Toxicological Profile for Chloroethane

Draft for Public Comment

January 2024

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

CS274127-A

DISCLAIMER

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

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.

Each profile includes the following:

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

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

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

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

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

Written comments may also be sent to: Agency for Toxic Substances and Disease Registry
Office of Innovation and Analytics
Toxicology Section
1600 Clifton Road, N.E.
Mail Stop S106-5
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.

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

VERSION HISTORY

Date	Description
January 2024	Draft for public comment toxicological profile released
April 2016	Addendum to the toxicological profile released
December 1998	Final toxicological profile released

CONTRIBUTORS & REVIEWERS

CHEMICAL MANAGER TEAM

Carolyn Harper, Ph.D. (Lead)
Nickolette Roney, M.P.H.
Rae T. Benedict, Ph.D.

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

Julie Melia, Ph.D., D.A.B.T.
Deborah Herber, Ph.D.
Ramsey Hanna, Ph.D.
Mario Citra, Ph.D.

SRC, Inc., North Syracuse, NY

REVIEWERS

Interagency Minimal Risk Level Workgroup:

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

Additional reviews for science and/or policy:

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

PEER REVIEWERS

1. David Williams, Ph.D.; University Distinguished Professor; Department of Environmental and Molecular Toxicology; Oregon State University; Corvallis, Oregon.

2. Robert Herrick, Sc.D.; Harvard School of Public Health; Department of Environmental Health; Boston, Massachusetts.

3. Edward Levin, Ph.D.; Professor; Duke University; Durham, North Carolina.

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

LIST OF FIGURES

LIST OF TABLES

CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Chloroethane is a volatile, low molecular weight halogenated colorless gas. In the past, the single largest use of chloroethane was in the production of tetraethyl lead. Chloroethane is currently used in the production of ethyl cellulose and in miscellaneous applications including as a solvent and topical anesthetic, and in the manufacture of dyes, chemicals, foamed plastics, and pharmaceuticals.

When chloroethane is released to the environment, most will quickly partition to the atmosphere. Once in the atmosphere, it will break down by reactions with photochemically generated hydroxyl radicals. If released to soil or water, chloroethane is expected to volatilize rapidly but it may leach into groundwater since it is expected to possess high mobility in soil. It may undergo biodegradation under both aerobic and anaerobic conditions and may also be broken down by hydrolysis. Direct photolysis is not expected to be an important environmental fate process since chloroethane does not absorb photons of light in the environmental ultraviolet (UV) spectrum.

The general population may be exposed to chloroethane by inhalation of ambient air and possibly through the ingestion of drinking water. Direct exposure may also occur when chloroethane is used as a topical anesthetic. Occupational exposure, inhalation or dermal, can occur at facilities were chloroethane is manufactured and used (e.g., printing and publishing, painting companies, and electric services). People have also been known to intentionally inhale chloroethane vapors from commercial products for its narcotic effects, which may result in unconsciousness or even death.

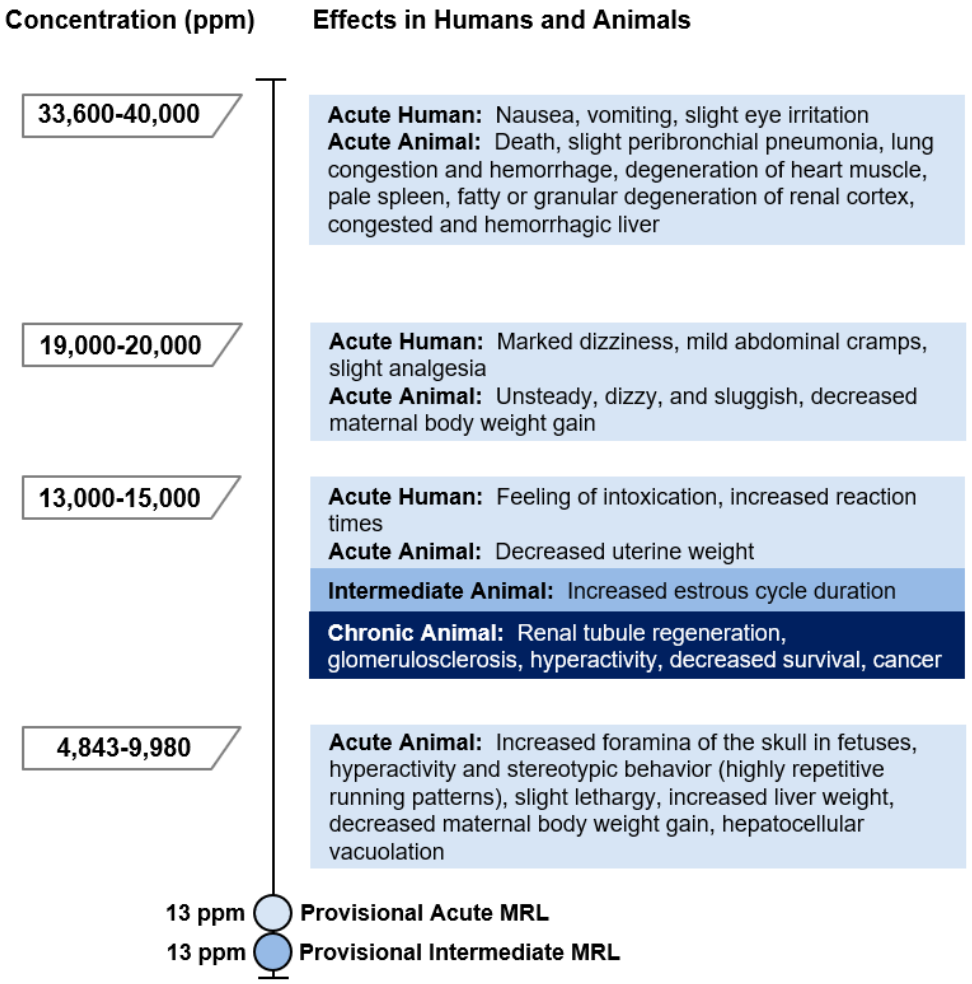
1.2 SUMMARY OF HEALTH EFFECTS

Information on the toxicity of chloroethane comes primarily from volunteer studies, case reports, and inhalation studies in animals. Most human studies have evaluated acute-duration inhalation exposure, while animal studies have predominantly focused on acute- and intermediate-duration inhalation exposure. A limited number of oral animal studies were identified. Animal inhalation studies were located for most of the health endpoints evaluated in this profile.

As shown in Figure 1-1, the most sensitive effects appear to be neurological, developmental, hepatic, renal, body weight, and reproductive effects. Hepatic and body weight effects were only observed in one or two studies and these changes were not reported in several other studies evaluating higher concentrations and/or longer durations (Figure 2-2). Therefore, only renal, neurological, reproductive, and developmental effects were further considered as potential health hazards. A systematic review of these noncancer endpoints resulted in the following hazard identification conclusions:

- Neurological effects are a presumed health effect for humans.
- Reproductive effects are an unclassifiable health effect for humans.
- Developmental effects are an unclassifiable health effect for humans.

Figure 1-1. Health Effects Found Following Inhalation Exposure to Chloroethane



Neurological Effects. Numerous human and animal studies have reported neurological effects following inhalation of chloroethane. Volunteers who inhaled 13,000–20,000 ppm reported marked dizziness, increased reaction times, and a feeling of intoxication (Davidson 1925; USBM 1929). People who intentionally misused chloroethane experienced slurred speech, dizziness, and difficulty walking (Demarest et al. 2011; Hes et al. 1979; Senussi and Chalise 2015). In addition, some studies reported that patients experienced visual hallucinations, tremors, nausea, abdominal cramps, and an unsteady gait after misusing chloroethane (Al-Ajmi et al. 2018; Kuthiah and Er 2019; Nordin et al. 1988). Other symptoms associated with chloroethane misuse included sleep disorders, tachycardia, ataxia, confusion, dysdiadochokinesia (inability to perform rapid, repeated alternating movements) of the arm, and sluggish or brisk lower limb reflexes (Finch and Lobo 2005; Hager et al. 2021; Hes et al. 1979; Kuthiah and Er 2019; Nordin et al. 1988). Neurological effects in animals have been seen after inhalation in both acute- and chronic-duration studies in several species.

Acute-duration inhalation exposure led to hyperactivity, stereotypic behavior, and/or loss of reflexes in mice (Dow 1985, 1995; Lazarew 1929); slight lethargy in rats (Landry et al. 1982); unsteadiness, dizziness, and sluggish behavior in guinea pigs (USBM 1929); and hyperactivity in dogs (Landry et al. 1982). In a 2-year inhalation study, female mice were hyperactive during the daily exposure (NTP 1989). Oral exposure to chloroethane via gavage led to female rats becoming unsteady 15–30 minutes after receiving chloroethane (Dow 1992); no effects were seen when chloroethane was administered in drinking water (Dow 1995).

Reproductive Effects. Studies of reproductive effects in humans exposed to chloroethane were not identified. Several studies investigated reproductive endpoints in animals after inhalation exposure. In intermediate-duration studies, a small increase in the average duration of the estrous cycle was observed in mice exposed to high concentrations of chloroethane, in the absence of any changes in serum estradiol and progesterone (Bucher et al. 1995). Histopathological effects have not been observed in reproductive organs of animals exposed to chloroethane for ≤2 or 13 weeks (Landry et al. 1982, 1987, 1989; NTP 1989). Decreased uterine motility and muscle tone was observed in dogs anesthetized with chloroethane (van Liere et al. 1966). In acute-duration inhalation studies, chloroethane has been shown to decrease uterine glutathione (GSH) levels in both rats and mice (Fedtke et al. 1994b). No effects on pregnancy rate, number of litters, number of live and dead fetuses, or number and position of resorption sites were observed in mice exposed for 6 hours/day on gestation days (GDs) 6–15 to 4,946 ppm (Scortichini et al. 1986) or up to 15,000 ppm of chloroethane (Dow 1985). Chloroethane has also been shown to produce

uterine cancer in mice, but not rats, exposed to 15,000 ppm chloroethane for approximately 2 years (NTP 1989). The relevance of these uterine effects in animals to humans is not known.

Developmental. No studies were located on developmental effects of chloroethane in humans. Two prenatal inhalation studies were located for chloroethane (Dow 1985; Scortichini et al. 1986). In a study of pregnant mice exposed to chloroethane at concentrations up to 4,946 ppm for 6 hours/day on GDs 6–15, no significant treatment-related changes were observed in maternal body or liver weight, pregnancy rate, number of resorptions, number of live fetuses/litter, litter size, fetal sex ratio, fetal body weight, or incidence of external or visceral malformations in the fetuses (Scortichini et al. 1986). An increase in the incidence of delayed fetal foramina closure (DFFC) of the skull bones (developmental delay of ossification of small centers of unossified bone) was seen in the fetuses at 4,946 ppm. Dow (1985) exposed pregnant mice up to 15,000 ppm of chloroethane for 6 hours/day on GDs 6–15. No exposure-related changes in the number of resorptions, live fetuses/litter, or normal-appearing fetuses were observed. This study, however, did not examine fetuses for skeletal or visceral alterations.

Cancer. No studies were located regarding the carcinogenicity of chloroethane in humans. Animal cancer studies have observed specific carcinogenic outcomes but have not consistently identified a target organ across sexes or species. In a study by the National Toxicology Program (NTP 1989), 86% of female mice chronically exposed to chloroethane vapor developed highly malignant uterine carcinomas. Uterine tumors were not observed in any of the control mice. The incidence of hepatocellular carcinomas also increased significantly in female mice. Male mice had an increased incidence of alveolar and bronchiolar adenomas, but because male survival was substantially reduced toward the end of the study, these results are not conclusive. Male rats had marginally increased incidences of skin tumors, whereas female rats had marginally increased incidences of brain astrocytomas, providing evidence that chloroethane is carcinogenic in rats (NTP 1989). Based on limited evidence of carcinogenicity in animals and no human data, the International Agency for Research on Cancer (IARC) considers chloroethane to be in Group 3, not classifiable as to its carcinogenicity to humans (IARC 1999). The carcinogenicity of chloroethane has not been classified by the Department of Human Health Services (HHS) (NTP 2021). A provisional carcinogenicity assessment by the U.S. Environmental Protection Agency (EPA) determined that chloroethane was likely to be carcinogenic to humans (EPA 2007).

Due to the limited number of oral animal studies identified, no figure describing the health effects found in animals following oral exposure to chloroethane was created. The two acute-duration oral studies that

exposed rats to chloroethane in drinking water at levels up to 662 mg/kg/day did not report any health effects.

1.3 MINIMAL RISK LEVELS (MRLs)

Inhalation MRLs. As illustrated in Figure 1-2, available inhalation data for chloroethane suggest that the hepatic, developmental, neurological, body weight, reproductive, and renal systems are the most sensitive targets of toxicity; however, liver and body weight effects were not consistently observed, even at higher concentrations. The inhalation database was considered adequate for derivation of an acute- and intermediate-duration MRL. The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

Oral MRLs. The oral database was considered inadequate for derivation of acute-, intermediate-, and chronic-duration MRLs. The MRL findings are summarized in Table 1-1 and discussed in greater detail in Appendix A.

Figure 1-2. Summary of Sensitive Targets of Chloroethane – Inhalation

Available data indicate that the hepatic, developmental, renal, neurological, body weight, reproductive, and renal systems appear to be the most sensitive targets of chloroethane inhalation exposure; however, liver and body weight effects were not consistently observed, even at higher concentrations.

Numbers in triangles and circles are the lowest LOAELs among health effects in humans and animals, respectively

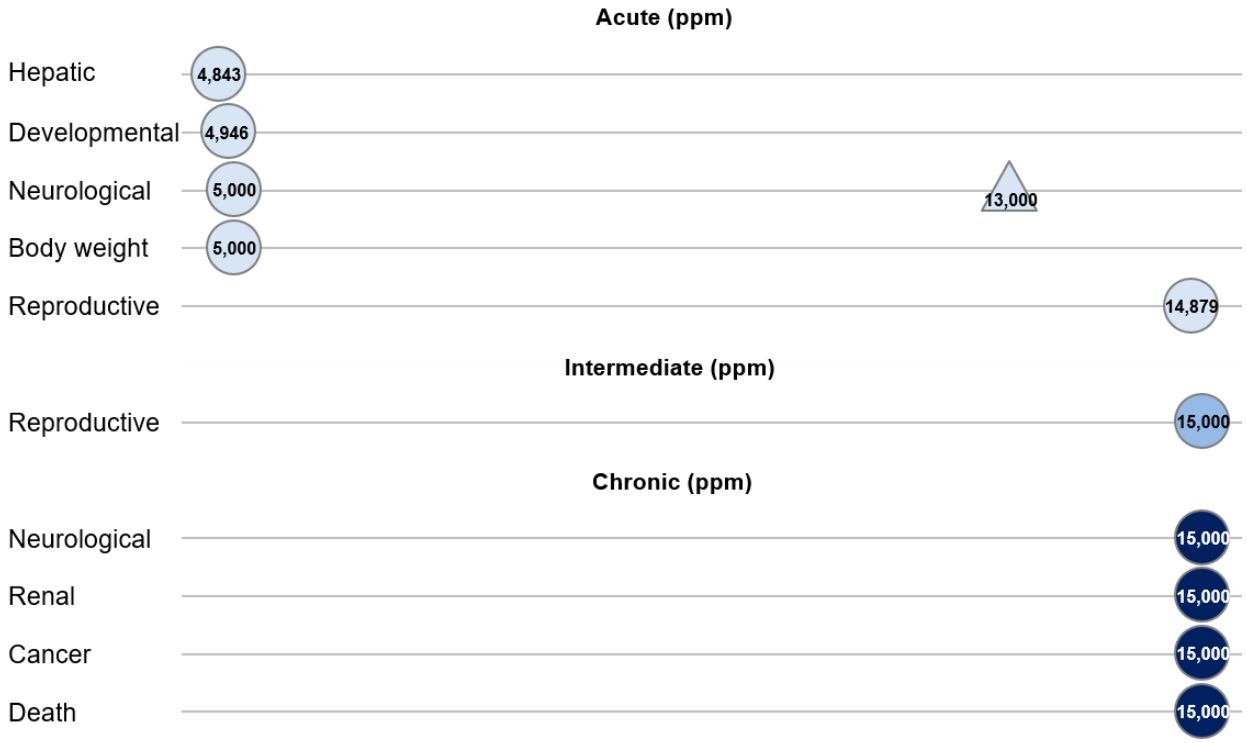


Table 1-1. Minimal Risk Levels (MRLs) for Chloroethane[a]

Exposure route	Exposure duration	Provisional MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	Acute	**13 ppm** (34 mg/m^3)	Increased incidence of delayed fetal foramina closure (DFFC) of the skull bones; developmental delay of ossification of small centers of unossified bone of the skull in mice.	$NOAEL_{HEC}$	376.0 ppm	UF: 30	Scortichini et al. 1986
	Intermediate	**13 ppm** (34 mg/m^3)	Increased estrous cycle in mice	$LOAEL_{HEC}$	3,750 ppm	UF: 300	Bucher et al. 1995
	Chronic	None	–	–	–	–	–
Oral	**No oral MRLs were derived for any duration.**						

[a]See Appendix A for additional information.

HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; POD = point of departure; UF = uncertainty factor

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

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

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

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

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to chloroethane, 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 chloroethane was also conducted; the results of this review are presented in Appendix C.

Summaries of the human observational studies and 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. Dermal studies are limited to human data on the use of chloroethane as a topical anesthetic or case reports describing neurological effects seen in patients that intentionally misused chloroethane. These studies are not summarized in tables or figures.

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.

Effects have been classified into “less serious LOAELs” or “serious LOAELs (SLOAELs).” “Serious” effects (SLOAELs) are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of chloroethane 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.

The health effects of chloroethane have been evaluated in human controlled studies, case reports, and experimental animal studies. As illustrated in Figure 2-1, most of the health effects data come from inhalation exposure in animals. These animal studies are primarily acute-duration studies, with a lesser number of intermediate- and chronic-duration studies. Animal inhalation data are available for all health effects categories. The largest number of human studies pertain to the use of chloroethane as a topical anesthetic, followed by case reports of neurological effects seen in patients who intentionally misused chloroethane. Although case reports are useful for assessing clinical pathology, they typically lack exposure information useful to evaluate dose-response.

Based on human and animal studies, the most sensitive effects appear to be neurological, reproductive, and developmental effects. Hepatic effects were observed in two studies; however, these changes were not reported in several other studies evaluating higher concentrations and/or longer durations (Figure 2-2). Therefore, hepatic effects were not further considered as a potential health hazard for chloroethane.

- **Neurological effects:** Neurological effects following inhalation are a presumed health effect based on a high level of evidence in animal studies; evidence in human studies is low primarily

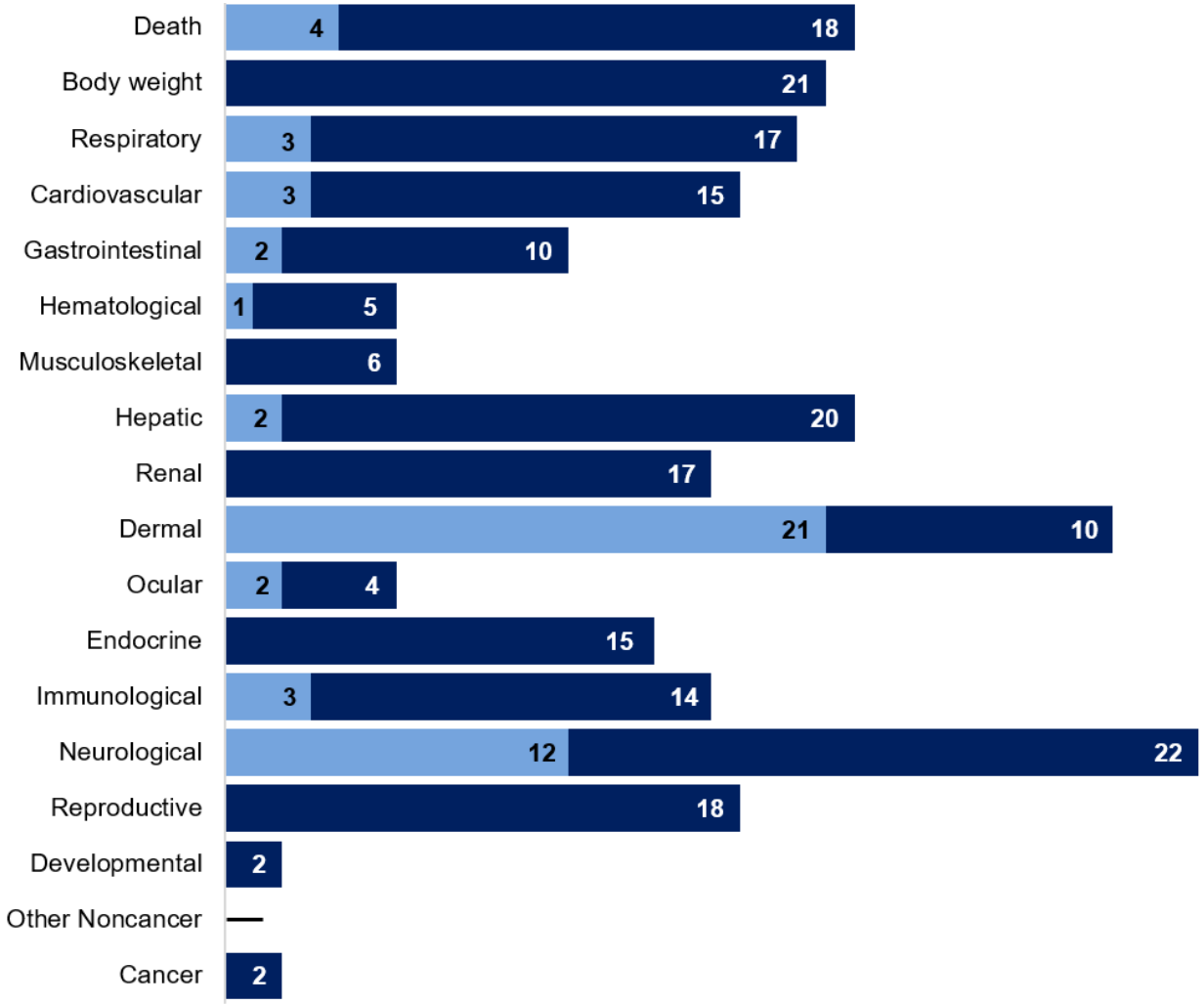
due to lack of quality studies. Dizziness, feeling of intoxication, increased reaction time, slurred speech, sleep disturbances, rapid eye movement, visual hallucination, tremor, and altered reflexes have been reported in people who voluntarily inhaled chloroethane. Animal studies have shown hyperactivity in mice and dogs, slight lethargy in rats, and unsteadiness, dizziness, and sluggish behavior in guinea pigs.

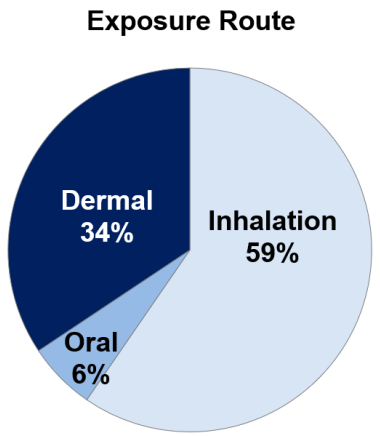
- **Developmental effects:** Developmental effects following inhalation are an unclassifiable health effect based on low level evidence in animal studies; there is inadequate evidence in humans to make a conclusion. Increased incidence of DFFC of the skull bones (developmental delay of ossification of small center of unossified bone of the skull) was seen in mouse pups exposed *in utero* on GDs 6–15.

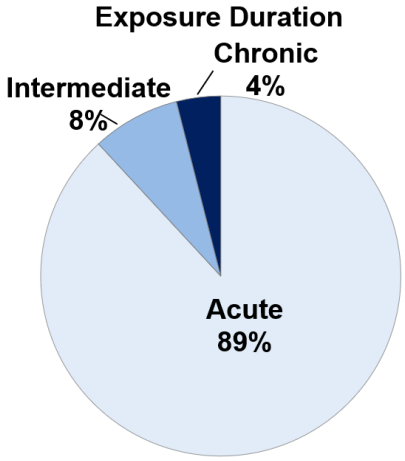
- **Reproductive effects:** Reproductive effects following inhalation exposure are an unclassifiable health effect based on low-level evidence in animal studies; there is inadequate evidence in humans to make a conclusion. Decreased uterine weight and increased estrous cycle length in mice, and decreased uterine motility and muscle tone in dogs were observed following inhalation exposure to chloroethane.

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

Most studies examined the potential neurological, dermal, and hepatic effects of chloroethane
Fewer studies evaluated health effects in humans than animals (counts represent studies examining endpoint)







*Includes studies discussed in Chapter 2. A total of 78 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to Chloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Davidson 1925									
1	Human 1–2	Up to 22 minutes (NS)	13,000, 19,000, 25,000, 33,600	CS, NX	Gastro	25,000	33,600		Nausea, vomiting during recovery from exposure
					Neuro		13,000	19,000	LOAEL: subjective feeling of intoxication, increased reaction times SLOAEL: distinct intoxication, slight analgesia, increased reaction times
USBM 1929									
2	Human 2	2–4 breaths (NS)	20,000, 40,000	CS	Gastro		20,000		Mild abdominal cramps
					Ocular	20,000	40,000		Slight eye irritation
					Neuro		20,000		Marked dizziness
Fedtke et al. 1994a									
3	Rat (Fischer-344) 2 M, 2 F	5 days 6 hours/day (WB)	M: 0, 14,090; F: 0, 14,393	BW, OW	Bd wt	14,393 F			
						14,090 M			
					Resp	14,393 F			
						14,090 M			
					Hepatic	14,393 F			
						14,090 M			
					Renal	14,393 F			
						14,090 M			
					Repro	14,393 F			
						14,090 M			

Table 2-1. Levels of Significant Exposure to Chloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Landry et al. 1982									
4	Rat (Fischer-344) 6 M, 6 F	2 weeks 5 days/week 6 hours/day (WB)	0, 1,590, 3,980, 9,980	LE, CS, BW, BC, GN, HP, OW, HE, UR	Bd wt	9,980			
					Resp	9,980			
					Cardio	9,980			
					Gastro	9,980			
					Hemato	9,980			
					Musc/skel	9,980			
					Hepatic	9,980			
					Renal	9,980			
					Dermal	9,980			
					Ocular	9,980			
					Endocr	9,980			
					Immuno	9,980			
					Neuro	3,980	9,980		Slight lethargy
					Repro	9,980			
NTP 1989									
5	Rat (Fischer-344/N) 5 M, 5 F	2 weeks 5 days/week 6 hours/day (WB)	0, 19,000	CS, LE, BW, GN, HP	Bd wt	19,000			
Breslin et al. 1988									
6	Mouse (B6C3F1) 10 F	14 days 6 hours/day (WB)	0, 14,955	LE, CS, BW, HP	Bd wt	14,955			
					Repro	14,955			

Table 2-1. Levels of Significant Exposure to Chloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Dow 1985									
7	Mouse (CF-1) 8–10 F	10 days 6 hours/day GDs 6–15 (WB)	0, 5,000, 10,000, 15,000	LE, CS, BW, FI, WI, OP, GN, OW, DX	Bd wt		5,000		13–15% decrease in maternal body weight gain
					Resp	15,000			
					Hepatic	15,000			
					Neuro		5,000		Increased activity and stereotypic behavior (highly repetitive running patterns)
					Develop	15,000			
Dow 1992									
8	Mouse (B6C3F1) 3 F	6 hours (WB)	0, 15,000	CS, BI	Neuro		15,000		Hyperactivity (constant running, jumping, and rearing)
Fedtke et al. 1994a									
9	Mouse (B6C3F1) 30 M, 30 F	5 days 6 hours/day (WB)	M: 0, 15,025; F: 0, 14,879	BW, OW	Bd wt	14,879 F			
						15,025 M			
					Resp	14,879 F			
						15,025 M			
					Hepatic	14,879 F			
						15,025 M			
					Renal	14,879 F			
						15,025 M			
					Repro	15,025 M	14,879 F		Approximately 35% decrease in absolute and relative uterine weight
Landry et al. 1987, 1989									
10	Mouse (B6C3F1) 7 M, 7 F	11 days 23 hours/day (WB)	0, 250, 1,247, 4,843	BW, OW, CS, HP, GN, HE, LE, NX, BC	Bd wt	4,843			
					Resp	4,843			
					Cardio	4,843			
					Gastro	4,843			

Table 2-1. Levels of Significant Exposure to Chloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Hemato	4,843			
					Musc/skel	4,843			
					Hepatic	1,247	4,843		Increased relative liver weight and slight increase in hepatocellular vacuolation
					Renal	4,843			
					Dermal	4,843			
					Ocular	4,843			
					Endocr	4,843			
					Immuno	4,843			
					Neuro	4,843			
					Repro	4,843			
Lazarew 1929									
11	Mouse (NS) NS	2 hours (WB)		LE	Death			56,860	Minimum lethal concentration
NTP 1989									
12	Mouse (B6C3F1) 5 M, 5 F	2 weeks 5 days/week 6 hours/day (WB)	0, 19,000	CS, LE, BW, GN, HP	Bd wt	19,000			
Scortichini et al. 1986									
13	Mouse (CF-1) 23–26 F	10 days 6 hours/day GDs 6–15 (WB)	0, 491, 1,504, 4,946	BW, CS, DX, OW, FI, WI, DX	Bd wt	4,946			
					Hepatic	4,946			
					Develop	1,504[b]	4,946		Increased incidence of delayed fetal foramina closure (DFFC) of skull bones developmental delay in ossification of skull bones)

Table 2-1. Levels of Significant Exposure to Chloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Landry et al. 1982									
14	Dog (Beagle) 2 M	2 weeks 5 days/week 6 hours/day (WB)	0, 1,590, 3,980, 9,980	GN, HP, OW, LE, HE, UR, CS, BC, BW, NX, OP	Bd wt	9,980			
					Resp	9,980			
					Cardio	9,980			
					Gastro	9,980			
					Hemato	9,980			
					Musc/skel	9,980			
					Hepatic	9,980			
					Renal	9,980			
					Dermal	9,980			
					Ocular	9,980			
					Endocr	9,980			
					Immuno	9,980			
					Neuro	3,980	9,980		Hyperactivity during exposure in 1/2 dogs
					Repro	9,980			
USBM 1929									
15	Guinea pig (NS) 2–12 NS	Up to 810 minutes (WB)	0, 10,000, 20,000, 40,000, 51,000, 64,000, 76,000, 80,000, 84,000, 87,000, 91,000, 127,000, 142,000, 153,000, 232,000,	LE, CS, GN, HP	Death			40,000	2/6 animals died
					Resp	20,000	40,000		Slight peribronchial pneumonia, congestion, and hemorrhage; labored breathing that became rapid and shallow
					Cardio	20,000		40,000	Degeneration of heart muscle of guinea pigs that died
					Gastro	40,000	80,000		Congestion and blood-tinged contents in small intestine; scattered hemorrhages in walls of large intestine
					Hemato	20,000	40,000		Pale spleen
					Hepatic	20,000	40,000		Congested and hemorrhagic

Table 2-1. Levels of Significant Exposure to Chloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
			241,000		Renal	20,000	40,000		Fatty or granular degeneration of the cortex
					Neuro	10,000	20,000		Unsteady, dizzy, and sluggish
INTERMEDIATE EXPOSURE									
Dow 1941									
16	Rat (NS) 6 M, 6 F	6.5 months 5 days/week 7.5–8 hours/day (WB)	0, 10,000	CS, BW, GN, HP	Bd wt	10,000			
					Resp	10,000			
					Hepatic	10,000			
					Renal	10,000			
					Endocr	10,000			
					Immuno	10,000			
NTP 1989									
17	Rat (Fischer-344/N) 10 M, 10 F	13 weeks 5 days/week 6 hours/day (WB)	0, 2,500, 5,000, 10,000, 19,000	CS, LE, BW, GN, HP, OW	Bd wt	19,000			
					Resp	19,000			
					Cardio	19,000			
					Gastro	19,000			
					Hepatic	19,000			
					Renal	19,000			
					Dermal	19,000			
					Endocr	19,000			
					Immuno	19,000			
					Neuro	19,000			
					Repro	19,000			

Table 2-1. Levels of Significant Exposure to Chloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Bucher et al. 1995									
18	Mouse (B6C3F1) 30 F	21 days 6 hours/day (WB)	0, 15,000	CS, BW, OW, HP, BC	Bd wt	15,000			
					Hepatic	15,000			
					Endocr	15,000			
					Repro		15,000[c]		Small increase in the average duration of the estrous cycle, no consistent changes in hormone levels
NTP 1989									
19	Mouse (B6C3F1) 10 M, 10 F	13 weeks 5 days/week 6 hours/day (WB)	0, 2,500, 5,000, 10,000, 19,000	CS, LE, BW, GN, HP, OW	Bd wt	19,000			
					Resp	19,000			
					Cardio	19,000			
					Gastro	19,000			
					Hepatic	19,000			
					Renal	19,000			
					Dermal	19,000			
					Endocr	19,000			
					Immuno	19,000			
					Neuro	19,000			
					Repro	19,000			
Dow 1941									
20	Rabbit (NS) 2 M, 2 F	6.5 months 5 days/week 7.5–8 hours/day (WB)	0, 10,000	CS, BW, OP, GN, HP	Bd wt	10,000			
					Resp	10,000			
					Hepatic	10,000			
					Renal	10,000			
					Ocular	10,000			
					Endocr	10,000			
					Immuno	10,000			

Table 2-1. Levels of Significant Exposure to Chloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
CHRONIC EXPOSURE									
NTP 1989									
21	Rat (Fischer-344/N) 50 M, 50 F	102 weeks 5 days/week 6 hours/day (WB)	0, 15,000	CS, LE, BW, GN, HP	Bd wt	15,000			
					Resp	15,000			
					Cardio	15,000			
					Gastro	15,000			
					Musc/skel	15,000			
					Hepatic	15,000			
					Renal	15,000			
					Dermal	15,000			
					Endocr	15,000			
					Immuno	15,000			
					Neuro	15,000			
					Repro	15,000			
					Cancer			15,000 F	CEL: 3/50 malignant brain astrocytomas significantly different from historical but not concurrent controls
								15,000 M	CEL: 5/50 skin trichoepithelioma, sebaceous gland adenoma, or basal cell carcinoma
NTP 1989									
22	Mouse (B6C3F1) 50 M, 50 F	100 weeks 5 days/week 6 hours/day (WB)	0, 15,000	CS, LE, BW, GN, HP	Death			15,000	39/50 males and 48/50 females died
					Bd wt	15,000			
					Resp	15,000			
					Cardio	15,000			
					Gastro	15,000			
					Musc/skel	15,000			
					Hepatic	15,000			

Table 2-1. Levels of Significant Exposure to Chloroethane – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Renal	15,000 M	15,000 F		Scattered foci of tubular regeneration, minimal glomerulosclerosis
					Dermal	15,000			
					Endocr	15,000			
					Immuno	15,000			
					Neuro	15,000 M	15,000 F		Hyperactivity during exposure
					Repro	15,000			
					Cancer			15,000 F	CEL: 43/50 uterine carcinomas; 8/48 hepatocellular carcinomas or adenomas
								15,000 M	CEL: 10/48 lung adenomas or carcinomas

Shaded rows indicate MRL principal study.

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive a provisional acute-duration inhalation MRL of 13 ppm. The NOAEL of 1,504 ppm was adjusted for continuous exposure and was converted to a HEC using the default animal:human blood gas partition coefficient ratio of 1 (1 x 1,504 ppm x 6 hours/24 hours = 376.0 ppm) and divided by an uncertainty factor of 30 (3 for animal to human after dosimetric adjustment and 10 for human variability), resulting in a provisional acute-duration MRL of 13 ppm. See Appendix A for more detailed information regarding the MRL.
[c]Used to derive a provisional intermediate-duration inhalation MRL of 13 ppm. The LOAEL of 15,000 ppm was adjusted for continuous exposure and was converted to a HEC using the default animal:human blood gas partition coefficient ratio of 1 (1 x 15,000 ppm x 6 hours/24 hours = 3,750 ppm) and divided by an uncertainty factor of 300 (10 for use of a LOAEL, 3 for animal to human after dosimetric adjustment, and 10 for human variability), resulting in a provisional intermediate-duration inhalation MRL of 13 ppm. See Appendix A for more detailed information regarding the MRL.

