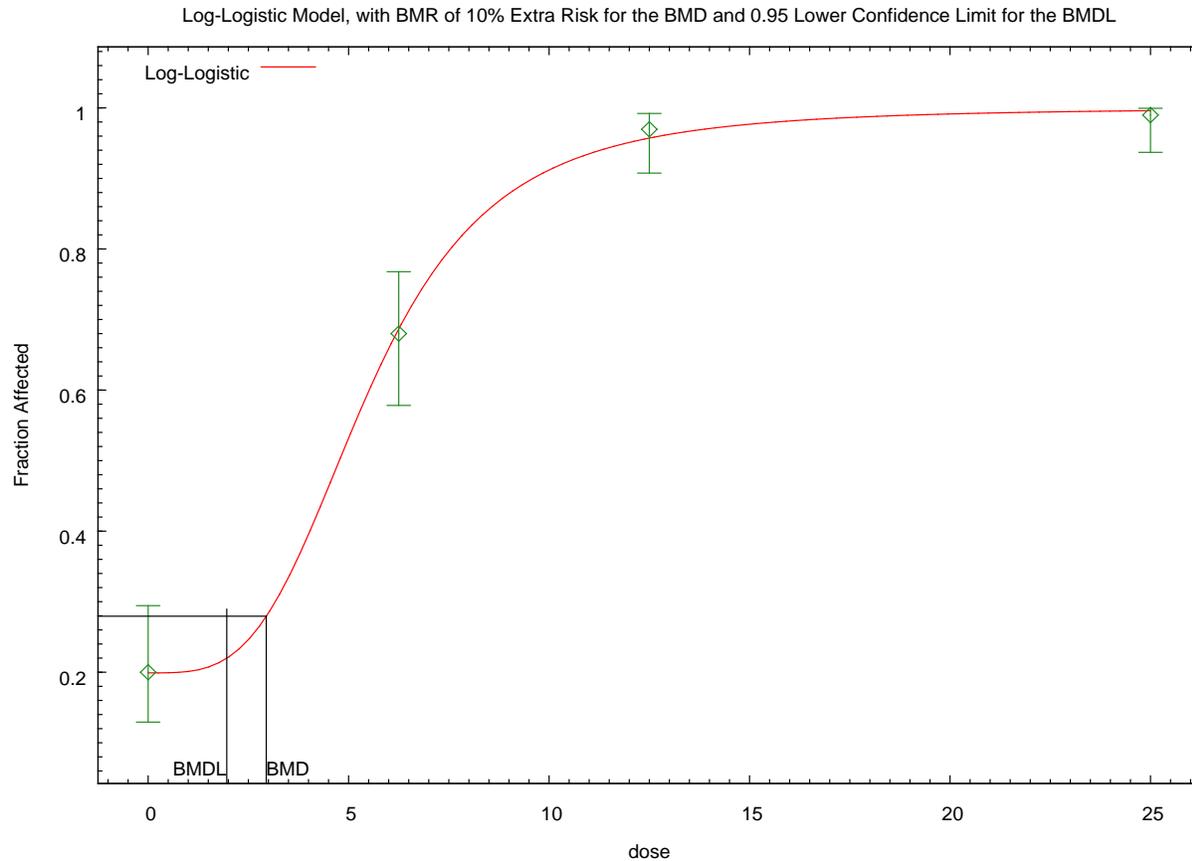


Table A-18 summarizes the BMC_{10} and $BMCL_{10}$ values for the nasal lesion incidences in the male and female mice exposed to 1,1-dichloroethene vapor for 6 hours/day, 5 days/week for 105 weeks (NTP 2015a). The BMC_{10} of 0.59 ppm for olfactory epithelium metaplasia in the male mice was selected because it represents the lowest BMC_{10} among the best-fitting models for nasal lesions. The corresponding $BMCL_{10}$ of 0.45 ppm serves as the POD for deriving a chronic-duration inhalation MRL for 1,1-dichloroethene.

APPENDIX A

Table A-18. BMC₁₀ and BMCL₁₀ Values from the Best-Fitting Models for Selected Nonneoplastic Nasal Lesions in B6C3F1/N Mice Exposed to 1,1-Dichloroethene Vapor 6 Hours/Day, 5 Days/Week for 105 Weeks

Lesion type	Sex	Model	BMC ₁₀ (ppm)	BMCL ₁₀ (ppm)
Turbinate Hyperostosis	Male	Multistage 1-degree	0.68	0.56
	Female	LogLogistic	4.44	3.46
	Combined	NA		
Olfactory epithelium Metaplasia	Male	Gamma	0.59^a	0.45
	Female	Probit	1.91	1.46
	Combined	LogLogistic	2.95	1.96

^aThe BMCL₁₀ of 0.45 mg/kg/day for metaplasia in the male mice was selected as the preferred POD for deriving a chronic-duration inhalation MRL for 1,1-dichloroethene because it corresponds to the lowest BMC₁₀ (0.59 mg/kg/day) among the group of best-fitting models for nasal lesions.

BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., ₁₀ = exposure concentration associated with 10% extra risk); MRL = minimum risk level; NA = not applicable (no model provided adequate fit to the combined data; goodness-of-fit p-value <0.1); POD = point of departure

Intermittent Exposure: The BMCL₁₀ of 0.45 ppm was adjusted from intermittent exposure to a continuous exposure scenario according to the following equation:

$$\text{BMCL}_{10\text{ADJ}} = \text{BMCL}_{10} (0.45 \text{ ppm}) \times 6 \text{ hours}/24 \text{ hours} \times 5 \text{ days}/7 \text{ days} = 0.080 \text{ ppm}$$

Human Equivalent Concentration: To calculate a HEC, the BMCL_{10ADJ} was multiplied by the regional gas dose ratio (mouse:human) for RGDR_{ET}. The RGDR_{ET} was calculated according to the EPA (1994) equation 4-18:

$$\text{RGDR}_{\text{ET}} = \frac{\left(\frac{V_E}{SA_{\text{ET}}}\right)_A}{\left(\frac{V_E}{SA_{\text{ET}}}\right)_H}$$

where:

ET = extrathoracic region

V_E = minute volume (mL/minute)

SA = surface area (cm²)

A = animal (mouse)

H = human

SA_{ET} values for the mouse (3 cm²) and humans (200 cm²) were taken from Table 4-4 of EPA (1994). The chronic minute volume (V_E) for the male B6C3F1 mouse was taken from Table 1-4 of EPA (1988a) in which it was presented as 0.063 m³/day (43.75 mL/minute). According to EPA (1994), the default minute volume for humans is 13,800 cm³/minute. Therefore:

$$\text{RGDR}_{\text{ET}} = \frac{\left(\frac{V_E}{SA_{\text{ET}}}\right)_A}{\left(\frac{V_E}{SA_{\text{ET}}}\right)_H} = \frac{\frac{43.75 \text{ mL}/\text{min}}{3 \text{ cm}^2}}{\frac{13,800 \text{ mL}/\text{min}}{200 \text{ cm}^2}} = 0.21$$

APPENDIX A

The $BMCL_{10HEC} = BMCL_{10ADJ} \times RGDR_{ET} = 0.080 \text{ ppm} \times 0.21 = 0.017 \text{ ppm}$

Uncertainty Factor: The $BMCL_{10HEC}$ of 0.017 ppm was divided by a total uncertainty factor of 30:

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

$$MRL = BMCL_{10HEC} \div UFs$$

$$0.017 \text{ ppm} \div (3 \times 10) = 0.0006 \text{ ppm (rounded up from 0.000567 ppm).}$$

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

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,1-Dichloroethene
CAS Numbers: 75-35-4
Date: December 2019
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

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

Rationale for Not Deriving an MRL: No dose-response data are available for humans. Many acute-duration studies employed fasted animals which are known to be more sensitive than nonfasted rats to 1,1-dichloroethene-induced adverse effects following oral exposure. The increased sensitivity to 1,1-dichloroethene in fasted animals appears to be related to toxicokinetic parameters. Levels of radioactivity in liver, kidneys, and lungs of fasted rats treated with ¹⁴C-1,1-dichloroethene were significantly greater than levels in nonfasted rats (McKenna et al. 1978b). 1,1-Dichloroethene-induced hepatic lesions appeared earlier and were more extensive in fasted rats compared to nonfasted rats (Jaeger et al. 1974; McKenna et al. 1978a; Reynolds and Moslen 1977). Liver mixed function oxidase activity in fasted animals following 1,1-dichloroethene exposure was greater than that in similarly-treated nonfasted animals (McKenna et al. 1978a; Nakajima et al. 1982). Due to increased sensitivity to 1,1-dichloroethene toxicity among fasted animals, only oral data from nonfasted animals (i.e., normal diet) were considered for MRL derivation. Some studies did not provide dose-response data because only a single dose level was used. Table A-19 summarizes available results from acute-duration oral studies in laboratory animals. Among studies that employed multiple dose levels and nonfasted animals, the lowest LOAEL is 100 mg/kg/day for 11% depressed body weight in female rats administered 1,1-dichloroethene by gavage for 14 days (NTP 1982). Given the limited database of information for the gavage exposure route and no information regarding the effects of acute-duration dietary or drinking water exposure, it is not considered appropriate to derive an acute-duration oral MRL for 1,1-dichloroethene at this time.

Table A-19. Summary of Potential Candidate Critical Effects for Deriving an Acute-Duration Oral MRL for 1,1-Dichloroethene

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

APPENDIX A

Table A-19. Summary of Potential Candidate Critical Effects for Deriving an Acute-Duration Oral MRL for 1,1-Dichloroethene

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

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

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,1-Dichloroethene
CAS Numbers: 75-35-4
Date: December 2019
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

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

Rationale for Not Deriving an MRL: No dose-response data are available for humans. Table A-20 summarizes potential candidate critical effect PODs from intermediate-duration oral studies in laboratory animals. The 90-day gavage studies of rats and mice (NTP 1982) were the only available intermediate-duration oral studies in which treatment-related adverse effects were observed. Given the limited database of information for the gavage exposure route and no information regarding the effects of intermediate-duration dietary or drinking water exposure, it is not considered appropriate to derive an intermediate-duration oral MRL for 1,1-dichloroethene at this time.

Table A-20. Summary of Potential Candidate Critical Effects for Deriving an Intermediate-Duration Oral MRL for 1,1-Dichloroethene

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

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

Agency Contacts (Chemical Managers): Malcolm Williams

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 1,1-Dichloroethene
CAS Numbers: 75-35-4
Date: December 2019
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic
MRL: 0.05 mg/kg/day (provisional)
Critical Effect: Hepatocellular midzonal fatty change
References: Humiston et al. 1978; Quast et al. 1983
Point of Departure: BMDL₁₀ of 4.61 mg/kg/day
Uncertainty Factor: 100
LSE Graph Key: 28
Species: Rat

MRL Summary: A provisional MRL of 0.05 mg/kg/day has been derived for chronic-duration oral exposure to 1,1-dichloroethene based on hepatic effects in female Sprague-Dawley rats receiving 1,1-dichloroethene from the drinking water for up to 2 years (Humiston et al. 1978; Quast et al. 1983).

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

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

Summary of the Principal Studies:

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

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

In the principal study, groups of Sprague-Dawley rats (48/sex/group; 80/sex for controls; 6–7 weeks of age) were administered 1,1-dichloroethene in the drinking water for 2 years at 50, 100, or 200 ppm (author-estimated doses of 7, 10, and 20 mg/kg/day, respectively, for males, and 9, 14, and 30 mg/kg/day, respectively, for females). Controls consisted of 80 rats/sex that received drinking water without 1,1-dichloroethene. Rats were monitored for survival, clinical signs, body weight, and food intake. Blood and urine were collected from at least five rats/sex/group at 6, 12, 18, and 23 months for hematology and urinalysis. Clinical chemistry evaluations were performed on 5 rats/sex/group at 6, 12, and 18 months, and from all surviving rats from each group in which <10 rats remained at terminal

APPENDIX A

sacrifice. At sacrifice, weights of brain, heart, liver, kidneys, and testes were recorded. Comprehensive gross pathological examinations were performed on all rats. Comprehensive histopathologic examinations were performed on control and high-dose rats; histopathology was also performed on selected target organs and grossly recognized neoplastic changes in low- and mid-dose rats.

There were no significant treatment-related differences from controls in appearance and demeanor, mortality, body weight, food consumption, water consumption, hematology, urinalysis, clinical chemistry, or organ weight. The sole treatment-related observation was microscopic changes in the liver (minimal amount of hepatocellular swelling with midzonal fatty change). The incidences of midzonal fatty change in the controls, low-, mid-, and high-dose rats were 14/80, 5/48, 13/48, and 19/47, respectively, for males, and 3/80, 7/48, 11/48, and 20/48, respectively, for females. Incidences of midzonal fatty change were significantly increased in the high-dose males (20 mg/kg/day; $p < 0.005$) and mid- (14 mg/kg/day; $p = 0.012$) and high-dose (30 mg/kg/day) females. Incidences of minimal hepatocellular swelling were significantly increased in females at all 1,1-dichloroethene dose levels. The mid-dose (10 mg/kg/day) and high-dose (20 mg/kg/day) are considered male rat NOAEL and LOAEL levels, respectively, for histopathologic liver effects. The low-dose (9 mg/kg/day) is considered a minimum LOAEL for the female rat, based on the minimal nature of hepatocellular swelling at that dose level.

Selection of the Point of Departure for the MRL: The lowest LOAEL identified in the 2-year rat study (Humiston et al. 1978; Quast et al. 1983) was 9 mg/kg/day for increased hepatocellular hypertrophy in female rats. Incidence data for these effects are presented in Table A-21.

Table A-21. Incidence Data for Selected Nonneoplastic Liver Lesions in Male and Female Sprague-Dawley Rats Administered 1,1-Dichloroethene in the Drinking Water for up to 2 Years

Lesion type	Males			
Time-weighted average dose (mg/kg/day)	0	7	10	20
Minimal hepatocellular hypertrophy	14/80	5/48	13/48	19/47 ^a
Minimal midzonal fatty change	0/80	1/48	2/48	3/47 ^b
	Females			
Time-weighted average dose (mg/kg/day)	0	9	14	30
Minimal hepatocellular hypertrophy	3/80	7/48 ^b	11/48 ^a	20/48 ^a
Minimal midzonal fatty change	10/80	12/48	14/48 ^b	22/48 ^a

^aSignificantly different from control incidence according to Fisher's exact test ($p < 0.01$).

^bSignificantly different from control incidence according to Fisher's exact test ($p < 0.05$).

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

APPENDIX A

The incidence data for hepatocellular hypertrophy and for midzonal fatty change in the female rats were fit to all standard dichotomous models in EPA's BMDS (version 2.7.0.1) using a BMR of 10% change in incidence from controls. Adequate model fit was judged by three criteria: goodness-of-fit statistics (p -value >0.1), scaled residuals (within ± 2 units) at the data points (except the control) closest to the predefined BMR, and visual inspection of the proximity of the predicted dose-response curve to the observed data points closest to the BMR. For each dataset, among all models providing adequate fit to the data, the lowest BMDL was selected as the POD when the difference between the BMDLs estimated from these models was >3 -fold; otherwise, the BMDL from the model with the lowest AIC was chosen.

The model predictions for hepatocellular hypertrophy are presented in Table A-22. All models provided adequate fit to the data. BMDLs for models providing adequate fit differed by <3 -fold; therefore, the model with the lowest AIC (1-degree Multistage) was selected as a potential POD. The 1-degree Multistage model fit is presented in Figure A-14.

Table A-22. Model Predictions for Hepatocellular Hypertrophy in Female Sprague-Dawley Rats Receiving 1,1-Dichloroethene from the Drinking Water for 2 Years (Humiston et al. 1978; Quast et al. 1983)

Model	DF	χ^2	χ^2 Goodness- of-fit p-value ^a	Scaled residuals ^b			AIC	BMD ₁₀ (mg/kg/day)	BMDL ₁₀ (mg/kg/day)
				Dose below BMD	Dose above BMD	Overall largest			
Gamma ^c	1	0.03	0.85	0.01	-0.11	0.14	188.38	7.70	4.93
Logistic	2	2.17	0.34	0.45	0.95	0.95	188.59	12.25	10.19
LogLogistic ^d	1	0.02	0.89	0.01	-0.09	0.11	188.36	7.87	4.27
LogProbit ^d	2	0.68	0.71	0.48	0.33	-0.55	187.00	9.89	7.83
Multistage (1-degree)^{e,f}	2	0.17	0.92	0.08	-0.36	-0.36	186.52	6.60	4.89
Multistage (2-degree) ^e	1	0.05	0.82	0.01	-0.16	0.17	188.40	7.42	4.92
Multistage (3-degree) ^e	1	0.05	0.82	0.01	-0.16	0.17	188.40	7.42	4.92
Probit	2	1.61	0.44	0.41	0.83	0.83	187.99	11.38	9.45
Weibull ^c	1	0.04	0.85	0.01	-0.12	0.15	188.38	7.64	4.93

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.

^cPower restricted to ≥ 1 .

^dSlope restricted to ≥ 1 .

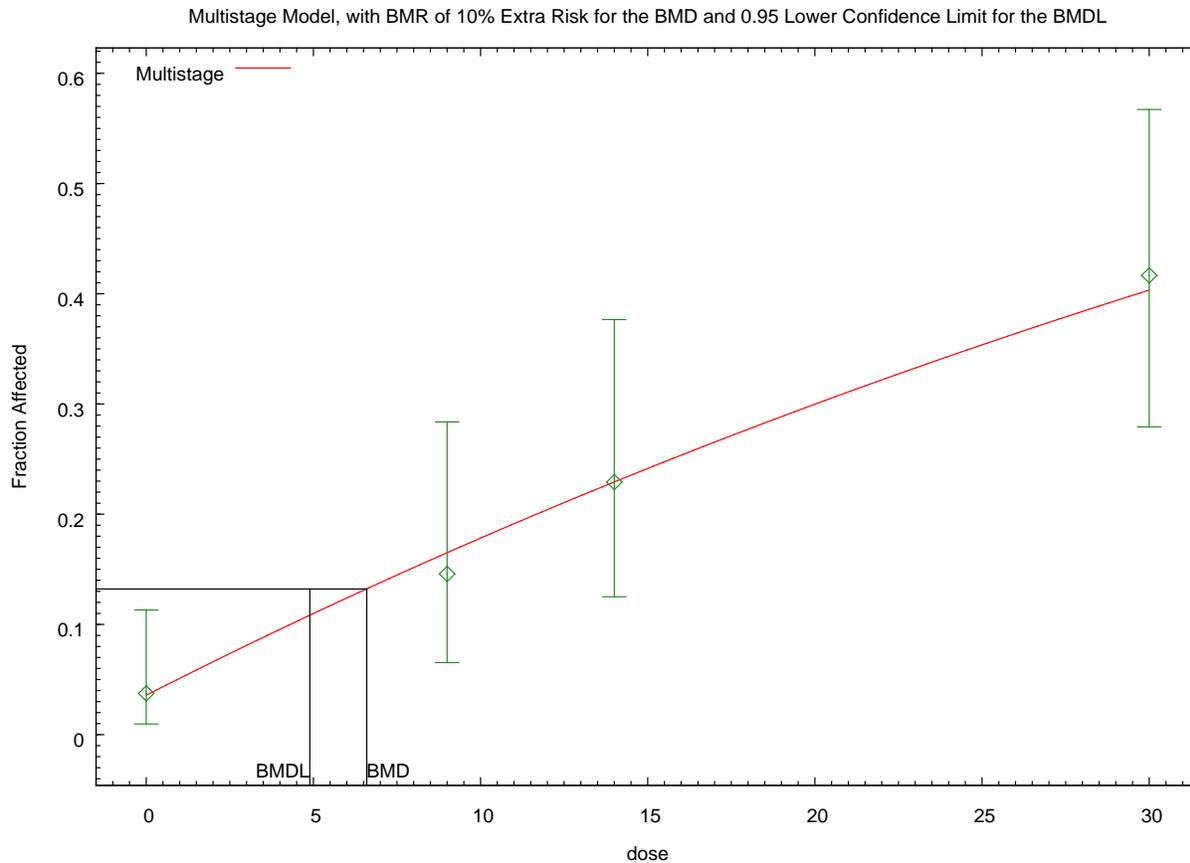
^eBetas restricted to ≥ 0 .

^fBMDL₁₀ values varied by <3 -fold; therefore, the model with the lowest AIC was selected as the best-fitting model (1-degree Multistage).

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

APPENDIX A

Figure A-14. Fit of 1-Degree Multistage Model for Hepatocellular Hypertrophy in Female Sprague-Dawley Rats Receiving 1,1-Dichloroethene from the Drinking Water for 2 Years (Dose in mg/kg/day)



The model predictions for midzonal fatty change are presented in Table A-23. All models provided adequate fit to the data. BMDLs for models providing adequate fit differed by <3-fold; therefore, the models with the lowest AIC were selected (Gamma, Multistage 1-degree and 2-degree, and Weibull) as a potential POD. The representative Weibull model fit is presented in Figure A-15.