BC = blood chemistry; Bd wt or BW = body weight; Cardio = cardiovascular; CEL = Cancer Effect Level; CS = clinical signs; Develop = developmental; DX = developmental effects; Endocr = endocrine; F = female(s); FI = food intake; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; HE = hematology; HEC = human equivalent concentration; Hemato = hematological; HP = histopathology; Immuno = immunological; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological effects; OP = ophthalmology; OW = organ weight; Repro = reproductive; Resp = respiratory; SLOAEL = serious LOAEL; UR = urinalysis; WB = whole body; WI = water intake

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

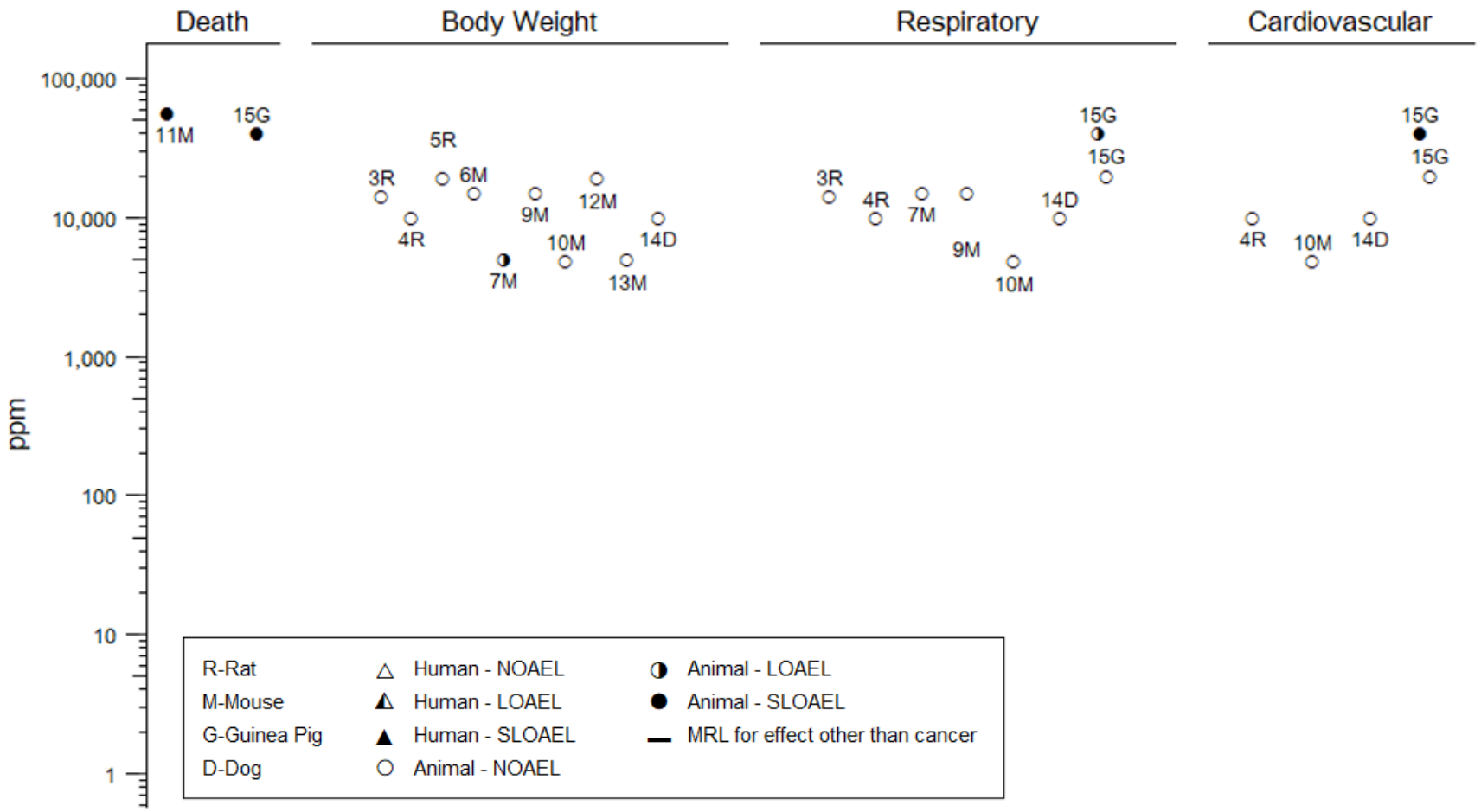


Figure 2-2. Levels of Significant Exposure to Chloroethane – Inhalation
Acute (≤14 days)

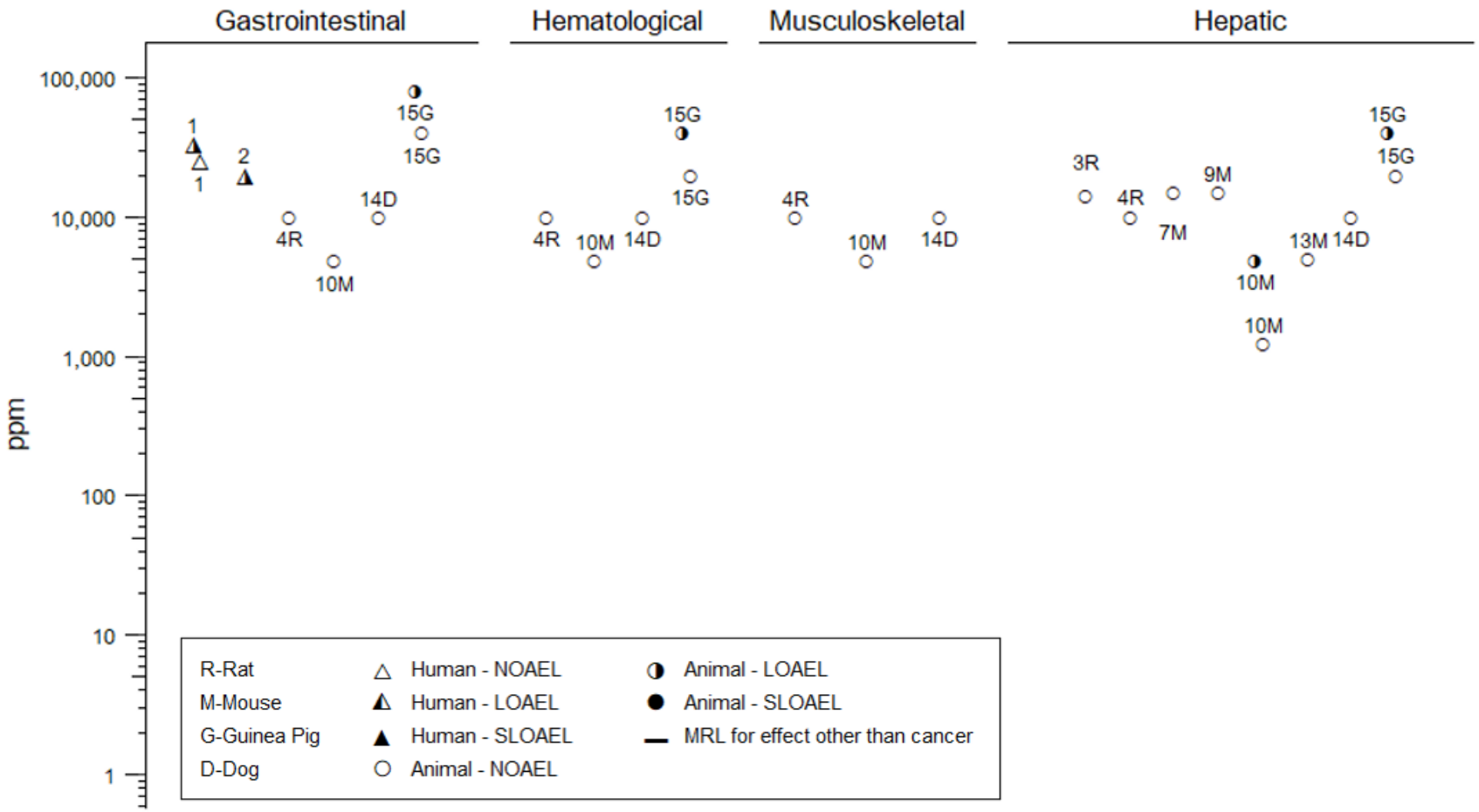


Figure 2-2. Levels of Significant Exposure to Chloroethane – Inhalation
Acute (≤14 days)

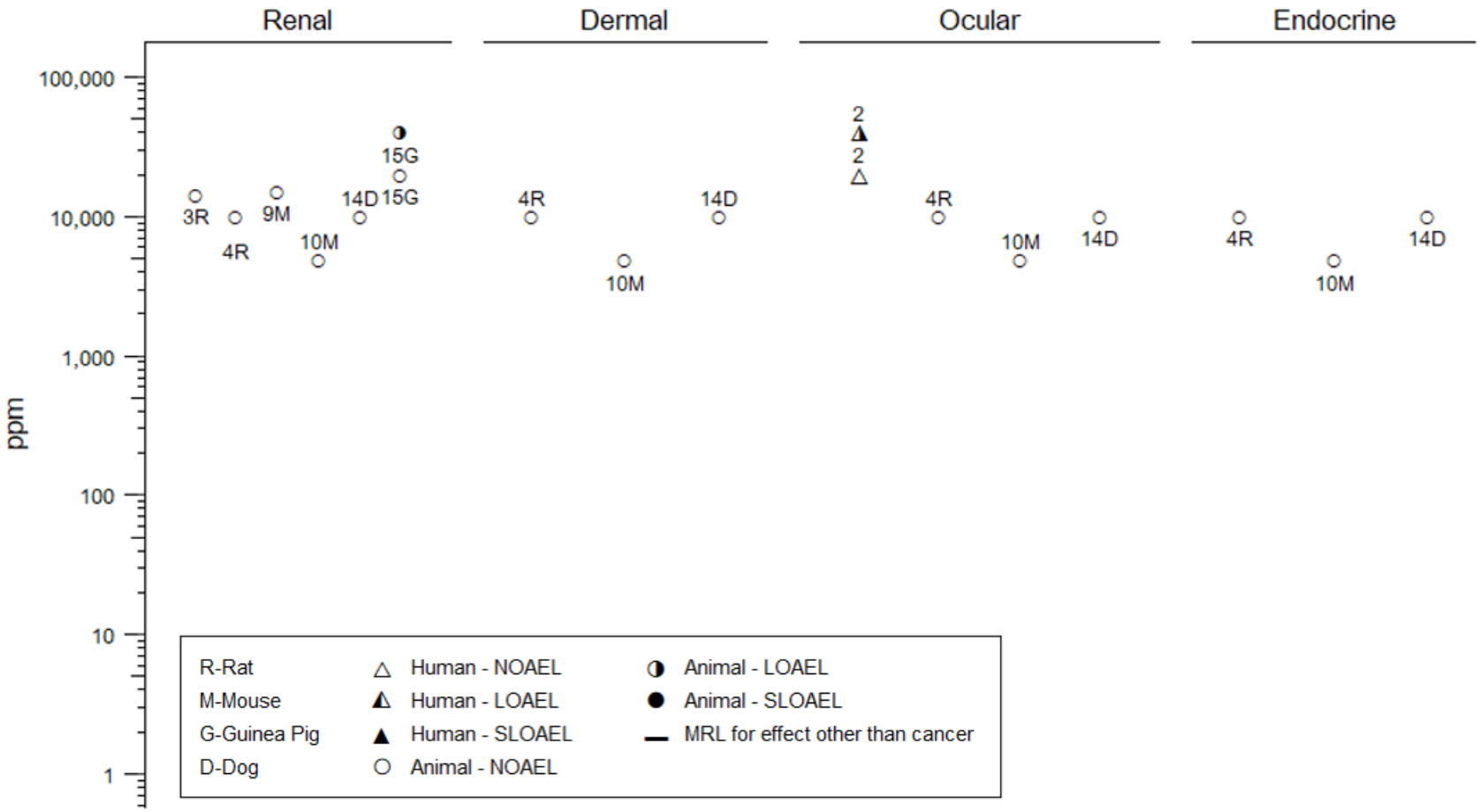


Figure 2-2. Levels of Significant Exposure to Chloroethane – Inhalation
Acute (≤14 days)

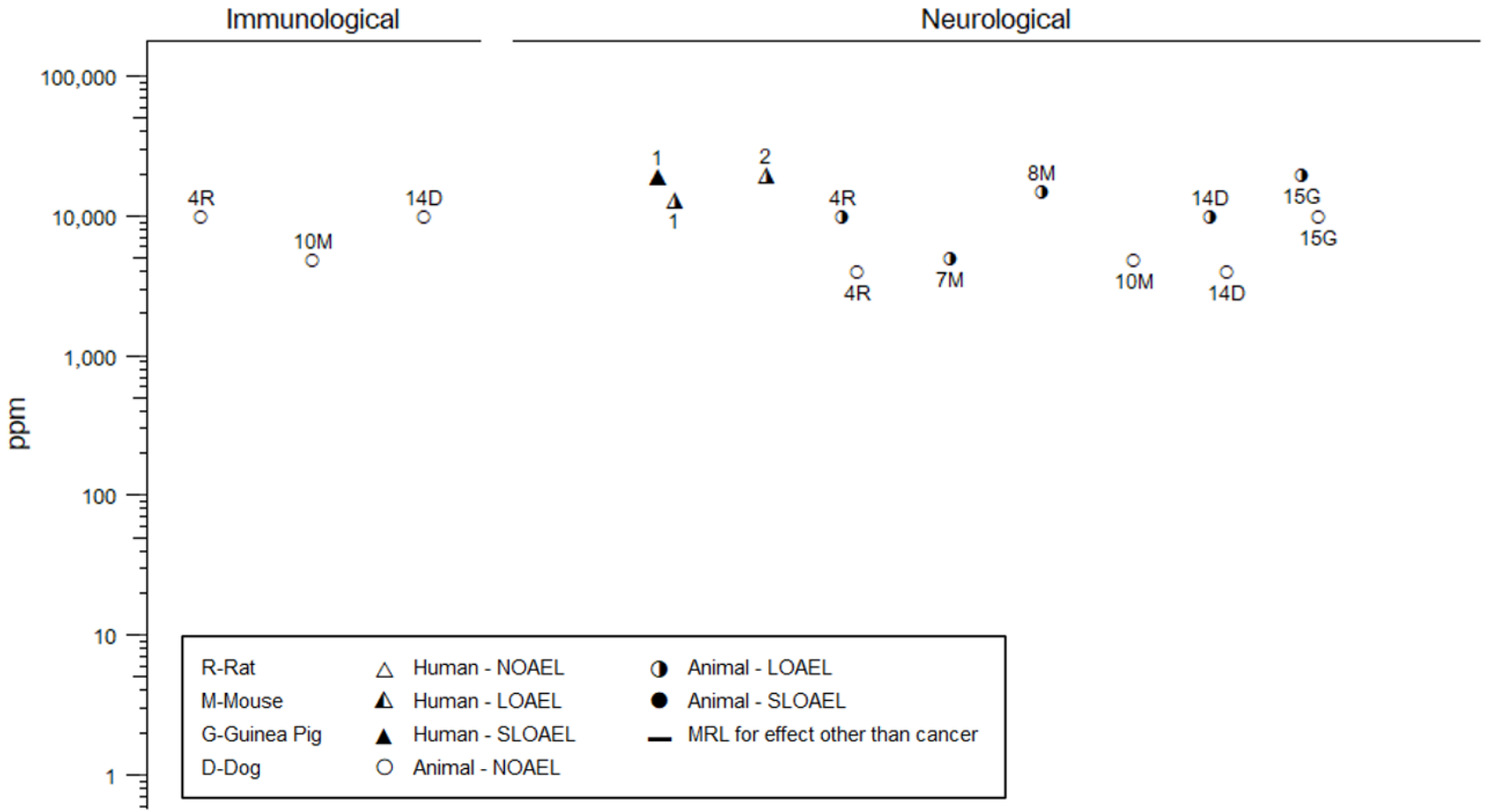


Figure 2-2. Levels of Significant Exposure to Chloroethane – Inhalation
Acute (≤14 days)

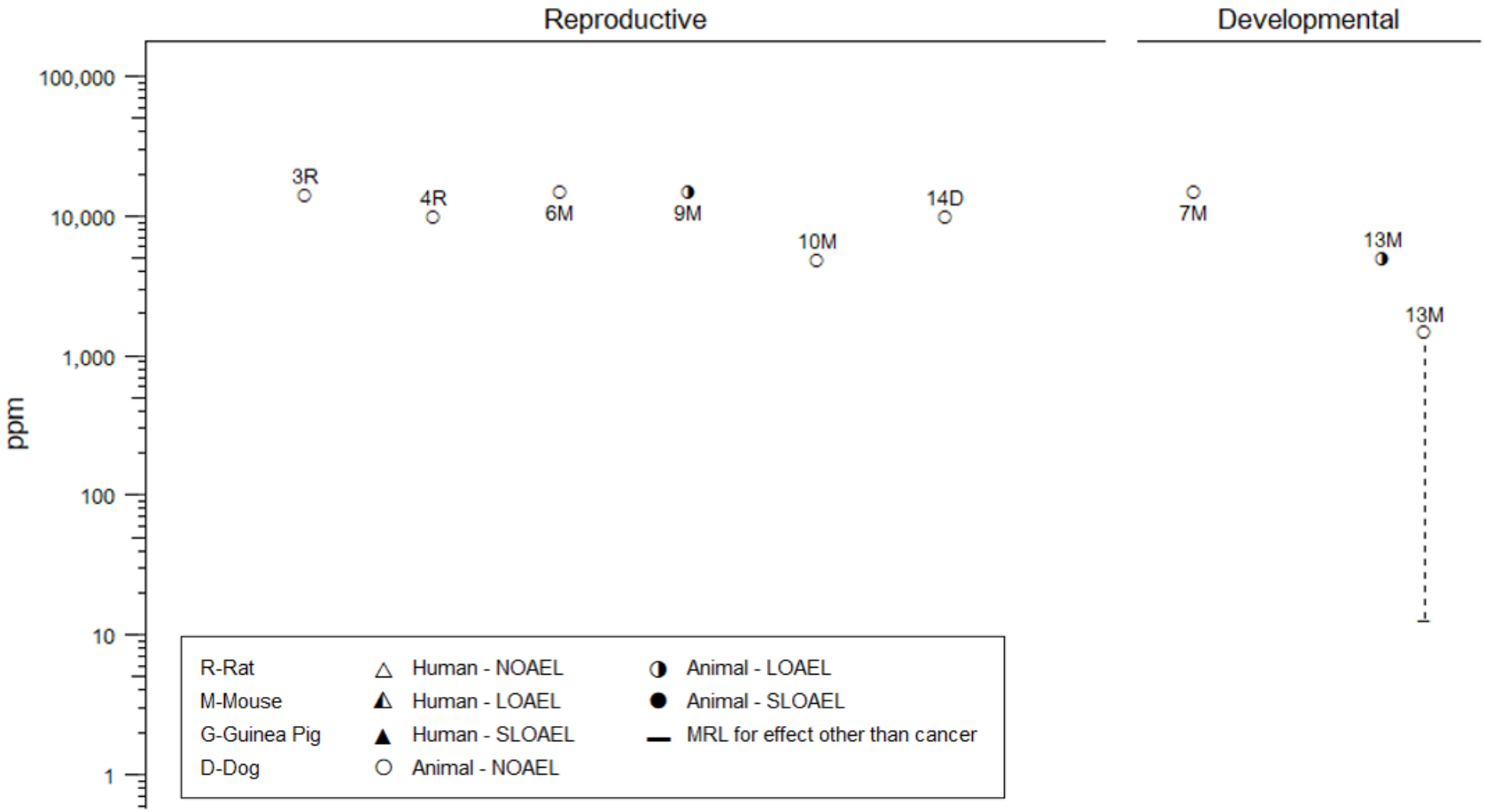


Figure 2-2. Levels of Significant Exposure to Chloroethane – Inhalation
Intermediate (15–364 days)

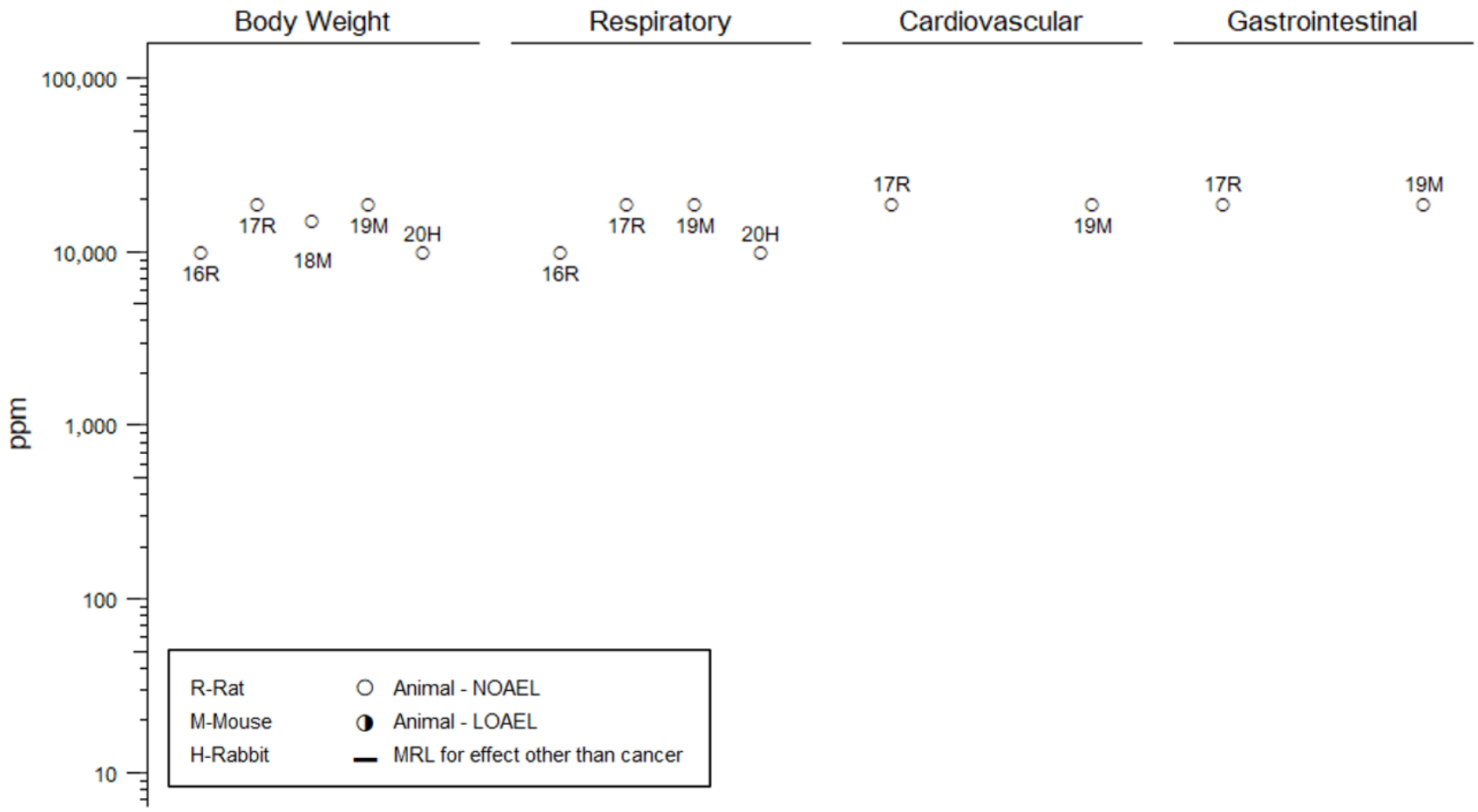


Figure 2-2. Levels of Significant Exposure to Chloroethane – Inhalation
Intermediate (15–364 days)

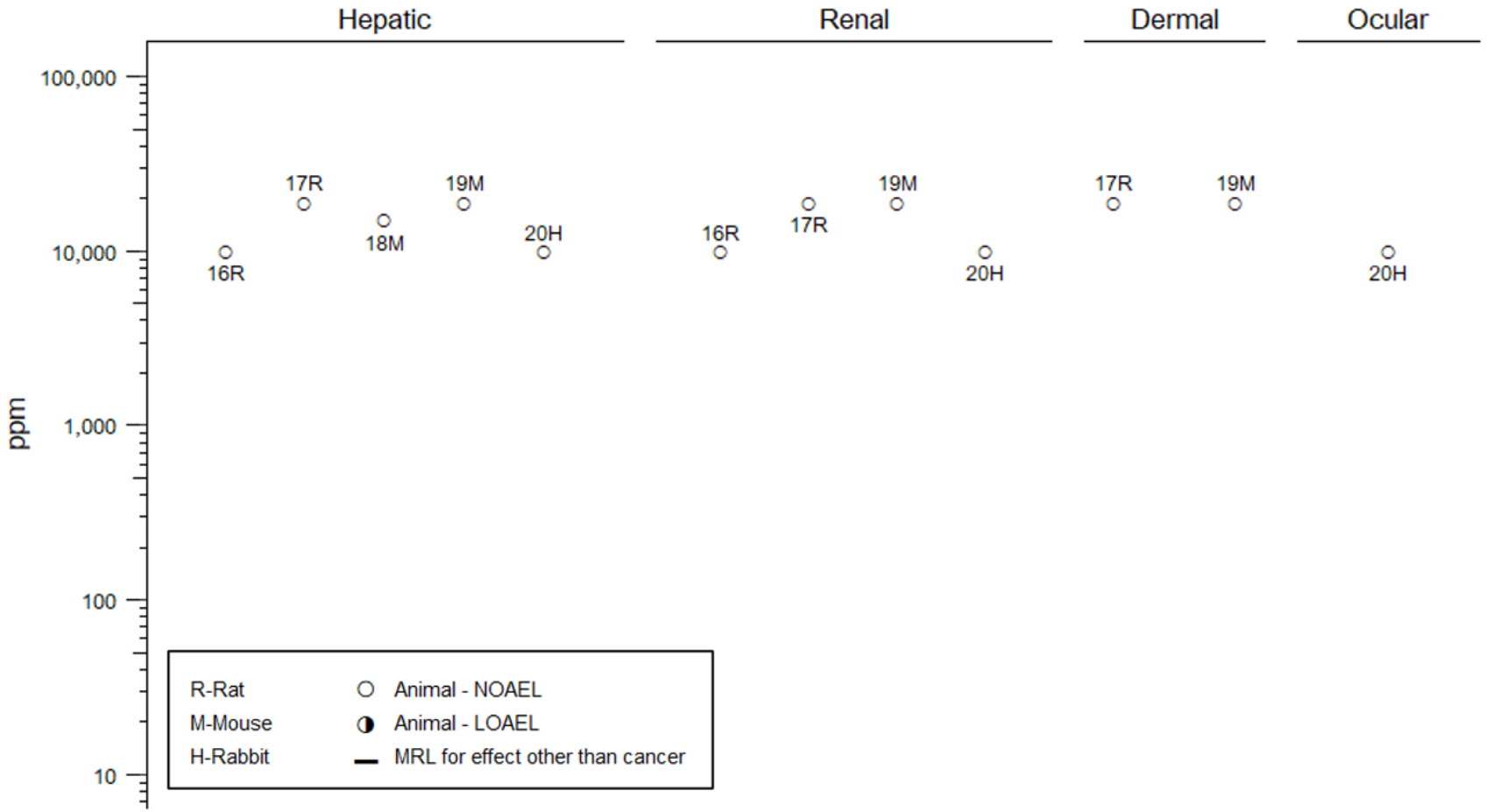


Figure 2-2. Levels of Significant Exposure to Chloroethane – Inhalation
Intermediate (15–364 days)

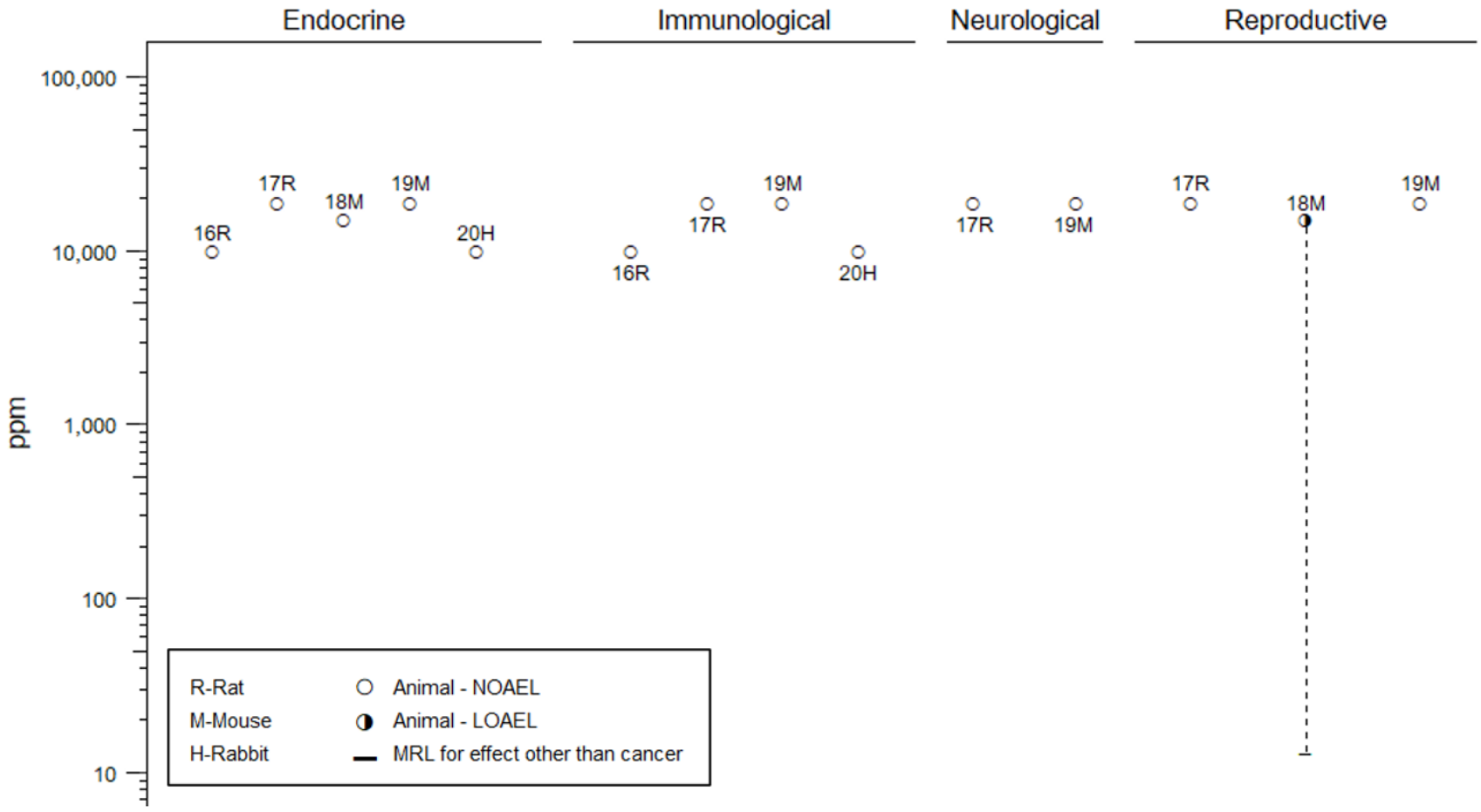


Figure 2-2. Levels of Significant Exposure to Chloroethane – Inhalation
Chronic (≥365 days)

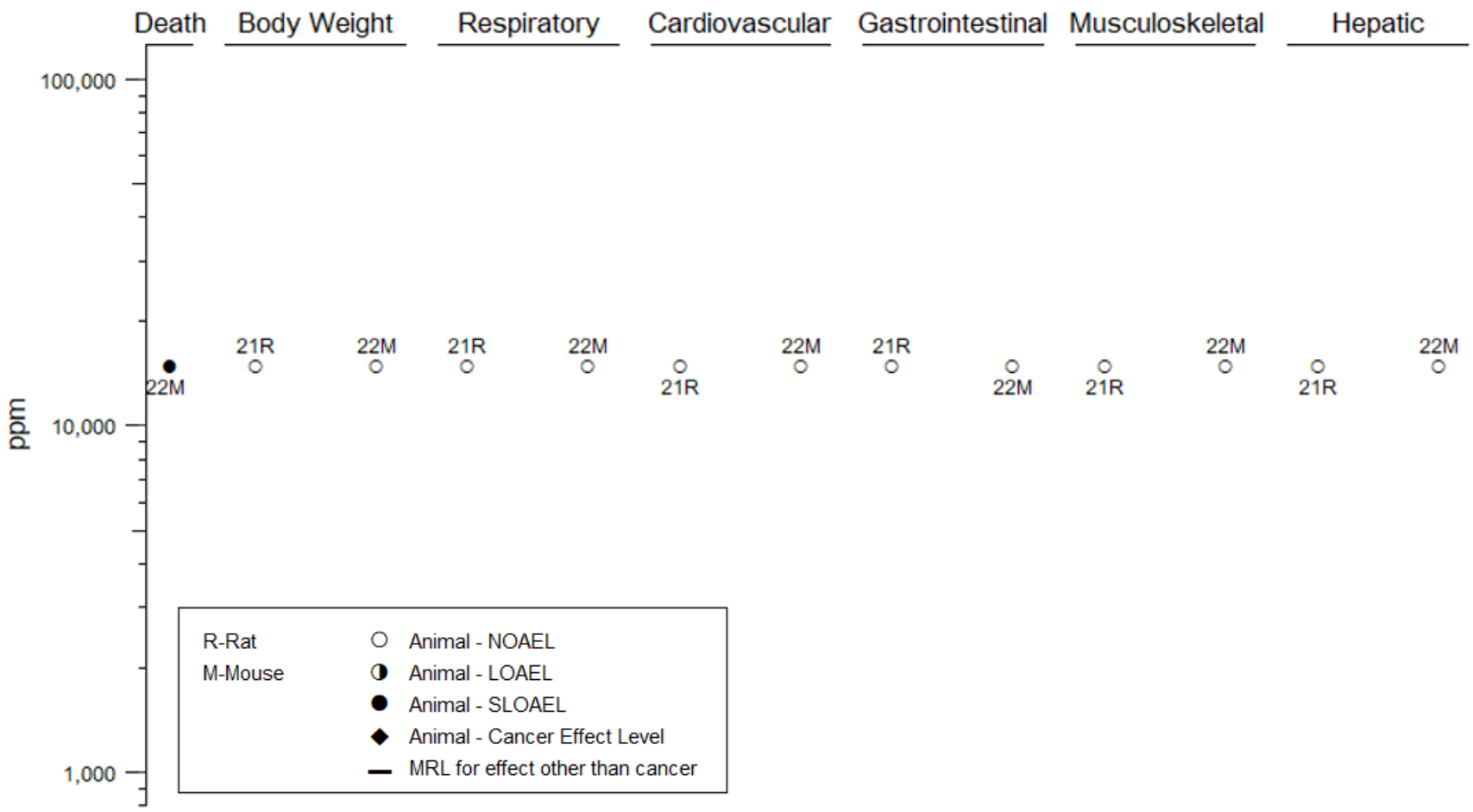


Figure 2-2. Levels of Significant Exposure to Chloroethane – Inhalation
Chronic (≥365 days)

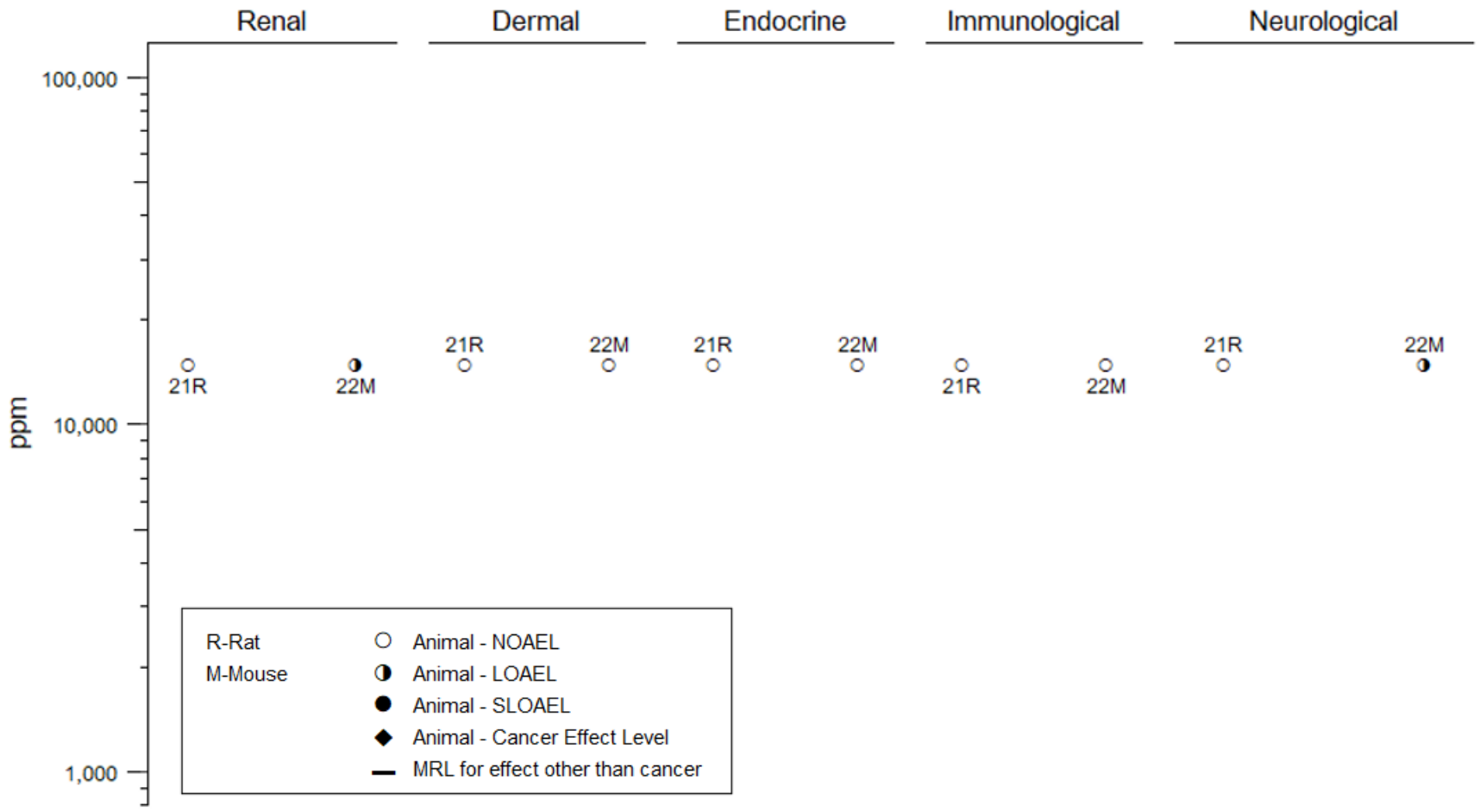


Figure 2-2. Levels of Significant Exposure to Chloroethane – Inhalation
Chronic (≥365 days)