APPENDIX A

Table A-23. Model Predictions for Midzonal Fatty Change in Female Sprague-Dawley Rats Receiving 1,1-Dichloroethene from the Drinking Water for up to 2 Years (Humiston et al. 1978; Quast et al. 1983)

Model	DF	χ^2 Goodness-of-fit		Scaled residuals ^b			AIC	BMD ₁₀ (mg/kg/day)	BMDL ₁₀ (mg/kg/day)
		χ^2	p-value ^a	Dose below BMD	Dose above BMD	Overall largest			
Gamma^{c,d,f}	2	0.03	0.98	-0.017	-0.13	0.13	242.46	6.64	4.61
Logistic	2	0.69	0.71	0.52	0.32	0.52	243.12	10.14	8.09
LogLogistic ^e	1	0.05	0.89	-0.012	0.13	-0.16	244.47	6.79	3.77
LogProbit ^e	2	1.0	0.61	0.75	0.19	0.75	243.4	10.47	7.69
Multistage (1-degree)^{d,f}	2	0.03	0.98	-0.017	-0.13	0.13	242.46	6.64	4.61
Multistage (2-degree)^{d,f}	2	0.03	0.98	-0.017	-0.13	0.13	242.46	6.64	4.61
Multistage (3-degree) ^d	1	0.03	0.86	-0.021	-0.14	0.14	244.46	6.67	4.61
Probit	2	0.55	0.76	0.49	0.27	0.49	242.98	9.64	7.65
Weibull^{c,f}	2	0.03	0.98	-0.017	-0.13	0.13	242.46	6.64	4.61

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

^bScaled residuals at doses immediately below and above the BMD; also the largest residual at any dose.

^cPower restricted to ≥ 1 .

^dSlope restricted to ≥ 1 .

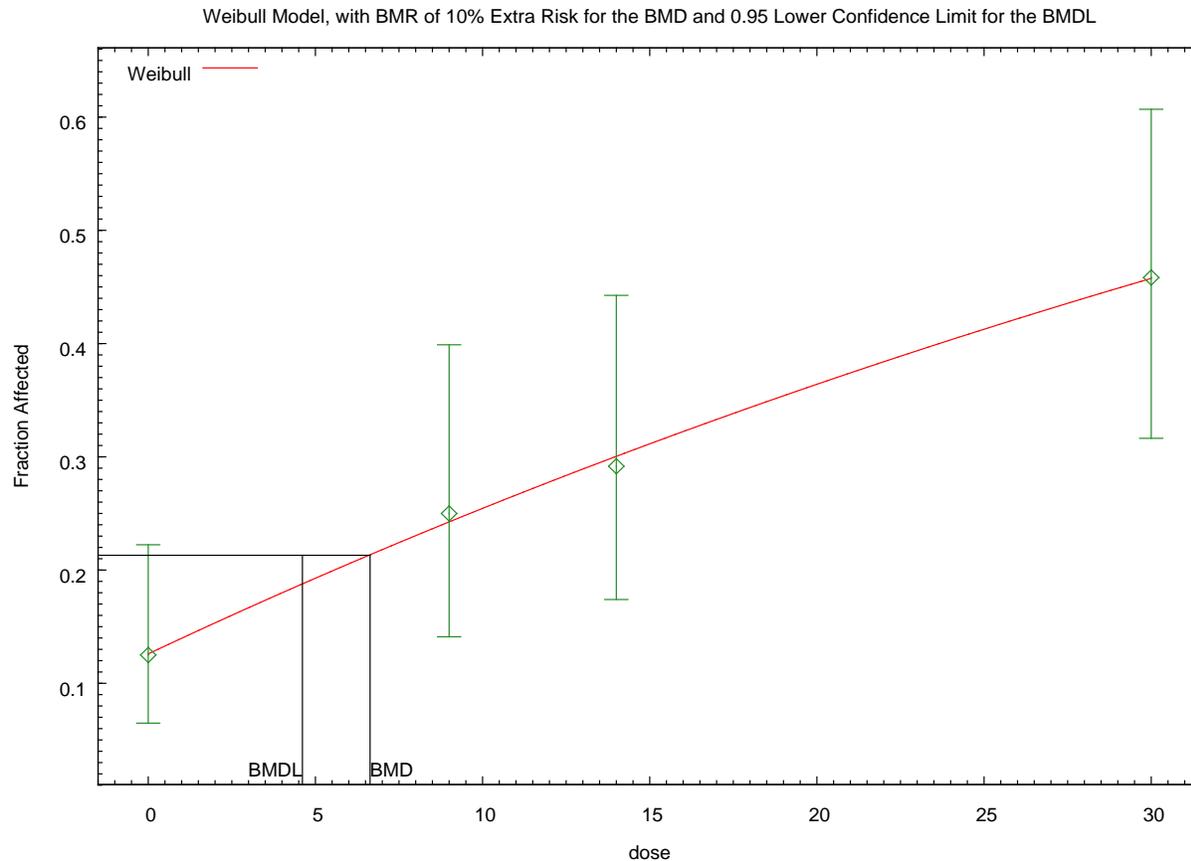
^eBetas restricted to ≥ 0 .

^fAll models provided adequate fit to the data. BMDLs differed by <3-fold; therefore, the models with the lowest AIC (Gamma, Multistage 1-degree and 2-degree, and Weibull models) were selected as best-fitting models.

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

APPENDIX A

Figure A-15. Fit of Weibull Model for Hepatic Midzonal Fatty Change in Female Sprague-Dawley Rats Receiving 1,1-Dichloroethene from the Drinking Water for 2 Years (Dose in mg/kg/day)



From the best-fitting models, the BMD₁₀ of 6.60 mg/kg/day for hepatocellular hypertrophy (Table A-22) is essentially the same as the BMD₁₀ of 6.64 mg/kg/day for midzonal fatty change (Table A-23). The BMDL₁₀ of 4.61 mg/kg/day for midzonal fatty change in the female rats is essentially the same as the BMDL₁₀ of 4.89 mg/kg/day for hepatocellular hypertrophy. Application of a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for individual variability) to either BMDL₁₀ (4.61 or 4.89 mg/kg/day) results in a provisional chronic-duration oral MRL of 0.05 mg/kg/day (rounded from 0.0461 mg/kg/day or 0.0489 mg/kg/day, respectively).

Uncertainty Factor: The BMDL₁₀ values were divided by a total uncertainty factor of 100:

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

$$\text{MRL} = \text{BMCL}_{10} \div \text{UFs}$$

$$\text{MRL} = 4.61 \text{ mg/kg/day or } 4.89 \text{ mg/kg/day} \div (10 \times 10) = 0.05 \text{ mg/kg/day (rounded from } 0.0461 \text{ mg/kg/day or } 0.0489 \text{ mg/kg/day).}$$

APPENDIX A

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

Agency Contacts (Chemical Managers): Malcolm Williams

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

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

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for 1,1-dichloroethene. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of 1,1-dichloroethene have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of 1,1-dichloroethene are presented in Table B-1.

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

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

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

Other noncancer effects
Cancer

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

B.1.1 Literature Search

The current literature search was intended to update the existing toxicological profile for 1,1-dichloroethene (ATSDR 1994), thus, the literature search was restricted to studies published between January 1992 to December 2016. The following main databases were searched in December 2016:

- PubMed
- National Library of Medicine's TOXLINE
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for 1,1-dichloroethene. The query strings used for the literature search are presented in Table B-2.

APPENDIX B

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to 1,1-dichloroethene were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
12/2016	((("vinylidene chloride"[nm] OR 21SK105J9D[rn] OR 75-35-4[rn]) AND (1992/01/01 : 3000[dp] OR 1992/01/01 : 3000[mhda])) OR (((("1,1-Dce"[tw] OR "1,1-Dichloroethene"[tw] OR "1,1-Dichloroethylene"[tw] OR "as-Dichloroethylene"[tw] OR "asym-Dichloroethylene"[tw] OR "Vinylidene chloride"[tw] OR "Vinylidene dichloride"[tw] OR "Vinylidine chloride"[tw]) AND (1992/01/01 : 3000[dp] OR 1992/01/01 : 3000[crdat] OR 1992/01/01 : 3000[edat])) NOT medline[sb]) OR (((("1,1"[tw] AND (dichloroethene[tw] OR dce[tw] OR Dichloroethylene[tw])) AND (1992/01/01 : 3000[dp] OR 1992/01/01 : 3000[crdat] OR 1992/01/01 : 3000[edat])) NOT medline[sb]))
Toxline	
12/2016	("1 1 dichloroethylene" OR "vinylidene chloride" OR "vinylidine chloride" OR "1 1 dichloroethene" OR "vinylidene dichloride" OR "1 1 dce" OR 75-35-4 [rn]) AND 1992:2016 [yr] AND (ANEUP [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR FEDRIP [org] OR HEEP [org] OR HMTG [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) [not] PubMed [org] [not] pubdart [org]
Toxcenter	
12/2016	=> d hist full (FILE 'HOME' ENTERED AT 16:04:43 ON 07 DEC 2016) FILE 'TOXCENTER' ENTERED AT 16:05:01 ON 07 DEC 2016 CHARGED TO COST=EH011.11.01.01.ODC L1 3620 SEA 75-35-4 L2 3456 SEA L1 NOT TSCATS/FS L3 3072 SEA L2 NOT PATENT/DT L4 1753 SEA L3 AND PY>1992 ACTIVATE TOXQUERY/Q ----- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT

APPENDIX B

Table B-2. Database Query Strings

Database search date	Query string
L9	QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
L10	QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
L11	QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
L12	QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
L13	QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
L14	QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
L15	QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
L16	QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
L17	QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
L18	QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
L19	QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
L20	QUE (ENDOCRIN? AND DISRUPT?)
L21	QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
L22	QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
L23	QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
L24	QUE (CARCINO? OR COCARCINO? OR CANCER? OR PRECANCER? OR NEOPLAS?)
L25	QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
L26	QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
L27	QUE (NEPHROTOX? OR HEPATOTOX?)
L28	QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
L29	QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
L30	QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29
L31	QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
L32	QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
L33	QUE L30 OR L31 OR L32
L34	QUE (NONHUMAN MAMMALS)/ORGN
L35	QUE L33 OR L34
L36	QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
L37	QUE L35 OR L36
L38	----- 691 SEA L4 AND L37

APPENDIX B

Table B-2. Database Query Strings

Database search date	Query string
L39	51 SEA L38 AND MEDLINE/FS
L40	63 SEA L38 AND BIOSIS/FS
L41	549 SEA L38 AND CAPLUS/FS
L42	28 SEA L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
L43	590 DUP REM L39 L40 L42 L41 (101 DUPLICATES REMOVED)
L*** DEL	51 S L38 AND MEDLINE/FS
L*** DEL	51 S L38 AND MEDLINE/FS
L44	51 SEA L43
L*** DEL	63 S L38 AND BIOSIS/FS
L*** DEL	63 S L38 AND BIOSIS/FS
L45	30 SEA L43
L*** DEL	549 S L38 AND CAPLUS/FS
L*** DEL	549 S L38 AND CAPLUS/FS
L46	484 SEA L43
L*** DEL	28 S L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
L*** DEL	28 S L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
L47	25 SEA L43
L48	539 SEA (L44 OR L45 OR L46 OR L47) NOT MEDLINE/FS SAVE TEMP L48 1,1-DICHLORO/A DICHLORO/A D SCAN L48

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS^a	
12/2016	Compounds searched: 75-35-4 [with received date of 1992-2000]
NTP	
12/2016	1,1-dichloroethene OR "vinylidene chloride" OR "Vinylidene dichloride" OR "Vinylidene chloride" OR "1,1-Dichloroethylene" OR "75-35-4"
NIH RePORTER	
12/2016	Active projects, "1,1-Dce" OR "1,1-Dichloroethene" OR "1,1-Dichloroethylene" OR "as-Dichloroethylene" OR "asym-Dichloroethylene" OR "Vinylidene chloride" OR "Vinylidene dichloride" OR "Vinylidene chloride" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects, 2017, 2016, 2015, 2014, 2013, 2012
Other	Identified throughout the assessment process

^aSeveral versions of the TSCATS database were searched, as needed, by CASRN including TSCATS1 via Toxline (no date limit), TSCATS2 via <https://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearch?OpenForm> (date restricted by EPA receipt date), and TSCATS via CDAT (date restricted by 'Mail Received Date Range'), as well as google for recent TSCA submissions.

APPENDIX B

The 2016 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 1,001
- Number of records identified from other strategies: 153
- Total number of records to undergo literature screening: 1,154

B.1.2 Literature Screening

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

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

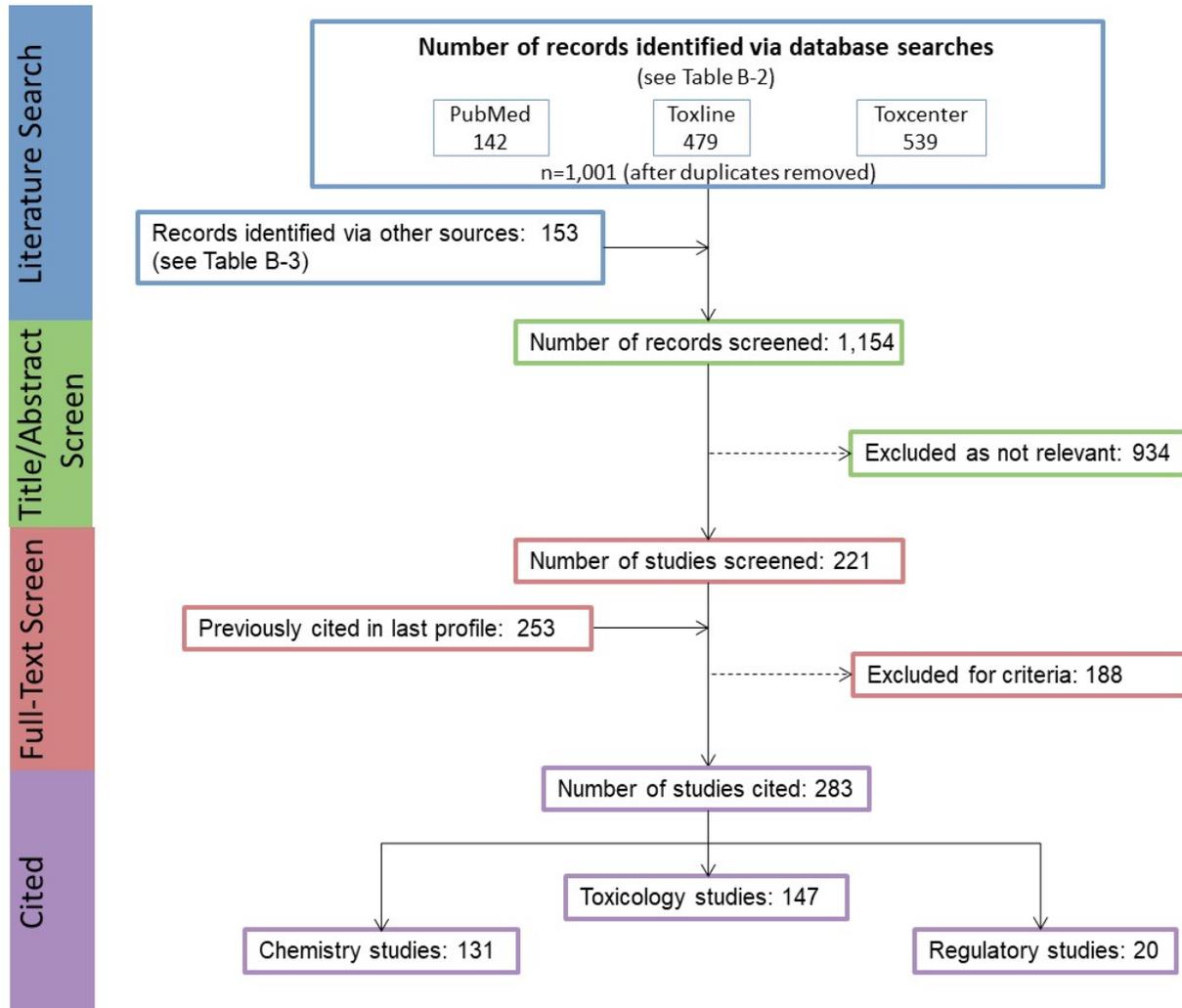
- Number of titles and abstracts screened: 1,154
- Number of studies considered relevant and moved to the next step: 221

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: 221
- Number of studies cited in the pre-public draft of the toxicological profile: 253
- Total number of studies cited in the profile: 283

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

APPENDIX B

Figure B-1. December 2017 Literature Search Results and Screen for 1,1-Dichloroethene

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

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

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

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to 1,1-dichloroethene. The inclusion criteria used to identify relevant studies examining the health effects of 1,1-dichloroethene are presented in Table C-1.

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

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

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen was conducted to identify studies examining the health effects of 1,1-dichloroethene. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the literature search to update the existing toxicological profile for 1,1-dichloroethene (ATSDR 1994) was restricted to studies published between January 1992 and December 2016. See Appendix B for the databases searched and the search strategy.

A total of 1,154 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

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

Title and Abstract Screen. In the Title and Abstract Screen step, 1,154 records were reviewed; 203 studies were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of the 160 health effects studies identified in the update literature was performed. Additionally, 43 studies cited in the LSE tables for the existing profile were included in the full study screen bringing the total number of studies for the qualitative review to 203.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

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

Table C-2. Data Extracted From Individual Studies

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

A summary of the extracted data for each study is presented in the Supplemental Document for 1,1-Dichloroethene and overviews of the results of the inhalation and oral exposure studies are presented in Sections 2.2–2.18 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (Tables 2-1 and 2-2, respectively).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for 1,1-dichloroethene identified in human and animal studies are presented in Tables C-3 and C-4, respectively. Studies examining these potential outcomes were carried through to Steps 4–8 of the systematic review. Ninety studies (published in 50 documents) examining these potential outcomes were carried through to Steps 4–8 of the systematic review.

APPENDIX C

Table C-3. Overview of the Health Outcomes for 1,1-Dichloroethene Evaluated In Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Cancer
Inhalation studies																	
Cohort					1		1	1									
					0		0	0									
Case control																	
Population																	
Case series																	
Oral studies																	
Cohort																	
Case control																	
Population															1		
															0		
Case series																	
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series																	
Number of studies examining endpoint			0	1	2	3	4	5-9	≥10								
Number of studies reporting outcome			0	1	2	3	4	5-9	≥10								

APPENDIX C

Table C-4. Overview of the Health Outcomes for 1,1-Dichloroethene Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological ^a	Neurological ^a	Reproductive ^a	Developmental	Other Noncancer	Cancer
Inhalation studies																	
Acute-duration	12	4	1	0	0	0	17	9	0	0	0	0	1	1	6	0	0
	6	1	1	0	0	0	13	8	0	0	0	0	1	0	4	0	0
Intermediate-duration	6	9	0	0	1	0	15	7	0	0	0	0	0	3	0	0	0
	3	4	0	0	0	0	14	4	0	0	0	0	0	2	0	0	0
Chronic-duration	8	8	0	0	3	0	10	8	0	0	1	0	0	0	0	0	4
	1	3	0	0	0	0	4	3	0	0	1	0	0	0	0	0	4
Oral studies																	
Acute-duration	3	3	1	1	1	0	11	4	0	0	0	0	0	0	1	0	0
	2	2	0	1	1	0	10	4	0	0	0	0	0	0	0	0	0
Intermediate-duration	3	0	0	0	1	0	3	1	0	0	0	0	0	0	0	0	0
	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Chronic-duration	4	4	2	1	1	0	5	5	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Dermal studies																	
Acute-duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Intermediate-duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Chronic-duration	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Number of studies examining endpoint				0	1	2	3	4	5-9	≥10							
Number of studies reporting outcome				0	1	2	3	4	5-9	≥10							

^aNumber of studies examining endpoint includes study evaluating histopathology, but not evaluating function.

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

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

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

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

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

Selection bias

Were the comparison groups appropriate?

Confounding bias

Did the study design or analysis account for important confounding and modifying variables?

Attrition/exclusion bias

Were outcome data complete without attrition or exclusion from analysis?

Detection bias

Is there confidence in the exposure characterization?

Is there confidence in outcome assessment?

Selective reporting bias

Were all measured outcomes reported?

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

Selection bias

Was administered dose or exposure level adequately randomized?

Was the allocation to study groups adequately concealed?

Performance bias

Were the research personnel and human subjects blinded to the study group during the study?

Attrition/exclusion bias

Were outcome data complete without attrition or exclusion from analysis?

Detection bias

Is there confidence in the exposure characterization?