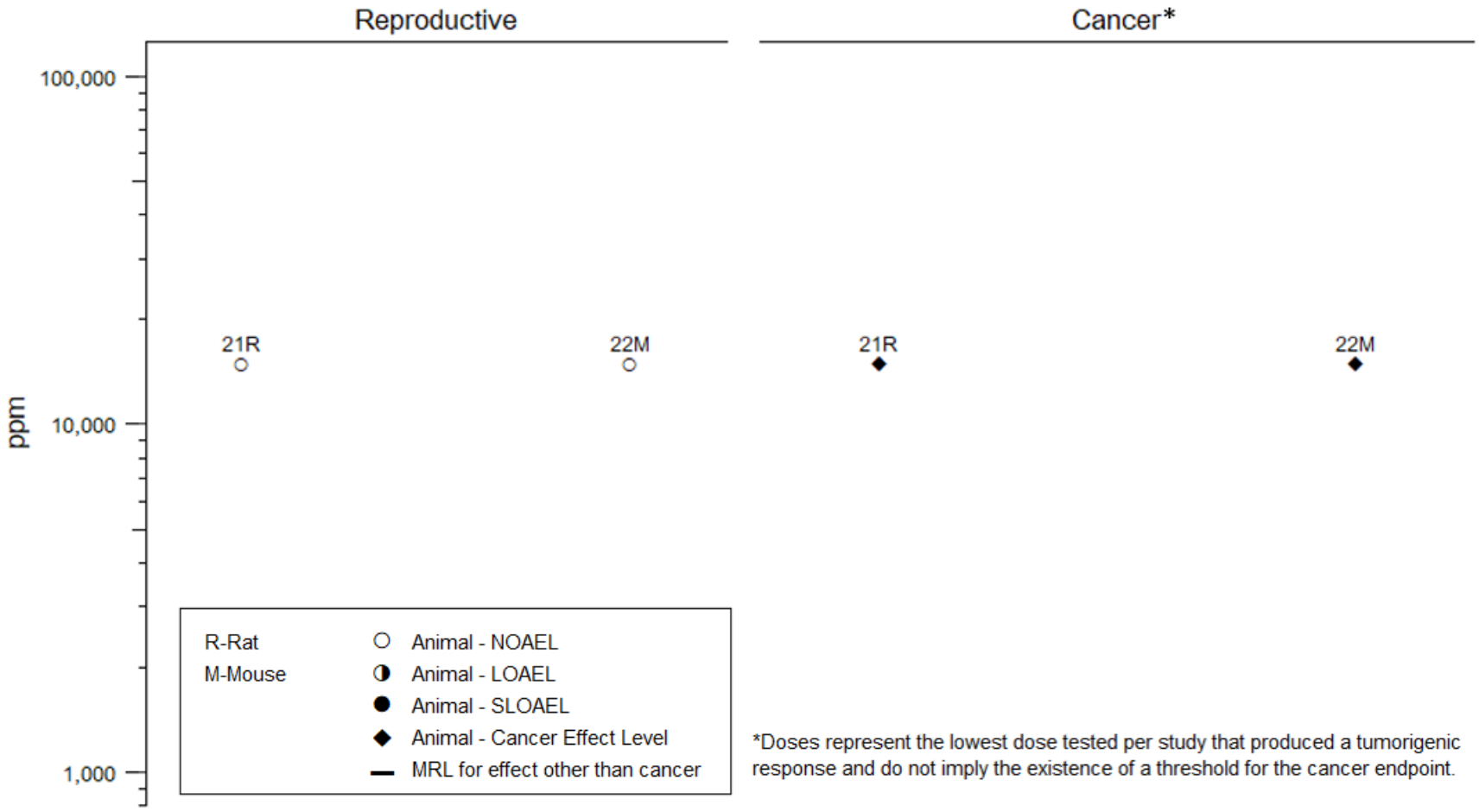


Table 2-2. Levels of Significant Exposure to Chloroethane – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Dow 1995									
1	Rat (Fischer-344) 5 M, 5 F	7 days (W)	M: 0, 613; F: 0, 662	CS, BW, FI, WI	Bd wt	662 F 613 M			
Dow 1995									
2	Rat (Fischer-344) 10 M, 10 F	14 days (W)	M: 0, 297; F: 0, 361	LE, CS, BW, FI, WI, HE, BC, OW, GN, HP	Bd wt	361 F 297 M			
					Cardio	361 F 297 M			
					Hemato	361 F 297 M			
					Hepatic	361 F 297 M			
					Renal	361 F 297 M			
					Endocr	361 F 297 M			
					Immuno	361 F 297 M			
					Neuro	361 F 297 M			

Table 2-2. Levels of Significant Exposure to Chloroethane – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Repro	361 F 297 M			

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

BC = blood chemistry; Bd wt or BW = body weight; Cardio = cardiovascular; CS = clinical signs; Endocr = endocrine; F = female(s); FI = food intake; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Neuro = neurological; NOAEL = no-observed-adverse-effect level; OW = organ weight; Repro = reproductive; WI = water intake

Figure 2-3. Levels of Significant Exposure to Chloroethane – Oral (mg/kg/day)
Acute (≤14 days)

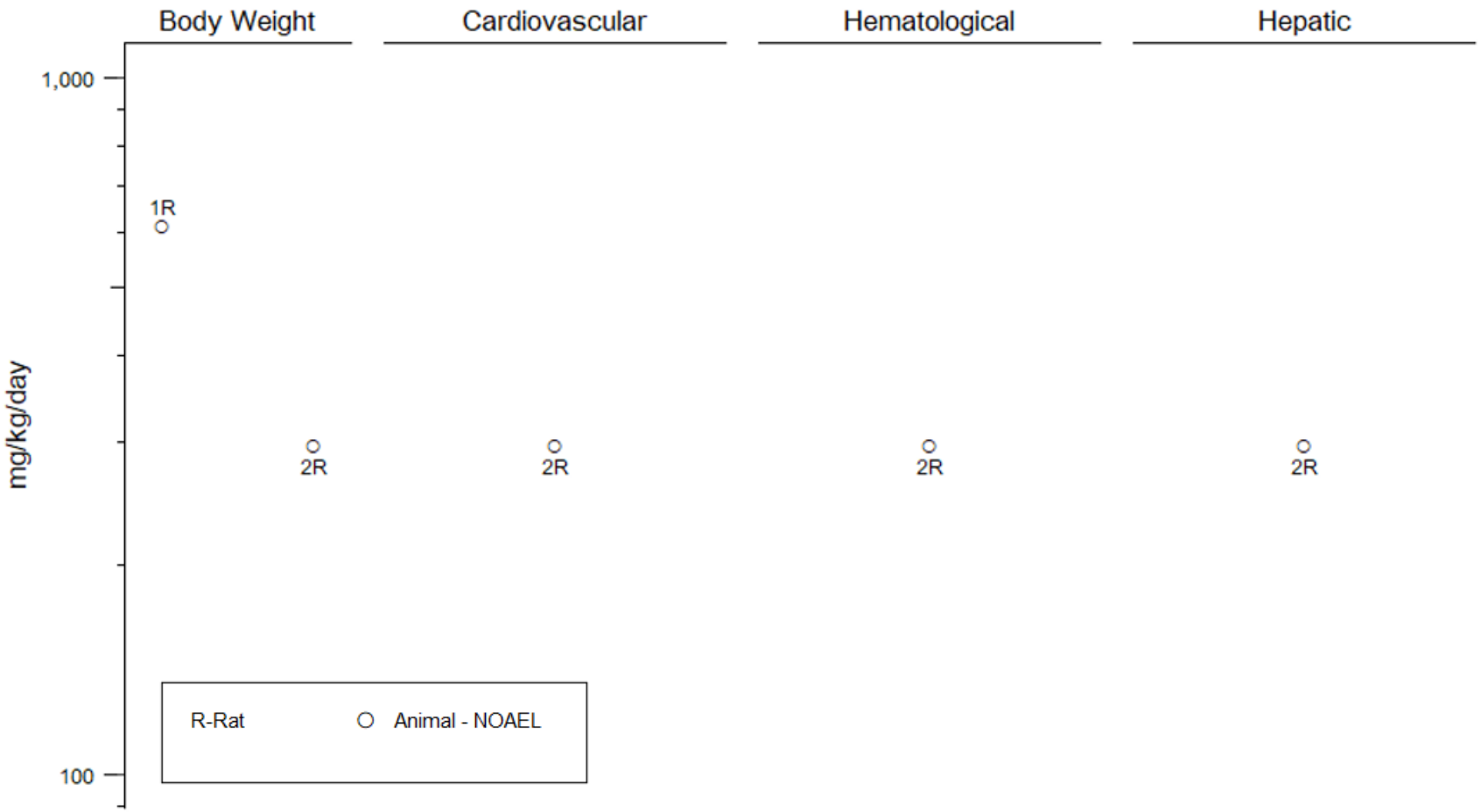
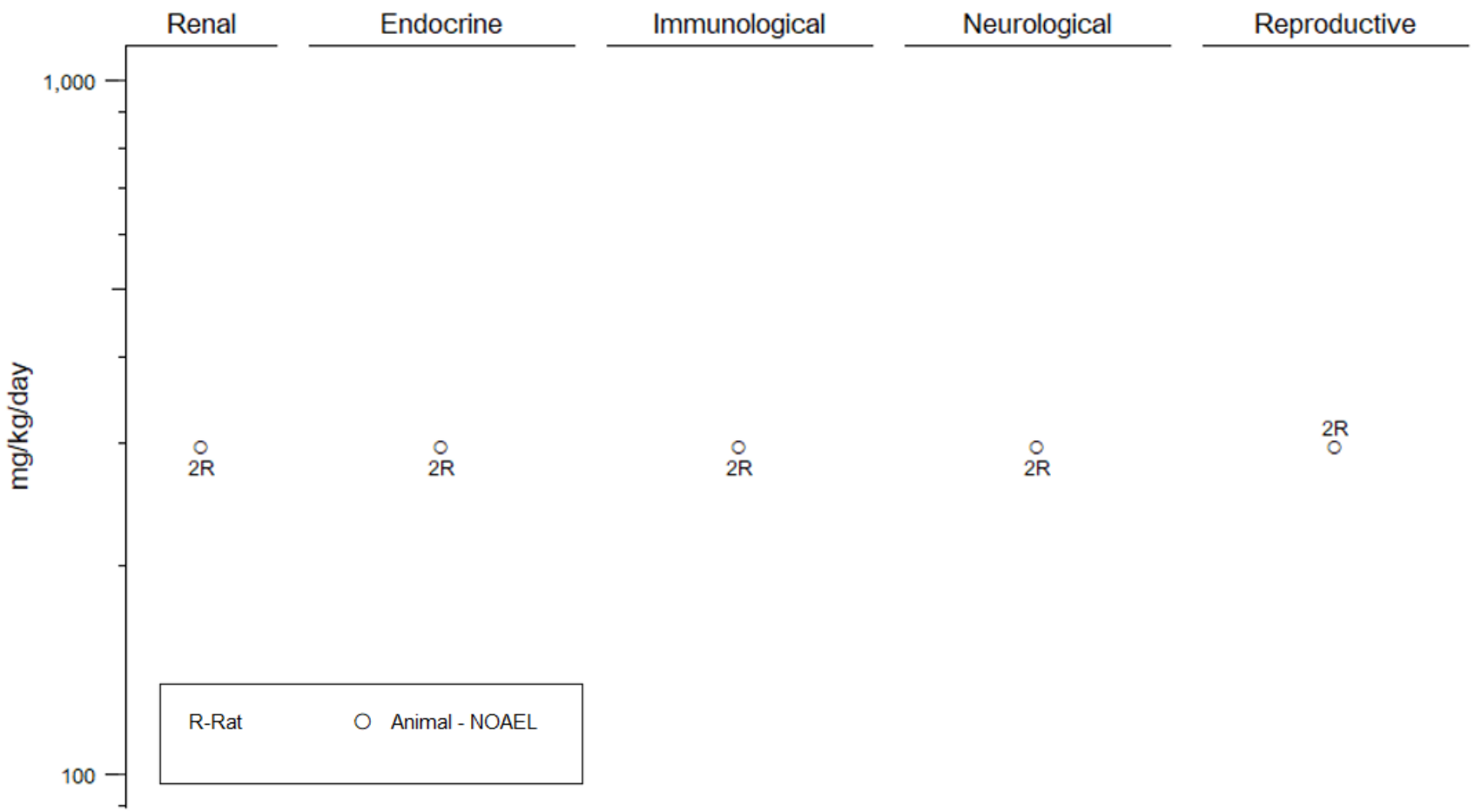


Figure 2-3. Levels of Significant Exposure to Chloroethane – Oral
Acute (≤14 days)



2.2 DEATH

Previous use of chloroethane as a general anesthetic resulted in the death of human patients (Dawkins 1964; Konietzko 1984; Kuschinsky 1970; Lawson 1965; Lehmann and Flury 1943). The cause of death from chloroethane anesthesia has been reported as respiratory paralysis (Kuschinsky 1970) and toxic injury to the heart (Lehmann and Flury 1943). Death has also been reported following intentional misuse of chloroethane as a recreational inhalant (Broussard et al. 2000; Schwark et al. 2022; Yacoub et al. 1993). In these cases, blood concentrations measured at autopsy ranged from 9 to 65 mg/dL; chloroethane was also detected in urine, lung, and brain tissues. Schwark et al. (2022) reported nonspecific signs of asphyxiation including fluidity of the blood, petechiae in the pleura and epicardium, and visceral congestion. Autopsy findings reported by Broussard et al. (2000) included cerebral edema and congestion, as well as visceral congestion. Levels of significant exposure are not reported in Table 2-1 or plotted in Figure 2-2 because concentrations of chloroethane lethal to humans are not known.

Mortality produced by inhalation of high concentrations of chloroethane vapor has been studied quantitatively in animals. The minimum lethal concentration of chloroethane in a 2-hour exposure study in mice was 56,860 ppm (Lazarew 1929). No deaths were seen in mice or rats after exposure to 19,000 ppm chloroethane for 4 hours (NTP 1989), or in a female monkey exposed to 10,000 ppm for 8 hours (Dow 1941). These studies are not included in Table 2-1 and were not plotted in Figure 2-2, because they did not include a control group. Lethality was dependent on concentration and exposure duration in guinea pigs exposed to chloroethane concentrations ranging from 10,000 to 241,000 ppm for 5 minutes to 13.5 hours (USBM 1929). Exposure to 20,000 ppm chloroethane for 9 hours was not lethal to guinea pigs in this study. Death was reported during or after exposure of guinea pigs to 40,000 ppm for 9 hours (2/6), 87,000 ppm for 4.5 hours (6/6), 76,000 ppm for 90 minutes (4/4), and 51,000 ppm for 40 minutes (1/3).

Studies in which animals were repeatedly exposed to chloroethane for ≤14 days did not report any deaths resulting from inhalation of this compound. No mortality was reported in mice exposed to 4,843 ppm 23 hours/day for 11 days (Landry et al. 1987, 1989); rats and dogs exposed to 9,980 ppm 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982); mice exposed to 14,955 ppm 6 hours/day for 14 days (Breslin et al. 1988); pregnant mice exposed to 15,000 ppm 6 hours/day on GDs 6–15 (Dow 1985); or rats and mice exposed to 19,000 ppm 6 hours/day, 5 days/week for 2 weeks (NTP 1989).

Mortality was not increased significantly by intermediate-duration chloroethane exposure (15–364 days). In the first week of a 13-week study, 1 of 10 male mice died when exposed to 10,000 ppm for 6 hours/day, 5 days/week. NTP (1989) did not discuss whether the death was exposure related; therefore, this death is not included in Table 2-1 and was not plotted in Figure 2-2.

In a chronic-duration inhalation study, rat survival was not reduced compared to controls following exposure to 15,000 ppm chloroethane 6 hours/day, 5 days/week for 102 weeks (NTP 1989). The concurrent controls, however, had abnormally low survival rates after week 90 of the study. Survival was significantly reduced in mice following exposure to 15,000 ppm chloroethane for 100 weeks; the effect was found in males after 330 days and in females after 574 days (NTP 1989). The final incidences of mortality were 22/50 and 39/50 in control and treated males, respectively, and 18/50 and 48/50 in control and treated females, respectively. An ascending urinary tract infection may have contributed to the reduced survival in male mice. The decreased survival in female mice was attributed to uterine cancer.

No deaths were seen in mice that drank chloroethane for 7 days (up to 662 mg/kg/day) or 14 days (up to 361 mg/kg/day) (Dow 1995).

2.3 BODY WEIGHT

No studies were located regarding body weight effects in humans after exposure to chloroethane.

Animal studies demonstrate that chloroethane exposure does not adversely affect body weight or weight gain. Indeed, 436 ppm chloroethane 4 hours/day for 8 of 10 days in rats (Gohlke and Schmidt 1972; Schmidt et al. 1972) did not affect body weight gain significantly. Gohlke and Schmidt (1972) and Schmidt et al. (1972) are not included in Table 2-1 and were not plotted in Figure 2-2 because methods and results were not adequately reported. Exposing mice, rats, and dogs to an order of magnitude higher chloroethane exposures also did not significantly affect body weight gain. Mice exposed up to 4,843 ppm for 23 hours/day for 11 days (Landry et al. 1987, 1989) and rats and dogs exposed to up to 9,980 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982) had no significant body weight gain effects. Furthermore, rodents exposed to chloroethane at 14,000–19,000 ppm did not exhibit significant body weight gain. Rats exposed to chloroethane at 14,000–15,000 ppm for five daily 6-hour exposures (Fedtke et al. 1994a) or 19,000 ppm 6 hours/day, 5 days/week for 2 weeks (NTP 1989) or mice exposed to 14,955 ppm 6 hours/day for 14 days (Breslin et al. 1988) did not have significant body weight gain. No effects on body weight gain were seen in pregnant mice exposed to chloroethane 6 hours/day on

GDs 6–15 at concentrations up to 4,946 ppm (Scortichini et al. 1986). In a similar study, Dow (1985) reported that terminal body weights of pregnant mice exposed to up to 15,000 ppm of chloroethane 6 hours/day on GDs 6–15 were within 10% of control group; however, body weight gain was decreased 13–15% at ≥5,000 ppm.

Longer-duration chloroethane exposures between 10,000 and 19,000 ppm that lasted for 6–8 hours/day for 21 days or 5 days/week for 13 weeks, 6.5 months, or approximately 2 years did not significantly affect body weight gain in rats, mice, or rabbits (Bucher e al. 1995; Dow 1941; NTP 1989).

Oral exposure to chloroethane did not affect body weight gains. Body weights of rats given drinking water containing chloroethane for 7 days (up to 662 mg/kg/day) or 14 days (up to 361 mg/kg/day) were within 10% of control values (Dow 1995). In a longer-term study, body weights appeared unaffected in rabbits given up to 1,000 mg/kg/day of chloroethane by gavage for 60 days (Dow 1941). This study is not included in Table 2-1 and was not plotted in Figure 2-2 because experimental conditions were not adequately described.

2.4 RESPIRATORY

Chloroethane, in combination with nitrous oxide and oxygen, was used to maintain anesthesia in human patients previously made unconscious by administration of either thiopentone (thiopental), nitrous oxide, or a mixture of nitrous oxide, chloroethane, and oxygen (Cole 1956). A concentration of 20,000 ppm chloroethane was initially required to maintain anesthesia, but this could slowly be reduced to as low as 5,000 ppm in some cases. Respiration usually remained smooth and even, but some cases of tachypnea were seen. Respiratory rate was stimulated in 16 of 23 patients tested in a second mixed exposure study using nitrous oxide, oxygen, and 36,000 ppm chloroethane (Cole 1967). These studies are not included in Table 2-1 and were not plotted in Figure 2-2 as a NOAEL or LOAEL for the acute respiratory effects of chloroethane in humans because the compound was administered in conjunction with other anesthetic agents. Respiratory paralysis was reported to be the cause of death of a 14-year-old child who died during anesthesia with chloroethane (Kuschinsky 1970). A level of significant exposure was not based on this report because the concentration of chloroethane administered was not known.

A few studies in animals indicated that inhalation of chloroethane may affect respiration, although the majority of studies reported no effects. No histological lesions were seen in the lungs of a female monkey exposed to 10,000 ppm of chloroethane for 8 hours (Dow 1941). This study is not included in Table 2-1

and was not plotted in Figure 2-2 because no comparison to a control animal was made. Guinea pigs initially displayed labored breathing within 10 minutes of exposure to ≥40,000 ppm chloroethane, which then became rapid and shallow after 25 minutes (USBM 1929). The lungs of guinea pigs had slight peribronchial pneumonia, congestion, and hemorrhage following exposure to ≥40,000 ppm; no changes in the lungs were seen at 20,000 ppm (USBM 1929).

Hypertrophic bronchial tubes and interstitial pneumonia were found in rats given eight 4-hour exposures to 436 ppm chloroethane; however, these effects were also present to a lesser extent in controls (Gohlke and Schmidt 1972). Consequently, these results were not considered to be indicative of adverse respiratory effects produced by chloroethane. The only other respiratory effect reported by this study was a mild transitory increase in relative lung weight, which was also not considered adverse (Schmidt et al. 1972). Gohlke and Schmidt (1972) and Schmidt et al. (1972) are not included in Table 2-1 and were not plotted in Figure 2-2 because methods and results were not adequately reported. Absolute and relative lung weights were not affected in rats or mice exposed to chloroethane at 14,000–15,000 ppm 6 hours/day for 5 days (Fedtke et al. 1994a). No gross lesions were present on the lungs of pregnant mice exposed to concentrations up to 15,000 ppm on GDs 6–15 (Dow 1985). Histopathological changes were not observed in the respiratory tracts of mice exposed to chloroethane at 4,843 ppm 23 hours/day for 11 days (Landry et al. 1987, 1989). Histopathological examinations of respiratory organs and tissues were performed following inhalation of chloroethane for 6 hours/day, 5 days/week for 2 weeks at a concentration up to 9,980 ppm in rats and dogs (Landry et al. 1982) and at 19,000 ppm in rats and mice (NTP 1989). No effects were reported in either study. The 2-week NTP (1989) study is limited in that organs of only 3 of 10 exposed rats and 3 of 10 exposed mice were examined microscopically. Therefore, the respiratory endpoint is not included in Table 2-1 and was not plotted in Figure 2-2 for this study.

In an intermediate-duration study, inhalation of concentrations up to 19,000 ppm chloroethane for 13 weeks (6 hours/day, 5 days/week) failed to produce lesions in the respiratory tissue of rats or mice as documented by complete histopathological examinations (NTP 1989). No gross or histological changes were seen in the lungs of rats or rabbits exposed to 10,000 ppm 7.5–8 hours/day, 5 days/week for 6.5 months (Dow 1941).

No non-neoplastic histopathological effects were observed on the respiratory system of rats and mice exposed to 15,000 ppm chloroethane for approximately 2 years (6 hours/day, 5 days/week) (NTP 1989).

2.5 CARDIOVASCULAR

There is some evidence that inhalation of chloroethane has cardiovascular effects in humans. Vagal stimulation occurred in children exposed briefly to high concentrations of chloroethane (Bush et al. 1952). This study is not included in Table 2-1 and was not plotted in Figure 2-2 because the effective concentration of chloroethane was not reported. A mixture of chloroethane, nitrous oxide, and oxygen was used to maintain anesthesia in patients previously made unconscious by administration of thiopentone (thiopental), or nitrous oxide, or the mixture described above (Cole 1956). A concentration of 20,000 ppm chloroethane was initially required to maintain anesthesia, but this could slowly be reduced to concentrations as low as 5,000 ppm in some cases. Pulse rate remained strong and no clinically detectable arrhythmias or changes in heart rate were observed. A similar study using 36,000 ppm chloroethane found increased systolic blood pressure and pulse rate in 16 of 25 patients tested, but again, no cardiac arrhythmias were detected (Cole 1967). These studies are not included in Table 2-1 and were not plotted in Figure 2-2 as a NOAEL or LOAEL for the acute cardiovascular effects of chloroethane in humans because the compound was administered in conjunction with other anesthetic agents.

The cardiovascular effects of chloroethane have also been studied in animals. In dogs, acute-duration exposure to anesthetic concentrations of chloroethane resulted in cardiac irregularities, including ventricular tachycardia and asystole (Haid et al. 1954; Morris et al. 1953). Chloroethane also sensitized the heart to the effects of epinephrine (Haid et al. 1954; Morris et al. 1953). Bush et al. (1952) found that cardiac depression occurred in dogs given anesthetic doses of chloroethane. This depression was initially due to stimulation of the vagus nerve and occurred within 2 minutes of the onset of anesthesia. Direct depression of the cardiac tissue followed and was preceded by tachycardia. With an increasing concentration of chloroethane, dogs had ventricular fibrillation or asystole, which resulted in death. None of the above studies are included in Table 2-1 or plotted in Figure 2-2 because effective chloroethane concentrations were not reported.

Degeneration of heart muscle was found in guinea pigs that died following exposure to $\geq$40,000 ppm chloroethane for 9 hours (USBM 1929). No effects were reported at lower concentrations.

Multiple acute-duration inhalation studies reported no significant cardiovascular effects. Rat heart weight was not affected by eight 4-hour exposures to 436 ppm chloroethane over a 10-day period (Gohlke and Schmidt 1972; Schmidt et al. 1972). These studies are not included in Table 2-1 and were not plotted in

Figure 2-2 because methods and results were not adequately reported. No cardiovascular effects were found on histopathological examination of rats and dogs exposed to concentrations up to 9,980 ppm chloroethane for 2 weeks (6 hours/day, 5 days/week) (Landry et al. 1982). Changes in heart weights and microscopic changes in the heart were not observed in mice exposed to chloroethane at concentrations up to 4,843 ppm 23 hours/day for 11 days (Landry et al. 1987, 1989). Inhalation of 19,000 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks or 13 weeks had no histopathological effect on the cardiovascular system of rats or mice (NTP 1989). Because histopathological examinations were completed on only a few animals in the 2-week study, this study is not included in Table 2-1 and was not plotted in Figure 2-2 for cardiovascular effects.

In the only chronic-duration inhalation study of chloroethane, histopathological examinations of the heart did not reveal any effects in rats or mice exposed to 15,000 ppm 6 hours/day, 5 days/week for up to 2 years (NTP 1989).

No changes in absolute or relative heart weight, or gross pathology were seen in rats that drank chloroethane in drinking water for 14 days (297 mg/kg/day for males; 361 mg/kg/day for females) (Dow 1995).

2.6 GASTROINTESTINAL

Gastrointestinal effects have been reported in humans exposed to chloroethane by inhalation. USBM (1929) reported that mild abdominal cramps occurred in healthy human subjects who inhaled two breaths of 40,000 ppm chloroethane or 2–4 breaths of 20,000 ppm chloroethane. Exposure to 33,600 ppm chloroethane caused nausea and vomiting in human subjects after approximately 8 minutes; subjects exposed to 25,000 ppm did not become nauseated even after 21 minutes (Davidson 1925). It is not clear if gastrointestinal effects are a direct irritant effect of chloroethane or if they are secondary to nervous system effects.

Gastrointestinal effects in animals were studied by necropsy and histopathological examination. Congestion and blood-tinged contents were seen in the small intestines and scattered hemorrhages in the walls of the large intestine were seen in guinea pigs that died following exposure to ≥80,000 ppm for up to 4.5 hours (USBM 1929). Chloroethane concentrations ≤40,000 ppm did not produce gastrointestinal effects in this study. Exposure to concentrations up to 9,980 ppm chloroethane for 2 weeks had no histopathological effects on the gastrointestinal organs of rats or dogs (Landry et al. 1982).

Histopathological changes were not observed in the gastrointestinal tracts of mice exposed to chloroethane at concentrations up to 4,843 ppm 23 hours/day for 11 days (Landry et al. 1987, 1989), or in rats or mice exposed to 19,000 ppm 6 hours/day, 5 days/week for 2 weeks (NTP 1989). The gastrointestinal endpoint for the 2-week NTP (1989) study is not included in Table 2-1 and was not plotted in Figure 2-2 because histopathological examinations were completed on only 3 of 10 exposed rats and 3 of 10 exposed mice.

No gastrointestinal effects were found by histopathological examination in longer-term studies. The gastrointestinal system was without effect in rats and mice exposed to chloroethane at 19,000 ppm for 6 hours/day, 5 days/week for 13 weeks or at 15,000 ppm for up to 2 years (NTP 1989)

2.7 HEMATOLOGICAL

There was a single report of a hematological effect following chloroethane inhalation in humans. A human subject exposed to 33,600 ppm chloroethane developed cyanosis within 8.5 minutes but only when the chloroethane was not mixed with oxygen (Davidson 1925). Therefore, this effect was likely due to lack of oxygen, and this result was not used as the basis for a LOAEL.

Slightly congested or pale spleens were observed in guinea pigs exposed to ≥40,000 ppm chloroethane for 90 minutes (USBM 1929). No effects on hematologic parameters (packed cell volume, hemoglobin, red blood cell counts, platelet counts, differential leukocyte counts, mean corpuscular volume, mean corpuscular hemoglobin) were noted in mice exposed to chloroethane at concentrations up to 4,843 ppm 23 hours/day for 11 days (Landry et al. 1987, 1989) or in rats or dogs exposed to concentrations up to 9,980 ppm 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982). Hematologic effects were not examined in other inhalation studies of chloroethane.

No treatment-related changes in hematologic parameters (hematocrit, hemoglobin concentration, red blood cells, white blood cells, platelet count, differential counts of 100 leukocytes, morphology of erythrocytes, leukocytes, and platelets) were seen in rats that drank chloroethane in drinking water for 14 days (297 mg/kg/day for males; 361 mg/kg/day for females) (Dow 1995).

2.8 MUSCULOSKELETAL

No toxicological studies examining musculoskeletal effects of chloroethane in humans were located. Histopathological examination of muscle and bone following exposure of mice to chloroethane at concentrations up to 4,843 ppm 23 hours/day for 11 days did not reveal any effects (Landry et al. 1987, 1989). Histopathologic changes in muscle and bone were also not observed in rats or dogs exposed to chloroethane at concentrations up to 9,980 ppm 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982). No increase in the occurrence of bone lesions was found in rats and mice exposed to 15,000 ppm chloroethane 6 hours/day, 5 days/week for approximately 2 years (NTP 1989). The NTP studies of shorter duration did not include examination of bone or muscle tissue.

One study investigated the musculoskeletal effects of dermally applied chloroethane in animals. Chloroethane sprayed onto a 1–2-cm^2 area on the thighs of rats until the skin was blanched produced local infiltration and disintegration of muscle fibers (Kenig 1956). This study, available only as an abstract, was not used as the basis for a LOAEL because the effective dose of chloroethane was not reported and few experimental details were provided.

Musculoskeletal effects occurring in fetuses following *in utero* exposure are discussed in the developmental section (Section 2.17).

2.9 HEPATIC

In a case report of a woman who sniffed chloroethane (about 200–300 mL/day) for 4 months, an enlarged liver and mild transient disturbance of liver function, which was not further described, were noted (Hes et al. 1979). The woman had previously misused other drugs but was reportedly not actively misusing substances for 2 years before starting to intentionally misuse chloroethane. Moderately elevated serum alanine aminotransferase (ALT) was observed in a man who intentionally misused (inhaled) chloroethane for 30 years (Nordin et al. 1988). During the 4 months before the man was examined, he had inhaled at least 100 mL/day chloroethane (Nordin et al. 1988). This subject also had a history of substance use disorder (alcohol and sedative misuse), so it is not known for certain if the liver effects were a result of exposure to chloroethane alone. Due to uncertainties of exposure level and possible co-exposure with other chemicals, these studies are not included in Table 2-1 and were not plotted in Figure 2-2.

Hepatic effects in animals have been studied by a number of researchers. No histological hepatic changes were seen in a female monkey exposed for 8 hours to 10,000 ppm of chloroethane (Dow 1941). This study is not included in Table 2-1 and was not plotted in Figure 2-2 because no comparison to a control animal was made. Edema, congestion, and degeneration were seen in the livers of guinea pigs exposed to ≥40,000 ppm chloroethane for up to 9 hours (USBM 1929).

In repeated-exposure studies, liver weights were not affected in rats or mice following five daily 6-hour exposures to chloroethane at 14,000–15,000 ppm (Fedtke et al. 1994a) or in pregnant mice exposed to concentrations up to 15,000 ppm 6 hours/day for 10 days (GDs 6–15) (Dow 1985). Serum aminotransaminase activity (alanine and aspartate), liver enzyme activity (succinate dehydrogenase, alpha-naphthyl acetate-esterase, and acid phosphatase), lipid content, histopathology, and liver weight were not significantly altered in rats given eight 4-hour exposures to 436 ppm chloroethane (Gohlke and Schmidt 1972; Schmidt et al. 1972). Histopathological effects were reported but apparently only in groups pretreated with ethanol. It did not appear that significant tissue changes occurred in rats exposed to chloroethane alone. These studies are not included in Table 2-1 and were not plotted in Figure 2-2 because methods and results were not adequately reported.

Mice exposed to 4,843 ppm chloroethane 23 hours/day for 11 days had increased relative liver weight (approximately 13%) and slightly increased hepatocellular vacuolation (Landry et al. 1987, 1989). No changes in liver weight were noted in mice exposed to chloroethane at concentrations up to 4,946 ppm 6 hours/day on GDs 6–15 and sacrificed on GD 18 (Scortichini et al. 1986). There was a slight increase in relative liver weight (5–8%) in male rats exposed to ≥3,980 ppm for 6 hours/day, 5 days/week for 2 weeks, but since there were no changes in clinical chemistry or liver histopathology, and only a small depletion of non-protein sulfhydryl, the change in relative weight was considered to be more adaptive and not an indication of significant liver toxicity (Landry et al. 1982). There were no hepatic effects in two dogs exposed to concentrations up to 9,980 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982). No significant hepatotoxicity was observed in rats or mice examined histologically following exposure to 19,000 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks (NTP 1989). The hepatic endpoint for the 2-week NTP (1989) study is not included in Table 2-1 and was not plotted in Figure 2-2 because histopathological examinations were completed on only 3 of 10 exposed rats and 3 of 10 exposed mice.

No changes in liver weight or histopathology were observed in mice exposed to 15,000 ppm chloroethane 6 hours/day for 21 days (Bucher et al. 1995); also, no histological changes were seen in the liver of rats or

rabbits following 6.5 months of exposure to 10,000 ppm 7.5 hours/day, 5 days/week (Dow 1941). Relative liver weights were significantly ($p<0.05$) increased in male rats (14%) and female mice (18%), but not in female rats or male mice exposed to 19,000 ppm chloroethane 6 hours/day, 5 days/week for 13 weeks (NTP 1989). Because histopathological changes were not observed, the increased relative liver weight is not considered adverse.

Chronic-duration exposure to 15,000 ppm chloroethane 6 hours/day, 5 days/week for approximately 2 years, produced no increase in the incidence of non-neoplastic hepatic lesions in rats or mice, although hepatocellular carcinomas/adenomas did appear in 8/48 female mice (NTP 1989).

No changes in absolute or relative liver weight, serum parameters (alkaline phosphatase, ALT, and aspartate aminotransferase [AST]) or histopathology were seen in rats that drank chloroethane in drinking water for 14 days (297 mg/kg/day for males; 361 mg/kg/day for females) (Dow 1995).

Adaptive Responses. Changes in adenosine triphosphate/adenosine diphosphate (ATP/ADP) ratio and GSH depletion were investigated as possible adaptive measures occurring in the liver following chloroethane exposure. A single 5-minute exposure to an unspecified concentration of chloroethane produced an increase in the ratio of ATP/ADP in the livers of mice (Oura et al. 1966). Liver non-protein sulfhydryl (NPSH) concentration was reduced in both rats and mice following a single 6-hour exposure to 3,980 ppm of chloroethane (Landry et al. 1982). This effect was not associated with histopathological changes in the rat (Landry et al. 1982). Histopathology was not evaluated in mice from this study. Following five daily 6-hour exposures to chloroethane at 15,000 ppm, GSH levels in the liver were reduced in male rats but not in female rats or in mice of either sex (Fedtke et al. 1994b).

2.10 RENAL

No studies were located regarding renal effects in humans after exposure to chloroethane.

Inhalation of chloroethane produced renal effects in only a single acute-duration inhalation study. Congestion and fatty or granular degeneration of the cortex were seen in the kidneys of guinea pigs exposed to ≥40,000 ppm for up to 9 hours (USBM 1929). No effects were found following exposure to concentrations ≤20,000 ppm for 9 hours.