Is there confidence in outcome assessment?

Selective reporting bias

Were all measured outcomes reported?

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

Was administered dose or exposure level adequately randomized?

Was the allocation to study groups adequately concealed?

Performance bias

Were experimental conditions identical across study groups?

Were the research personnel blinded to the study group during the study?

Attrition/exclusion bias

Were outcome data complete without attrition or exclusion from analysis?

Detection bias

Is there confidence in the exposure characterization?

Is there confidence in outcome assessment?

Selective reporting bias

Were all measured outcomes reported?

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

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

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

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

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

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

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

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

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

*Key question used to assign risk of bias tier

APPENDIX C

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

Reference	Risk of bias criteria and ratings									Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	Confidence in the outcome assessment?*	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	
Outcome: Respiratory effects										
<i>Inhalation acute exposure</i>										
Henck et al. 1979 (mouse; Ha[ICR])	+	+	++	+	+	++	++	+	na	First
Henck et al. 1979 (mouse; B6C3F1)	+	+	++	+	+	++	++	+	na	First
Henck et al. 1979 (mouse; CD-1)	+	+	++	+	+	++	++	+	na	First
Henck et al. 1979 (mouse; CF-W)	+	+	++	+	+	++	++	+	na	First
Zeller et al. 1979a (rat)	+	+	+	+	+	+	+	+	na	First
<i>Oral acute exposure</i>										
Chieco et al. 1981 (rat)	+	+	+	+	+	++	++	+	na	First
Forkert and Reynolds 1982 (mouse)	+	+	+	+	+	++	++	+	na	First
Forkert et al. 1985 (mouse)	+	na	na	na	na	++	++	+	na	First
<i>Inhalation intermediate exposure</i>										
Gage 1970 (rat)	+	+	+	+	+	++	++	+	na	First
Maltoni et al. 1985 (rat)	+	+	+	+	+	+	+	+	na	First
NTP 2015a (rat; 14 weeks)	+	+	++	+	+	++	++	+	na	First
NTP 2015a (mouse; 17 days)	+	+	++	+	+	++	++	+	na	First
NTP 2015a (mouse 14 weeks)	+	+	++	+	+	++	++	+	na	First
Prendergast et al. 1967 (rat)	+	+	++	+	+	++	++	+	na	First

APPENDIX C

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

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

APPENDIX C

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

Reference	Risk of bias criteria and ratings								Risk of bias tier	
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias		Other bias
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	Confidence in the outcome assessment?*	All measured outcomes reported?		Study design or analysis account for important confounding and modifying variables?

Outcome: Hepatic effects

Inhalation acute exposure

Henck et al. 1979 (mouse; Ha[ICR])	+	+	++	+	+	++	++	+	na	First
Henck et al. 1979 (mouse; B6C3F1)	+	+	++	+	+	++	++	+	na	First
Henck et al. 1979 (mouse; CD-1)	+	+	++	+	+	++	++	+	na	First
Henck et al. 1979 (mouse; CF-W)	+	+	++	+	+	++	++	+	na	First
Jaeger 1977 (rat)	+	na	na	na	+	+	+	+	na	First
Jaeger et al. 1973a (rat)	+	na	na	na	+	+	+	+	na	First
Jaeger et al. 1974 (rat; fasted)	+	+	+	+	+	++	+	+	na	First
Jaeger et al. 1974 (rat; nonfasted)	+	+	+	+	+	++	+	+	na	First
Maltoni et al. 1985 (mouse)	+	+	+	+	+	+	+	+	na	First
McKenna et al. 1978b (rat)	+	+	+	+	+	++	+	+	na	First
Murray et al. 1979 (rat; 80 ppm)	+	+	+	+	+	+	+	+	na	First
Murray et al. 1979 (rat; 160 ppm)	+	+	+	+	+	+	+	+	na	First
Murray et al. 1979 (rabbit; 80 ppm)	+	+	+	+	+	+	+	+	na	First
Murray et al. 1979 (rabbit; 160 ppm)	+	+	+	+	+	+	+	+	na	First
Reitz et al. 1980 (mouse)	+	+	+	+	+	+	+	+	na	First
Short et al. 1977c, 1977d (rat)	+	+	+	+	+	+	+	+	na	First
Short et al. 1977c, 1977d (mouse)	+	+	+	+	+	+	+	+	na	First

APPENDIX C

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

Reference	Risk of bias criteria and ratings								Risk of bias tier	
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias		Other bias
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	Confidence in the outcome assessment?*	All measured outcomes reported?		Study design or analysis account for important confounding and modifying variables?
<i>Oral acute exposure</i>										
Chieco et al. 1981 (rat; 200 mg/kg/day)	+	+	+	+	+	++	+	+	na	First
Chieco et al. 1981 (rat; 50–200 mg/kg/day)	+	+	+	+	+	++	+	+	na	First
Jaeger et al. 1973b (rat)	+	+	+	+	+	++	+	+	na	First
Jenkins and Andersen 1978 (rat)	+	+	+	+	+	++	+	+	na	First
Kanz and Reynolds 1986 (rat)	+	+	+	+	+	++	+	+	na	First
Kanz et al. 1991 (rat)	+	+	+	+	+	++	+	+	na	First
Moslen et al. 1985 (rat)	+	+	+	+	+	++	+	+	na	First
Murray et al. 1979 (rat)	+	+	+	+	+	+	+	+	na	First
NTP 1982 (rat)	+	+	+	+	+	++	+	+	na	First
NTP 1982 (mouse)	+	+	+	+	+	++	+	+	na	First
Reynolds et al. 1984 (rat)	+	+	+	+	+	++	+	+	na	First
<i>Inhalation intermediate exposure</i>										
Balmer et al. 1976 (rat)	+	+	+	+	+	+	+	+	na	First
Gage 1970 (rat)	+	+	+	+	+	++	++	+	na	First
Maltoni et al. 1985 (rat)	+	+	+	+	+	+	+	+	na	First
NTP 2015a (rat; 16 days)	+	+	++	+	+	++	++	+	na	First
NTP 2015a (rat; 14 weeks)	+	+	++	+	+	++	++	+	na	First
NTP 2015a (mouse; 17 days)	+	+	++	+	+	++	++	+	na	First

APPENDIX C

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

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	Risk of bias tier
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	Confidence in the outcome assessment?*	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?	
NTP 2015a (mouse; 14 weeks)	+	+	++	+	+	++	++	+	na	
Plummer et al. 1990 (rat; continuous)	+	+	+	+	+	+	+	+	na	First
Plummer et al. 1990 (rat; intermittent)	+	+	+	+	+	+	+	+	na	First
Prendergast et al. 1967 (monkey)	+	+	++	+	+	++	++	+	na	First
Prendergast et al. 1967 (rat)	+	+	++	+	+	++	++	+	na	First
Prendergast et al. 1967 (guinea pig)	+	+	++	+	+	++	++	+	na	First
Prendergast et al. 1967 (dog)	+	+	++	+	+	++	++	+	na	First
Quast 1976 (rat)	+	+	+	+	+	+	+	+	na	First
Quast et al. 1986 (rat)	+	+	++	+	+	++	++	++	na	First
<i>Oral intermediate exposure</i>										
NTP 1982 (rat)	+	+	+	+	+	++	++	+	na	First
NTP 1982 (mouse)	+	+	+	+	+	++	++	+	na	First
Quast et al. 1983 (dog)	+	+	+	+	+	++	++	+	na	First
<i>Inhalation chronic exposure</i>										
Lee et al. 1977, 1978 (rat)	+	+	+	+	+	++	+	+	na	First
Lee et al. 1977, 1978 (mouse)	+	+	+	+	+	++	+	+	na	First
Maltoni et al. 1985 (rat; 104 weeks)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (rat; 52 weeks)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (mouse; 10, 25 ppm)	+	+	+	+	+	+	+	+	na	First

APPENDIX C

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

Reference	Risk of bias criteria and ratings										Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias		
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	Confidence in the outcome assessment?*	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?		
Maltoni et al. 1985 (mouse; 25 ppm)	+	+	+	+	+	+	+	+	na	First	
Maltoni et al. 1985 (hamster)	+	+	+	+	+	+	+	+	na	First	
NTP 2015a (rat; 105 weeks)	+	+	++	+	+	++	++	++	na	First	
NTP 2015a (mouse; 105 weeks)	+	+	++	+	+	++	++	++	na	First	
<i>Oral chronic exposure</i>											
Maltoni et al. 1985 (rat; 0.5 mg/kg/day)	+	+	+	+	+	+	+	+	na	First	
Maltoni et al. 1985 (rat; multidose)	+	+	+	+	+	+	+	+	na	First	
NTP 1982 (rat)	+	+	++	+	+	++	++	++	na	First	
NTP 1982 (mouse)	+	+	++	+	+	++	++	++	na	First	
Quast et al. 1983 (rat)	+	+	++	+	+	++	++	++	na	First	
Outcome: Renal effects											
<i>Inhalation acute exposure</i>											
Henck et al. 1979 (mouse; Ha[ICR])	+	+	++	+	+	++	++	+	na	First	
Henck et al. 1979 (mouse; B6C3F1)	+	+	++	+	+	++	++	+	na	First	
Henck et al. 1979 (mouse; CD-1)	+	+	++	+	+	++	++	+	na	First	
Henck et al. 1979 (mouse; CF-W)	+	+	++	+	+	++	++	+	na	First	
Jackson and Conolly 1985 (rat)	+	+	++	+	+	++	++	+	na	First	
Maltoni et al. 1985 (mouse)	+	+	+	+	+	+	+	+	na	First	
McKenna et al. 1978b (rat)	+	+	+	+	+	++	+	+	na	First	

APPENDIX C

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

Reference	Risk of bias criteria and ratings										Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias		
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	Confidence in the outcome assessment?*	All measured outcomes reported?	Study design or analysis account for important confounding and modifying variables?		
Short et al. 1977c, 1977d (rat)	+	+	+	+	+	+	+	+	+	na	First
Short et al. 1977c, 1977d (mouse)	+	+	+	+	+	+	+	+	+	na	First
<i>Oral acute exposure</i>											
Chieco et al. 1981 (rat)	+	+	+	+	+	++	+	+	+	na	First
Jenkins and Andersen 1978 (rat; single dose)	+	+	+	+	+	++	+	+	+	na	First
Jenkins and Andersen 1978 (rat; multidose)	+	+	+	+	+	++	+	+	+	na	First
Jenkins and Andersen 1978 (rat; single dose)	+	+	+	+	+	++	+	+	+	na	First
<i>Inhalation intermediate exposure</i>											
Maltoni et al. 1985 (rat)	+	+	+	+	+	+	+	+	+	na	First
NTP 2015a (rat; 16 days)	+	+	++	+	+	++	++	+	+	na	First
NTP 2015a (rat; 14 weeks)	+	+	++	+	+	++	++	+	+	na	First
NTP 2015a (mouse; 17 days)	+	+	++	+	+	++	++	+	+	na	First
NTP 2015a (mouse; 14 weeks)	+	+	++	+	+	++	++	+	+	na	First
Prendergast et al. 1967 (rat)	+	+	++	+	+	++	++	+	+	na	First
Prendergast et al. 1967 (dog)	+	+	++	+	+	++	++	+	+	na	First
<i>Oral intermediate exposure</i>											
Quast et al. 1983 (dog)	+	+	+	+	+	++	++	+	+	na	First