No histological changes in the kidneys were seen in a female monkey exposed for 8 hours to 10,000 ppm of chloroethane (Dow 1941). This study is not included in Table 2-1 and was not plotted in Figure 2-2 because no comparison to a control animal was made. Exposure to 436 ppm chloroethane for 4 hours/day for 8 days had no effect on rat kidney histopathology, fat content, or weight (Gohlke and Schmidt 1972; Schmidt et al. 1972). These studies are not included in Table 2-1 and were not plotted in Figure 2-2 because methods and results were not adequately reported. Inhalation of chloroethane at concentrations up to 4,843 ppm 23 hours/day for 11 days in mice did not produce renal effects detectable by serum chemistry analysis or histopathological examination (Landry et al. 1987, 1989). Absolute and relative kidney weights were not affected in rats or mice exposed to 14,000–15,000 ppm chloroethane for five daily 6-hour exposures (Fedtke et al. 1994a). Blood urea nitrogen (BUN) was decreased slightly (percent not reported) in female rats following inhalation of ≥3,980 ppm for 2 weeks (Landry et al. 1982). However, the study authors did not consider this effect to be toxicologically significant because decreased BUN is not a direct indicator of kidney toxicity, and no associated pathological lesions were found. No other renal effects were found in rats or dogs exposed to up to 9,980 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982). Histopathological examination of 3 of 10 exposed rats and 3 of 10 exposed mice showed no evidence of nephrotoxicity after exposure to 19,000 ppm 6 hours/day, 5 days/week for 2 weeks (NTP 1989). Because of the small number of animals examined microscopically, the renal endpoint for this study is not included in Table 2-1 and was not plotted in Figure 2-2.

Exposure to concentrations as high as 19,000 ppm chloroethane 6 hours/day, 5 days/week for 13 weeks had no effect on the occurrence of kidney lesions in rats or mice (NTP 1989). No renal lesions were seen in rats or rabbits following 6.5 months of exposure to 10,000 ppm 7.5–8 hours/day, 5 days/week (Dow 1941).

Chloroethane vapor at a concentration of 15,000 ppm produced signs of mild nephrotoxicity in mice exposed 6 hours/day, 5 days/week for 100 weeks (NTP 1989). There was an increase in the incidence of scattered foci of tubular regeneration and minimal glomerulosclerosis in treated female mice, while treated male mice exhibited only slight enlargement of renal tubular cell nuclei. No renal effects were found in rats exposed to 15,000 ppm chloroethane 6 hours/day, 5 days/week for 102 weeks (NTP 1989).

No changes in absolute or relative kidney weight or gross pathology were seen in rats that drank chloroethane in drinking water for 14 days (297 mg/kg/day for males; 361 mg/kg/day for females) (Dow 1995).

2.11 DERMAL

Physicians often use chloroethane as a local spray anesthetic. When sprayed on the skin, chloroethane rapidly evaporates and causes the skin to freeze, which produces a numbing sensation (Im et al. 2012). Dermally applied chloroethane, typically for ≤30 seconds, has been shown to reduce pain if sprayed on the skin prior to venous or arterial puncture or cannulation (Fossum et al. 2016; Rao et al. 2019; Rüsch et al. 2017; Schlieve and Miloro 2015; Selby and Bowles 1995; Soueid and Richard 2007), spinal injection (Firdaus et al. 2018; Walsh et al. 2010), injection into joints (Moon et al. 2017, 2020; Shah et al. 2018), botulinum toxin injection (Irkoren et al. 2015; Richards 2009), skin puncture for allergy testing (Waibel and Katial 2005), and during needle electromyography (Moon and Kim 2014). Chloroethane is used for procedures such as skin biopsy and ear piercing that require short periods of surface anesthesia in a small area (Florentine et al. 1997; Noble 1979). It is also used topically to relieve pain in facial muscles during physical therapy for those suffering from temporomandibular pain and dysfunction syndrome (also known as temporomandibular joint disorder, or TMD) (Merbach 1996) and reduced the pain associated with dressing changes for negative pressure wound therapy (Tank et al. 2021). Use of chloroethane spray during exercise for 4 weeks following total knee arthroplasty resulted in reduced pain and decreased consumption of analgesics (Rui et al. 2017). Pain relief was also observed following chloroethane spray in children and adolescents with spastic torticollis (i.e., involuntary, uncontrollable positioning of head due to painful muscle spasms of the neck) (Nibhanipudi 2015). Chloroethane was useful in preventing pruritus (i.e., severe itching) in skin prick tests without affecting the flare and wheal reactions that are indicative of an allergic response (Gal-Oz et al. 2010, 2015; Waibel and Katial 2005). These studies were not included in the LSE table because the effective dose of chloroethane was not reported.

Symptoms of frostbite can result from prolonged exposures. Three children who had their earlobes sprayed with chloroethane for several minutes all developed chemical frostbite on their ears and necks (Noble 1979). Mild pain was reported when chloroethane was sprayed on a small area of one hand each of 40 women (Selby and Bowles 1995). These studies were not included in the LSE table because the effective dose of chloroethane was not reported. The chloroethane was sprayed for 10 seconds, from a height of 20 cm. This procedure was used as analgesia for venous cannulation, a procedure that was reported to be more painful without pretreatment with chloroethane. Dermal contact sensitivity reactions to chloroethane are described in Section 2.14 (Immunological).

Chloroethane has the same topical anesthetic qualities in animals as it does in humans (Dobkin and Byles 1971). Chloroethane applied to a 1–2-cm^2 area on the thighs of rats until the skin was blanched produced edema in the subcutaneous tissue of the application site (Kenig 1956). This study, available only as an abstract, was not used as the basis for a LOAEL because the effective dose of chloroethane was not reported and few experimental details were provided.

Non-neoplastic dermal effects following inhalation exposure to chloroethane were not reported in animal studies. No histopathological effects on the skin were found in mice exposed to up to 4,843 ppm 23 hours/day for 11 days (Landry et al. 1987, 1989); in rats or dogs exposed to up to 9,980 ppm 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982); or in rats or mice exposed 6 hours/day, 5 days/week to 19,000 ppm for 2 weeks (NTP 1989), up to 19,000 ppm for 13 weeks (NTP 1989), or 15,000 ppm for approximately 2 years. The dermal endpoint from the 2-week NTP (1989) study is not included in Table 2-1 and was not plotted in Figure 2-2 because histopathological examinations were completed on only 3 of 10 exposed rats and 3 of 10 exposed mice. Dermal carcinogenic effects observed in male rats (NTP 1989) are discussed in Section 2.19.

2.12 OCULAR

Mild eye irritation occurred in volunteers exposed briefly to 40,000 ppm chloroethane (USBM 1929). No eye irritation was reported following exposure to 20,000 ppm. Rodriguez and Ascaso (2012) described a case where a patient suffered an acute burn of the ocular surface following chloroethane spray exposure. The patient had undergone excision of a papilloma on his superior right eyelid after slight freezing with the chloroethane spray. No additional reports of ocular toxicity in humans during exposure to chloroethane vapor were identified.

Histopathological examinations of the eyes did not reveal any effects in mice exposed to up to 4,843 ppm chloroethane 23 hours/day for 11 days (Landry et al. 1987, 1989) or in rats or dogs exposed to up to 9,980 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982). Ophthalmoscopic examination of the eyes of the chloroethane-exposed dogs also did not reveal any effects. In addition, no ocular lesions were seen during ophthalmoscopic examination in rabbits following whole-body exposure to 10,000 ppm 7.5–8 hours/day, 5 days/week for 6.5 months (Dow 1941).

2.13 ENDOCRINE

No studies were located regarding endocrine effects in humans after exposure to chloroethane.

Studies in animals did not report any effects of chloroethane on endocrine endpoints. No histological changes were seen in the adrenals or pancreas of a female monkey exposed to 10,000 ppm chloroethane for 8 hours (Dow 1941). This study is not included in Table 2-1 and was not plotted in Figure 2-2 because no comparison to a control animal was made. No effects on thyroid weight, thyroid histopathology, pituitary weight, adrenal weight and histology, or adrenocorticotropic hormone activity were noted in rats exposed to 436 ppm chloroethane 4 hours/day for 8 exposures over 10 days (Gohlke and Schmidt 1972; Schmidt et al. 1972). These studies are not included in Table 2-1 and were not plotted in Figure 2-2 because methods and results were not adequately reported. Histopathologic changes were not observed in the adrenals, pancreas, parathyroids, pituitary, or thyroid glands of mice exposed to chloroethane at concentrations as high as 4,843 ppm 23 hours/day for 11 days (Landry et al. 1987, 1989), or rats or dogs exposed to up to 9,980 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982). No histological changes were seen in the pituitary or adrenal glands in mice exposed to 15,000 ppm chloroethane 6 hours/day for 21 days (Bucher et al. 1995). Microscopic examination of the adrenals, pancreas, parathyroids, pituitary, and thyroid glands from 3 of 10 rats and 3 of 10 mice exposed to 19,000 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks did not reveal any effects (NTP 1989). Because histopathological examinations were completed on only a few animals, this study is not included in Table 2-1 and was not plotted in Figure 2-2 for endocrine effects.

Histopathologic changes were not observed in the adrenals, pancreas, parathyroid glands, pituitary, or thyroid glands of rats or mice exposed to concentrations as high as 19,000 ppm chloroethane 6 hours/day, 5 days/week for 13 weeks, or 15,000 ppm 6 hours/day, 5 days/week for approximately 2 years (NTP 1989). No histological changes were seen in the adrenals or pancreas of rats and rabbits exposed to 10,000 ppm 7.5–8 hours/day, 5 days/week for 6.5 months (Dow 1941).

No changes in absolute or relative thyroid (including parathyroid) weight or gross pathology were seen in rats that drank chloroethane in drinking water for 14 days (297 mg/kg/day in males; 361 mg/kg/day for females) (Dow 1995).

2.14 IMMUNOLOGICAL

No studies were located regarding immunological effects in humans after inhalation or oral exposure to chloroethane.

Dermal exposure to chloroethane can result in contact sensitivity. Patch tests performed on two patients with eczema were strongly positive for chloroethane, while a third patient suffered an eczematous reaction after the use of chloroethane as a local anesthetic. Patch tests on 15 control volunteers were negative (van Ketel 1976). Kriechbaumer et al. (1998) also demonstrated contact sensitization in a patch test of a single female athlete. Severity of the infiltrated, vesicular, and non-urticarial reaction was similar for occluded and non-occulated sites. A punch biopsy taken from a woman with a positive patch test to chloroethane revealed observations consistent with a T-cell-mediated allergic reaction (Bircher et al. 1994). Microscopic examination showed marked spongiosis and a lymphohistiocytic infiltrate. There was a marked dermal infiltrate of CD3+T cells (pan T cells), with a predominance of CD4 T cells (helper/ suppressor cell subtypes). Most of the cells expressed lymphocyte function-associated antigen. A considerable number of CD1+Langerhans cells were also found in the epidermis.

Immunological effects in animals exposed to chloroethane were mostly negative. No histological changes were seen in the spleen of a female monkey exposed to 10,000 ppm of chloroethane for 8 hours (Dow 1941). This study is not included in Table 2-1 and was not plotted in Figure 2-2 because no comparison to a control animal was made. Rat spleen and thymus weights were not affected by exposure to 436 ppm chloroethane for 4 hours/day for 8 days (Gohlke and Schmidt 1972; Schmidt et al. 1972). White blood cell counts were also unaffected in this study (Gohlke and Schmidt 1972; Schmidt et al. 1972). These studies are not included in Table 2-1 and were not plotted in Figure 2-2 because methods and results were not adequately reported. Histological changes in the thymus, spleen, and lymph nodes were not observed in mice exposed to concentrations up to 4,843 ppm chloroethane 23 hours/day for 11 days (Landry et al. 1987, 1989). There were no compound-related effects on organs or tissues of the immune system after exposure to up to 9,980 ppm 6 hours/day, 5 days/week for 2 weeks in rats or dogs (Landry et al. 1982); 19,000 ppm 6 hours/day, 5 days/week for 2 weeks in rats or mice (NTP 1989); 10,000 ppm 7.5–8 hours/day, 5 days/week for 6.5 months in rats or rabbits (Dow 1941); up to 19,000 ppm 6 hours/day, 5 days/week for 13 weeks in rats or mice (NTP 1989); or 15,000 ppm 6 hours/day, 5 days/week for approximately 2 years in rats or mice (NTP 1989). The immunological endpoint for the 2-week NTP (1989) study is not included in Table 2-1 and was not plotted in Figure 2-2 because histopathological examinations were completed for only 3 of 10 exposed rats and 3 of 10 exposed mice.

No changes in absolute or relative spleen weight or gross pathology were seen in rats that drank chloroethane in drinking water for 14 days (297 mg/kg/day in males; 361 mg/kg/day for females) (Dow 1995).

2.15 NEUROLOGICAL

There are numerous reports of neurological effects in humans exposed to chloroethane by inhalation. Marked dizziness was reported in volunteers who were given three breaths of 20,000 ppm chloroethane (USBM 1929). A subjective feeling of intoxication occurred at 17 minutes and increased reaction times at 3 minutes were reported in persons during exposure to 13,000 ppm (Davidson 1925). At 19,000 ppm, slight intoxication was recorded within 1 minute of exposure and increased reaction times were noted (similar to those observed at 13,000 ppm). This effect progressed to distinct intoxication and mild analgesia within 12 minutes. At higher concentrations, more pronounced effects appeared, such as slight incoordination within 15 minutes at 25,000 ppm and marked incoordination within 8 minutes at 33,600 ppm. Inhalation of 33,600 ppm chloroethane in oxygen produced unconsciousness in 13–17 minutes (Davidson 1925). Neurological effects (intoxication, talkativeness, aggression, and incoordination) occurred earlier when chloroethane was delivered in air compared to oxygen (Davidson 1925). The number of subjects exposed at each concentration was not clearly stated in this study, and there was no discussion regarding how long it took for the subjects to recover fully from the effects of chloroethane. Anesthetic concentrations of chloroethane also produced vagus nerve stimulation in subjects studied by Bush et al. (1952); however, the concentration of chloroethane was not specified. Use of chloroethane as a topical anesthetic is described in Section 2.11 (Dermal).

Several case reports of intentional solvent inhalation using chloroethane have described significant neurological symptoms in people, who generally recover following cessation of exposure. People who intentionally inhaled chloroethane experienced slurred speech, dizziness, and difficulty walking (Demarest et al. 2011; Hes et al. 1979; Senussi and Chalise 2015). In addition, some studies reported that patients experienced visual hallucinations, tremors, nausea, abdominal cramps, and an unsteady gait after intentionally inhaling chloroethane (Al-Ajmi et al. 2018; Kuthiah and Er 2019; Nordin et al. 1988). Other symptoms associated with intentional chloroethane inhalation included sleep disorders, tachycardia, ataxia, confusion, dysdiadochokinesia (inability to perform rapidly repeated alternating movements) of the arm, and sluggish or brisk lower limb reflexes (Finch and Lobo 2005; Hager et al. 2021; Hes et al. 1979; Kuthiah and Er 2019; Nordin et al. 1988). Blood tests and neuroimaging were generally negative

for these intentional solvent inhalation cases (Finch and Lobo 2005; Senussi and Chalise 2015); however, a single case report showed neuropathy of motor and sensory neurons by electrophysiology in a subject that intentionally inhaled chloroethane periodically for approximately 30 years, and then began inhaling chloroethane daily 4 months prior to examination (Nordin et al. 1988). This subject also experienced a grand mal seizure and short-term memory loss; however, full recovery was observed after approximately 6 weeks after exposure cessation.

Neurological effects of chloroethane inhalation have also been studied in animals. A female monkey exposed to 10,000 ppm for 8 hours did not show any signs of intoxication throughout the exposure (Dow 1941). Female B6C3F1 mice became hyperactive (running, jumping, boxing, and rearing) within 1.5–2 hours of being exposed to 15,000 ppm of ^{14}C-chloroethane or chloroethane for 6 hours; this increased activity continued for approximately 1 hour after cessation of exposure (Dow 1992). Similarly, pregnant mice exposed to ≥5,000 ppm of chloroethane (6 hours/day on GDs 6–15) became hyperactive and exhibited stereotypic behavior (highly repetitive running patterns) within the 2 hours of exposure; however, the level of activity did not appear to be dose dependent (Dow 1985). Loss of reflexes was seen in mice after 2 hours of exposure to 53,053 ppm (Lazarew 1929). This study is not included in Table 2-1 and was not plotted in Figure 2-2 for neurological effects because a concurrent control group was not included. Unlike mice, no change in activity was seen in female Fischer 344 rats following inhalation of up to 15,000 ppm ^{14}C-chloroethane (Dow 1992). This study is also not included in Table 2-1 and was not plotted in Figure 2-2 due to lack of a concurrent control group. Guinea pigs exposed to 20,000 ppm chloroethane were unsteady, sluggish, and dizzy during a 9-hour exposure (USBM 1929). Those exposed to 40,000 ppm were unsteady and dizzy after 3 minutes of exposure. At higher concentrations (>51,000 ppm), these effects were seen after shorter exposure durations, and more severe effects were found, such as inability to stand, lying on the side, convulsions, and unconsciousness. In dogs, concentrations of chloroethane that produced anesthesia also produced stimulation of the vagus nerve and, consequently, cardiac depression (Bush et al. 1952). Pretreatment with anticholinergic drugs inhibited vagal stimulation (Bush et al. 1952). Muscle twitching and tremors have also been observed in dogs during chloroethane anesthesia (Morris et al. 1953). LOAELs were not taken from these studies because the effective concentrations of chloroethane were not reported.

There were few reports of neurological effects in studies of longer duration. Brain histopathology and weight in the rat were unaffected by eight 4-hour exposures to 436 ppm chloroethane (Gohlke and Schmidt 1972; Schmidt et al. 1972). These studies are not included in Table 2-1 and were not plotted in Figure 2-2 because methods and results were not adequately reported. Slight lethargy was observed in

rats and hyperactivity was observed in one of two dogs exposed to 9,980 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982). Brain weight and brain or peripheral nerve histopathology were not affected. Evaluation of the dogs for gait, posture, cranial nerve reflexes, postural reactions, spinal cord reflexes, muscle tone, and pain perception also did not reveal any chloroethane-related effects (Landry et al. 1982). When mice received 11 days of near-continuous exposure to up to 4,843 ppm chloroethane, no neurological effects were found by function testing or histopathological examination (Landry et al. 1987, 1989). No compound-related neurological effects were found in histopathological examinations of rats and mice exposed to up to 19,000 ppm chloroethane 6 hours/day, 5 days/week for 2 or 13 weeks (NTP 1989). Since histopathological examinations were completed on only a few animals in the 2-week study, it is not included in Table 2-1 and was not plotted in Figure 2-2 for neurological effects.

No increase in the occurrence of non-neoplastic lesions was found in nervous system organs or tissues following exposure of rats and mice to 15,000 ppm chloroethane 6 hours/day, 5 days/week for approximately 2 years (NTP 1989). This study did, however, report hyperactivity of female mice during the daily exposure period.

Neurological effects after oral exposure to chloroethane have been studied in rats and mice. Female rats given a single gavage of 1998 mg/kg chloroethane became unsteady for 15–30 minutes after dosing; no effects were seen at 57 mg/kg (Dow 1992). Unlike inhalation studies, no neurological effects were seen in female B6C3F1 female mice after a gavage dose of 1,970 mg/kg (Dow 1992). These data are not included in Table 2-1 and were not plotted in Figure 2-2 because no control groups were included. No changes in absolute or relative brain weight or gross pathology were seen in rats that drank chloroethane in drinking water for 14 days (297 mg/kg/day for males; 361 mg/kg/day for females) (Dow 1995).

There is one study of the neurological effects of dermally applied chloroethane in animals. Rats were sprayed with chloroethane until their skin was blanched, and examination of the nerve fibers at the site of application (a 1–2-cm^2 area of the thigh) revealed thickening of the fibers and swelling of the Schwann cell nuclei (Kenig 1956). These effects subsided within 10 days of application. This study, available only as an abstract, was not used as the basis for a LOAEL because the effective dose of chloroethane was not reported and few experimental details were provided.

2.16 REPRODUCTIVE

No studies were located regarding reproductive effects in humans after exposure to chloroethane.

Several studies investigated reproductive endpoints in animals. Absolute and relative uterine weights were decreased by approximately 35% in mice exposed to 14,879 ppm chloroethane 6 hours/day for 5 days, compared to unexposed controls (Fedtke et al. 1994a). This study did not undertake histopathological examination, therefore the reason for the decreased uterine weight is unknown. No effect on uterine weights was seen in rats exposed to the same levels (Fedtke et al. 1994a). Uterine GSH levels were significantly decreased in both rats and mice following exposure, in fact to a greater degree than decreases observed in the liver, lungs, and kidneys in the same animals (Fedtke et al. 1994b).

A small, but significant increase in the average duration of the estrous cycle was observed in mice after exposure to 15,000 ppm 6 hours/day for 21 days (Bucher et al. 1995). Before the exposure, estrous cycle duration was 5.15±0.15 days, while during the exposure, estrous cycle duration increased to 5.52±0.19 days. The proportion of time spent in the stages of the cycle during exposure was significantly different compared to pre-exposure in both the exposed and control group. Mice spent shorter time in metestrus and longer time in the other stages. No changes were seen in serum estradiol or progesterone levels, uterine and ovarian weight, or uterine and ovarian histopathology in these mice (Bucher et al. 1995). Breslin et al. (1988) also studied the length of the estrous cycle in mice after 14 days of exposure to 14,955 ppm for 6 hours/day. No significant increase in the estrous cycle length was seen during exposure compared to pre-exposure (5.0±0.7 days pre-exposure versus 5.6±0.8 days during exposure). No histological changes in the ovaries, oviduct, uterus, cervix, or vagina were observed after exposure. The discrepancy between the two studies regarding increased estrous cycle length may be due to duration of exposure (14 versus 21 days) or number of animals studied. Bucher et al. (1995) studied 30 females/group, whereas Breslin et al. (1988) studied 10 females/group. The larger sample size would lend itself to greater statistical power to distinguish differences. In dogs anesthetized with chloroethane, decreased uterine motility and muscle tonus were observed (van Liere et al. 1966). This study was not used as the basis for a LOAEL because the effective concentration of chloroethane was not reported. In addition, the relevance of this endpoint to other reproductive effects is unclear.

Testes weights and histology were not affected in rats exposed to 436 ppm chloroethane 4 hours/day for 8 days during a l0-day time period (Gohlke and Schmidt 1972; Schmidt et al. 1972). These studies are

not included in Table 2-1 and were not plotted in Figure 2-2 because methods and results were not adequately reported.

Histopathological changes in reproductive organs were not observed in mice exposed to concentrations as high as 4,843 ppm chloroethane 23 hours/day for 11 days (Landry et al. 1987, 1989) or in rats and dogs exposed to up to 9,980 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks (Landry et al. 1982). Microscopic examination of the reproductive organs of 3 of 10 rats and 3 of 10 mice exposed to 19,000 ppm chloroethane 6 hours/day, 5 days/week for 2 weeks did not reveal any effects (NTP 1989). Because histopathological examinations were completed on only a few animals, this study is not included in Table 2-1 and was not plotted in Figure 2-2 for reproductive effects. No non-neoplastic compound-related histopathological changes were found in the reproductive organs of rats or mice exposed to 19,000 ppm chloroethane 6 hours/day, 5 days/week for 13 weeks, or to 15,000 ppm 6 hours/day, 5 days/week for approximately 2 years (NTP 1989). However, metastatic uterine cancer was observed in in female mice after 100 weeks of exposure to 15,000 ppm (NTP 1989) (Section 2.19).

No changes in absolute or relative ovarian or testes weights, or gross pathology of these organs were seen in rats that drank chloroethane in drinking water for 14 days (297 mg/kg/day for males; 361 mg/kg/day for females) (Dow 1995). Prenatal studies in mice exposed to chloroethane on GDs 6–15 did not report changes in pregnancy rate, resorptions, or live fetuses/litter (Dow 1985; Scortichini et al. 1986). These studies are further described in Section 2.17 (Developmental).

2.17 DEVELOPMENTAL

No studies were located on developmental effects of chloroethane in humans.

Two prenatal inhalation studies were located for chloroethane (Dow 1985; Scortichini et al. 1986). In a study of pregnant mice exposed to chloroethane at concentrations up to 4,946 ppm for 6 hours/day on GDs 6–15, no significant treatment-related changes were observed in maternal body or liver weight, pregnancy rate, number of resorptions, number of live fetuses/litter, litter size, fetal sex ratio, fetal body weight, or incidence of external, or visceral malformations in the fetuses (Scortichini et al. 1986).

An increase in incidence of DFFC of the skull bones (developmental delay of ossification of small centers of unossified bone of the bone) was seen in the mouse fetuses at 4,946 ppm. Incidences based on number of fetuses affected were 1/126, 1/142, 1/147, and 5/116 at 0, 491, 1,504, and 4,946 ppm, respectively.

These data were significant for trend (p=0.0488), but not in a pairwise comparison to the control group. Incidence data for number of litters affected were 1/22, 1/24, 1/25, and 5/22 at 0, 491, 1,504, and 4,946 ppm, respectively. Although the incidences of number of litters affected were not statistically different from controls (by pairwise or trend tests), this effect was considered to be biologically relevant. An increase in supernumerary ribs was also found, although this effect was not statistically significant and not dose related.

Dow (1985) exposed pregnant mice up to 15,000 ppm of chloroethane for 6 hours/day on GDs 6–15. No exposure-related changes in the number of resorptions, live fetuses/litter, or normal-appearing fetuses were observed. This study, however, did not examine fetuses for skeletal or visceral alterations.

2.18 OTHER NONCANCER

No studies were identified that examined other noncancer effects in humans or animals following inhalation, oral, or dermal exposure to chloroethane.

2.19 CANCER

No studies were located regarding cancer and chloroethane exposure in humans.

Inhalation exposure to 15,000 ppm chloroethane 6 hours/day, 5 days/week for 102 weeks, produced evidence of carcinogenicity in both male and female rats (NTP 1989). The combined incidences of skin trichoepitheliomas, sebaceous gland adenomas, and basal cell carcinomas were 10% (5/50) in treated male rats and 0% (0/50) in concurrent controls. The increase was statistically significant when compared to the mean historical inhalation control incidence of 0.7% (n=300) and the historical untreated control incidence of 2% (n=1,936). It is reasonable to combine incidence data of these neoplasms because they are morphologically similar (all are epithelial tumors arising from the epidermis or associated structures).

Malignant brain astrocytomas were found in 6% (3/50) of the treated female rats and 0% (0/50) of the concurrent controls. This increase was statistically significant compared to the historical inhalation control incidence of 0.3% (n=297) and the historical untreated glial cell tumor incidence of 1.2% (n=1,969), but not when compared to the concurrent control. All three affected rats died before the end of the study, and it was suggested that the brain tumors may have been the cause of death. NTP (1989)

concluded that this study provides equivocal evidence of the carcinogenicity of chloroethane in both male and female rats.

There was a highly significant increase in the incidence of uterine carcinomas of endometrial origin in female mice exposed to 15,000 ppm chloroethane 6 hours/day, 5 days/week for 100 weeks (NTP 1989). These tumors, which were highly malignant and metastasized to a wide variety of organs, were found in 86% (43/50) of treated females and 0% (0/49) of concurrent controls. Picut et al. (2003) reevaluated the pathology and incidence data of the NTP (1989) study and confirmed the high incidence of uterine neoplasms and metastases to a large number of organs including the lung, lymph nodes, and ovaries. The characterization of the uterine neoplasms as adenocarcinomas of endometrial origin was also confirmed.

The NTP (1989) study also reported a significant increase in hepatocellular carcinomas/adenomas, which occurred in treated female mice at an incidence of 17% (8/48) and concurrent controls at 6% (3/49). A significant increase in the occurrence of hematopoietic lymphomas in treated female mice was discounted because concurrent control values were abnormally low compared to historical control values. In male mice, the combined incidence of alveolar and bronchiolar adenomas/carcinomas was 21% (10/48), a significant increase compared to the 10% (5/50) incidence in concurrent controls. The study authors concluded that this study provides clear evidence of the carcinogenicity of chloroethane in female mice but that the study was inadequate for male mice because of low survival (50%). A CEL of 15,000 ppm for mice is reported in Table 2-1 and plotted in Figure 2-2.

Based on limited evidence of carcinogenicity in animals and no human data, IARC (1999) considers chloroethane to be in Group 3, not classifiable as to its carcinogenicity to humans. The carcinogenicity of chloroethane has not been classified by the HHS (NTP 2021). A provisional carcinogenicity assessment by the U.S. Environmental Protection Agency (EPA) determined chloroethane was likely to be carcinogenic to humans (EPA 2007).

2.20 GENOTOXICITY

No studies were located regarding genotoxic effects in humans following exposure to chloroethane. Limited *in vivo* and *in vitro* studies suggest that chloroethane is nongenotoxic to mice following inhalation exposure and may be mutagenic to bacteria and mammalian cells *in vitro* at high concentrations.

Results of mutagenicity tests performed *in vivo* and *in vitro* are shown in Tables 2-3 and 2-4, respectively. Chloroethane did not increase the number of micronuclei in bone marrow cells or affect deoxyribonucleic acid (DNA) synthesis in mice exposed nose-only to 25,000 ppm chloroethane 6 hours/day for 3 days (Ebert et al. 1994). The investigators indicated that the exposure concentration used in this study was about 66% of the flammability limit and that it was the highest concentration that could be safely administered.

Table 2-3. Genotoxicity of Chloroethane *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Mouse bone marrow cells	Micronuclei	–	Ebert et al. 1994
Mouse hepatocytes	Unscheduled DNA synthesis	–	Ebert et al. 1994

– = negative result

Table 2-4. Genotoxicity of Chloroethane *In Vitro*

		Results		
		Activation		
Species (test system)	Endpoint	With	Without	Reference
Prokaryotic organisms				
Salmonella typhimurium[a]				
Strain TA 1535	Gene mutation	+	+	NTP 1989
Strain TA100	Gene mutation	+	–	NTP 1989
Strain TA98 (dessicator test for exposure to gases)	Gene mutation	–	–	NTP 1989
Strains TA1535, TA100	Gene mutation	+	+	Milman et al. 1988
Eukarytotic organisms				
Mammalian cells				
Mouse BALB/c-3T# cells	Cell transformation	No data	–	Milman et al. 1988; Tu et al. 1985
Chinese hamster ovary cells	Gene mutation	+	+	Ebert et al. 1994
Mouse B6C3F1 hepatocyte primary culture	DNA repair	No data	–	Milman et al. 1988
Mouse B6C3F1 hepatocyte primary culture	DNA repair	No data	–	Williams 1983

[a]Mutagenic activity consistent with an alkylating agent; positive in base substitution strains.

+ = positive results; – = negative results

In bacteria, chloroethane gas (>10,000 ppm) was mutagenic in *Salmonella typhimurium* strain TA1535 but not in strain TA98 both with and without activation (Milman et al. 1988; NTP 1989). In strain

TA100, one study reported positive results only with metabolic activation (NTP 1989), while another showed positive results both with and without activation (Milman et al. 1988). Results in mammalian cells *in vitro* are inconsistent. Chloroethane was positive for gene mutation in Chinese hamster ovary cells exposed to 625–2,480 µg/mL chloroethane (Ebert et al. 1994), whereas negative results were reported for chloroethane in a cell transformation assay using mouse BALB/c-3T3 cells (up to 467 µg/mL) (Tu et al. 1985) and in a DNA repair synthesis assay using mouse primary hepatocytes at the highest nontoxic concentration (Milman et al. 1988; Williams 1983).

Existing data are inconclusive concerning the genotoxicity of chloroethane. Additional genotoxicity tests are needed to determine whether it is possible that chloroethane is genotoxic in humans.

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

3.1 TOXICOKINETICS

A single volunteer study provides limited quantitative information on absorption and excretion. No additional human studies were located. Chloroethane toxicokinetic studies in rats and mice provide limited qualitative data for absorption and distribution and some quantitative data on metabolism and excretion. In summary:

- Chloroethane is readily absorbed following inhalation exposure in humans, rats and mice and oral exposure in rats. Following a 30-second inhalation exposure in humans, approximately 82% of the inhaled dose was retained in the body. The extent of absorption was not quantified in studies using rats and mice. The dermal absorption potential is low, as indicated by the estimated dermal flux rate of 0.99 mg/cm^2 hour.

- Rat partition coefficients indicate that chloroethane, once absorbed, would have a greater affinity for fat than for muscle or the liver. Distribution was widespread in rats following inhalation and oral exposure, with the highest concentrations found in ovaries, adrenals, fat, and skin.

- In rats and mice, the two major pathways of chloroethane metabolism are the production of acetaldehyde by cytochrome P450 (CYP), and conjugation of chloroethane with GSH to form S-ethyl-glutathione.

- Acetaldehyde is rapidly metabolized to acetic acid. The GSH metabolites are further metabolized to S-ethyl-L-cysteine in mice and S-ethyl-N-acetyl-L-cysteine in both rats and mice. GSH conjugate metabolites of chloroethane (i.e., mercapturic acids) are detected in the urine of rats and mice.

- Following a 30-second inhalation exposure in humans, 30% of the retained dose was excreted in expired air in the first hour. The rate of urinary excretion in the first hour was described as slow (i.e., <0.01% per minute).

- In animals exposed to relatively low concentrations or doses of chloroethane, excretion as exhaled CO_2 predominates, suggesting complete metabolism. At higher concentrations or doses in rats, where metabolism is saturated, exhalation of unchanged chloroethane is the primary excretion pathway. A similar pattern is observed in mice following exposure to high oral doses (i.e., exhalation of chloroethane is predominant); however, a shift towards higher urinary excretion of chloroethane metabolites occurs following inhalation of high concentrations in mice.

3.1.1 Absorption

Chloroethane is readily absorbed following inhalation exposure in humans, rats, and mice and oral exposure in rats (Dobkin and Byles 1971; Dow 1992; Finer 1966; Konietzko 1984; Lawson 1965;

Lehmann and Flury 1943; Morgan et al. 1970; Torkelson and Rowe 1981). Inhalation absorption of chloroethane is rapid in humans, which is demonstrated by the rapidity of anesthesia in humans following inhalation exposure (Dobkin and Byles 1971; Finer 1966; Lawson 1965). Human subjects were exposed to about 5 mg ^{38}Cl-labeled chloroethane for 30 seconds by taking one breath through the mouth and then holding it for 30 seconds (Morgan et al. 1970). Approximately 18% of the radioactivity was exhaled in the first two breaths, indicating that about 82% was retained.

Chloroethane is readily absorbed through the lungs and gastrointestinal tract in laboratory animals; however, the extent of absorption has not been quantified (Dow 1992; Konietzko 1984; Lehmann and Flury 1943; Torkelson and Rowe 1981). A dermal flux rate of 0.99 mg/cm^2/hour was estimated based on the physical-chemical properties of chloroethane (Fiserova-Bergerova et al. 1990). Based on the estimated dermal flux rate, the study authors considered chloroethane to have no significant dermal absorption potential. No quantitative studies were located regarding absorption in humans or animals following dermal exposure to chloroethane.

3.1.2 Distribution

Representative partition coefficients for chloroethane in humans, rats, and mice are provided in Table 3-1. These partition coefficients were measured *in vitro* using a vial equilibration method. The data for rats indicate that chloroethane has a higher affinity for fat than for blood, liver, or muscle (Gargas et al. 1989).

Table 3-1. Chloroethane Partition Coefficients

			Partition coefficient			
Species	Strain	Sex	Blood/air	Liver/air	Muscle/air	Fat/air
Human[a]	NA	NR	1.9	–	–	–
Human[b]	NA	NR	2.69±0.20	–	–	–
Rat[b]	Fischer 344	M	4.08±0.39[c]	3.61±0.32	3.22±0.68	38.6±0.7
Mouse[d]	B6C3F1	F	5.1±1.8	–	–	–

[a]Morgan et al. 1970.
[b]Gargas et al. 1989.
[d]This value was adjusted to 5.5 using the Gargas et al. (1990) PBPK model.
[c]Gargas et al. 2008.

– = no data; F = female; M = male; NA = not applicable; NR = not reported; PBPK = physiologically based pharmacokinetic

Distribution was widespread in rats following inhalation and oral exposure, with the highest concentrations found in ovaries, adrenals, fat, and skin (Dow 1992). In female Fischer 344 rats and B6C3F1 mice exposed to ^{14}C-chloroethane by inhalation (15,000 ppm for 6 hours) or gavage (single dose of 37 or 1750 mg/kg in corn oil), detectable levels of radioactivity were found in all organs examined (adrenal, blood, brain, fat, heart, liver, lung, muscle, kidney, ovary, uterus, skin, and remaining carcass) (Dow 1992). The highest levels of radioactivity were found in the ovaries, adrenals, fat (oral exposure only), and skin (inhalation exposure only). No accumulation was found in the uterus of rats or mice following inhalation or oral exposure.

Review articles provided some additional information about the distribution of chloroethane; however, the species in which the information was obtained was not stated (Konietzko 1984; Lehmann and Flury 1943). In the blood, approximately 75% of the chloroethane is bound to red blood cells and 25% is in the plasma (Konietzko 1984). The highest concentration of chloroethane in the animal body was found in fatty tissue around the kidney and the lowest was found in the cerebrospinal fluid (Konietzko 1984). The brain was said to accumulate a concentration 2 times that of the blood. Lehmann and Flury (1943) reported that chloroethane content in the brain and medulla oblongata was especially high.