APPENDIX C

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

Reference	Risk of bias criteria and ratings								Risk of bias tier	
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias		Other bias
	Administered dose or exposure level adequately randomized?	Allocation to study groups adequately concealed?	Experimental conditions identical across study groups?	Research personnel blinded to the study group during the study?	Outcome data complete without attrition or exclusion from analysis?	Confidence in the exposure characterization?	Confidence in the outcome assessment?*	All measured outcomes reported?		Study design or analysis account for important confounding and modifying variables?
<i>Inhalation chronic exposure</i>										
Maltoni et al. 1985 (rat; 104 weeks)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (rat; 52 weeks)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (mouse; 10, 25 ppm)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (mouse; 25 ppm)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (hamster)	+	+	+	+	+	+	+	+	na	First
NTP 2015a (rat; 105 weeks)	+	+	++	+	+	++	++	++	na	First
NTP 2015a (mouse; 105 weeks)	+	+	++	+	+	++	++	++	na	First
Quast et al. 1986 (rat)	+	+	++	+	+	++	++	++	na	First
<i>Oral chronic exposure</i>										
Maltoni et al. 1985 (rat; single dose)	+	+	+	+	+	+	+	+	na	First
Maltoni et al. 1985 (rat; multidose)	+	+	+	+	+	+	+	+	na	First
NTP 1982 (rat)	+	+	++	+	+	++	++	++	na	First
NTP 1982 (mouse)	+	+	++	+	+	++	++	++	na	First
Quast et al. 1983 (mouse)	+	+	++	+	+	++	++	++	na	First

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

*Key question used to assign risk of bias tier

C.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including HHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to 1,1-dichloroethene and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** the true effect may be reflected in the apparent relationship
- **Low confidence:** the true effect may be different from the apparent relationship
- **Very low confidence:** the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

C.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to 1,1-dichloroethene and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions in Distiller, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure, and experimental animal studies are presented in Tables C-10, C-11, and C-12, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".
- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".
- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".
- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

APPENDIX C

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

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

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

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

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

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

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

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

APPENDIX C

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

Reference	Key features				Initial study confidence
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	
Outcome: Hepatic effects					
Inhalation-cohort Ott et al. 1976	No	Yes	Yes	Yes	Moderate
Outcome: Renal effects					
Oral-cross-sectional Ott et al. 1995	No	Yes	Yes	Yes	Moderate

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

Reference	Key feature				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Outcome: Respiratory effects					
<i>Inhalation acute exposure</i>					
Henck et al. 1979 (mouse; Ha[ICR])	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; B6C3F1)	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; CD-1)	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; CF-W)	Yes	Yes	Yes	Yes	High
Zeller et al. 1979a (rat)	No	Yes	No	No	Very Low
<i>Oral acute exposure</i>					
Chieco et al. 1981 (rat)	Yes	No	No	No	Very Low
Forkert and Reynolds 1982 (mouse)	Yes	No	Yes	No	Low
Forkert et al. 1985 (mouse)	Yes	No	Yes	No	Low
<i>Inhalation intermediate exposure</i>					
Gage 1970 (rat)	Yes	No	No	No	Very Low
Maltoni et al. 1985 (rat)	Yes	Yes	No	No	Low
NTP 2015a (rat; 14 weeks)	Yes	Yes	Yes	Yes	High

APPENDIX C

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

Reference	Key feature				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
NTP 2015a (mouse; 17 days)	Yes	Yes	Yes	Yes	High
NTP 2015a (mouse 14 weeks)	Yes	Yes	Yes	Yes	High
Prendergast et al. 1967 (rat)	Yes	Yes	No	No	Low
Prendergast et al. 1967 (guinea pig)	Yes	Yes	No	No	Low
Prendergast et al. 1967 (dog)	Yes	No	No	No	Very Low
Quast et al. 1986 (rat)	Yes	No	No	No	Very Low
<i>Inhalation chronic exposure</i>					
Maltoni et al. 1985 (rat; 104 weeks)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (rat; 52 weeks)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (mouse; 10, 25 ppm)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (mouse; 25 ppm)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (hamster)	Yes	Yes	No	No	Low
NTP 2015a (rat)	Yes	Yes	Yes	Yes	High
NTP 2015a (mouse)	Yes	Yes	Yes	Yes	High
Quast et al. 1986 (rat)	Yes	Yes	No	No	Low
<i>Oral chronic exposure</i>					
Maltoni et al. 1985 (rat; 0.5 mg/kg/day)	Yes	Yes	Yes	No	Moderate
Maltoni et al. 1985 (rat; 5, 10, 20 mg/kg/day)	Yes	Yes	Yes	No	Moderate
NTP 1982 (rat)	Yes	Yes	Yes	Yes	High
NTP 1982 (mouse)	Yes	Yes	Yes	Yes	High
Outcome: Hepatic effects					
<i>Inhalation acute exposure</i>					
Henck et al. 1979 (mouse; Ha[ICR])	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; B6C3F1)	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; CD-1)	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; CF-W)	Yes	Yes	Yes	Yes	High
Jaeger 1977 (rat)	Yes	Yes	No	No	Low
Jaeger et al. 1973a (rat)	Yes	No	No	No	Very Low
Jaeger et al. 1974 (rat; fasted)	No	No	No	No	Very Low
Jaeger et al. 1974 (rat; nonfasted)	No	No	No	No	Very Low
Maltoni et al. 1985 (mouse)	Yes	Yes	Yes	No	Moderate
McKenna et al. 1978b (rat)	No	No	Yes	No	Very Low
Murray et al. 1979 (rat; 80 ppm)	Yes	Yes	No	Yes	Moderate
Murray et al. 1979 (rat; 160 ppm)	Yes	Yes	No	Yes	Moderate

APPENDIX C

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

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

APPENDIX C

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

Reference	Key feature				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
<i>Oral intermediate exposure</i>					
NTP 1982 (rat)	Yes	Yes	Yes	Yes	High
NTP 1982 (mouse)	Yes	Yes	Yes	Yes	High
Quast et al. 1983 (dog)	Yes	Yes	Yes	Yes	High
<i>Inhalation chronic exposure</i>					
Lee et al. 1977, 1978 (rat)	Yes	Yes	Yes	No	Moderate
Lee et al. 1977, 1978 (mouse)	Yes	Yes	Yes	No	Moderate
Maltoni et al. 1985 (rat; 104 weeks)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (rat; 52 weeks)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (mouse; 10, 25 ppm)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (mouse; 25 ppm)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (hamster)	Yes	Yes	No	No	Low
NTP 2015a (rat; 105 weeks)	Yes	Yes	Yes	Yes	High
NTP 2015a (mouse; 105 weeks)	Yes	Yes	Yes	Yes	High
Quast et al. 1986 (rat)	Yes	Yes	Yes	Yes	High
<i>Oral chronic exposure</i>					
Maltoni et al. 1985 (rat; 0.5 mg/kg/day)	Yes	Yes	Yes	No	Moderate
Maltoni et al. 1985 (rat; multidose)	Yes	Yes	Yes	No	Moderate
NTP 1982 (rat)	Yes	Yes	Yes	Yes	High
NTP 1982 (mouse)	Yes	Yes	Yes	Yes	High
Quast et al. 1983 (rat)	Yes	Yes	Yes	Yes	High
Outcome: Renal effects					
<i>Inhalation acute exposure</i>					
Henck et al. 1979 (mouse; Ha[ICR])	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; B6C3F1)	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; CD-1)	Yes	Yes	Yes	Yes	High
Henck et al. 1979 (mouse; CF-W)	Yes	Yes	Yes	Yes	High
Jackson and Conolly 1985 (rat)	Yes	Yes	Yes	Yes	High
Maltoni et al. 1985 (mouse)	Yes	Yes	Yes	No	Moderate
McKenna et al. 1978b (rat)	No	No	Yes	No	Very Low
Short et al. 1977c, 1977d (rat)	Yes	No	Yes	Yes	Moderate
Short et al. 1977c, 1977d (mouse)	Yes	No	Yes	Yes	Moderate
<i>Oral acute exposure</i>					
Chieco et al. 1981 (rat)	Yes	No	Yes	No	Low

APPENDIX C

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

Reference	Key feature				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Jenkins and Andersen 1978 (rat; single dose)	Yes	No	Yes	Yes	Moderate
Jenkins and Andersen 1978 (rat; multidose)	Yes	No	Yes	Yes	Moderate
Jenkins and Andersen 1978 (rat; single dose)	Yes	No	Yes	Yes	Moderate
<i>Inhalation intermediate exposure</i>					
Maltoni et al. 1985 (rat)	Yes	Yes	No	No	Low
NTP 2015a (rat; 16 days)	Yes	Yes	Yes	Yes	High
NTP 2015a (rat; 14 weeks)	Yes	Yes	Yes	Yes	High
NTP 2015a (mouse; 17 days)	Yes	Yes	Yes	Yes	High
NTP 2015a (mouse; 14 weeks)	Yes	Yes	Yes	Yes	High
Prendergast et al. 1967 (rat)	Yes	Yes	No	No	Low
Prendergast et al. 1967 (dog)	Yes	No	No	No	Very Low
<i>Oral intermediate exposure</i>					
Quast et al. 1983 (dog)	Yes	Yes	Yes	Yes	High
<i>Inhalation chronic exposure</i>					
Maltoni et al. 1985 (rat; 104 weeks)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (rat; 52 weeks)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (mouse; 10, 25 ppm)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (mouse; 25 ppm)	Yes	Yes	No	No	Low
Maltoni et al. 1985 (hamster)	Yes	Yes	No	No	Low
NTP 2015a (rat; 105 weeks)	Yes	Yes	Yes	Yes	High
NTP 2015a (mouse; 105 weeks)	Yes	Yes	Yes	Yes	High
Quast et al. 1986 (rat)	Yes	Yes	Yes	Yes	High
<i>Oral chronic exposure</i>					
Maltoni et al. 1985 (rat; single dose)	Yes	Yes	Yes	No	Moderate
Maltoni et al. 1985 (rat; multidose)	Yes	Yes	Yes	No	Moderate
NTP 1982 (rat)	Yes	Yes	Yes	Yes	High
NTP 1982 (mouse)	Yes	Yes	Yes	Yes	High
Quast et al. 1983 (mouse)	Yes	Yes	Yes	Yes	High