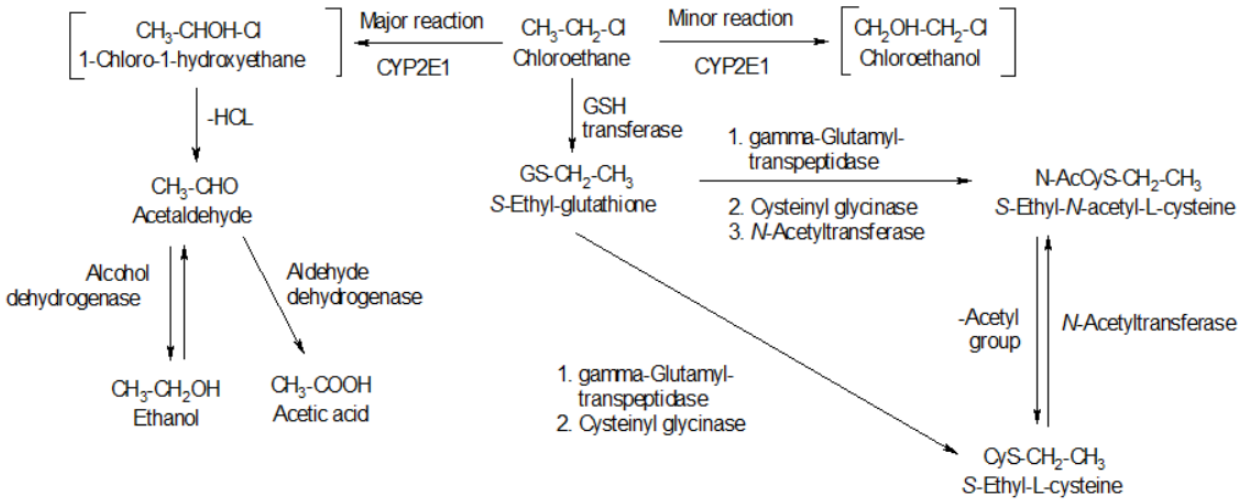
One study determined that chloroethane can be detected in the breast milk of nursing mothers (Pellizzari et al. 1982). The study was not quantitative and did not offer data concerning the percentage of nursing mothers that might excrete the compound in milk after exposure. It did not provide a range of concentrations of the compound in this medium. No studies were identified that determined if chloroethane was stored in maternal tissues. However, the rapid clearance of chloroethane, as well as its volatility, suggest that it would not be stored within the body for an extended period of time, so preconception maternal exposure is not likely to result in exposure to children during gestation or lactation.

3.1.3 Metabolism

Although no studies were located regarding metabolism of chloroethane by humans, the proposed metabolic pathways for chloroethane in rats and mice (Fedtke et al. 1994b; Figure 3-1) are relevant for humans. The two major pathways are the production of acetaldehyde by CYP and the conjugation of chloroethane with GSH to form S-ethyl-glutathione.

The metabolism of chloroethane to acetaldehyde was studied *in vitro* using livers from rats and mice exposed to chloroethane at 0 or approximately 15,000 ppm 6 hours/day for 5 days (Fedtke et al. 1994a). The amounts of acetaldehyde detected ranged from 26.9 to 49.3% of the chloroethane metabolized, depending on pre-exposure to chloroethane, for the individual microsome preparations from rats and mice. The investigators found that exposure to chloroethane induced its own metabolism by approximately 100% in mice and female rats, with no effect in male rats. Based on studies using specific CYP enzyme inducers and inhibitors, the investigators concluded that CYP2El was responsible for chloroethane metabolism. CYP2E1 also metabolizes alcohols, aldehydes, and ketones, and plays a role in gluconeogenesis within the body (Vieira et al. 1996). Most acetaldehyde is rapidly metabolized to acetic acid by aldehyde dehydrogenase; a small portion may be reduced by alcohol dehydrogenase to ethanol. Therefore, increased acetaldehyde relative to normal levels was not detected in the serum of chloroethane-exposed rats or mice (15,000 ppm) or in the urine of exposed rats (Fedtke et al. 1994a). Small increases in acetaldehyde were detected in the urine of chloroethane-exposed mice (Section 3.1.4, Excretion). Except for the approximately 3-fold greater metabolism of chloroethane in mice compared to rats, there was little difference between the species.

Figure 3-1. Metabolic Pathways for Chloroethane Biotransformation



Source: Fedtke et al. (1994b)

[ ] = known metabolites that were not detected in the referenced study; GSH = glutathione

GSH levels were studied in rats and mice exposed to chloroethane at 0 or 15,000 ppm 6 hours/day for 5 days (Dow 1992; Fedtke et al. 1994b). The animals were sacrificed immediately after the last exposure.

Compared to controls, GSH concentrations were significantly decreased in exposed animals. The significant GSH decreases occurred in the livers of male rats, in the kidneys of female rats, in the lungs of both sexes of rats and mice, and in the uterus of both rats and mice that were exposed to 15,000 ppm. The decreases in GSH levels were greatest in chloroethane exposed animals, particularly in the uterus of both species and in the lungs of mice, in which levels were approximately two-thirds lower than in controls (Fedtke et al. 1994b). Exposure to 15,000 ppm for 6 hours depleted tissue GSH levels to a greater extent in female mice than in female rats (Table 3-2); however, the species differences were less pronounced in the uterus and ovary compared to the liver, kidney, brain, and lung (Dow 1992). The time course of hepatic GSH depletion from chloroethane exposure demonstrated rapid depletion and recovery in female mice. Hepatic GSH depletion occurred more slowly in female rats; however, the rate of recovery was similar to mice, showing complete recovery by 18 hours after chloroethane exposure. Chloroethane exposure did not exhibit species differences for the rates of kidney and uterine GSH depletion and recovery. GSH depletion was not observed in rats and mice exposed to 150 or 3,000 ppm chloroethane for 6 hours (Dow 1992).

Table 3-2. Glutathione Depletion in Tissues of Female Fischer 344 Rats and B6C3F1 Mice Exposed to 15,000 ppm Chloroethane for 6 Hours

	Percent decrease in glutathione levels	
Tissue	Rats	Mice
Liver	35	79
Kidney	22	41
Brain	10	20
Lung	21	68
Ovary	43	44
Adrenal	68	32
Uterus	32	45

Source: Dow 1992

In vitro studies of chloroethane conjugation to GSH, using liver cytosolic fractions from control and chloroethane-exposed rats and mice, indicated that the conjugation was catalyzed by glutathione-S-transferase enzymes (Fedtke et al. 1994b). GSH conjugation rates, in nmol chloroethane conjugated/minute mg protein, were greater in mice (0.71±0.19 in males; 1.01±0.19 in females) than in rats (0.17±0.19 in males; 0.16±0.03 in females). Chloroethane exposure had no effect on these rates in rats and slightly decreased the rates in mice. When urine was analyzed for GSH metabolites, S-ethyl-N-acetyl-L-cysteine was detected in both rats and mice. However, only S-ethyl-L-cysteine was detected

in the urine of mice. The total amount of GSH metabolites excreted during the 5-day exposure period was about 5-fold higher in mice than in rats. The study authors concluded that rats completely metabolized S-ethyl-L-cysteine to more hydrophilic metabolites before urinary excretion, while these metabolic pathways were not available to the same extent in mice under the conditions of this study.

After GSH conjugation of chloroethane, three other enzymes convert the conjugate to a more hydrophilic form to be excreted by the body. These enzymes are γ-glutamyltranspeptidase, cysteinyl glycinase, and N-acetyltransferase (NAT) (Sipes and Gandolfi 1991). These three enzymes convert relatively hydrophobic GSH conjugates to their respective mercapturic acids, which can be excreted more readily.

The metabolic rates for chloroethane were estimated for male Fischer 344 rats using a gas uptake method (Gargas et al. 1990) (Table 3-3). The rats were exposed to an initial concentration of 100, 535, 1,200, or 2,350 ppm, and the disappearance of the gas was studied for about 5 hours. A physiologically based pharmacokinetic (PBPK) model that assumed metabolism occurred exclusively in the liver was used to analyze the data. The metabolism of chloroethane was best described by a combination of a saturable pathway and a first-order pathway.

Table 3-3. Estimates of Metabolic Parameters Obtained from Gas Uptake Experiments in Male Fischer 344 Rats

V_{maxc}, mg/hour*kg	4.0
V_{maxc}, µmol/hour	62.0
K_m, mg/L	0.1
K_m, µM	1.55
k_{tc}, $hour^{-1}*kg^{-1}$	1.0

V_{maxc} = maximum reaction velocity (scaled to 1 kg animal); K_m = concentration at ½ V_{max} (Michaelis constant); k_{tc} = first-order rate constant (scaled to 1 kg animal)

Source: Gargas et al. 1990

3.1.4 Excretion

Excretion of chloroethane by the lungs is rapid in humans and animals (Konietzko 1984; Lehmann and Flury 1943; Torkelson and Rowe 1981). In animals exposed to relatively low concentrations or doses of chloroethane, excretion as exhaled CO_2 predominates, suggesting complete metabolism (Dow 1992). At higher concentrations or doses in rats, where metabolism is saturated, exhalation of unchanged chloroethane is the primary excretion pathway (Dow 1992). A similar pattern is observed in mice

following exposure to high oral doses (i.e., exhalation of chloroethane is predominant); however, a shift towards higher urinary excretion of chloroethane metabolites occurs following inhalation of high concentrations in mice (Dow 1992).

In humans exposed briefly by inhalation to chloroethane, 30% of the retained dose was excreted in the breath within 1 hour (Morgan et al. 1970). Excretion over a longer period of time could not be measured because of the short half-life of the ^{38}Cl radioisotope used in this study. Morgan et al. (1970) found that the rate of excretion of radioactivity in the urine of humans was very slow (i.e., <0.01% per minute) 1 hour after inhalation.

The excretion pattern was similar in rats and mice exposed to 150 ppm for 6 hours, with the highest percentage of radioactivity recovered as expired CO_2, followed by tissues and carcass, urine, and feces (Table 3-4). Less than 2% was found as unchanged chloroethane in expired air in animals exposed to 150 ppm, suggesting that most of the radioactivity was eliminated as metabolites at this concentration. Exposure to 15,000 ppm chloroethane caused a shift in the excretion pattern which differed in rats and mice. In rats, the highest percentage of radioactivity was recovered as unchanged chloroethane; decreases in recovered radioactivity were observed in expired CO_2, urine, feces, and tissue/carcass compared to the 150-ppm group. In mice, expired chloroethane was also increased, but to a much lesser extent than seen in rats (i.e., 60-fold in rats versus 4-fold in mice). The time course of excretion was characterized by rapid exhalation of unchanged chloroethane (i.e., within the first hour). Exhalation as ^{14}C-CO_2 occurred primarily during the first 12 hours, while urinary excretion occurred over the first 24 hours.

Table 3-4. Excretion of Chloroethane and Metabolites Following Inhalation Exposure in Female Fischer 344 Rats and B6C3F1 Mice

	Percent of recovered radioactivity 48 hours after a 6-hour inhalation exposure	
Media	150 ppm	15,000 ppm
Rats		
Expired chloroethane	1.12	62.81
Expired CO_2	53.57	19.17
Urine	9.66	8.68
Feces	3.15	1.60
Tissues and carcass	32.03	7.64
Total	99.53	99.90

Table 3-4. Excretion of Chloroethane and Metabolites Following Inhalation Exposure in Female Fischer 344 Rats and B6C3F1 Mice

	Percent of recovered radioactivity 48 hours after a 6-hour inhalation exposure	
Media	150 ppm	15,000 ppm
Mice		
Expired chloroethane	1.72	6.96
Expired CO_2	41.76	31.80
Urine	15.86	38.37
Feces	6.02	7.05
Tissues and carcass	34.65	16.02
Total	100.01	100.20

Source: Dow 1992

Following single gavage exposures of 57 mg/kg in Fisher 344 rats or 37 mg/kg in B6C3F1 mice, the excretion pattern suggested more excretion as unchanged chloroethane in rats compared to mice and more excretion as expired ^{14}C-CO_2 in mice compared to rats (Table 3-5). Repeated administration of 37 mg/kg for eight daily doses in mice showed a similar excretion pattern as seen after a single gavage dose. Administration of a higher oral dose (1,999 mg/kg in rats, 1,970 mg/kg in mice) enhanced the excretion of unchanged chloroethane in expired air in both species, suggesting that metabolic pathways may be saturated at high doses. The time course of excretion was similar for oral and inhalation exposure with unchanged chloroethane excreted within the first hour, exhalation as ^{14}C-CO_2 occurring primarily during the first 12 hours and urinary excretion occurring over the first 24 hours.

Table 3-5. Excretion of Chloroethane and Metabolites Following Oral Exposure in Female Fischer 344 Rats and B6C3F1 Mice

Media	Percent of recovered radioactivity 48h after oral gavage dosing	
Rats (single dose)	57 mg/kg	1,998 mg/kg
Expired chloroethane	42.78	84.28
Expired CO_2	40.34	4.53
Urine	2.09	0.81
Feces	0.77	0.19
Tissues and carcass	7.04	0.76
Total	93.02	90.57

Table 3-5. Excretion of Chloroethane and Metabolites Following Oral Exposure in Female Fischer 344 Rats and B6C3F1 Mice

Media	Percent of recovered radioactivity 48h after oral gavage dosing		
Mice	34 mg/kg (single dose)	37 mg/kg (eight daily doses)	1,970 mg/kg (single dose)
Expired chloroethane	16.75	13.82	73.60
Expired CO_2	60.82	64.29	9.62
Urine	2.88	2.93	1.68
Feces	1.44	1.19	0.37
Tissues and carcass	7.02	5.80	1.14
Total	88.91	88.03	86.41

Source: Dow 1992

Small increases in acetaldehyde were detected in the urine of chloroethane-exposed mice but not rats (Fedtke et al. 1994a). Acetaldehyde concentrations in the urine were 7.9–20.3 and 0–18.1 µmol/L, respectively, in control male and female mice and 15.4–70.1 and 11.6–17 µmol/L, respectively, in mice exposed to 15,000 ppm chloroethane for 6 hours. Acetaldehyde is rapidly metabolized to acetic acid; therefore, it would be difficult to detect in whole animal studies. GSH conjugates have also been detected in the urine of rats and mice exposed to chloroethane (Fedtke et al. 1994b). Rats excreted the more hydrophilic S-ethyl-N-acetyl-L-cysteine, while mice excreted both S-ethyl-N-acetyl-L-cysteine and S-ethyl-L-cysteine. During the 5 days that rats and mice were exposed to chloroethane at 15,000 ppm for 6 hours/day, the total amount of GSH metabolites excreted in the urine was about 5-fold higher in mice than in rats.

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

Models are simplified representations of a system with the intent of reproducing or simulating its structure, function, and behavior. PBPK models are more firmly grounded in principles of biology and biochemistry. They use mathematical descriptions of the processes determining uptake and disposition of chemical substances as a function of their physicochemical, biochemical, and physiological characteristics (Andersen and Krishnan 1994; Clewell 1995; Mumtaz et al. 2012a; Sweeney and Gearhart 2020). PBPK models have been developed for both organic and inorganic pollutants (Ruiz et al. 2011) and 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 (Mumtaz et al. 2012b; Ruiz et al. 2011; Sweeney and Gearhart 2020; Tan et al. 2020). PBPK models can also be used to more accurately extrapolate from animal to human,

high dose to low dose, route to route, and various exposure scenarios and to study pollutant mixtures (El-Masri et al. 2004). 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 (Clewell 1995).

Gargas et al. 1990

Gargas et al. (1990) used a rat dosimetry model to analyze gas uptake curves from closed-chamber exposures to chloroethane. Three rats placed in a closed chamber were exposed to target concentrations of 100, 535, 1,200, or 2,350 ppm chloroethane for 3–6 hours. The chamber atmosphere was sampled every 10 minutes and analyzed by gas chromatography to monitor the time course of gas uptake. The series of uptake curves was analyzed using the rat dosimetry model which included physiological parameters (body and organ weights, alveolar ventilation blood flow) and blood and tissue solubility as reported by Gargas et (1989). The dosimetry model included compartments for fat, liver, other rapidly perfused tissues (i.e., adrenals, kidney, brain, uterus, ovaries, and testes) and slowly perfused tissues. Metabolism was assumed to occur solely in the liver and the mass balance equation accounted for saturable metabolism, defined by V_{maxc} and $K_{m,}$ and a first order rate constant (k_{tc}) (Table 3-3). Chamber uptake curves were simulated and compared to the experimental data. Kinetic constants were adjusted, and simulations were repeated to obtain an adequate visual fit and computer optimization was performed by varying V_{maxc} and k_{tc} values until the best least-square fit was achieved.

Chloroethane metabolism was described as a combination of saturable and first-order processes. Uptake kinetics in rats exposed to a chamber concentration of 600 ppm were significantly altered by pretreatment with pyrazole. Analysis using the PBPK model showed near complete inhibition of oxidative CYP metabolism by pyrazole pretreatment.

Gargas et al. 2008

Gargas et al. (2008) expanded the existing PBPK model for rats (Gargas et al. 1990) and developed chloroethane PBPK models for mice and humans (women) to facilitate species comparisons. Tissue compartments represented in the model include gas exchange in the lung, fat, adrenals, kidneys, brain, uterus, ovaries/testes, liver, other richly perfused tissues, and slowly perfused tissues. The tissue:blood partition coefficients for mice and humans were calculated by dividing the rat tissue:air partition

coefficients by the mouse or human blood air partition coefficients. Blood:air partition coefficients for rats, mice, and humans are shown in Table 3-1 (Gargas et al. 1989, 1990, 2008).

Oxidative metabolism by CYP was saturable with respect to chloroethane concentration and GSH conjugation was considered saturable with respect to both chloroethane concentration and GSH level. Tissue GSH concentrations were evaluated as a balance between zero-order synthesis or delivery and first order loss due to use (i.e., GSH conjugation), degradation, or export. Reported tissue levels of GSH (liver, kidney, brain, ovary, adrenal gland, and uterus) and GSH depletion data (Dow 1992) were used to calculate GSH-conjugation rates for rats and mice. GSH levels and conjugation rates in humans were estimated using a parallelogram method. Parameter fitting for oxidative (mouse only) and GSH metabolism (rats and mice) was accomplished using closed chamber uptake (Gargas et al. 1990) and GSH depletion data (Dow 1992). Validation of the rat and mouse models was accomplished by comparing measured (Fedtke et al. 1994b; Landry et al. 1982) and model-predicted GSH values in the liver, kidney, and uterus. Predicted GSH values were reasonably accurate following a single chloroethane exposure but were somewhat less accurate following repeated exposure. Limited data are available for validating the human model. The volunteer study of chloroethane uptake and retention (Morgan et al. 1970) was used for this purpose and modeled estimates of retention were similar to the measured values.

Species comparisons using the rat, mouse, and human models predict CYP saturation to occur at 200–500 ppm chloroethane in rats, >1,000 ppm in mice, and between 1,000 and 3,000 ppm in humans. Saturation of GSH metabolism is predicted to occur between 6,000 and 9,000 ppm in all three species. Mice were predicted to produce more GSH metabolites of chloroethane, compared to rats and humans. The PBPK modeling results are consistent with the hypothesis that a GSH-derived metabolite of chloroethane, formed via oxidation by CYP (likely producing acetaldehyde), and conjugation with GSH may be involved with the mode of action for uterine tumors in mice. Model limitations include the small number of animals used for the closed chamber uptake experiments and the inability of the GSH submodel to account for an increase in GSH levels that exceed initial concentrations. In addition, validation of the human model is limited by the availability of human data.

3.1.6 Animal-to-Human Extrapolations

Inhalation absorption of chloroethane and excretion in expired air and urine occurs in humans, rats, and mice. Data are not available to compare the extent of absorption or excretion in humans and animals. The distribution and metabolism of chloroethane have not been studied in humans. A PBPK model was

developed to compare the internal dosimetry of chloroethane following inhalation in rats, mice, and humans (Gargas et al. 2008); however, limited data were available to validate the human model.

Animals and humans appear to have similar respiratory, cardiovascular, and neurological toxicity. Stimulation of the respiratory rate was seen in humans and guinea pigs (Cole 1967; USBM 1929). Stimulation of the vagus nerve and cardiac depression was observed in humans and dogs (Bush et al. 1952). The symptoms of intoxication and the anesthetic properties of chloroethane were similar in humans, guinea pigs, and dogs (Bush et al. 1952; Davidson 1925; Demarest et al. 2011; Morris et al. 1953; USBM 1929). Animal data are extensive for respiratory, cardiovascular, and neurological effects; however, data in humans are limited to case reports of poisoning following use as a recreational inhalant and reports of chloroethane used as a local or general anesthetic.

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 chloroethane are discussed in Section 5.7, Populations with Potentially High Exposures.

There are limited reports concerning children being exposed to chloroethane. Effects observed in humans exposed to chloroethane have resulted primarily from inhalation exposure. Respiratory paralysis was reported to be the cause of death of a 14-year-old child who died during anesthesia with chloroethane (Kuschinsky 1970); however, the concentration of chloroethane administered was not known. Another

study reported vagal stimulation in children briefly exposed to reportedly high concentrations of chloroethane; the specific levels were not indicated (Bush et al. 1952).

Chloroethane has also been used and sometimes misused as a topical anesthetic in both children and adults (Nibhanipudi 2015; Noble 1979; Ramsook et al. 2001; Soueid and Richard 2007; van Ketel 1976). Misuse occurs when excessive amounts of chloroethane are sprayed on the skin for long periods of time. Three children suffered frostbite on the exposed skin of their ears and necks after having their earlobes sprayed with chloroethane for several minutes (Noble 1979).

Effects seen in adults exposed to chloroethane are also expected in children. In particular, the nervous system is likely to be a sensitive target of chloroethane, as it is in adults. Since infants and young children have a larger proportion of their bodies as brain mass with a greater cerebral blood flow than adults (Swenberg et al. 1992), the pharmacokinetics indicate a higher potential for chloroethane to reach the brain of a child. Infants and young children (ages not specified) would therefore be more susceptible to the anesthetic effects of chloroethane than adults.

No studies were identified that reported effects in adults from chloroethane exposure that occurred during childhood. There is no information on the health effects of exposures in young animals after birth. There are no data concerning the effects of chloroethane exposure on human development and there are only two developmental studies in animals (Dow 1985; Scortichini et al. 1986). Inhalation of chloroethane doses (≤4,946 ppm) during GDs 6–15 were not maternally toxic, although a trend for an increased incidence of mouse fetuses with increased skull foramina was observed (Scortichini et al. 1986). Dow (1985) reported that the fetuses exposed *in utero* (GDs 6–15) to 5,000 ppm appeared normal; however, fetuses were not examined for skeletal or visceral alterations.

There are no data available concerning the pharmacokinetics of chloroethane in children. There are no human or animal studies available concerning the ability of chloroethane or its metabolites to reach and cross the placenta.

One study determined that chloroethane is present in the breast milk of nursing mothers (Pellizzari et al. 1982). The study was not quantitative and did not offer data concerning the percentage of nursing mothers who might excrete the compound in milk after exposure. Further, the study did not provide a range of concentrations of the compound in this medium.

No studies were identified that determined if chloroethane was stored in maternal tissues. However, the rapid clearance of chloroethane, as well as its volatility, suggest that it would not be stored within the body for an extended period of time, so preconception maternal exposure is not likely to result in exposure to children during gestation or lactation.

No data are available to indicate that distribution of chloroethane is different in children. However, chloroethane distribution may be very different in children relative to adults due to the difference in fat and water content and lean body mass in children. Physical-chemical properties of chloroethane indicate that it would be readily soluble in fat. In the newborn and young infant, fat tissue is relatively scarce (15% of body weight) (Morselli et al. 1980) as compared to an adult, indicating that distribution of lipophilic chloroethane will differ in infants and young children relative to adults. In addition, infants and younger children have much more water (total body and extracellular) relative to body weight than adults. Given this, the distribution of water-soluble compounds, such as chloroethane metabolites, will differ in children as compared with adults (Morselli et al. 1980).

No data are currently available to indicate that the metabolism of chloroethane is different in children when compared to adults. However, the chloroethane metabolism scheme has enzyme families that are developmentally regulated. Chloroethane is metabolized by both CYP and by glutathione S-transferase. Studies have shown that liver glutathione S-transferase activities are low in prepubertal male and female rats, but as the rats reach sexual maturity (at around 30–50 days of age), GSH-conjugating activity is 2–3-fold higher in males than females (Lamartiniere and Lucier 1983). The difference in glutathione S-transferase activity was dependent on pituitary secretions. Further research on hypophysectomized male and female rats revealed that growth hormones may contribute to the establishment of glutathione S-transferase activities (Lamartiniere 1981). No data are available to indicate that glutathione S-transferase activity is also developmentally or sexually expressed in humans.

During the process of metabolism, NAT enzymes may convert the chloroethane conjugate to a less hydrophilic form, allowing it to be excreted (Sipes and Gandolfi 1991). There are two NAT enzyme families, NAT 1 and NAT2. Of these enzymes, only NAT2 is developmentally regulated. It is unknown which NAT enzyme metabolizes chloroethane; therefore, it is unknown whether chloroethane is developmentally regulated by this pathway.

Studies have shown that CYP2E1 is developmentally expressed in humans (Vieira et al. 1996). This enzyme is not detectable from livers of fetuses at 14–40 gestational weeks. However, the level of the

protein rises sharply in the first day after birth (1 unit/mg protein) and continues to increase until it reaches adult values of approximately 5 units/mg protein, in children from 1 to 10 years of age (Vieira et al. 1996).

It is unknown whether children differ from adults in their susceptibility to chloroethane, despite the theoretical reasons for which they might potentially differ, as discussed above.

In humans, there are no data concerning parental exposure affecting children, including preconception exposure. There are no data concerning preconception exposure of either parent to germ line mutations, developmental defects, childhood cancer, or other health effects in humans. Chloroethane is mutagenic in bacterial and mammalian cells incubated *in vitro*. However, chloroethane is negative for mutagenicity of mammalian cells *in vivo*. These inconclusive results do not allow the prediction of chloroethane genotoxicity in humans.

No population has been identified that is unusually susceptible to toxic effects resulting from chloroethane exposure. Since chloroethane is metabolized by CYP2E1 (Fedtke et al. 1994b), it is possible that individuals with polymorphisms in CYP2E1 may be more susceptible to toxic effects of chloroethane. Also, CYP2E1 is induced in people who frequently drink alcohol, as well as people with medical conditions such as diabetes. Therefore, populations that frequently drink alcohol or have diabetes, may be more susceptible to effects of chloroethane.

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 2006).

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 2006). 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 chloroethane are discussed in Section 3.3.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 2006). 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 chloroethane 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

Chloroethane levels can be measured in the blood with a limit of detection of 0.045 µg/L. These measurements were added to the National Health and Nutrition Examination Survey (NHANES) study in 2013 to evaluate exposure in the U.S. population (CDC 2017, 2018, 2020). Because a portion of the chloroethane inhaled is exhaled, measurement of chloroethane in breath may also serve as a useful biomarker of exposure.

In rats and mice, chloroethane is metabolized to acetaldehyde and the GSH conjugates, S-ethyl-N-acetyl-L-cysteine and S-ethyl-L-cysteine (Fedtke et al. 1994a, 1994b). The GSH conjugates, S-ethyl-N-acetyl-E-cysteine and S-ethyl-L-cysteine, would not be biomarkers unique to chloroethane exposure. Acetaldehyde forms adducts with plasma proteins. Ethanol is also metabolized to acetaldehyde; thus, measurement of adducts, or of antibodies produced in response to these adducts, would also indicate ethanol exposure (Worrall et al. 1994); these therefore would not be a specific biomarker for chloroethane.

3.3.2 Biomarkers of Effect

Clinical signs of toxicity in volunteers exposed to 13,000–20,000 ppm chloroethane for short exposure durations include neurological (e.g., intoxication) and gastrointestinal effects (e.g., abdominal cramps and vomiting) (Davidson 1925; USBM 1929). Anesthesia occurs in humans by inhalation of chloroethane at a concentration of approximately 40,000 ppm (Dobkin and Byles 1971). Other effects reported at anesthetic concentrations include cardiac irregularities, respiratory paralysis, and nausea. Since these effects occur following exposure to many chemicals, they would not serve as useful biomarkers for chloroethane exposure.

3.4 INTERACTIONS WITH OTHER CHEMICALS

In the past, chloroethane, combined with nitrous oxide and oxygen, was used to maintain anesthesia in patients previously made unconscious by administration of either thiopentone (thiopental), nitrous oxide, or a mixture of nitrous oxide, chloroethane, and oxygen (Cole 1956). A concentration of 20,000 ppm chloroethane was initially required to maintain anesthesia, but this could slowly be reduced to as low as 5,000 ppm in some cases. Anesthesia could be maintained up to an hour using chloroethane in this manner. In a similar study using 36,000 ppm chloroethane, the length of time required to recover from anesthesia varied from 3 to 15 minutes in 33 subjects (Cole 1967). Vomiting occurred in 10 of 23 patients who were anesthetized with 36,000 ppm chloroethane combined with nitrous oxide and oxygen (Cole 1967).

A study in cats demonstrated that the extent of methemoglobinemia induced by intravenous administration of aniline was significantly reduced in cats anesthetized with chloroethane compared to unanesthetized cats (McLean et al. 1967). The rate at which the methemoglobin disappeared, however, was also significantly reduced in the anesthetized cats compared with unanesthetized cats. The results suggest that concurrent exposure to aniline and chloroethane may induce less methemoglobin than exposure to aniline alone, but the methemoglobin induced by the combined exposure would persist longer than that induced by exposure to aniline alone. A similar effect was not observed when cats were anesthetized with chloralose and treated with phenylhydroxylamine, the aniline metabolite that results in methemoglobin formation. Therefore, the study authors concluded that chloralose acts by inhibiting the metabolism of aniline. It is not known if chloroethane acts in the same manner.

No studies were available investigating the interactions of chloroethane with other chemicals in children or in adults.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of chloroethane is presented in Table 4-1.

Table 4-1. Chemical Identity of Chloroethane

Characteristic	Information	Reference
Chemical name	Ethyl chloride; chloroethane	Lide 2005
Synonym(s) and registered trade name(s)	Aethylis; chloridum; chlorethyl; ether chloratus; ether hydrochloric; ether muriatic; ethyl chloride; monochloro-ethane; Anodynon; Chelen; chloryl anesthetic; Kelene; Narcotile	NLM 2023
Chemical formula	C_2H_5Cl	Budavari et al. 1989
SMILES	CCCl	NLM 2023
Chemical structure	$CH_3–CH_2–Cl$	Lide 2005
CAS Registry Number	75-00-3	NLM 2023

CAS = Chemical Abstracts Service; SMILES = simplified molecular-input line-entry system

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of chloroethane is presented in Table 4-2.

Table 4-2. Physical and Chemical Properties of Chloroethane

Property	Information	Reference
Molecular weight	64.52 g/mol	Budavari et al. 1989
Color	Colorless	Morris and Tasto 1979
Physical state	Gas	Budavari et al. 1989
Melting point	-138.7°C	Budavari et al. 1989
Boiling point	32.5°C at 2 atm; 12.3°C at 760 torr	Budavari et al. 1989, 1996
Specific gravity at 0°C	0.9214	Budavari et al. 1996
Density at 20°C	0.8970	Morris and Tasto 1979
Odor	Ethereal, pungent	NLM 2023
Odor threshold:		
Water	0.019 ppm (w/v)	Amoore and Hautala 1983
Air	4.2 ppm (v/v) (11.3 g/L)	Amoore and Hautala 1983

Table 4-2. Physical and Chemical Properties of Chloroethane

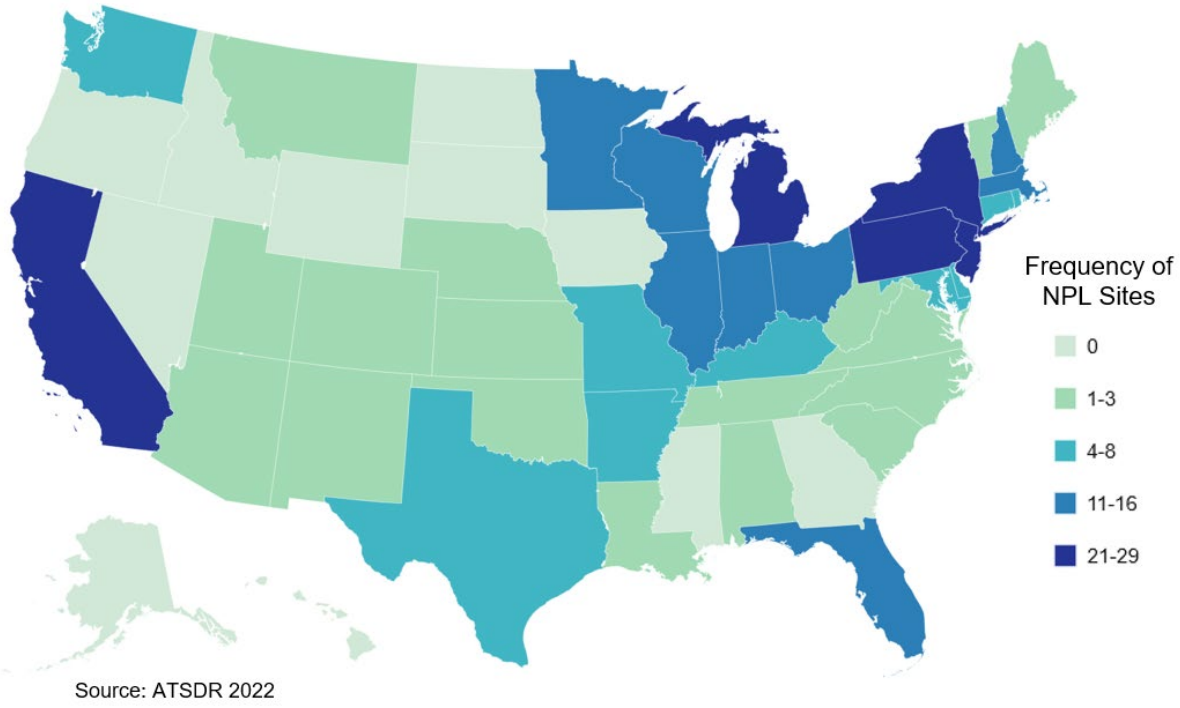
Property	Information	Reference
Solubility:		
Water at 20°C	0.574 g/100 mL	Budavari et al. 1989
Organic solvents	Alcohol: 48.3 g/100 mL	Budavari et al. 1989
Partition coefficients:		
Log K_{ow}	1.43	NLM 2023
Log K_{oc}	1.52 (estimated using equation 4–7)	Lyman 1982
K_{oc}	143; 33 (using log K_{oc} of 1.52)	Lyman 1982
Vapor pressure at 20°C	1,008 mmHg	Daubert and Danner 1985
Henry's law constant at 25°C	$1.11x10^{-2}$ atm•m^3/mole (24.8 C)	Gossett 1987
Autoignition temperature	519°C	Morris and Tasto 1979
Flashpoint		
Open cup	-43°C	Budavari et al. 1989
Closed cup	-50°C	Budavari et al. 1989
Conversion factors:		
ppm (v/v) to mg/m^3 in air (20°C)	ppm (v/v) x 2.68 = mg/m^3	Budavari et al. 1989
mg/m^3 to ppm in air (20°C)	mg/m^3 x 0.373 = ppm (v/v)	Budavari et al. 1989
Explosive limits in air	3.6–14.8 volume %	Budavari et al. 1989

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Chloroethane has been identified in at least 315 of the 1,868 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2022a). However, the number of sites in which chloroethane has been evaluated is not known. The number of sites in each state is shown in Figure 5-1.

Figure 5-1. Number of NPL Sites with Chloroethane Contamination



- Ambient air may contain chloroethane since there are fugitive emissions from use of chloroethane as a chemical intermediate. Ambient air and possible consumption of contaminated drinking groundwater are the primary sources of exposure to the general population.
- Exposure can also occur from the direct use of chloroethane as a topical anesthetic.
- People have also been known to intentionally inhale chloroethane vapors from commercial products for its narcotic effects.
- Occupational exposure where chloroethane is manufactured and used is likely to result in higher exposures than for the general population.

- Since chloroethane has a very high vapor pressure and Henry's law constant it is expected to exist primarily in the vapor phase. In the atmosphere, the main degradation pathway will be through its reaction with photochemically generated hydroxyl radicals.
- If released to soil or water, chloroethane is expected to volatilize rapidly but it may leach into groundwater since it is expected to possess high mobility in soil.
- Degradation in soil and water may occur through both biotic and abiotic mechanisms.

Chloroethane is a compound that occurs in the environment as the result of anthropogenic activity. Chloroethane exposure may occur from process and fugitive emissions from its production and use as a chemical intermediate and from landfill leaching. Chloroethane is also known to evaporate from wastewater streams, landfills, solvents, and anesthetics. The combustion of plastics, refuse, and biomass may also release chloroethane. The anaerobic biodegradation of some chlorinated solvents and chloroethane's formation during water chlorination are other sources of exposure. Most chloroethane released in the environment eventually enters the atmosphere.

When released to the atmosphere, the dominant removal mechanism is expected to be reaction with photochemically-generated hydroxyl radicals (half-life of 40 days). Potential exists for removal from the atmosphere in precipitation; however, most chloroethane removed by this mechanism is likely to reenter the atmosphere by volatilization. When released to surface water, volatilization is expected to be the primary fate process (half-life of 2.4 hours in a model river). When released to soil, chloroethane either volatilizes rapidly from soil surfaces or leaches through subsurface soil where it becomes a potential groundwater contaminant. In groundwater, chloroethane would be subject to chemical hydrolysis to give ethanol. Sufficient data are not available to establish the rate of chloroethane degradation in groundwater.

The general population may be exposed to low levels (<2 ppbv; Table 5-7) of chloroethane through inhalation of contaminated ambient air. Exposure may also occur through possible consumption of contaminated drinking water (0.1–228 ppb; Table 5-5). Dermal contact can occur from the intentional use of chloroethane as a topical anesthetic. Occupational exposure may occur by inhalation and/or dermal contact.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Table 5-1 summarizes information on companies that reported the production, import, or use of chloroethane for the Toxics Release Inventory (TRI) in 2021 (TRI21 2023). TRI data should be used with caution since only certain types of industrial facilities are required to report. This is not an exhaustive list.

The production of chloroethane in the United States has decreased as the use of leaded gasoline has been regulated. In 1960, approximately 247,000 metric tons (1 metric ton=1,000 kg) of chloroethane were produced, while in 1988, production of chloroethane was approximately 69,000 metric tons (IARC 1991). Data from the EPA Chemical Data Reporting (CDR) database indicates that there are two domestic producers of chloroethane: Nouryon Chemicals LLC and Westlake Chemical Corporation (EPA 2020). Much of the data from these two entities is listed as confidential business information (CBI), but national production volumes from 2016 to 2019 were estimated to range from 20,000,000 to <100,000,000 pounds (from 9,072 to <45,359 metric tons). Table 5-1 summarizes TRI information regarding facilities that produced, processed, or used chloroethane in 2021 (TRI21 2023).

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	1	0	99	1, 13
AR	2	1,000	9,999	6, 9, 12
IL	2	1,000	999,999	1, 5, 6, 13
KY	1	10,000	99,999	1, 3, 6
LA	16	0	49,999,999	1, 3, 4, 5, 6, 10, 12, 13, 14
MI	3	10,000	999,999	1, 5, 6, 12, 13
MO	1	1,000	9,999	1, 5, 14
NJ	1	100	999	1, 5
NY	1	0	99	1, 5
TX	14	100	999,999	1, 3, 5, 6, 9, 10, 12, 13, 14

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
VA	1	100,000	999,999	6
WV	1	100	999	1, 5

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

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

Source: TRI21 2023 (Data are from 2021)

5.2.2 Import/Export

From 1979 to 1988, the United States exported 8,562–13,868 metric tons, with the maximum occurring in 1986 and the minimum occurring in 1988 (IARC 1991). The recent amounts that were imported or exported by the two entities that manufactured chloroethane from 2016 to 2019 in the CDR were declared as CBI (EPA 2020).

5.2.3 Use

In the past, the single largest use of chloroethane was in the production of tetraethyl lead. In 1984, 80% of the chloroethane consumed in the United States was used in domestic production of tetraethyl lead, 15% was used in the production of ethyl cellulose, and 5% was used for miscellaneous applications including use as a solvent and topical anesthetic, and in the manufacture of dyes, chemicals, and pharmaceuticals (Budavari et al. 1996; Morris and Tasto 1979). Government-mandated reduction in the amount of lead additives used in gasoline in the United States and a shift to the use of unleaded gasoline caused a drastic reduction in the amount of chloroethane required to produce tetraethyl lead (CMR 1982; EPA 1985; IARC 1991).

Chloroethane is a local spray anesthetic used by physicians and is also available over the counter to alleviate pain associated with insect bites and stings, and sports injuries. Dermally applied chloroethane is used to reduce pain prior to venous or arterial puncture or cannulation (Fossum et al. 2016; Rao et al. 2019; Rüsch et al. 2017; Schlieve and Miloro 2015; Selby and Bowles 1995). Other dermal uses include

spinal injection (Firdaus et al. 2018; Walsh et al. 2010), botulinum toxin injection (botox) (Irkoren et al. 2015; Richards 2009), skin puncture for allergy testing (Waibel and Katial 2005), and during needle electromyography (Moon and Kim 2014).

Chloroethane is used for procedures such as skin biopsy and ear piercing that require short periods of surface anesthesia in a small area (Florentine et al. 1997; Noble 1979). It is also used topically to relieve pain in facial muscles during physical therapy for those suffering from temporomandibular pain and dysfunction syndrome (also known as temporomandibular joint disorder, or TMD) (Marbach 1996) and reduced the pain associated with dressing changes for negative pressure wound therapy (Tank et al. 2021). Use of chloroethane spray is used to relieve muscle pain associated with exercise (Rui et al. 2017) and spastic torticollis (i.e., involuntary, uncontrollable positioning of head due to painful muscle spasm of the neck) (Nibhanipudi 2015), and to prevent pruritus (i.e., severe itching) in skin prick tests without affecting the flare and wheal reactions that are indicative of an allergic response (Gal-Oz et al. 2010, 2015; Waibel and Katial 2005).

Chloroethane is also used as a recreational inhalant, which is an off label and illegal use. It is desired for its narcotic effects (Juliá-Romero et al. 2021; Kuthiah and Er 2019; Pothiawala et al. 2021; Schwark et al. 2022; Senussi and Chalise 2015). The compound is manufactured in pressurized canisters and sold commercially.

5.2.4 Disposal

Chloroethane is listed as a toxic substance under Section 3 13 of the Emergency Planning and Community Right to Know Act (EPCRA) under Title III of the Superfund Amendments and Reauthorization Act (SARA) (EPA 1998). Disposal of wastes containing chloroethane is controlled by federal regulations (Chapter 7).

Chloroethane may be disposed of by controlled incineration. It is recommended that chloroethane be mixed with another combustible fuel prior to incineration; however, sufficient oxygen and an adequate operating temperature are mandatory to avoid incomplete combustion resulting in the formation of phosgene. In a study of the thermal destruction of chloroethane, the minimum temperature required for 99.99% destruction with a 1-second residence time was 727°C (Fisher and Koshland 1990). Among the chlorinated methanes and ethanes studied, chloroethane had the lowest temperature required for destruction. Chloroethane is also a constituent of some wastewater streams; it is susceptible to removal

by air stripping (Gould et al. 1983). Placing chloroethane in a landfill is not recommended (Gould et al. 1983).

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 2022). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility's North American Industry Classification System (NAICS) codes is covered under EPCRA Section 313 or is a federal facility; and if their facility manufactures (defined to include importing) or processes any TRI chemical in excess of 25,000 pounds, or otherwise uses any TRI chemical in excess of 10,000 pounds, in a calendar year (EPA 2022).

5.3.1 Air

Estimated releases of 166,717 pounds (~75.62 metric tons) of chloroethane to the atmosphere from 44 domestic manufacturing and processing facilities in 2021, accounted for about 99.8% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2023). These releases are summarized in Table 5-2.

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Chloroethane[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	1	249	0	0	0	0	249	0	249
AR	2	13	0	0	0	0	13	0	13
IL	2	4,115	0	0	0	0	4,115	0	4,115
KY	1	9	0	0	0	0	9	0	9
LA	16	29,141	27	0	1	0	29,168	1	29,169
MI	3	993	110	0	0	0	1,103	0	1,103
MO	1	691	5	0	0	0	696	0	696
NJ	1	12,229	1	0	0	0	12,230	0	12,230
NY	1	5	0	0	0	0	5	0	5
TX	14	32,507	32	0	5	0	32,542	2	32,544
VA	1	81,476	4	0	0	0	81,476	4	81,480

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Chloroethane[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
WV	1	5,290	114	0	0	0	5,404	0	5,404
Total	44	166,717	293	0	6	0	167,009	7	167,016

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

RF = reporting facilities; UI = underground injection

Source: TRI21 2023 (Data are from 2021)

Chloroethane may be released to the environment through process and fugitive emissions related to its production and use as a chemical intermediate; evaporative losses from waste-water streams, landfills, solvents, and anesthetics; and emissions from combustion of plastics, refuse, and biomass (EPA 1977; Graedel et al. 1986; Vogt and Walsh 1985; Young and Parker 1984).

EPA's National Emission Inventory (NEI) database contains information regarding sources that emit criteria air pollutants (CAPs) and their precursors, and hazardous air pollutants (HAPs) for the 50 United States, Washington DC, Puerto Rico, and the U.S. Virgin Islands. Emissions are estimated from multiple sources, including state and local environmental agencies, the TRI database, computer models for on- and off-road emissions, and databases related to EPA's Maximum Achievable Control Technology (MACT) programs to reduce emissions of HAPs. Chloroethane emissions estimated from the 2017 inventory are summarized in Table 5-3.

Table 5-3. Pounds of Chloroethane Emitted by Sector

Emission sector	Pounds of chloroethane emitted
Agriculture; livestock waste	520,626.10
Fuel combustion; commercial/institutional; coal	52.92
Fuel combustion; commercial/institutional; other	56.16
Fuel combustion; electric generation; biomass	17,821.72
Fuel combustion; electric generation; coal	9,855.79
Fuel combustion; electric generation; natural gas	28.84
Fuel combustion; electric generation; other	256.30
Fuel combustion; industrial boilers, internal combustion engines; biomass	1.25
Fuel combustion; industrial boilers, internal combustion engines; coal	406.28
Fuel combustion; industrial boilers, internal combustion engines; natural gas	3,585.09
Fuel combustion; industrial boilers, internal combustion engines; other	278.33
Industrial processes; cement manufacturing	213.52
Industrial processes; chemical manufacturing	85,707.71
Industrial processes; ferrous metals	88.93
Industrial processes; non-ferrous metals	2,028.93
Industrial processes; not elsewhere classified	39,176.00
Industrial processes; oil and gas production	81.27
Industrial processes; petroleum refineries	40.80
Industrial processes; pulp and paper	60.26
Industrial processes; storage and transfer	250.43
Miscellaneous; bulk gasoline terminals	1.16
Miscellaneous; gas stations	1.25
Miscellaneous; waste disposal	33,968.25
Solvent; industrial surface coating and use	75,374.00
Solvent; degreasing	52.00

Source: EPA 2023a

5.3.2 Water

Estimated releases of 293 pounds (~0.13 metric tons) of chloroethane to surface water from 44 domestic manufacturing and processing facilities in 2021, accounted for <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2023). This estimate includes releases to wastewater treatment and publicly owned treatment works (POTWs) (TRI21 2023). These releases are summarized in Table 5-2.

Limited data are available regarding the release of chloroethane to water. This compound may be released to the environment as a constituent of wastewater streams from various industries, particularly those that use chloroethane as an intermediate. The following industries have been identified as potential sources of release of chloroethane: electroplating, organic chemicals, steam electric, asbestos, timber products processing, metal finishing, paving and roofing, paint and ink formulating, gum and wood, and carbon black (EPA 1988). It is possible that chloroethane forms in some wastewater streams from chlorination (EPA 1977; Gould et al. 1983; Otson 1987). Because of its volatility, the majority of chloroethane released to surface water is expected to enter the atmosphere. This compound can leach into groundwater from waste disposal sites, and it may form in groundwater as an anaerobic biodegradation product of chlorinated solvents (e.g., 1,1,1-trichloroethane and cis-1,1-dichloroethylene) (Barrio-Lage et al. 1986; Vogel and McCarty 1987).

5.3.3 Soil

Estimated releases of 6 pounds (~0.003 metric tons) of chloroethane to soil from 44 domestic manufacturing and processing facilities in 2021, accounted for <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2023). These releases are summarized in Table 5-2.

Chloroethane can occur in soil from the disposal of waste products that contain this compound and from formation as an anaerobic biodegradation product of various chlorinated compounds (e.g., 1,1,1-trichloroethane and cis-1,2-dichloroethylene) (Barrio-Lage et al. 1986; Vogel and McCarty 1987).

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Air. The relatively high water solubility of chloroethane suggests that potential exists for removal of this compound from the atmosphere via washout. However, most chloroethane removed by this mechanism is likely to reenter the atmosphere by volatilization.

Water. The dominant removal process for chloroethane in surface water is expected to be volatilization. Based on a measured Henry's law constant of 1.11×10^{-2} atm-m^3/mole at 24.8°C, the

volatilization half-life of chloroethane from a model river 1 m deep, flowing 1 m/second with a wind speed of 3 m/second was estimated to be 2.4 hours (Gossett 1987; Thomas 1982).

Bioconcentration factors (BCF) of 7 and 5 have been estimated for chloroethane using linear regression equations based on a log of the octanol-water partition coefficient (K_{ow}) of 1.43 and a water solubility of 5,678 mg/L at 20°C, respectively (Bysshe 1982; Horvath 1982; NLM 2023). These BCF values indicate that this compound would not bioconcentrate significantly in aquatic organisms.

Adsorption coefficients (K_{oc}) of 143 and 33 were estimated for chloroethane using linear regression equations based on log K_{ow} and water solubility data, respectively (Lyman 1982). These values suggest that adsorption of chloroethane to suspended solids and sediments in water would not be a significant fate process.

Sediment and Soil. The likely insignificant sorption of chloroethane to soil, indicated by the relatively low K_{oc} value for the compound, suggests that it would be highly mobile in soil and might undergo significant leaching (Swann et al. 1983). The relatively high vapor pressure of chloroethane and its volatility from water suggest that it would evaporate rapidly from soil surfaces, and that volatilization would probably be a major removal process. The calculated value of K_{oc}, 0.347 at 17.5°C (Washington 1996), indicates that chloroethane in soil has a propensity to become dissolved in soil water and will then enter soil gas. The concentrations of chloroethane in soil water and the vapor phase will approach equilibrium.

5.4.2 Transformation and Degradation

Air. The dominant atmospheric removal process for chloroethane is predicted to be removal by reaction with photochemically-generated hydroxyl radicals in the troposphere. This will proceed via hydrogen abstraction; other atmospheric oxidants such as nitrate radicals and ozone will not have a significant role in the atmospheric oxidation of chloroethane (Atkinson 1985; Howard and Evenson 1976).

The half-life for this reaction has been estimated to be 40 days based on a reaction rate constant of 4.0×10^{-13} m^3/molecule-second at 25°C and a typical hydroxyl radical concentration of 5.0×10^5 molecules/m^3 (Atkinson 1985; Howard and Evenson 1976). This tropospheric half-life suggests that <1% of the chloroethane released to the atmosphere would diffuse into the stratosphere, where it

would be destroyed by photolysis (EPA 1979). Chloroethane is not expected to photolyze in the atmosphere below the ozone layer since it contains no chromophores that absorb light in the visible part of the spectrum (wavelengths about 300–700 nm) (EPA 1982; Hubrich and Stuhl 1980; Jaffe and Orchin 1962).

Water. Chloroethane is susceptible to slow chemical hydrolysis and forms ethanol and hydrochloric acid as reaction products. The hydrochloric acid formed dissociates at the neutral pH of most natural waters and forms a chloride salt.

The hydrolytic half-life of chloroethane is not known with certainty. The hydrolytic half-life in water at 25°C and pH 7 was estimated to be 38 days based on a reaction rate constant extrapolated from experimental data at 100°C (Laughton and Robertson 1959; Mabey and Mill 1978).

An anaerobic dehalogenation study of 1,1,1-trichloroethane studied the formation of chloroethane as a degradation byproduct of this reaction (Vogel and McCarty 1987). The study found that chloroethane degradation rates were similar in biologically active samples and controls; based on this, the study authors concluded that abiotic hydrolysis was the primary mechanism of degradation for chloroethane. The data for the rate of decrease in chloroethane were used to estimate a pseudo first-order hydrolysis rate constant of approximately 0.37 $years^{-1}$, corresponding to a half-life of approximately 1.9 years, which is considerably longer than the value estimated by Mabey and Mill (1978).

In another study conducted by Jeffers and Wolfe (1996), the hydrolysis of chloroethane in 0.01 M hydrochloric acid (assumed to be the same rate constant under neutral conditions) and 0.01 M NaOH at 25°C was determined. The reaction in 0.01 M hydrochloric acid at 25°C was found to predominate, with a rate constant of $5.1x10^{-7}$, resulting in an estimated half-life for chloroethane of 2.6 years. Although studies (above) report conflicting data, chemical hydrolysis may be an important fate process in groundwater when losses from other degradation and transport processes are expected to be negligible.

The high volatility of chloroethane indicates that this compound will volatilize from groundwater and enter soil as a gas. In addition, chloroethane is susceptible to biodegradation in groundwater and other media. Vogel and McCarty (1987) have shown that chloroethane, formed by the anaerobic biodegradation of trichloroethylene in a batch fermenter, was further dechlorinated by methanogenic bacteria. This study, however, provided no rate constant for this reaction that could be compared to the rate for hydrolysis.

Oxidation of chloroethane in water via reaction with singlet oxygen or peroxy radicals is too slow to be environmentally relevant (EPA 1982). Direct photolysis in surface waters is not expected to be an environmentally relevant fate process due to lack of absorption in the environmental UV spectrum (EPA, 1982).

Sediment and Soil. In moist subsurface soils, chloroethane is expected to be susceptible to chemical hydrolysis. However, this pathway is expected to be slow, and other fate and transport processes may predominate. A large body of data exists on the biodegradation of chlorinated alkenes and alkanes under anaerobic or aerobic conditions. Most of these data, however, deal with polychlorinated compounds that are biodegraded to chloroethane or a structurally similar alkane or alkene (Ahlert and Enzminger 1992; Barrio-Lage et al. 1986; Chang and Alvarez-Cohen 1996; Tabak et al. 1981; Vogel and McCarty 1987).

Chloroethane can undergo reductive dehalogenation by methanogenic bacteria in an anaerobic cell suspension or packed column environment (Baek et al. 1990; Holliger et al. 1992). Ethane and hydrochloric acid are formed by the reductive dechlorination of chloroethane (Holliger et al. 1992). In addition, chloroethane can be oxidized by aerobic nitrifying bacteria (Rasche et al. 1990). Both acetaldehyde and 2-chloroethanol are produced from the oxidation of chloroethane, with acetaldehyde predominating at >98% of the total product (Rasche et al. 1990).

Although these studies provided maximum product formation rates, first-order rate constants were not estimated; therefore, no comparisons could be made to determine which biodegradation pathway would more rapidly clear chloroethane from a contaminated environment. The pathways do not directly compete, because they occur in different environments: one in an oxygen-deficient environment and the other in an oxygen-rich environment. For example, methanogenic environments are found at landfills and deep aquifers high in nutrient rich organic compounds. Denitrifying environments are common to agricultural land use as well as areas that have onsite wastewater treatment systems (Ahlert and Enzminger 1992).

Further, optimal biodegradation of chloroethane in aquifers or saturated sediments or soils is highly dependent on the presence of appropriate metabolizing bacteria, migration of the contaminant to the bacteria, and availability and concentration of necessary reactants such as carbon sources, reducers, and/or oxidizers. While laboratory studies indicate that biodegradation can be a significant pathway for

clearance of chloroethane and other contaminants from affected media, the importance of this pathway in the environment is still unknown.

Nitrifying activity was stimulated to study co-oxidation of monohalogenated hydrocarbons by native populations of ammonia-oxidizing bacteria. These slurries actively degraded chloroethane at maximum rates of 20–30 nmol/mL/hour that could be sustained for approximately 12 hours (Duddleston et al. 2002).

Hommes et al. (1998) examined the influence of soil upon the co-oxidation of a variety of halogenated and nonhalogenated hydrocarbons by *Nitrosomonas europaea*. Small quantities of Willamette silt loam (organic carbon content, 1.8%; cation-exchange capacity, 15 mmol/kg of soil) were suspended with *N. europaea* cells in a soil-slurry-type reaction mixture. The oxidations of ammonia and chloroethane were compared to results for controls in which no soil was added. Raising the ammonium concentration in the reaction mixture from 10 to 50 mM reduced the effects of soil on nitrite production and chloroethane co-oxidation (Hommes et al. 1998).

Other Media. The dechlorinating activity of a methanogenic granular sludge from a methanol-fed upflow anaerobic sludge blanket reactor was investigated with chlorinated ethanes. Findings revealed that this unadapted methanogenic consortium degraded all chloroethanes tested and that reductive hydrogenolysis was an important dechlorinating mechanism (van Eekert et al. 1999).

Wu et al. (2013) found that a *Bacillus* strain capable of degrading chloroethane grew more readily when at a pH value of 7.0, the immobilized microorganism ratio was at 5%, and the temperature was maintained at 30°C.

5.5 LEVELS IN THE ENVIRONMENT

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

Table 5-4. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air	0.01 ppb	EPA 2023c
Drinking water	0.008 ppb	EPA 1986a
Surface water and groundwater	0.008 ppb	EPA 1986a
Soil	24 ppm	EMMI 1997

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

Table 5-5. Summary of Environmental Levels of Chloroethane

Media	Low	High	For more information
Outdoor air (ppbv)	0.016	1.42	Section 5.5.1
Indoor air (ppbv)	0.76	1.08	Section 5.5.1
Drinking water (ppb)	0.10	228	Section 5.5.2

ppbv = parts per billion based on volume

Detections of chloroethane in air, water, and soil at NPL sites are summarized in Table 5-6.

Table 5-6. Chloroethane 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)	23	34.8	10.1	116	78
Soil (ppb)	48	45.6	6.94	15	14
Air (ppbv)	0.330	0.399	3.76	7	7

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

ppbv = parts per billion based on volume

5.5.1 Air

Chloroethane is a pollutant monitored for in the national Air Quality System (AQS) database, which contains ambient air pollution data collected by EPA, state, local, and tribal air pollution control agencies from monitors throughout the country. Table 5-7 shows the yearly mean 24-hour ambient air concentrations of chloroethane at monitoring stations across the United States.

Table 5-7. Summary of Annual Concentration of Chloroethane (ppbv) Measured in Ambient Air at Locations Across the United States[a,b]

Year	Number of sites	Mean of all detections for all locations	Maximum concentration
2018	83	0.022	1.19
2019	85	0.016	0.19
2020	88	0.031	0.45
2021	139	0.076	1.42
2022[c]	65	0.048	0.63

[a]Values were originally reported in parts per billion carbon (ppbC) and converted to ppbv.
[b]24-hour sampling period.
[c]As of January 23, 2023.

Source: EPA 2023b

Current ambient levels of chloroethane are markedly lower than levels found during the mid-1970s and early 1980s because of a substantial decrease in the production of chloroethane in the United States and a phaseout of leaded gasoline. Monitoring data from the early 1980s indicated that levels of chloroethane in ambient air at various urban/suburban locations in the United States had maximum and minimum values of 10 and 1,248 pptv, respectively. The average concentrations ranged from 41 to 140 pptv (EPA 1981; Shepson et al. 1987). Marine air samples collected in the Northern Hemisphere during 1981 contained an average concentration of 19 pptv (Singh et al. 1983). Rural air samples collected in 1974–1975 in the northwest United States contained <5 pptv chloroethane (Grimsrud and Rasmussen 1975).

Chloroethane was detected in the air samples of landfill gas collected from a municipal/industrial landfill in the United Kingdom and a municipal landfill simulator (Vogt and Walsh 1985; Young and Parker 1984). These data indicate that chloroethane may be found in the air above some landfills. However, sufficient data are not available to determine whether elevated levels of chloroethane typically occur at, or in the vicinity of, waste disposal sites. Chloroethane was detected in indoor air of a newspaper printing operation at 0.76 ppbv (760 pptv) and a small facility that printed scientific material at 1.08 ppbv

(1,080 pptv) (Alabdulhadi et al. 2019). Chloroethane was detected in various media (indoor air, groundwater, or outdoor air) at 10 sites that ATSDR evaluated for indoor air exposures from soil vapor intrusion between 2002 and 2009 (Burk and Zarus 2013). Chloroethane was detected in indoor air samples at three of the sites ranging from 0.03 to 10 ppbv, in one outdoor air sample at 0.095 ppbv, and in groundwater samples at seven of the sites ranging from 0.81 to 170 ppb.

Barletta et al. (2009) identified chloroethane among a suite of tracer gases (OCS, CH_3Cl, 1,2-dichloroethane, ethyl chloride, and Halon-1211) that scientists can use to trace contaminants originating in China to determine if they might be moving with wind currents into the United States, becoming a source of U.S. population exposure.

5.5.2 Water

The Water Quality Portal (WQP) is a source of discrete water-quality data in the United States and beyond. This cooperative service integrates publicly available water-quality data from the United States Geological Survey (USGS), EPA, and over 400 state, federal, tribal, and local agencies. Analysis of compiled data from the WQP that spans 4 decades (1981–2023) indicates that chloroethane is not a common surface water pollutant. Of 144,292 samples analyzed, chloroethane was detected in 19,166 (0.13% of samples). Of those 19,166 samples, only 1,060 had values >10 µg/L, with a median value of 2.5 µg/L (WQP 2023).

Chloroethane was monitored as part of the Unregulated Contaminant Monitoring Rule from 1988 to 1997 (UCMR Round 1 monitoring data). This program collects data for contaminants suspected to be present in drinking water, but that do not have health-based standards set under the Safe Drinking Water Act (SDWA). Chloroethane was subsequently regulated under the SDWA. Chloroethane was monitored in 39,180 public water systems (PWS) and was detected above its reporting level (0.10 ppb) in 0.004% of the PWS (EPA 2001). The maximum observed level was reported as 288 ppb and the mean value of all detections was 5.34 ppb.

USGS (2006) reported that chloroethane was detected at a concentration >0.2 µg/L in 0.29% of groundwater samples from aquifer studies (1,710–3,498 samples), 0.083% of domestic water-supply wells (1,190–1,208 samples), 0.28% of public water-supply wells (828–1,096 samples), and 6.3% of statewide groundwater samples (1,305–4,086 samples) in Wisconsin. Chloroethane contamination of groundwater has occurred at U.S. Department of Defense facilities (USGS 2006) and various waste

disposal sites throughout the United States (ATSDR 1989, 1991; Cline and Viste 1985; EPA 1986b, 1986c; Myers 1983; Sabel and Clark 1984).

5.5.3 Sediment and Soil

No recent data were located regarding levels of chloroethane in sediment and soil. In a 1982 survey of U.S. wastewater treatment plants receiving both municipal and industrial waste streams, chloroethane was found in undigested sewage sludge from 2 of 13 plants at concentrations ranging from 14.5 to 24 mg/kg dry weight. Assuming that the sludge was disposed of by land application, the application rate of chloroethane to soil was projected to be 0.16–0.17 kg/hectare (dry weight) and the resulting concentration of chloroethane in the top 15 cm of soil was predicted to be 0.08–0.085 mg/kg (Naylor and Loehr 1982).

5.5.4 Other Media

Few reports are available concerning the identification of chloroethane in other media. Chloroethane at a mean concentration of 7.6 ng/g was found in oysters collected from Lake Pontchartrain, Louisiana (Ferrario et al. 1985).

5.6 GENERAL POPULATION EXPOSURE

Limited data indicate that the general population is exposed to chloroethane by inhalation of contaminated air and ingestion of contaminated drinking water (EPA 2023b; WQP 2023). Medical use of chloroethane as a topical anesthetic, results in direct dermal exposure of the general population to this compound (Gal-Oz et al. 2010, 2015; Nibhanipudi 2015; Rui et al. 2017; Tank et al. 2021; Waibel and Katial 2005). Chloroethane blood level measurements were added to the NHANES study in 2013. Blood levels above the limit of detection (i.e., 0.045 µg/L) were <0.1%, with blood concentrations reported up to 0.617 µg/L (CDC 2017, 2018, 2020).

ATSDR's three-compartment Shower and Household-Use Exposure (SHOWER) model predicts air concentrations in the shower stall, bathroom, and main house throughout the day by estimating the contribution from showering or bathing and the contribution from other water sources in the house, such as the dishwasher, clothes washer, and faucets. This information, along with human activity patterns, is used to calculate a daily time-weighted average exposure concentration via inhalation exposure and from dermal uptake from skin contact. ATSDR's SHOWER model is available by sending a request to

showermodel@cdc.gov. Using median treated water levels as discussed in Section 5.5.2 (2.5 µg/L, based on WQP data; WQP 2023) and representative outdoor air levels discussed in Section 5.5.1 (0.048 µg/L based on AQS; EPA 2023b) Reasonable Maximum Exposure levels for chloroethane were calculated for different exposure groups (Table 5-8).

Table 5-8. Reasonable Maximum Exposure Inhalation Daily Exposure Concentration and Administered Dermal Dose of Chloroethane for the Target Person

Exposure group	Inhalation (ug/m3)	Dermal (ug/kg/day)
Birth–<1 year	5.3	0.0056
1–<2 years	5.3	0.0052
2–<6 years	5.3	0.0044
6–<11 years	5.3	0.0036
11–<16 years	5.3	0.0029
16–<21 years	5.3	0.0027
Adults	5.3	0.0026
Pregnant and breastfeeding women	5.3	0.0027

Source: ATSDR 2022b

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Occupational workers who come into contact with chloroethane are expected to have higher exposure levels than the general population. Workers may be exposed to chloroethane by inhalation and/or dermal exposure. There are two chemical companies producing chloroethane in the United States according to the Chemical Data Reporting system (EPA 2020). The number of workers at the manufacturing locations in Cook County, Illinois and Harris County, Texas were not reported. In addition, workers from the 44 domestic manufacturing and processing facilities that utilize chloroethane may potentially be exposed to chloroethane (TRI21 2023).

Emissions data suggest that workers in the following industries may be exposed to chloroethane: chemical manufacturing, cement manufacturing, pulp and paper, oil and gas production, petroleum refining, waste disposal, and agriculture (EPA 2023a). Since chloroethane is used in cleaning solvents and degreasers, plumbers, pipe fitters, and automotive mechanics can be exposed (Fidler et al. 1987; Parker et al. 1979). Persons working in the printing industry may have a greater potential for high exposures than the general population, as volatile organic compounds (VOCs), including chloroethane, may be used in these industries. Alabdulhadi et al. (2019) detected chloroethane levels ranging from

0.76 to 1.08 ppbv in the air of a scientific literature printing facility and a newspaper printing operation. Chloroethane is increasing used as a blowing agent for the manufacturing of foam plastic; workers in these industries have increased potential for exposure (Matsunaga et al. 1976). Medical personnel who use chloroethane to anaesthetize the skin, or people who self-administer chloroethane for muscle or joint pain may also have a higher potential for exposure than the general population.

People who intentionally misuse chloroethane for recreational purposes typically spray it on a piece of cloth and then inhale the substance (Schwark et al. 2022). Chloroethane misuse may result in severe health effects such as slurred speech, dizziness, difficulty walking, cardiac depression, respiratory paralysis, and death. These effects are generally reversible following cessation of exposure (Demarest et al. 2011; Hes et al. 1979; Pothiawala et al. 2021; Schwark et al. 2022; Senussi and Chalise 2015).

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 chloroethane 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 chloroethane.

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

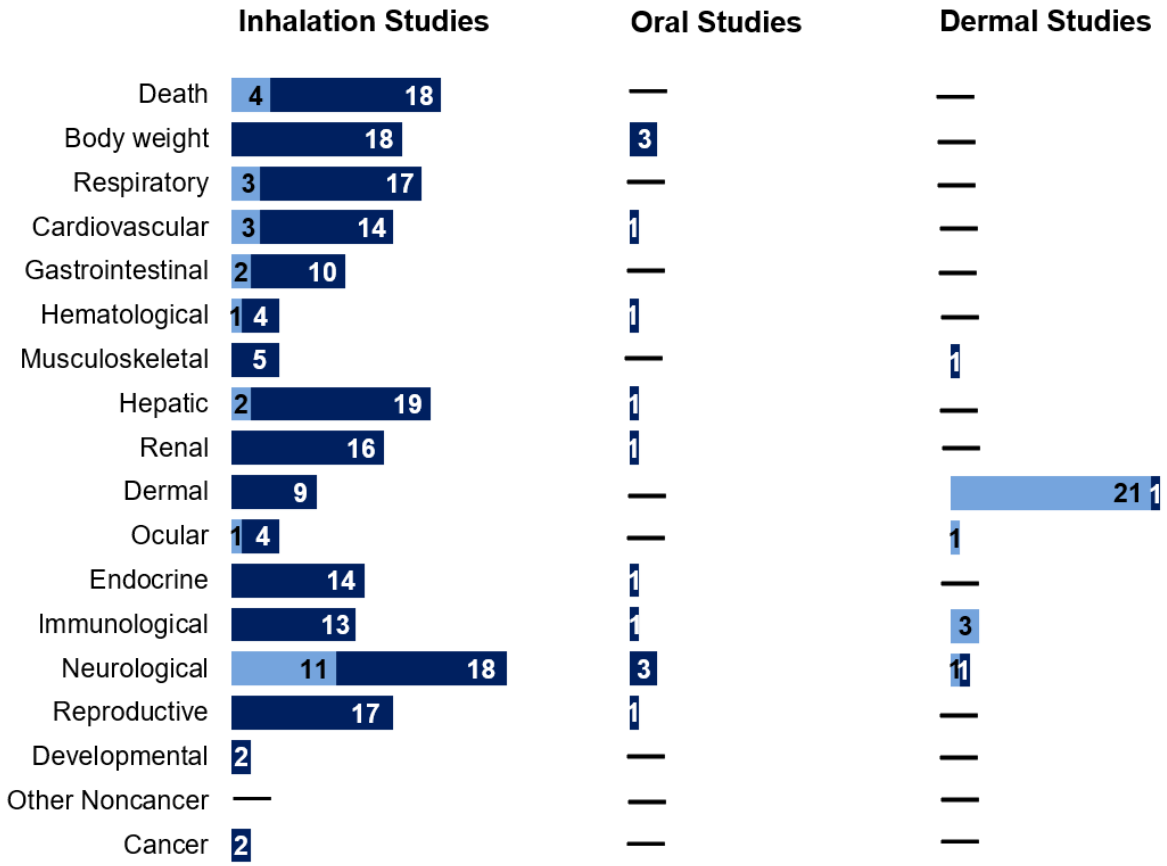
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to chloroethane that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of chloroethane. The number of human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

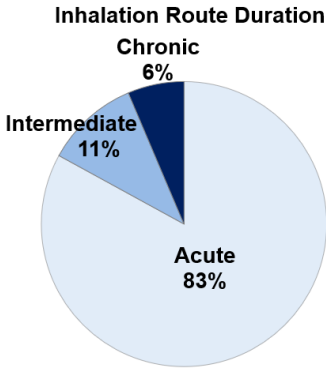
As illustrated in Figure 6-1, most of the data on the toxicity of chloroethane come from inhalation exposure in humans and animals. In humans, the inhalation data are from a few volunteer exposure studies and several case reports of intentional solvent misuse. In animals, most inhalation studies are acute-duration studies and neurological effects are the most common health endpoints studied. No oral studies in humans were located, and only a couple of oral animal studies were identified. Dermal exposure studies were almost exclusively performed in humans and were related to the use of chloroethane for topical anesthesia.

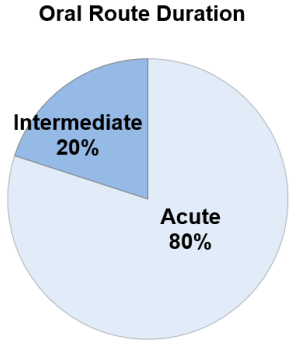
Figure 6-1. Summary of Existing Health Effects Studies on Chloroethane by Route and Endpoint*

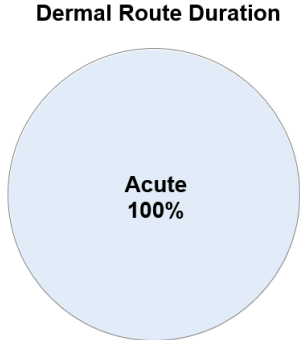
Potential neurological, hepatic, and dermal effects were the most studied endpoints

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; studies may have examined more than one endpoint.

6.2 IDENTIFICATION OF DATA NEEDS

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

Acute-Duration MRLs. The inhalation database is adequate to derive an acute-duration inhalation MRL. Although an acute-duration inhalation MRL was derived, additional studies that establish a dose-response relationship for neurological effects would be useful. The oral database is inadequate to derive an acute-duration oral MRL. Oral studies in animals are limited to two acute-duration gavage studies that did not include a control group and two drinking water studies that reported no health effects. Additional acute-duration oral studies examining a wide range of potential health endpoints are needed to identify the most sensitive targets of toxicity and to establish a dose-response relationship. However, since the predominant route expected for human exposure is inhalation, oral data may be less relevant to ongoing exposure scenarios in humans.

Intermediate-Duration MRLs. The inhalation database is adequate to derive an intermediate-duration inhalation MRL. Although an intermediate-duration inhalation MRL was derived, additional studies that investigate a dose-response relationship for reproductive effects would be useful. In animals, intermediate-duration inhalation studies in rats, mice, and rabbits suggest that systemic effects are unlikely at high exposure concentrations (up to 19,000 ppm). However, neurological effects were not observed in these studies. Further investigation of neurological endpoints may be useful because neurological effects were noted in both acute- and chronic-duration inhalation studies. The oral database is inadequate to derive an intermediate-duration MRL. Only one poorly reported (and not listed in the LSE table), intermediate-duration oral study in animals was identified. Additional intermediate-duration oral studies are needed examining a wide range of potential endpoints to identify the most sensitive targets of toxicity and to establish a dose-response relationship. However, since the predominant route expected for human exposure is inhalation, oral data may be less relevant to ongoing exposure scenarios in humans.