APPENDIX C

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

	Initial study confidence	Initial confidence rating
Outcome: Respiratory effects		
<i>Inhalation acute exposure</i>		
Animal studies		
Henck et al. 1979 (mouse; Ha[ICR])	High	High
Henck et al. 1979 (mouse; B6C3F1)	High	
Henck et al. 1979 (mouse; CD-1)	High	
Henck et al. 1979 (mouse; CF-W)	High	
Zeller et al. 1979a (rat)	Very Low	
<i>Inhalation intermediate exposure</i>		
Animal studies		
Gage 1970 (rat)	Very Low	High
Maltoni et al. 1985 (rat)	Low	
NTP 2015a (rat; 14 weeks)	High	
NTP 2015a (mouse; 17 days)	High	
NTP 2015a (mouse 14 weeks)	High	
Prendergast et al. 1967 (rat)	Low	
Prendergast et al. 1967 (guinea pig)	Low	
Prendergast et al. 1967 (dog)	Very Low	
Quast et al. 1986 (rat)	Very Low	
<i>Inhalation chronic exposure</i>		
Animal studies		
Maltoni et al. 1985 (rat; 104 weeks)	Low	High
Maltoni et al. 1985 (rat; 52 weeks)	Low	
Maltoni et al. 1985 (mouse; 10, 25 ppm)	Low	
Maltoni et al. 1985 (mouse; 25 ppm)	Low	
Maltoni et al. 1985 (hamster)	Low	
NTP 2015a (rat)	High	
NTP 2015a (mouse)	High	
Quast et al. 1986 (rat)	Low	
<i>Oral acute exposure</i>		
Animal studies		
Chieco et al. 1981 (rat)	Very Low	Low
Forkert and Reynolds 1982 (mouse)	Low	
Forkert et al. 1985 (mouse)	Low	
<i>Oral chronic exposure</i>		
Animal studies		
Maltoni et al. 1985 (rat; 0.5 mg/kg/day)	Moderate	High
Maltoni et al. 1985 (rat; 5, 10, 20 mg/kg/day)	Moderate	
NTP 1982 (rat)	High	
NTP 1982 (mouse)	High	

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

	Initial study confidence	Initial confidence rating	
Outcome: Hepatic effects			
<i>Inhalation acute exposure</i>			
Animal studies			
Henck et al. 1979 (mouse; Ha[ICR])	High	High	
Henck et al. 1979 (mouse; B6C3F1)	High		
Henck et al. 1979 (mouse; CD-1)	High		
Henck et al. 1979 (mouse; CF-W)	High		
Jaeger 1977 (rat)	Low		
Jaeger et al. 1973a (rat)	Very Low		
Jaeger et al. 1974 (rat; fasted)	Very Low		
Jaeger et al. 1974 (rat; nonfasted)	Very Low		
Maltoni et al. 1985 (mouse)	Moderate		
McKenna et al. 1978b (rat)	Very Low		
Murray et al. 1979 (rat; 80 ppm)	Moderate		
Murray et al. 1979 (rat; 160 ppm)	Moderate		
Murray et al. 1979 (rabbit; 80 ppm)	Moderate		
Murray et al. 1979 (rabbit; 160 ppm)	Moderate		
Reitz et al. 1980 (mouse)	Very Low		
Short et al. 1977c, 1977d (rat)	Moderate		
Short et al. 1977c, 1977d (mouse)	Moderate		
<i>Inhalation intermediate exposure</i>			
Animal studies			
Balmer et al. 1976 (rat)	High		High
Gage 1970 (rat)	Low		
Maltoni et al. 1985 (rat)	Low		
NTP 2015a (rat; 16 days)	High		
NTP 2015a (rat; 14 weeks)	High		
NTP 2015a (mouse; 17 days)	High		
NTP 2015a (mouse; 14 weeks)	High		
Plummer et al. 1990 (rat; continuous)	Low		
Plummer et al. 1990 (rat; intermittent)	Low		
Prendergast et al. 1967 (monkey)	Low		
Prendergast et al. 1967 (rat)	Low		
Prendergast et al. 1967 (guinea pig)	Low		
Prendergast et al. 1967 (dog)	Very Low		
Quast 1976 (rat)	High		
Quast 1986 (rat)	Moderate		
<i>Inhalation chronic exposure</i>			
Human studies			
Ott et al. 1976	Moderate	Moderate	
Animal studies			
Lee et al. 1977, 1978 (rat)	Moderate	High	
Lee et al. 1977, 1978 (mouse)	Moderate		

APPENDIX C

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

	Initial study confidence	Initial confidence rating	
Maltoni et al. 1985 (rat; 104 weeks)	Low	High	
Maltoni et al. 1985 (rat; 52 weeks)	Low		
Maltoni et al. 1985 (mouse; 10, 25 ppm)	Low		
Maltoni et al. 1985 (mouse; 25 ppm)	Low		
Maltoni et al. 1985 (hamster)	Low		
NTP 2015a (rat; 105 weeks)	High		
NTP 2015a (mouse; 105 weeks)	High		
Quast et al. 1986 (rat)	High		
<i>Oral acute exposure</i>			
Animal studies			
Chieco et al. 1981 (rat; 200 mg/kg/day)	Low	Moderate	
Chieco et al. 1981 (rat; 50–200 mg/kg/day)	Low		
Jaeger et al. 1973b (rat)	Moderate		
Jenkins and Andersen 1978 (rat)	Low		
Kanz and Reynolds 1986 (rat)	Moderate		
Kanz et al. 1991 (rat)	Moderate		
Moslen et al. 1985 (rat)	Low		
Murray et al. 1979 (rat)	Moderate		
NTP 1982 (rat)	Moderate		
NTP 1982 (mouse)	Moderate		
Reynolds et al. 1984 (rat)	Very Low		
<i>Oral intermediate exposure</i>			
Animal studies			
NTP 1982 (rat)	High	High	
NTP 1982 (mouse)	High		
Quast et al. 1983 (dog)	High		
<i>Oral chronic exposure</i>			
Animal studies			
Maltoni et al. 1985 (rat; 0.5 mg/kg/day)	Moderate	High	
Maltoni et al. 1985 (rat; multidose)	Moderate		
NTP 1982 (rat)	High		
NTP 1982 (mouse)	High		
Quast et al. 1983 (rat)	High		
Outcome: Renal effects			
<i>Inhalation acute exposure</i>			
Animal studies			
Henck et al. 1979 (mouse; Ha[ICR])	High	High	
Henck et al. 1979 (mouse; B6C3F1)	High		
Henck et al. 1979 (mouse; CD-1)	High		
Henck et al. 1979 (mouse; CF-W)	High		
Jackson and Conolly 1985 (rat)	High		
Maltoni et al. 1985 (mouse)	Moderate		
McKenna et al. 1978b (rat)	Very Low		

APPENDIX C

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

	Initial study confidence	Initial confidence rating
Short et al. 1977c, 1977d (rat)	Moderate	
Short et al. 1977c, 1977d (mouse)	Moderate	
<i>Inhalation intermediate exposure</i>		
Animal studies		
Maltoni et al. 1985 (rat)	Low	High
NTP 2015a (rat; 16 days)	High	
NTP 2015a (rat; 14 weeks)	High	
NTP 2015a (mouse; 17 days)	High	
NTP 2015a (mouse; 14 weeks)	High	
Prendergast et al. 1967 (rat)	Low	
Prendergast et al. 1967 (dog)	Very Low	
<i>Inhalation chronic exposure</i>		
Human studies		
Ott et al. 1976	Moderate	Moderate
Animal studies		
Maltoni et al. 1985 (rat; 104 weeks)	Low	High
Maltoni et al. 1985 (rat; 52 weeks)	Low	
Maltoni et al. 1985 (mouse; 10, 25 ppm)	Low	
Maltoni et al. 1985 (mouse; 25 ppm)	Low	
Maltoni et al. 1985 (hamster)	Low	
NTP 2015a (rat; 105 weeks)	High	
NTP 2015a (mouse; 105 weeks)	High	
Quast et al. 1986 (rat)	High	
<i>Oral acute exposure</i>		
Animal studies		
Chieco et al. 1981 (rat)	Low	Moderate
Jenkins and Andersen 1978 (rat; single dose)	Moderate	
Jenkins and Andersen 1978 (rat; multidose)	Moderate	
Jenkins and Andersen 1978 (rat; single dose)	Moderate	
<i>Oral intermediate exposure</i>		
Animal studies		
Quast et al. 1983 (dog)	High	High
<i>Oral chronic exposure</i>		
Animal studies		
Maltoni et al. 1985 (rat; single dose)	Moderate	High
Maltoni et al. 1985 (rat; multidose)	Moderate	
NTP 1982 (rat)	High	
NTP 1982 (mouse)	High	
Quast et al. 1983 (mouse)	High	

C.6.2 Adjustment of the Confidence Rating

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

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

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

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

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

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

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-8 and C-9). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
 - No downgrade if most studies are in the risk of bias first tier
 - Downgrade one confidence level if most studies are in the risk of bias second tier
 - Downgrade two confidence levels if most studies are in the risk of bias third tier
- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below

APPENDIX C

are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:

- No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
 - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
 - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect
- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
 - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
 - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
 - Nature of the exposure in human studies and route of administration in animal studies— inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
 - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:

- No downgrade if none of the factors are considered indirect
 - Downgrade one confidence level if one of the factors is considered indirect
 - Downgrade two confidence levels if two or more of the factors are considered indirect
- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥ 10 for tests of ratio measures (e.g., odds ratios) and ≥ 100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
 - No downgrade if there are no serious imprecisions
 - Downgrade one confidence level for serious imprecisions
 - Downgrade two confidence levels for very serious imprecisions
 - **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
 - Downgrade one level of confidence for cases where there is serious concern with publication bias

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

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.