Chronic-Duration MRLs. The inhalation and oral databases are inadequate to derive chronic-duration MRLs. Available inhalation data in humans is limited to a case study and a poorly reported occupational

exposure study. In animals, additional inhalation studies are needed that investigate a dose-response relationship for health effects, particularly neurotoxicity. No chronic-duration oral studies were identified in either humans or animals. Chronic-duration oral studies examining a wide range of potential effects are needed to identify the most sensitive targets of toxicity and establish dose-response relationships. However, since the predominant route expected for human exposure is via inhalation, oral data may be less relevant to ongoing exposure scenarios in humans.

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

Neurotoxicity. Studies of chloroethane inhalation in humans and animals have provided information on the neurological clinical signs resulting from acute-duration exposure to chloroethane and the levels at which they occur. It would be useful to have studies that quantified the neurobehavioral changes occurring during exposure, and that measure recovery times. Studies that evaluate specific neurobehavioral outcomes, such as learning and memory, may also be useful. Oral studies investigating neurological effects are limited to two gavage studies and a 14-day drinking water study. A control group was not included in the gavage studies. Reliable studies of neurotoxicity focusing on dose-related responses following oral exposure are needed. Chloroethane spray is used as a topical anesthetic; studies are needed examining the potential effects that applying this chemical to the skin has on the neurological system.

Reproductive. No human studies evaluating reproductive toxicity were identified. Several animal inhalation studies identified reproductive effects including decreased uterine weight and GSH levels and increased estrous cycle duration. The relevance of uterine effects in animals to human chloroethane exposure is not known, and further studies to examine the mechanisms of uterine effects observed in chloroethane-exposed mice are needed. A multigeneration study to determine if uterine effects, estrous cycle effects, and effects on sperm motility impact reproductive performance is also needed. Available oral studies are not adequate for evaluating potential reproductive toxicity; therefore, additional oral studies evaluating this endpoint would be useful. Chloroethane spray is used as a topical anesthetic; studies are needed examining the potential effects that applying this chemical to the skin has on the reproductive system.

Developmental. No studies were located on developmental effects of chloroethane in humans. Two prenatal inhalation studies were located for chloroethane and an increase in incidence of

DFFC of the skull bones (developmental delay of ossification of small centers of unossified bone of the skull) was seen in the fetuses of one study. The second study did not perform visceral or skeletal examinations. No significant treatment-related changes were observed on other developmental parameters in these studies. Additional developmental studies by inhalation and oral routes are needed. Chloroethane spray is used as a topical anesthetic; studies are needed examining the potential effects that applying this chemical to the skin has on fetal development.

Epidemiology and Human Dosimetry Studies. Most of the human inhalation studies are case reports with no exposure level reported. Epidemiological studies of occupationally exposed workers or people living near industries releasing chloroethane or near hazardous waste sites are needed.

Biomarkers of Exposure and Effect. Although a couple of case studies reported the levels of chloroethane in blood and urine plus lung and brain tissue, these levels are not correlated with an exposure concentration. Other studies lacked environmental concentrations of chloroethane and levels of chloroethane in the breath, fluids, and body tissues. Studies examining the association between air and breath levels of chloroethane are needed. Although NHANES reported on concentration of chloroethane in the blood, these values were not correlated to exposure level (CDC 2017, 2018, 2020). Research is needed to ascertain whether there are biomarkers specific only for chloroethane exposure. Further research is required to determine if urinary excretion of GSH conjugates would serve as a useful biomarker following exposure of humans to chloroethane.

Unique biomarkers of effect have not been identified for exposure to chloroethane. Further research regarding the biochemical effects of chloroethane is needed to identify biomarkers of effect for chloroethane.

Absorption, Distribution, Metabolism, and Excretion. A single breath absorption study (Morgan et al. 1970) is the only quantitative study regarding the absorption, distribution, metabolism, and excretion of chloroethane in humans. Studies in rats and mice indicate that chloroethane is readily absorbed following inhalation exposure and is metabolized to acetaldehyde and GSH conjugates (Fedtke et al. 1994a, 1994b). Additional quantitative studies of the pharmacokinetics of chloroethane are needed.

Comparative Toxicokinetics. A study that compares the metabolism of chloroethane in rats and mice indicates that mice have a greater capacity to metabolize chloroethane than rats (Fedtke et al. 1994a, 1994b). An *in vitro* study using human liver preparations to study the metabolism of chloroethane is

needed to determine which species is the most appropriate model for the metabolism of chloroethane. It is currently unknown whether children differ from adults in their weight-adjusted intake of chloroethane. Changes in the skin surface area to body weight ratio as children grow may affect the tolerable dermal dose. This is demonstrated in model calculation of the Reasonable Maximum Exposure level (see Table 5-8). Therefore, studies investigating this issue are needed.

Children's Susceptibility. No studies involving exposure of children or immature animals to chloroethane have provided quantitative dose-response information. There are several qualitative studies in children associated with the use of chloroethane as an anesthetic (Nibhanipudi 2015; Noble 1979; Ramsook et al. 2001; Soueid and Richard 2007). Studies with immature animals or children exposed to the compound are needed to investigate any differences in toxicokinetics and the presence and severity of effects. Current knowledge of differences in physiology and biochemistry between children and adults indicate that distribution and metabolism might differ between children and adults. Definitive studies do not exist evaluating whether chloroethane pharmacokinetic parameters are different in children as compared with adults, and no PBPK models exist on any age of children or immature animals. Changes in skin surface area to body weight ratios can help to model Reasonable Maximum Exposure levels; however, this model cannot predict difference in absorption that may occur. Studies evaluating qualitative and quantitative differences in these processes would greatly facilitate the understanding of adverse effects of chloroethane in the developing human.

Studies are needed to determine whether chloroethane or its metabolites cross the placenta, and no studies have evaluated placental or cord blood concentrations of chloroethane or its metabolites in humans or animals. Experiments evaluating these parameters are needed, as well as experiments to determine whether chloroethane significantly accumulates in breast milk. One study detected the compound in breast milk (Pellizzari et al. 1982), but the maternal exposure route and chloroethane concentration in the milk were not identified. In addition, studies determining whether chloroethane would be stored in maternal tissues would be informative, although the volatility of the compound, as well as data indicating its rapid clearance from the body following inhalation exposure (Morgan et al. 1970), indicate that tissue storage is not expected.

Adequate data do not exist on the effect, if any, that chloroethane exposure has on fetal development. Reliable studies of this type are needed in determining the fetotoxicity of chloroethane, as well as the potential of the compound for disrupting normal child development. Studies on postnatal exposures and their influence on development in immature animals would also be useful.

Physical and Chemical Properties. Data on the physical and chemical properties of chloroethane are available. A K_{oc} value provides a means for predicting whether a compound will partition significantly into suspended solids and sediments in water or adsorb strongly to soil. A K_{oc} for chloroethane was estimated using regression equations based on log K_{ow} and water solubility data (Lyman 1982). This estimation technique is believed to provide a reasonable approximation of K_{oc}, so no further studies are needed.

Production, Import/Export, Use, Release, and Disposal. Data are adequate for the production and disposal of chloroethane (IARC 1991; TRI21 2023). Information on the use pattern for chloroethane is not available after 1988. Information would have to be supplied by the chemical industry to establish the percentage breakdown of the current chloroethane uses. This type of information is needed to establish the sources of chloroethane release and the potential for general population and occupational exposure.

Environmental Fate. Conflicting data (days or years) are available concerning the hydrolytic half-life of chloroethane in water (Jeffers and Wolfe 1996; Laughton and Robertson 1959; Mabey and Mill 1978; Vogel and McCarty 1987). Experimental data obtained from a hydrolysis study carried out in distilled water under environmental conditions (at 25°C and pH 5–9) are needed to predict the half-life of chloroethane (Haider 1980; Kobayashi and Rittmann 1982) in natural water and moist soil. Available data regarding biodegradation of chloroethane are insufficient for predicting the importance of biodegradation as a removal process for chloroethane. Natural water grab sample biodegradation studies and soil metabolism studies carried out under both aerobic and anaerobic conditions are needed to estimate the biodegradation half-life of chloroethane.

Although volatilization from soil is expected to be an important fate process (Washington 1996), data pertaining to the rate of volatilization from soil surfaces were not located in the available literature. Studies involving the measurement of the volatilization rate of chloroethane from soil surfaces are needed to evaluate the persistence of this compound upon release to soil.

The dominant removal mechanism for chloroethane in air is expected to be reaction with photochemically-generated hydroxyl radicals (Atkinson 1985; Howard and Evenson 1976). However, no data are available concerning the products of this reaction. These data are needed to understand the mechanism by which this compound degrades in the atmosphere.

Bioavailability from Environmental Media. Chloroethane is readily absorbed following inhalation exposure, the major route of exposure (Konietzko 1984; Lehmann and Flury 1943; Torkelson and Rowe 1981). Data regarding the bioavailability of chloroethane from different media for other routes of exposure were not identified. Studies examining the absorption of chloroethane from various media following oral and dermal exposure are needed to predict exposure to chloroethane at hazardous waste sites.

Food Chain Bioaccumulation. Based on bioconcentration factors of 7 and 5 estimated from log K_{ow} and water solubility (Bysshe 1982; Horvath 1982; NLM 2023), chloroethane is not expected to bioconcentrate significantly in aquatic organisms. Studies in which chloroethane is measured in biota and environmental media are needed to determine if this prediction is correct.

Exposure Levels in Environmental Media. Relatively large amounts of chloroethane are released to the environment on an annual basis (TRI21 2023). Levels in the ambient air are monitored throughout the United States and reported in the AQS database (EPA 2023b). The WQP, monitoring water-quality in the United States and beyond, indicates that chloroethane is not a common surface water pollutant (WQP 2023). Reliable monitoring data for the levels of chloroethane in contaminated media at hazardous waste sites are needed so that the information obtained on levels of chloroethane in the environment can be used in combination with the known body burdens of chloroethane to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Available data indicate that the general population may be exposed to chloroethane by inhalation, ingestion of drinking water, and dermal contact. Maximum inhalation and dermal exposure levels were calculated with the ATSDR (2022b) SHOWER model using data from the WQP (2023) and EPA (2023b). Even though chloroethane is a fairly large volume commercial compound, limited data are available concerning occupational exposure. There are no quantitative data relating type of occupation to level and route of exposure. Monitoring of workplace air is needed to evaluate exposure to occupational workers. Continued monitoring of air and water levels are needed to ensure accurate estimation of exposure to the general population and occupational workers.

Exposures of Children. Children are exposed to chloroethane via many different exposure pathways. Cardiovascular effects were observed in children exposed to a mixture of gases including chloroethane (Bush et al. 1952). However, the study lacked specificity for the chloroethane dose, and the use of a

gaseous mixture obscures the health effect finding. Reliable exposure and body burden studies in children are needed to relieve this data gap. In addition, because many older children may be exposed to chloroethane through sniffing the compound directly, there is a need to explore the prevalence of this behavior, the frequency of the misuse, and resulting exposure doses.

6.3 ONGOING STUDIES

No ongoing studies were identified in the National Institute of Health (NIH) RePORTER (2023) database.

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding chloroethane 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 chloroethane.

Table 7-1. Regulations and Guidelines Applicable to Chloroethane

Agency	Description	Information	Reference
	Air		
EPA	RfC	10 mg/m^3 (4 ppm)	IRIS 1991
	Provisional peer reviewed toxicity values		EPA 2007
	Provisional subchronic RfC	4 mg/m^3 (1.5 ppm)	
WHO	Air quality guidelines	No data	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories	Not listed	EPA 2018a
	National primary drinking water regulations	Not listed	EPA 2009
	RfD	Not evaluated	IRIS 1991
	Provisional peer reviewed toxicity values		
	Provisional subchronic RfD	0.1 mg/kg/day	EPA 2007
WHO	Drinking water quality guidelines	No data	WHO 2022
FDA	Substances added to food (formerly EAFUS)	Not listed	FDA 2023
	Cancer		
HHS	Carcinogenicity classification	No data	NTP 2021
EPA	Carcinogenicity classification	No data	IRIS 1991
	Provisional peer reviewed toxicity values		EPA 2007
	Provisional carcinogenicity assessment	Likely to be carcinogenic to humans	
IARC	Carcinogenicity classification	Group 3[a]	IARC 1999
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction	1,000 ppm	OSHA 2021a, 2021b, 2021c

Table 7-1. Regulations and Guidelines Applicable to Chloroethane

Agency	Description	Information	Reference
NIOSH	REL (up to 10-hour TWA)	Handle with caution in the workplace[b]	NIOSH 2018, 2019
	IDLH	3,800 ppm[c]	NIOSH 1994
	Emergency Criteria		
EPA	AEGLs-air	No data	EPA 2018b
DOE	PACs-air		DOE 2018a
	PAC-1[d]	300 ppm	
	PAC-2[d]	5,100 ppm[e]	
	PAC-3[d]	20,000 ppm[f]	

[a]Group 3: not classifiable as to carcinogenicity to humans.
[b]Due to structural similarity to other chloroethanes shown to be carcinogenic in animals.
[c]10% of the LEL for chloroethane.
[d]Definitions of PAC terminology are available from DOE (2018b).
[e]Between 10 and 50% of the LEL.
[f]Between 50 and 100% of the LEL.

AEGL = acute exposure guideline levels; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; LEL = lower explosive limit; 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; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

Ahlert RC, Enzminger JD. 1992. Anaerobic processes for the dechlorination of 1,1,1-trichloroethane. J Environ Sci Health A 27(7):1675-1699. https://doi.org/10.1080/10934529209375820.

Alabdulhadi A, Ramadan A, Devey P, et al. 2019. Inhalation exposure to volatile organic compounds in the printing industry. J Air Waste Manag Assoc 69(10):1142-1169. https://doi.org/10.1080/10962247.2019.1629355.

Al-Ajmi AM, Morad MA, Cooper PE, et al. 2018. Reversible ethyl chloride neurotoxicity: A case report. Can J Neurol Sci 45(1):119-120. https://doi.org/10.1017/cjn.2017.262.

Amoore JE, Hautala E. 1983. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J Appl Toxicol 3(6):272-290. https://doi.org/10.1002/jat.2550030603.

Andersen ME, Krishnan K. 1994. Relating in vitro to in vivo exposures with physiologically based tissue dosimetry and tissue response models. In: Salem H, ed. Animal test alternatives: Refinement, reduction, replacement. New York, NY: Marcel Dekker, Inc., 9-25.

Atkinson R. 1985. Kinetics and mechanisms of the gas-phase reactions of hydroxyl radical with organic compounds under atmospheric conditions. Chem Rev 86(1):69-201. https://doi.org/10.1021/cr00071a004.

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. 1991. Health assessment for Beacon Heights Landfill Site, Beacon Falls, Connecticut, Region 1. Cerclis No. CTD072122062. Addendum. Agency for Toxic Substances and Disease Registry. PB91205666. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB91205666.xhtml. April 12, 2023.

ATSDR. 2022a. Chloroethane. Full SPL data. Substance priority list (SPL) resource page. Agency for Toxic Substances and Disease Registry. https://www.atsdr.cdc.gov/SPL/resources/index.html. June 8, 2023.

ATSDR. 2022b. Sanders2015 HLCs used in SHOWER Model v3 and PHAST. Atlanta, GA: Agency for Toxic Substances and Disease Registry.

Baek NH, Jaffe PR, Shingal N. 1990. Simulating the degradation of TCE under methanogenesis. J Environ Sci Health A 25(8):987-1005. https://doi.org/10.1080/10934529009375612.

Barletta B, Meinardi S, Simpson IJ, et al. 2009. Characterization of volatile organic compounds (VOCs) in Asian and north American pollution plumes during INTEX-B: identification of specific Chinese air mass tracers. Atmos Chem Phys 9(14):5371-5388. https://doi.org/10.5194/acp-9-5371-2009.

Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8(4):471-486. https://doi.org/10.1016/0273-2300(88)90047-5.

Barrio-Lage G, Parsons FZ, Nassar RS, et al. 1986. Sequential dehalogenation of chlorinated ethenes. Environ Sci Technol 20(1):96-99. https://doi.org/10.1021/es00143a013.

Bircher AJ, Hampl K, Hirsbrunner P, et al. 1994. Allergic contact dermatitis from ethyl chloride and sensitization to dichlorodifluoromethane (CFC 12). Contact Dermatitis 31(1):41-44. https://doi.org/10.1111/j.1600-0536.1994.tb01904.x.

Breslin WJ, Berdasco NM, Phillips JE, et al. 1988. Ethyl chloride effects on estrous cycling in B6C3F1 mice (final report) with cover letter dated 112188. Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0517350. 86-890000040. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0517350.xhtml. January 10, 2023.

Broussard LA, Broussard AK, Pittman TS, et al. 2000. Death due to inhalation of ethyl chloride. J Forensic Sci 45(1):223-225.

8. REFERENCES

Bucher JR, Morgan DL, Adkins B, et al. 1995. Early changes in sex hormones are not evident in mice exposed to the uterine carcinogens chloroethane or bromoethane. Toxicol Appl Pharmacol 130(1):169-173. https://doi.org/10.1006/taap.1995.1022.

Budavari S, O'Neil MJ, Smith A, et al. 1989. Ethyl chloride. In: The Merck index: An encyclopedia of chemicals, drugs, and biologicals. 11th ed. Rahway, NJ: Merck & Co., 597.

Budavari S, O'Neil MJ, Smith A, et al. 1996. Ethyl chloride. In: The Merck index: An encyclopedia of chemicals, drugs, and biologicals. 12th ed. Rahway, NJ: CRC Press, 645.

Burk T, Zarus G. 2013. Community exposures to chemicals through vapor intrusion: A review of past ATSDR public health evaluations. J Environ Health 75(9):36-41.

Bush OF, Bittenbender G, Adriani J. 1952. Electrocardiographic changes during ethyl chloride and vinyl ether anesthesia in the dog and man. Anesthesiology 13(2):197-202. https://doi.org/10.1097/00000542-195203000-00013.

Bysshe SE. 1982. Bioconcentration factors in aquatic organisms. In: Lyman WJ, Reehl WF, Rosenblatt DH, eds. Handbook of chemical property estimation methods. New York, NY: McGraw-Hill Book Co., 5-1 to 5-30.

CDC. 2017. Volatile organic compounds and trihalomethanes/MTBE - Blood (VOCWB_H). National health and nutrition examination survey: 2013-2014 Data documentation, codebook, and frequencies. https://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/VOCWB_H.htm. August 1, 2023.

CDC. 2018. Volatile organic compounds and trihalomethanes/MTBE - Blood - Special sample (VOCWBS_I). National health and nutrition examination survey: 2015-2016 Data documentation, codebook, and frequencies. https://wwwn.cdc.gov/Nchs/Nhanes/2015-2016/VOCWB_I.htm. August 1, 2023.

CDC. 2020. Volatile organic compounds and trihalomethanes/MTBE - Blood (VOCWB_J). National health and nutrition examination survey: 2017-2018 Data documentation, codebook, and frequencies. https://wwwn.cdc.gov/Nchs/Nhanes/2017-2018/VOCWB_J.htm. August 1, 2023.

Chang HL, Alvarez-Cohen L. 1996. Biodegradation of individual and multiple chlorinated aliphatic hydrocarbons by methane-oxidizing cultures. Appl Environ Microbial 62(9):3371-3377. https://doi.org/10.1128/aem.62.9.3371-3377.1996.

Clewell HJ. 1995. The application of physiologically based pharmacokinetic modeling in human health risk assessment of hazardous substances. Toxicol Lett 79(1-3):207-217. https://doi.org/10.1016/0378-4274(95)03372-r.

Clewell HJ, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1(4):111-113. https://doi.org/10.1177/074823378500100408.

Cline PV, Viste DR. 1985. Migration and degradation patterns of volatile organic compounds. Waste Management Research 3(4):351-360. https://doi.org/10.1016/0734-242X(85)90128-4.

CMR. 1982. Ethyl chloride production cuts tied to EPA lead phasedown; exports, future seen doubtful. Vol. 7. Chemical Marketing Reporter. 13-14.

Cole WH. 1956. Ethyl chloride as a gaseous anesthetic. Anesthesia 11:156-159.

Cole WH. 1967. A re-evaluation of the pharmacology of ethyl chloride. Med J Aust 1(17):853-855. https://doi.org/10.5694/j.1326-5377.1967.tb21831.x.

Daubert TE, Danner RP. 1985. Chloroethane. In: Data compilation tables of properties of pure compounds. New York, NY: American Institute of Chemical Engineers.

Davidson BM. 1925. Studies of intoxication: V. The action of ethyl chloride. J Pharmacol Exp Ther 26:137-142.

Dawkins CJM. 1964. Safety of vinyl ether. Br Med J 2(5382):538. https://doi.org/10.1136/bmj.1.5382.563.

Demarest C, Torgovnick J, Sethi NK, et al. 2011. Acute reversible neurotoxicity associated with inhalation of ethyl chloride: a case report. Clin Neurol Neurosurg 113(10):909-910. https://doi.org/10.1016/j.clineuro.2011.05.004.

Dobkin AB, Byles PH. 1971. The pharmacodynamics of divinyl ether, ethylchloride, fluroxene, nitrous oxide and trichloroethylene. In: Soma LR, ed. Textbook of veterinary anesthesia. Baltimore, MD: Williams & Wilkins, 94-104.

DOE. 2018a. Table 2: Protective action criteria (PAC) rev. 29a based on applicable 60-minute AEGLs, ERPGs, or TEELs. The chemicals are listed in alphabetical order. June 2018. U.S. Department of Energy. https://edms3.energy.gov/pac/docs/Revision_29A_Table2.pdf. March 15, 2023.

DOE. 2018b. Protective action criteria (PAC) with AEGLs, ERPGs, & TEELs: Rev. 29A, June 2018. U.S. Department of Energy. https://edms3.energy.gov/pac/. July 6, 2022.

Dow. 1941. Toxicity of ethyl chloride. Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0517041. 86-870002251. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0517041.xhtml. January 10, 2023.

Dow. 1985. Initial submission: Ethyl chloride: Inhalation teratology probe study in CF-1 mice (final report) with cover letter dated 102591 (sanitized). Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8E. OTS0534634. 88-9200000184S. 8EHQ-1091-1538S. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0534634.xhtml. January 10, 2023.

Dow. 1992. Ethyl chloride: Disposition and metabolism in female Fischer 344 rats and B6C3F1 mice following inhalation exposure with cover letter dated 012893. Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0543464. 86930000120. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0543464.xhtml. August 15, 2022.

Dow. 1995. Ethyl chloride: Palatability and 14-day drinking water toxicity study in Fischer 344 rats, with cover letter dated 12/22/1998. (sanitized). Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0573872. 86990000022S. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0573872.xhtml. January 12, 2023.

Duddleston KN, Arp DJ, Bottomley PJ. 2002. Biodegradation of monohalogenated alkanes by soil NH(3)-oxidizing bacteria. Appl Microbiol Biotechnol 59(4-5):535-539. https://doi.org/10.1007/s00253-002-1031-7.

Ebert R, Fedtke N, Certa H, et al. 1994. Genotoxicity studies with chloroethane. Mutat Res 322(1):33-44. https://doi.org/10.1016/0165-1218(94)90030-2.

El-Masri HA, Mumtaz MM, Yushak ML. 2004. Application of physiologically-based pharmacokinetic modeling to investigate the toxicological interaction between chlorpyrifos and parathion in the rat. Environ Toxicol Pharmacol 16(1-2):57-71. https://doi.org/10.1016/j.etap.2003.10.002.

EMMI. 1997. Method 211.1: Organochlorine residues for fatty foods: Used by: FDA. Environmental monitoring methods index. U.S. Environmental Protection Agency.

EPA. 1977. Industrial process profiles for environmental use: Chapter 6. The industrial organic chemical industry. Research Triangle Park, NC: U.S. Environmental Protection Agency. PB281478. EPA600277023F. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB281478.xhtml. April 12, 2023.

EPA. 1979. Water-related environmental fate of 129 priority pollutants. Vol. II: Halogenated aliphatic hydrocarbons, halogenated ethers, monocyclic aromatics, phthalate esters, polycyclic aromatic hydrocarbons, nitrosamines, and miscellaneous compounds. Washington, DC: U.S. Environmental Protection Agency. PB80204381. EPA440479029b. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB80204381.xhtml. April 12, 2023.

EPA. 1981. Atmospheric measurements of selected hazardous organic chemicals. Research Triangle Park, NC: U.S. Environmental Protection Agency. PB81200628. EPA600381032. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB81200628.xhtml#. April 12, 2023.

EPA. 1982. Aquatic fate process data for organic priority pollutants. Washington, DC: U.S. Environmental Protection Agency. PB87169090. EPA400481014. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB87169090.xhtml. June 15, 2023.

EPA. 1985. Regulations of fuel and fuel additives, gasoline lead content. U.S. Environmental Protection Agency. Fed Regist 50(45):9386-9399.

EPA. 1986a. Methods for the determination of organic compounds in finished drinking water and raw source water. Cincinnati, OH: U.S. Environmental Protection Agency. EPA601B860001. F0115-08. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=940034LY.txt. April 12, 2023.

EPA. 1986b. Superfund record of decisions (EPA Region 3): Tybouts Corner Landfill, New Castle County, Delaware, March 1986. Washington, DC: U.S. Environmental Protection Agency. EPARODR0386019. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=91003AMA.txt. April 12, 2023.

EPA. 1986c. Superfund record of decision: Blosenski Landfill, PA. Washington, DC: U.S. Environmental Protection Agency. EPARODR0386029. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=91002Z6I.txt. April 12, 2023.

EPA. 1988. Analysis of Clean Water Act effluent guidelines pollutants. Summary of the chemicals regulated by industrial point source category. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR Parts 400-475. https://www.ecfr.gov/current/title-40/chapter-I/subchapter-N. April 12, 2023.

EPA. 1998. Toxic chemical release reporting: Community right-to-know. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372. https://www.ecfr.gov/current/title-40/chapter-I/subchapter-J/part-372?toc=1. April 12, 2023.

EPA. 2001. Occurrence data from the unregulated contaminant monitoring rule. U.S. Environmental Protection Agency. https://www.epa.gov/sites/default/files/2015-09/r1r2.zip. March 3, 2023.

EPA. 2007. Provisional peer-reviewed toxicity values for chloroethane (CASRN 75-00-3). Cincinnati, OH: U.S. Environmental Protection Agency. EPA690R07007F. https://cfpub.epa.gov/ncea/pprtv/documents/Chloroethane.pdf. March 14, 2023.

EPA. 2009. National primary drinking water regulations. Washington, DC: U.S. Environmental Protection Agency. EPA816F09004. https://www.epa.gov/sites/production/files/2016-06/documents/npwdr_complete_table.pdf. August 2, 2019.

EPA. 2018a. 2018 Edition of the drinking water standards and health advisories. Washington, DC: U.S. Environmental Protection Agency. EPA822F18001. https://www.epa.gov/system/files/documents/2022-01/dwtable2018.pdf. June 15, 2022.

EPA. 2018b. Compiled AEGL values. U.S. Environmental Protection Agency. https://www.epa.gov/sites/production/files/2018-08/documents/compiled_aegls_update_27jul2018.pdf. April 12, 2020.

EPA. 2020. CDR data. U.S. Environmental Protection Agency. https://www.epa.gov/chemical-data-reporting/access-cdr-data#2020. October 26, 2022.

EPA. 2022. Toxic chemical release inventory reporting forms and instructions: Revised 2021 version. U.S. Environmental Protection Agency. EPA740B22002. https://ordspub.epa.gov/ords/guideme_ext/guideme_ext/guideme/file/ry_2021_rfi.pdf. August 22, 2023.

EPA. 2023a. 2017 NEI data: Chloroethane. U.S. Environmental Protection Agency. https://www.epa.gov/air-emissions-inventories/2017-national-emissions-inventory-nei-data. October 24, 2022.

EPA. 2023b. Air Quality System (AQS) data. U.S. Environmental Protection Agency. https://www.epa.gov/aqs. December 5, 2022.

EPA. 2023c. Chloroethane. Sampling methods for HAPS (Core HAPS and VOCs). U.S. Environmental Protection Agency. https://aqs.epa.gov/aqsweb/documents/codetables/methods_haps.html. August 1, 2023.

FDA. 2023. Substances added to food. U.S. Food and Drug Administration. https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=FoodSubstances. March 14, 2023.

Fidler AT, Baker EL, Letz RE. 1987. Estimation of long term exposure to mixed solvents from questionnaire data: a tool for epidemiological investigations. Br J Ind Med 44(2):133-141. https://doi.org/10.1136/oem.44.2.133.

Fedtke N, Certa H, Ebert R, et al. 1994a. Species differences in the biotransformation of ethyl chloride: I. Cytochrome P450-dependent metabolism. Arch Toxicol 68:158-166. https://doi.org/10.1007/s002040050049.

Fedtke N, Certa H, Ebert R, et al. 1994b. Species differences in the biotransformation of ethyl chloride: II. GSH-dependent metabolism. Arch Toxicol 68(4):217-223. https://doi.org/10.1007/s002040050060.

Ferrario JB, Lawler GC, Deleon IR, et al. 1985. Volatile organic pollutants in biota and sediments of Lake Pontchartrain. Bull Environ Contam Toxicol 34(2):246-255. https://doi.org/10.1007/BF01609730.

Finch CK, Lobo BL. 2005. Acute inhalant-induced neurotoxicity with delayed recovery. Ann Pharmacother 39(1):169-172. https://doi.org/10.1345/aph.1E159.

Finer B. 1966. Divinyl ether and ethyl chloride for outpatients. Acta Anaesthesiol Scand Suppl 25:410-412.

Firdaus R, Sukmono B, Melati AC, et al. 2018. Comparison between vapocoolant spray and eutectic mixture of local anesthetics cream in reducing pain during spinal injections. Anesthesiol Res Pract 2018:5050273. https://doi.org/10.1155/2018/5050273.

Fiserova-Bergerova V, Pierce JT, Droz PO. 1990. Dermal absorption potential of industrial chemicals: Criteria for skin notation. Am J Ind Med 17(5):617-635. https://doi.org/10.1002/ajim.4700170507.

Fisher EM, Koshland CP. 1990. Numerical simulation of the thermal destruction of some chlorinated C1 and C2 hydrocarbons. J Air Waste Manage Assoc 40(10):1384-1390. https://doi.org/10.1080/10473289.1990.10466790.

Florentine BD, Frankel K, Raza A, et al. 1997. Local anesthesia for fine-needle aspiration biopsy of palpable breast masses: the effectiveness of a jet injection system. Diagn Cytopathol 17(6):472-476. https://doi.org/10.1002/(sici)1097-0339(199712)17:6<472::aid-dc18>3.0.co;2-j.

Fossum K, Love SL, April MD. 2016. Topical ethyl chloride to reduce pain associated with venous catheterization: a randomized crossover trial. Am J Emerg Med 34(5):845-850. https://doi.org/10.1016/j.ajem.2016.01.039.

Gal-Oz A, Rogowski O, Swartzon M, et al. 2010. Ethyl chloride as an antipruritic agent: a double-blind placebo-controlled prospective study. Dermatology 221(4):373-377. https://doi.org/10.1159/000321720.

Gal-Oz A, Kivity S, Shacham Y, et al. 2015. Prevention of pruritus with ethyl-chloride in skin prick test: a double-blind placebo-controlled prospective study. Allergy Asthma Clin Immunol 11(1):25. https://doi.org/10.1186/s13223-015-0091-z.

Gargas ML, Burgess RJ, Voisard DE, et al. 1989. Partition coefficients of low-molecular weight volatile chemicals in various liquids and tissues. Toxicol Appl Pharmacol 98(1):87-99. https://doi.org/10.1016/0041-008X(89)90137-3.

Gargas ML, Clewell HJ, Andersen ME. 1990. Gas uptake inhalation techniques and the rates of metabolism of chloromethanes, chloroethanes, and chloroethylenes in the rat. Inhal Toxicol 2(3):295-319. https://doi.org/10.3109/08958379009145260.

Gargas ML, Sweeney LM, Himmelstein MW, et al. 2008. Physiologically based pharmacokinetic modeling of chloroethane disposition in mice, rats, and women. Toxicol Sci 104(1):54-66. https://doi.org/10.1093/toxsci/kfn064.

Gohlke R, Schmidt P. 1972. [Subacute action of low concentrations of chlorinated ethanes on rats with and without additional ethanol-treatment. II. Histological, histochemical and morphometrical studies]. Int Arch Arbeitsmed 30:298-312. (German)

Gossett JM. 1987. Measurement of Henry's Law constants for C1 and C2 chlorinated hydrocarbons. Environ Sci Technol 21(2):202-208. https://doi.org/10.1021/ES00156A012.

Gould JP, Ramsey RE, Giabbai M, et al. 1983. Formation of volatile haloorganic compounds in the chlorination of municipal landfill leachates. In: Jolley RA, ed. Water chlorination environment impact and health effects. Vol. 4. Michigan: Ann Arbor Science, 525-539.

Graedel TE, Hawkins DT, Claxton LD. 1986. Chlorinated hydrocarbons. In: Atmospheric chemical compounds sources, occurrence and bioassay. New York, NY: Academic Press, 461.

Grimsrud EP, Rasmussen RA. 1975. Survey and analysis of halocarbons in the atmosphere by gas chromatography-mass spectrometry. Atmos Environ 9(11):1014-1017. https://doi.org/10.1016/0004-6981(75)90022-0.

Hager L, Kamp F, Proebstl L, et al. 2021. Inhalant abuse of ethyl chloride spray: A case report. Fortschr Neurol Psychiatr 89(07/08):382-384. https://doi.org/10.1055/a-1483-9865.

Haid B, White JM, Morris LE. 1954. Observations of cardiac rhythm during ethyl chloride anesthesia in the dog. Curr Res Anesth Analg 33(5):315-325.

Haider K. 1980. Degradation of chlorinated aliphatic and aromatic compounds by aerobic and anaerobic soil microorganisms. In: Second environmental research programme 1976-80: Reports on research sponsored under the first phase: 1976-80. Luxembourg: Commission of the European Communities, 200-204.

Hes JP, Cohn DF, Streifler M. 1979. Ethyl chloride sniffing and cerebellar dysfunction (case report). Isr Ann Psychiatr Relat Discip 17(2):122-125.

Holliger C, Schraa G, Stupperich E, et al. 1992. Evidence for the involvement of corrinoids and factor F430 in the reductive dechlorination of 1,2-dichloroethane by Methanosarcina barkeri. J Bacterial 174(13):4427-4434. https://doi.org/10.1128/jb.174.13.4427-4434.1992.

Hommes NG, Russell SA, Bottomley PJ, et al. 1998. Effects of soil on ammonia, ethylene, chloroethane, and 1,1,1-trichloroethane oxidation by Nitrosomonas europaea. Appl Environ Microbiol 64(4):1372-1378. https://doi.org/10.1128/aem.64.4.1372-1378.1998.

Horvath AL. 1982. Chloroethane. In: Halogenated hydrocarbons solubility-miscibility with water. New York, NY: Marcel Dekker, Inc., 494-495.

Howard CJ, Evenson KM. 1976. Rate constants for the reactions of OH with ethane and some halogen substituted ethanes at 296K. J Chem Phys 64(11):4303-4306. https://doi.org/10.1063/1.432115.

Hubrich C, Stuhl F. 1980. The ultraviolet absorption of some halogenated methanes and ethanes of atmospheric interest. J Photochem 12(2):93-107. https://doi.org/10.1016/0047-2670(80)85031-3.

IARC. 1991. Volume 52: Chlorinated drinking-water; chlorination by-products; some other halogenated compounds; cobalt and cobalt compounds. IARC Monographs on the evaluation of carcinogenic risks to humans. Lyon, France: International Agency for Research on Cancer. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono52.pdf. April 12, 2023.

IARC. 1999. Volume 71: Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. IARC Monographs on the evaluation of carcinogenic risks to humans. Lyon, France: International Agency for Research on Cancer. https://monographs.iarc.who.int/wp-content/uploads/2018/06/mono71.pdf. April 12, 2023.

Im YG, Park HJ, Chae HY, et al. 2012. Comparison of changes in facial skin temperature caused by ethyl chloride spraying, ice block rubbing and cold gel packing in healthy subjects. J Oral Rehabil 39(12):931-940. https://doi.org/10.1111/joor.12007.

IRIS. 1991. Chemical assessment summary: Ethyl chloride; CASRN 75-00-3. Integrated Risk Information System. Washington, DC: U.S. Environmental Protection Agency. https://iris.epa.gov/static/pdfs/0523_summary.pdf. March 14, 2023.

Irkoren S, Ozkan HS, Karaca H. 2015. A clinical comparison of EMLA cream and ethyl chloride spray application for pain relief of forehead botulinum toxin injection. Ann Plast Surg 75(3):272-274. https://doi.org/10.1097/sap.0000000000000121.

Jaffe HH, Orchin M. 1962. Chloroethane. In: Theory and application of ultraviolet spectroscopy. New York, NY: John Wiley and Sons, Inc., 173-174.