APPENDIX C

- Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias
- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
 - Upgrade one confidence level for evidence of a monotonic dose-response gradient
 - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies
- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., “healthy worker” effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
 - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect
- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:

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

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

In the seventh step of the systematic review of the health effects data for 1,1-dichloroethene, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome OR very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

APPENDIX C

A summary of the level of evidence of health effects for 1,1-dichloroethene is presented in Table C-18.

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

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

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

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

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

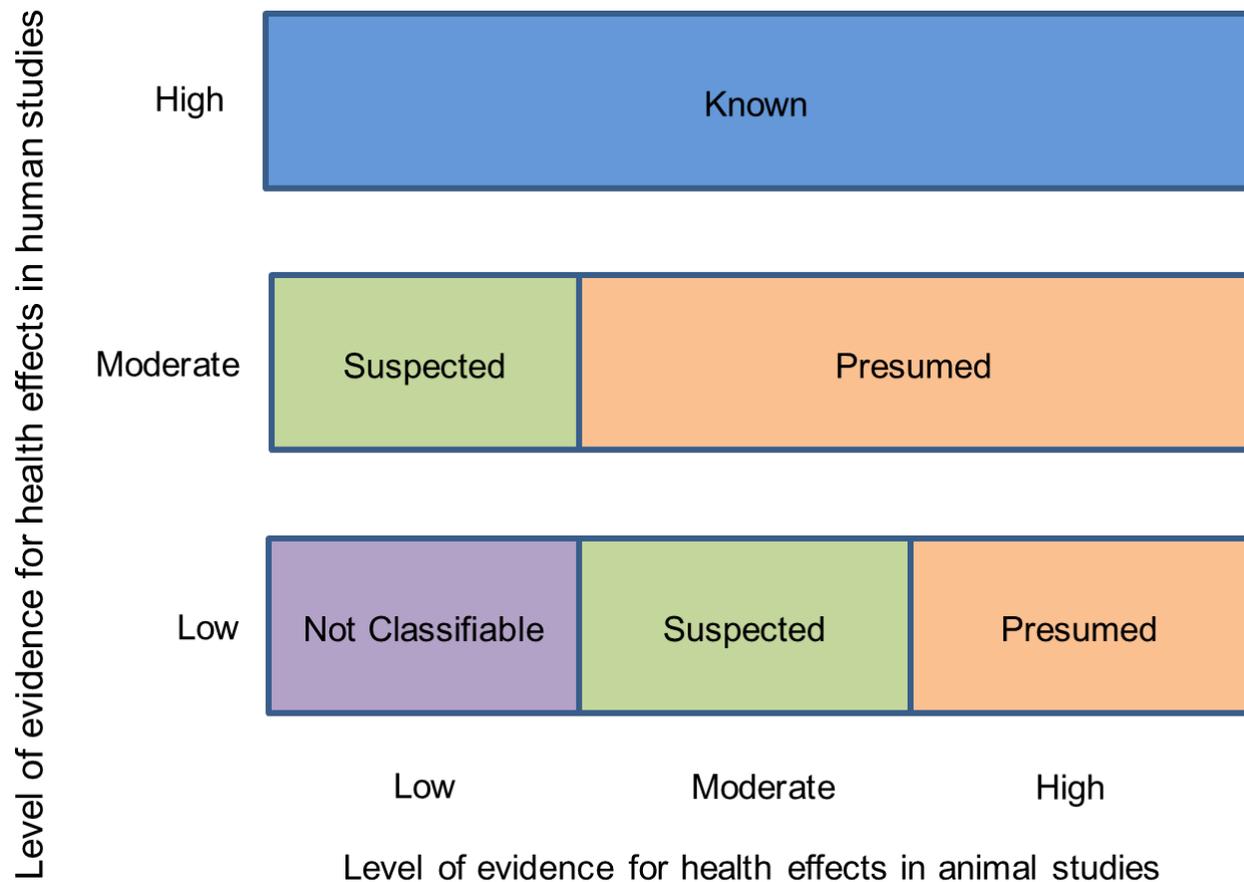
The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the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

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

APPENDIX C

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

Figure C-1. Hazard Identification Scheme



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

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

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

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

APPENDIX C

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

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

Presumed Health Effects

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

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

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

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

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

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

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

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

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

APPENDIX D

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

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

TABLE LEGEND

See Sample LSE Table (page C-5)

- (1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.
- (2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥ 365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.
- (3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).
- (4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.
- (5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to "Chemical X" via feed for 2 years. For a

APPENDIX D

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

- (6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).
- (7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.
- (8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.
- (9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.
- (10) Reference. The complete reference citation is provided in Chapter 8 of the profile.
- (11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page C-6)

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

- (13) 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.

APPENDIX D

- (14) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.
- (15) 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/m³ or ppm and oral exposure is reported in mg/kg/day.
- (16) 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).
- (17) 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.
- (18) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

APPENDIX D

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

	4 Species	5 Exposure parameters	5 Doses (mg/kg/day)	6 Parameters monitored	7 Endpoint	8 NOAEL (mg/kg/day)	8 Less serious LOAEL (mg/kg/day)	9 Serious LOAEL (mg/kg/day)	Effect
2 → CHRONIC EXPOSURE									
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	<u>Bd wt</u> <u>Hemato</u> <u>Hepatic</u>	25.5 138.0	138.0	6.1 ^c	Decreased body weight gain in males (23–25%) and females (31–39%) Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
10 ↓ Aida et al. 1992									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	<u>Hepatic</u> <u>Renal</u> <u>Endocr</u>	36.3 20.6 36.3	36.3		Increased incidence of renal tubular cell hyperplasia
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									

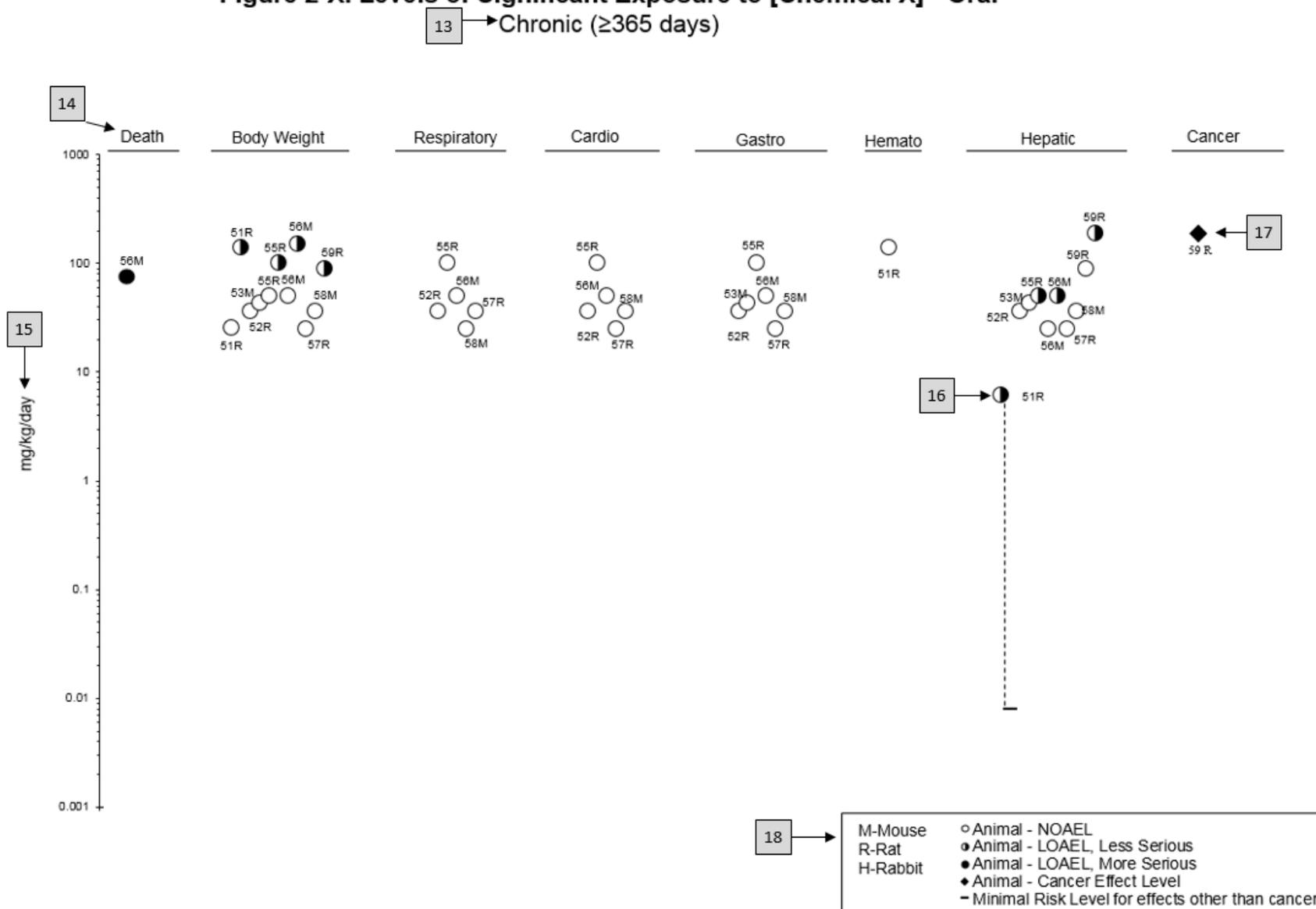
^aThe number corresponds to entries in Figure 2-x.

^bUsed to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the BMDL₀₅ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

^cUsed to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the BMDL₁₀ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

APPENDIX D

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



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 **Children and Other Populations that are Unusually Susceptible**
Section 3.3 **Biomarkers of Exposure and Effect**

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)

Internet: <http://www.atsdr.cdc.gov>

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see <https://www.atsdr.cdc.gov/csem/csem.html>).

Managing Hazardous Materials Incidents is a 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>).

APPENDIX E

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: <https://www.cdc.gov/nceh/>.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: <https://www.cdc.gov/niosh/>.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: <https://www.niehs.nih.gov/>.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: <http://www.aoec.org/>.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: <http://www.acoem.org/>.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: <http://www.acmt.net>.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at <http://pehsu.net/findhelp.html>.

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

APPENDIX F. GLOSSARY

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

APPENDIX F

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.

APPENDIX F

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₎ (LC₅₀)—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₎ (LD₅₀)—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time₍₅₀₎ (LT₅₀)—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.

APPENDIX F

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.

APPENDIX F

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.

APPENDIX F

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

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

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

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

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

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

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

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

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

APPENDIX G

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
kgg	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

APPENDIX G

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

APPENDIX G

VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q ₁ *	cancer slope factor
-	negative
+	positive
(+)	weakly positive result
(-)	weakly negative result