Jeffers PM, Wolfe NL. 1996. Homogeneous hydrolysis rate constants-Part II: Additions, corrections, and halogen effects. Environ Toxicol Chem 15(7):1066-1070. https://doi.org/10.1002/etc.5620150708.

Juliá-Romero C, Valls-Gil N, Amaya-Paladino L. 2021. Acute poisoning due to inhaled ethyl chloride. Med Clin (Barc) 157(11):550-551. https://doi.org/10.1016/j.medcli.2020.12.027.

Kenig EE. 1956. [Changes in the peripheral nervous system through the effects of ethyl chloride] (abstract). Biological Abstracts 35:18811.

Kobayashi H, Rittmann BE. 1982. Microbial removal of hazardous organic compounds. Environ Sci Technol 16(3):170a-183a. https://doi.org/10.1021/es00097a002.

Konietzko H. 1984. Chlorinated ethanes: Sources, distribution, environmental impact and health effects. In: Hazard Assessment of Chemicals: Current Developments. Vol. 3. Academic Press, Inc., 401-448.

Kriechbaumer N, Hemmer W, Focke M, et al. 1998. Sensitization to ethyl chloride in a handball player. Contact Dermatitis 38(4):227-228. https://doi.org/10.1111/j.1600-0536.1998.tb05724.x.

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.

Kuschinsky G. 1970. [Death caused by general anesthesia with ethyl chloride]. Dtsch Med Wochenschr 95(49):2499. (German)

Kuthiah N, Er C. 2019. "High" on muscle spray - ethyl chloride abuse. Ann Acad Med Singap 48(2):67-68.

Lamartiniere CA. 1981. The hypothalamic-hypophyseal-gonadal regulation of hepatic glutathione Stransferases in the rat. Biochem J 198(1):211-217. https://doi.org/10.1042/bj1980211.

Lamartiniere CA, Lucier GW. 1983. Endocrine regulation of xenobiotic conjugation enzymes. Basic Life Sci 24:295-312. https://doi.org/10.1007/978-1-4684-4400-1_16.

Landry TD, Ayres JA, Johnson KA, et al. 1982. Ethyl chloride: a two-week inhalation toxicity study and effects on liver non-protein sulfhydryl concentrations. Fundam Appl Toxicol 2(5):230-234. https://doi.org/10.1016/s0272-0590(82)80032-8.

Landry TD, Johnson KA, Momany-Pfruender JJ, et al. 1987. Ethyl chloride: 11-day continuous exposure inhalation toxicity study in B6C3F1 mice. Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA section 8. OTS0517040. 86-870002250. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0517040.xhtml. April 12, 2023.

Landry TD, Johnson KA, Phillips JE, et al. 1989. Ethyl chloride: 11-day continuous exposure inhalation toxicity study in B6C3F1 mice. Fundam Appl Toxicol 13(3):516-522. https://doi.org/10.1016/0272-0590(89)90288-1.

Laughton PM, Robertson RE. 1959. Solvolysis in hydrogen and deuterium oxide. Can J Chem 37(9):1491-1497. https://doi.org/10.1139/v59-219.

Lawson JIM. 1965. Ethyl chloride. Brit J Anaesth 37(9):667-670. https://doi.org/10.1093/bja/37.9.667.

Lazarew NW. 1929. [Concerning the strength of the narcotic effects of the vapors of the chlorine derivatives of the methanes, ethanes and ethylenes]. Arch Exp Pathol Pharmakol 141:19-24. (German)

Lehmann KB, Flury F. 1943. Chloroethane. In: Toxicology and hygiene of industrial solvents. Baltimore, MD: William and Wilkins Co., 154-157.

Lide DR. 2005. Chloroethane. In: CRC Handbook of chemistry and physics. Boca Raton, FL: CRC Press, 3-110 to 113-111.

Lyman WJ. 1982. Adsorption coefficient for soils and sediments. In: Lyman WJ, Reehl WF, Rosenblatt DH, eds. Handbook of chemical property estimation methods. New York, NY: McGraw-Hill Book Co., 4-1 to 5-29.

Mabey W, Mill T. 1978. Critical review of hydrolysis of organic compounds in water under environmental conditions. J Phys Chem Ref Data 7(2):383-415. https://doi.org/10.1063/1.555572.

Marbach JJ. 1996. Temporomandibular pain and dysfunction syndrome. History, physical examination, and treatment. Rheum Dis Clin North Am 22(3):477-498. https://doi.org/10.1016/s0889-857x(05)70283-0.

Matsunaga H, Tsuji K, Saito T. 1976. Foamed plastics of resin compositions comprising pullulan type resins and thermoplastic resins and process for producing the same. United States Patent. US3976605A. https://patents.google.com/patent/US3976605. November 27, 2023.

McLean S, Robinson J, Starmer GA, et al. 1967. The influence of anaesthetic agents on the formation of methaemoglobin induced by aniline in cats. J Pharm Pharmac 19(12):803-809. https://doi.org/10.1111/j.2042-7158.1967.tb09547.x.

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

Moon YE, Kim SH. 2014. Effects of ethyl chloride spray on pain and parameters of needle electromyography in the upper extremity. Am J Phys Med Rehabil 93(10):869-875. https://doi.org/10.1097/phm.0000000000000106.

Moon YE, Lee MY, Kim DH. 2017. Preventive effect of a vapocoolant spray on propofol-induced pain: a prospective, double-blind, randomized study. J Anesth 31(5):703-708. https://doi.org/10.1007/s00540-017-2386-3.

Moon YE, Kim SH, Seok H, et al. 2020. Comparison of the effects of vapocoolant spray and topical anesthetic cream on pain during intraarticular injection of the shoulder: A randomized double-blind controlled trial. Arch Phys Med Rehabil 101(10):1689-1695. https://doi.org/10.1016/j.apmr.2020.04.021.

Morgan A, Black A, Belcher DR. 1970. The excretion in breath of some aliphatic halogenated hydrocarbons following administration by inhalation. Ann Occup Hyg 13(4):219-233. https://doi.org/10.1093/annhyg/13.4.219.

Morris TE, Tasto WD. 1979. Ethyl chloride. In: Grayson M, Eckroth D, eds. Kirk-Othmer encyclopedia of chemical technology. Vol. V. 3rd ed. New York, NY: John Wiley and Sons, Inc., 714-722.

Morris LE, Noltensmeyer MH, White JM. 1953. Epinephrine induced cardiac irregularities in the dog during anesthesia with trichloroethylene, cyclopropane, ethyl chloride and chloroform. Anesthesiology 14(2):153-158. https://doi.org/10.1097/00000542-195303000-00006.

Morselli PL, France-Morselli R, Bossi L. 1980. Clinical pharmacokinetics in newborns and infants. Clin Pharmacokin 5(6):485-527. https://doi.org/10.2165/00003088-198005060-00001.

Mumtaz MM, Ray M, Crowell SR, et al. 2012a. Translational research to develop a human PBPK models tool kit-volatile organic compounds (VOCs). J Toxicol Environ Health A 75(1):6-24. https://doi.org/10.1080/15287394.2012.625546.

Mumtaz M, Fisher J, Blount B, et al. 2012b. Application of physiologically based pharmacokinetic models in chemical risk assessment. J Toxicol 2012:904603. https://doi.org/10.1155/2012/904603.

Myers V. 1983. Remedial activity at the Miami Drum Site, Florida. In: National conference management of uncontrolled hazardous waste sites, October 31-November 2, 1983. Silver Spring, MD: Hazardous Materials Control Research Institute, 354-357.

NAS/NRC. 2006. Human biomonitoring for environmental chemicals. Washington, DC: The National Academies Press, National Research Council. https://doi.org/10.17226/11700.

Naylor LM, Loehr RC. 1982. Priority pollutants in municipal sewage sludge. Biocycle 23(6):18-22.

Nibhanipudi KV. 2015. Effect of chloroethane spray in the treatment of spastic torticollis in children and adolescents. Glob Pediatr Health 2(Jun):2333794x15591567. https://doi.org/10.1177/2333794x15591567.

NIOSH. 1994. Ethyl chloride. Immediately dangerous to life or health concentrations (IDLH). National Institute for Occupational Safety and Health. https://www.cdc.gov/niosh/idlh/75003.html. March 14, 2023.

NIOSH. 2018. Appendix C. Supplementary exposure limits. NIOSH pocket guide to chemical hazards. National Institute for Occupational Safety and Health. https://www.cdc.gov/niosh/npg/nengapdxc.html. March 14, 2023.

NIOSH. 2019. Ethyl chloride. NIOSH pocket guide to chemical hazards. National Institute for Occupational Safety and Health. https://www.cdc.gov/niosh/npg/npgd0267.html. March 14, 2023.

NLM. 2023. PubChem compound summary: Chloroethane (CASRN: 75-00-3). https://pubchem.ncbi.nlm.nih.gov/compound/6337. April 13, 2023.

Noble DA. 1979. Another hazard of pierced ears [letter]. Br Med J 1(6156):125. https://doi.org/10.1136/bmj.1.6156.125-c.

Nordin C, Rosenqvist M, Hollstedt C. 1988. Sniffing of ethyl chloride - An uncommon form of abuse with serious mental and neurological symptoms. Int J Addict 23(6):623-627. https://doi.org/10.3109/10826088809039224.

NTP. 1989. Toxicology and carcinogenesis studies of chloroethane (ethyl chloride) (CAS No. 75-00-3) in F344/N rats and B6C3F1 mice (inhalation studies). Research Triangle Park, NC: National Toxicology Program. PB90225053. NTP TR 346. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr346.pdf. April 12, 2023.

NTP. 2013. Draft OHAT approach for systematic review and evidence integration for literature-based health assessments - February 2013. National Toxicology Program. https://ntp.niehs.nih.gov/ntp/ohat/evaluationprocess/draftohatapproach_february2013.pdf. March 14, 2023.

NTP. 2015. OHAT risk of bias rating tool for human and animal studies. National Toxicology Program. https://ntp.niehs.nih.gov/ntp/ohat/pubs/riskofbiastool_508.pdf. March 19, 2019.

NTP. 2021. CASRN index. In: Report on carcinogens. 15th ed. National Toxicology Program, https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/roc/index.html. January 10, 2022.

OSHA. 2021a. Occupational safety and health standards. Subpart Z - Toxic and hazardous substances. Air contaminants. Table Z-1: Limits for air contaminants. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000. https://www.govinfo.gov/content/pkg/CFR-2021-title29-vol6/pdf/CFR-2021-title29-vol6-sec1910-1000.pdf. August 28, 2022.

OSHA. 2021b. Occupational safety and health standards for shipyard employment. Subpart Z - Toxic and hazardous substances. Air contaminants. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1915.1000. https://www.govinfo.gov/content/pkg/CFR-2021-title29-vol7/pdf/CFR-2021-title29-vol7-sec1915-1000.pdf. August 28, 2022.

OSHA. 2021c. Safety and health regulations for construction. Subpart D - Occupational health and environment controls. Gases, vapors, fumes, dusts, and mists. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.55. https://www.govinfo.gov/content/pkg/CFR-2021-title29-vol8/pdf/CFR-2021-title29-vol8-sec1926-55.pdf. August 28, 2022.

Otson R. 1987. Purgeable organics in Great Lakes raw and treated water. Int J Environ Anal Chem 31(1):41-53. https://doi.org/10.1080/03067318708077128.

Oura E, Raiha NC, Suomalaimen H. 1966. Influence of some alcohols and narcotics on the adenosine phosphates in the liver of the mouse. Ann Med Exp Biol Fenn 45(1):57-62.

Parker JC, Casey GE, Bahlman LJ, et al. 1979. NIOSH current intelligence bulletin No. 27. Chloroethanes: review of toxicity. Am Ind Hyg Assoc J 40(3):A46-60.

Pellizzari ED, Hartwell TD, Harris BSH, et al. 1982. Purgeable organic compounds in mother's milk. Bull Environ Contam Toxicol 28(3):322-328. https://doi.org/10.1007/BF01608515.

Picut CA, Aoyama H, Holder JW, et al. 2003. Bromoethane, chloroethane and ethylene oxide induced uterine neoplasms in B6C3F1 mice from 2-year NTP inhalation bioassays: pathology and incidence data revisited. Exp Toxicol Pathol 55(1):1-9. https://doi.org/10.1078/0940-2993-00303.

Pothiawala S, Yong CK, Charles R. 2021. Inhaling muscle spray: A rising trend of abuse. World J Crit Care Med 10(3):43-46. https://doi.org/10.5492/wjccm.v10.i3.43.

8. REFERENCES

Ramsook C, Kozinetz CA, Moro-Sutherland D. 2001. Efficacy of ethyl chloride as a local anesthetic for venipuncture and intravenous cannula insertion in a pediatric emergency department. Pediatr Emerg Care 17(5):341-343. https://doi.org/10.1097/00006565-200110000-00005.

Rao PB, Mohanty CR, Singh N, et al. 2019. Effectiveness of different techniques of ethyl chloride spray for venepuncture-induced pain: A randomised controlled trial. Anesth Essays Res 13(3):568-571. https://doi.org/10.4103/aer.AER_103_19.

Rasche ME, Hicks RE, Ilyman MR, et al. 1990. Oxidation of monohalogenated ethanes and n-chlorinated alkanes by whole cells of Nitrosomonas europaea. J Bacterial 172(9):5368-5373. https://doi.org/10.1128/jb.172.9.5368-5373.1990.

RePORTER. 2023. Chloroethane. Research Portfolio Online Reporting Tools. National Institutes of Health. https://reporter.nih.gov/. March 17, 2023.

Richards RN. 2009. Ethyl chloride spray for sensory relief for botulinum toxin injections of the hands and feet. J Cutan Med Surg 13(5):253-256. https://doi.org/10.2310/7750.2009.08072.

Rodriguez NA, Ascaso FJ. 2012. Ocular surface frostbite secondary to ethyl chloride spray. Cutan Ocul Toxicol 31(1):77-80. https://doi.org/10.3109/15569527.2011.607201.

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. https://doi.org/10.1289/ehp.1307972.

Rui W, Long G, Li G, et al. 2017. Effects of ethyl chloride spray on early recovery after total knee arthroplasty: A prospective study. J Orthop Sci 22(1):89-93. https://doi.org/10.1016/j.jos.2016.10.005.

Ruiz P, Ray M, Fisher J, et al. 2011. Development of a human Physiologically Based Pharmacokinetic (PBPK) Toolkit for environmental pollutants. Int J Mol Sci 12(11):7469-7480. https://doi.org/10.3390/ijms12117469.

Rüsch D, Koch T, Seel F, et al. 2017. Vapocoolant spray versus lidocaine infiltration for radial artery cannulation: A prospective, randomized, controlled clinical trial. J Cardiothorac Vasc Anesth 31(1):77-83. https://doi.org/10.1053/j.jvca.2016.06.008.

Sabel GV, Clark TP. 1984. Volatile organic compounds as indicators of municipal solid waste leachate contamination. Waste Manag Res 2(2):119-130. https://doi.org/10.1016/0734-242X(84)90135-6.

Schlieve T, Miloro M. 2015. Topical refrigerant spray for pediatric venipuncture for outpatient surgery. Oral Maxillofac Surg Cases 1(2):29-32. https://doi.org/10.1016/j.omsc.2015.05.004.

Schmidt P, Binnewies S, Gohlike R, et al. 1972. [Subacute action of low concentrations of chlorinatedethanes on rats with and without additional ethanol treatment. I. Subacute and chronic toxicity studies with 1,1,2,2-tetrachloroethane]. Int Arch Arbeitsmed 38:283-298. (German)

Schwark T, Schaul M, Schneider S, et al. 2022. Two cases of fatal inhalation of easily available "recreational" substances. Am J Forensic Med Pathol 43(2):186-190. https://doi.org/10.1097/paf.0000000000000740.

Scortichini BH, Johnson KA, Momany-Pfruenderd JJ, et al. 1986. Ethyl chloride: Inhalation teratology study in CF-1 mice. Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA section FYI. OTS0001135. FYI-OTS-0794-1135. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0001135.xhtml. April 12, 2023.

Selby IR, Bowles BJM. 1995. Analgesia for venous cannulation: A comparison of EMLA (5 minute application), lignocaine, ethyl chloride, and nothing. J R Soc Med 88(5):264-267.

Senussi MH, Chalise S. 2015. Acute reversible neurologic deficits due to ethyl chloride sniffing: a case report and review of literature. Am J Ther 22(2):e40-e42. https://doi.org/10.1097/MJT.0b013e3182a32dba.

Shah A, Vidoni A, McGarry S, et al. 2018. Ethyl chloride spray for musculoskeletal ultrasound-guided injections: An alternative to subcutaneous injection of local anesthetic solution. J Clin Ultrasound 46(2):129-131. https://doi.org/10.1002/jcu.22561.

Shepson PB, Kleindiemst TE, Mcelhoe HB. 1987. A cryogenic trap/porous polymer sampling technique for the quantitative determination of ambient volatile organic compound concentrations. Atmos Environ 21(3):579-587. https://doi.org/10.1016/0004-6981(87)90040-0.

Singh HB, Salas LJ, Stiles RE. 1983. Selected man-made halogenated chemicals in the air and oceanic environment. J Geophys Res 88(C6):3675-3683. https://doi.org/10.1029/JC088iC06p03675.

Sipes IG, Gandolfi AJ. 1991. General principles of toxicology. In: Amdur MO, Doull J, Klaassen CD, eds. Casarett and Doull's toxicology: The basic science of poisons. 4th ed. New York, NY: Pergamon Press, 108.

Soueid A, Richard B. 2007. Ethyl chloride as a cryoanalgesic in pediatrics for venipuncture. Pediatr Emerg Care 23(6):380-383. https://doi.org/10.1097/01.pec.0000278396.25129.3f.

Swann RL, Laskowski DA, McCall PJ, et al. 1983. A rapid method for the estimation of the environmental parameters octanol/water partition coefficient, soil sorption constant, water to air ratio and water solubility. Res Rev 85:17-28. https://doi.org/10.1007/978-1-4612-5462-1_3.

Sweeney LM, Gearhart JM. 2020. Examples of physiologically based pharmacokinetic modeling applied to risk assessment. In: Fisher JW, Gearhart JM, Lin Z, eds. Physiologically based pharmacokinetic (PBPK) modeling. Academic Press: 281-299. https://doi.org/10.1016/B978-0-12-818596-4.00011-4.

Swenberg JA, Fedtke N, Fishbein L. 1992. Age-related differences in DNA adduct formation and carcinogenesis of vinyl chloride in rats. In: Guzelian PS, Henry CJ, Olin SS, eds. Similarities and differences between children and adults: Implications for risk assessment. Washington, DC: International Life Sciences Institute Press, 163-171.

Tabak HH, Quave SA, Mashni CI, et al. 1981. Biodegradability studies with organic priority pollutant compounds. J Water Pollut Control Fed 53:1503-1518.

Tan YM, Chan M, Chukwudebe A, et al. 2020. PBPK model reporting template for chemical risk assessment applications. Regul Toxicol Pharmacol 115:104691. https://doi.org/10.1016/j.yrtph.2020.104691.

Tank JC, Georgiadis GM, Bair JM, et al. 2021. Does the use of ethyl chloride improve patient-reported pain scores with negative pressure wound therapy dressing changes? A prospective, randomized controlled trial. J Trauma Acute Care Surg 90(6):1061-1066. https://doi.org/10.1097/ta.0000000000003157.

Thomas R. 1982. Volatilization from water. In: Lyman WJ, Reehl WF, Rosenblatt DH, eds. Handbook of chemical property estimation methods. New York, NY: McGraw Hill Book Co., Chapter 15.

Torkelson TR, Rowe VK. 1981. Ethyl chloride. In: Clayton GD, Clayton FE, eds. Patty's industrial hygiene and toxicology. Vol. 2B. 3rd ed. New York, NY: John Wiley and Sons, Inc., 3480-3483.

TRI21. 2023. Chloroethane. TRI explorer: Providing access to EPA's toxics release inventory data. Washington, DC: U.S. Environmental Protection Agency. https://www.epa.gov/enviro/tri-search. January 21, 2023.

Tu AS, Murray TA, Hatch KM, et al. 1985. In vitro transformation of BALB/c-3T3 cells by chlorinated ethanes and ethylenes. Cancer Lett 28(1):85-92. https://doi.org/10.1016/0304-3835(85)90096-5.

USBM. 1929. Physiological response attending exposure to vapors of methyl bromide, methyl chloride, ethyl bromide and ethyl chloride. U.S. Bureau of Mines. US Public Health Bull 185:1-56.

USGS. 2006. Description, properties, and degradation of selected volatile organic compounds detected in ground water - a review of selected literature. Reston, VA: U.S. Geological Survey. Open-File Report 2006-1338. https://pubs.usgs.gov/of/2006/1338/. June 15, 2023.

van Eekert MHA, Stams AJM, Field JA, et al. 1999. Gratuitous dechlorination of chloroethanes by methanogenic granular sludge. Appl Microbiol Biotechnol 51(1):46-52. https://doi.org/10.1007/s002530051361.

van Ketel WG. 1976. Allergic contact dermatitis from propellants in deodorant sprays in combination with allergy to ethyl chloride. Contact Dermatitis 2(2):115-119. https://doi.org/10.1111/j.1600-0536.1976.tb02996.x.

van Liere EJ, Mazzocco TR, Northup DW. 1966. The effect of cyclopropane, trichloroethylene and ethyl chloride on the uterus of the dog. Am J Obstet Gynecol 994(6):861-867.

Vieira I, Sonnier M, Cresteil T. 1996. Developmental expression of CYP2E1 in the human liver: Hypermethylation control of gene expression during the neonatal period. Eur J Biochem 238(2):476-483. https://doi.org/10.1111/j.1432-1033.1996.0476z.x.

Vogel TM, McCarty PL. 1987. Abiotic and biotic transformations of 1,1,1-trichloroethane under methanogenic conditions. Environ Sci Technol 21(12):1208-1213. https://doi.org/10.1021/es00165a008.

Vogt WG, Walsh JJ. 1985. Volatile organic compounds in gases from landfill simulators. Proc Air Pollution Control Association Annu Meet 78:2-17.

Waibel KH, Katial RK. 2005. Effect of topical vapocoolant spray on skin test wheal, flare, and pain responses. Ann Allergy Asthma Immunol 95(2):149-153. https://doi.org/10.1016/s1081-1206(10)61204-5.

Walsh P, Columb M, Russell R. 2010. A comparison of a Neuropen monofilament and ethyl chloride for assessing loss of touch sensation during combined spinal-epidural anaesthesia for caesarean section. Int J Obstet Anesth 19(4):365-372. https://doi.org/10.1016/j.ijoa.2010.06.010.

Washington JW. 1996. Gas partitioning of dissolved volatile organic compounds in the vadose zone: Principles, temperature effects and literature review. Ground Water 34(4):709-718. https://doi.org/10.1111/j.1745-6584.1996.tb02059.x.

WHO. 2010. Guidelines for indoor air quality: Selected pollutants. World Health Organization. http://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf. April 25, 2012.

WHO. 2022. Guidelines for drinking-water quality. Fourth edition incorporating the first and second addenda. World Health Organization. https://www.who.int/publications/i/item/9789240045064. June 22, 2022.

Williams GM. 1983. DNA repair tests of 11 chlorinated hydrocarbon analogs final report EPA contract. Naylor Dana Institute. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0509403. 40-8324292. 47007 B3C43. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0509403.xhtml. January 10, 2023.

Worrall S, De Jersey J, Wilce PA, et al. 1994. Studies on the usefulness of acetaldehyde-modified proteins and associated antibodies as markers of alcohol abuse. Alcohol & Alcoholism Suppl 2:503-507.

WQP. 2023. Water Quality Portal data: Chloroethane. National Water Quality Monitoring Council. https://www.epa.gov/waterdata/water-quality-data. April 12, 2023.

Wu X, Qu Y, Chemg G, et al. 2013. Molecular identification and conditions for preliminary application of a Bacillus sp. CIESC Journal 64(4):1459-1465. https://doi.org/10.3969/j.issn.0438-1157.2013.04.046. (Chinese)

Yacoub I, Robinson CA, Simmons GT. 1993. Death attributed to ethyl chloride. J Anal Toxicol 17(6):384--385. https://doi.org/10.1093/jat/17.6.384.

Young P, Parker A. 1984. Vapors, odors and toxic gases from landfills. In: Jackson LP, Rohlik AR, Conway RA, eds. Hazardous and industrial waste management and testing: Third symposium. STP851-EB. Philadelphia, PA: ASTM Technical Publication, 24-41.

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. LOAELs for serious health effects (such as irreparable damage to the liver or kidneys, or serious birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

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

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S106-5, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chloroethane
CAS Numbers: 75-00-3
Date: January 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute
MRL: 13 ppm (provisional) (34 mg/m^3)
Critical Effect: Increased incidence of DFFC of skull bones
Reference: Scortichini et al. 1986
Point of Departure: NOAEL of 1,504 ppm ($NOAEL_{HEC}$ of 376 ppm)
Uncertainty Factor: 30
LSE Graph Key: 13
Species: Mouse

MRL Summary: A provisional acute-duration MRL of 13 ppm was derived for chloroethane based on a NOAEL of 1,504 ppm for developmental effects (increased incidence of DFFC of skull bones) in mouse fetuses exposed for 6 hours/day on GDs 6–15 (Scortichini et al. 1986). The NOAEL was adjusted for continuous exposure and converted to a human equivalent concentration ($NOAEL_{HEC}$) of 376.0 ppm and divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans after dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: Developmental and neurological effects were observed at approximately 5,000 ppm following acute-duration inhalation exposure of chloroethane in animals (Table A-1). Two studies looked at developmental effects of chloroethane. In pregnant mice exposed to chloroethane for 6 hours/day on GDs 6–15, an increase in incidence of DFFC of the skull bones (a developmental delay of ossification of small centers of unossified bone of the skull) was seen in the fetuses at 4,946 ppm (Scortichini et al. 1986). Incidence based on number of fetuses affected was significant for dose-response trend, but not in a pairwise comparison to the control group. Incidence data for number of litters affected were not statistically different from controls (by pairwise or trend tests); however, this effect was considered biologically relevant. The second developmental study reported that mouse fetuses exposed to 15,000 ppm for 6 hours/day on GDs 6–15 appeared normal; however, fetuses were not examined for skeletal or visceral alterations (Dow 1985). This study was not included in Table A-1 because no developmental effects occurred in the only treatment group.

Neurological effects have been reported in humans and several animal species. These effects consisted of a feeling of dizziness and intoxication in humans, hyperactivity in mice and dogs, lethargy in rats, and unsteadiness in guinea pigs; however, the study with the lowest LOAEL for neurological effects (Dow 1985) did not report a NOAEL value. Developmental toxicity (increased incidence of DFFC of the skull in fetuses) was selected as the critical effect because Scortichini et al. (1986) provided the lowest LOAEL with an accompanying NOAEL value.

Table A-1. Selected NOAEL and LOAEL Values in Animals Following Acute-Duration Inhalation Exposure to Chloroethane

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Developmental effects					
Mouse (CF-1)	10 days 6 hours/day GDs 6–15	1,504	4,946	Increased incidence of delayed fetal foramina closure (DFFC) of the skull bones (developmental delay of ossification of bones of the skull of fetuses)	Scortichini et al. 1986
Neurological effects					
Human	Up to 22 minutes	ND	13,000	LOAEL: subjective feeling of intoxication, increased reaction times	Davidson 1925
Fisher-344 rat	2 weeks 5 days/week 6 hours/day	3,980	9,980	Slight lethargy	Landry et al. 1982
CD-1 mouse	10 days 6 hours/day GDs 6–15	ND	5,000	Increased activity and stereotypic behavior (highly repetitive running patterns) in dams	Dow 1985
Beagle dog	2 weeks 5 days/week 6 hours/day	3,980	9,980	Hyperactivity during exposure in 1/2 dogs	Landry et al. 1982

[a]Selected study/endpoint for derivation of acute-duration inhalation MRL.

LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level; SLOAEL = serious LOAEL

Selection of the Principal Study: Of the two developmental studies, Scortichini et al. (1986) was selected as the principal study because visceral and skeletal examinations were performed. In addition, this study provided a LOAEL with an accompanying NOAEL value.

Summary of the Principal Study:

Scortichini BH, Johnson KA, Momany-Pfruenderd JJ, et al. 1986. Ethyl chloride: Inhalation teratology study in CF-1 mice. Dow Chemical Company. Submitted to the U.S. Environmental Protection Agency under TSCA section FYI. OTS0001135. FYI-OTS-0794-1135. https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0001135.xhtml. April 12, 2023.

Pregnant CF-1 mice (23–26/group) were exposed to 99.9% pure chloroethane at 0, 491, 1,504, or 4,946 ppm 6 hours/day on GDs 6–15. Body weights were recorded on GDs 6, 9, 12, 15, and 18, and food and water intakes were measured. The animals were sacrificed on GD 18 and the following data were recorded: maternal liver weight; number and position of fetuses *in utero*; number of live and dead fetuses; number and position of resorption sites; weight and sex of each fetus; and gross external alterations. Half of each litter was examined for visceral alterations, and the other half was examined for skeletal alterations.

No maternal toxicity (body weight, food and water intake, liver weight) was observed. There were no effects on pregnancy rate, resorption rate, litter size, sex ratio, or fetal body weight. No changes in gross external or visceral alterations were seen in the exposed fetuses compared to controls. An increase in supernumerary ribs was found, although the effect was not indicated as statistically significant. The incidences of fetuses with supernumerary ribs were 2/257, l/299, 6/311, and 2/242 at 0, 491, 1,504, and 4,946 ppm, respectively. The incidences in litters were 2/22, l/25, 5/26, and 4/22 at 0, 491, 1,504, and 4,946 ppm, respectively.

A small increase in the incidence of DFFC of the skull bones (developmental delay of ossification of small centers of unossified bone of the skull) was observed at the high dose. The incidence data based on number of fetuses affected were 1/126, 1/142, 1/147, and 5/116 at 0, 491, 1,504, and 4,946 ppm, respectively. The study authors indicated that the foramina data were statistically significant. ATSDR's analysis of the data determined that there was a significant trend (p=0.0488) for the fetal data, but no significance in a pairwise comparison to the control group for the fetal data. Incidence data for number of litters affected were 1/22, 1/24, 1/25, and 5/22 at 0, 491, 1,504, and 4,946 ppm, respectively. The study authors indicated that the litter data were not significantly different from control. ATSDR's analysis determined that there were no significant differences in the pairwise comparison to control or trend test for the litter data.

Selection of the Point of Departure for the MRL: The NOAEL of 1,504 ppm for developmental effects (increased incidence of DFFC of the skull) in fetuses exposed 6 hours/day on GDs 6–15 (Scortichini et al. 1986) was selected as the point of departure (POD). Benchmark dose (BMD) modeling was not done on litter data due to lack of statistical significance by both pairwise comparison and for trend.

Adjustment for Intermittent Exposure: The intermittent NOAEL of 1,504 ppm was adjusted to a 24-hour continuous exposure using the following equation:

$$NOAEL_{ADJ} = NOAEL \times \frac{6\ hours}{24\ hours} = 1{,}504\ ppm \times \frac{6\ hours}{24\ hours} = 376.0\ ppm$$

Human Equivalent Concentration: The HEC was calculated by multiplying the $NOAEL_{ADJ}$ by the ratio of the chloroethane air:blood partition coefficient for humans and mice. The reported blood:gas (air) partition coefficient ($H_{b/g}$) values for chloroethane are 5.1 for mice and 1.9 or 2.69 for humans (Gargas et al. 1989, 2008; Morgan et al. 1970). Since the ratio of mouse to human blood:gas (air) partition coefficient is >1, a default value of 1 was used. The duration-adjusted $LOAEL_{HEC}$ was 1,237 ppm.

$$NOAEL_{HEC} = NOAEL_{ADJ} \times \frac{(H_{b/g})_A}{(H_{b/g})_H} = 376.0\ ppm \times 1 = 376.0\ ppm$$

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

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

$$MRL = NOAEL_{HEC} \div UFs$$
$$376.0\ ppm \div 30 = 12.53\ ppm \approx 13\ ppm$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: No supporting studies or pertinent information were available.

Agency Contacts (Chemical Managers): Carolyn Harper

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chloroethane
CAS Numbers: 75-00-3
Date: January 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate
MRL: 13 ppm (34 mg/m^3) (provisional)
Critical Effect: Increased estrous cycle length in mice
Reference: Bucher et al. 1995
Point of Departure: LOAEL of 15,000 ppm ($LOAEL_{HEC}$ of 3,750 ppm)
Uncertainty Factor: 300
LSE Graph Key: 18
Species: Mouse

MRL Summary: A provisional intermediate-duration inhalation MRL of 13 ppm was derived for chloroethane based on a LOAEL of 15,000 ppm for reproductive effects (increased estrous cycle length) in mice exposed 6 hours/day for 21 days (Bucher et al. 1995). The LOAEL was adjusted to continuous-duration exposure and converted to a human equivalent concentration ($LOAEL_{HEC}$) of 3,750 ppm and divided by a total uncertainty factor of 300 (10 for use of a LOAEL, 3 for extrapolation from animals to humans after dosimetric adjustment, and 10 for human variability).

Selection of the Critical Effect: The only adverse effect identified in intermediate-duration inhalation studies is related to the estrous cycle. The average duration of the estrous cycle increased significantly by 7% from 5.15 to 5.52 days in mice exposed to 15,000 ppm (only concentration tested) for 21 days, although no consistent effects on estradiol or progesterone were noted (Bucher et al. 1995). Breslin et al. (1988) also studied the length of the estrous cycle in mice after 14 days of exposure to 14,955 ppm for 6 hours/day. No significant increase in the estrous cycle length was seen during exposure compared to pre-exposure (5.0±0.7 days pre-exposure versus 5.6±0.8 days during exposure). The discrepancy between the two studies regarding increased estrous cycle length may be due to duration of exposure (14 versus 21 days) or number of animals studied. Bucher et al. (1995) studied 30 females/group, whereas Breslin et al. (1988) studied 10 females/group. The larger sample size would lend itself to greater statistical power to distinguish differences. In 13-week inhalation studies, no adverse effects (including histopathology on a complete panel of tissues) were observed in rats or mice exposed up to 19,000 ppm (NTP 1989). No adverse effects were observed in rats or rabbits exposed to 10,000 ppm (only concentration tested) for 6.5 months (Dow 1941).

Selection of the Principal Study: The intermediate-duration inhalation study investigating estrous cycle length was selected as the principal study (Bucher et al. 1995). No other intermediate-duration study reported a toxicologically relevant adverse effect.

Summary of the Principal Study:

Bucher JR, Morgan DL, Adkins B, et al. 1995. Early changes in sex hormones are not evident in mice exposed to the uterine carcinogens chloroethane or bromoethane. Toxicol Appl Pharmacol 130:169-173. http://doi.org/10.1006/taap.1995.1022.

Female B6C3F1 mice (30/group) were exposed to chloroethane at 0 or 15,000 ppm 6 hours/day for 21 days. Before the exposures, all the mice were sham-exposed for 21 days, and vaginal cytology studies were completed daily during the sham exposures and during the 21-day exposure period. Body weights

were measured at least weekly. At necropsy, blood was drawn for measurement of serum estradiol and progesterone. The liver and uterus were weighed. The liver, uterus, pituitary gland, adrenal glands, and ovaries were examined microscopically.

No clinical signs of toxicity were observed. Body weights were not different from control (data not shown). In the exposed group, mean estrous cycle length significantly increased from 5.15±0.15 days prior to exposure to 5.52±0.19 days during exposure (a 7% increase). In the control group, mean estrous cycle length was not different between the pre-exposure period and exposure period (5.02±0.2 versus 5.0±0.2, pre-exposure and exposure, respectively). The proportion of time spent in the stages of the cycle during exposure was significantly different compared to pre-exposure in both the exposed and control group. Mice spent shorter time in metestrus and longer time in the other stages. No significant difference in serum estradiol or progesterone were seen at the end of the exposure. No significant differences in weights of liver, uterus, or ovary were seen compared to control (data not shown). No histological changes were observed in the ovaries, pituitary, uterus, or adrenal glands.

Selection of the Point of Departure for the MRL: The LOAEL of 15,000 ppm for reproductive effects (increased duration of estrous cycle) in mice exposed 6 hours/day for 21 days (Bucher et al. 1995) was selected as the POD.

Adjustment for Intermittent Exposure: The intermittent 6 hours/day LOAEL of 15,000 ppm was adjusted to a 24-hour continuous exposure using the following equation:

$$LOAEL_{ADJ} = LOAEL \times \frac{6\ hours}{24\ hours} = 15{,}000\ ppm \times \frac{6\ hours}{24\ hours} = 3{,}750\ ppm$$

Human Equivalent Concentration: The HEC was calculated by multiplying the $LOAEL_{ADJ}$ by the ratio of the chloroethane air:blood partition coefficient for humans and mice. The reported blood:gas (air) partition coefficient ($H_{b/g}$) values for chloroethane are 5.1 for mouse and 1.9 or 2.69 for humans (Gargas et al. 1989, 2008; Morgan et al. 1970). Since the ratio of mouse to human blood:gas (air) partition coefficient is >1, a default value of 1 was used.

$$LOAEL_{HEC} = LOAEL_{ADJ} \times \frac{(H_{b/g})_A}{(H_{b/g})_H} = 3{,}750\ ppm \times 1 = 3{,}750\ ppm$$

Uncertainty Factor: The $LOAEL_{HEC}$ was divided by a total uncertainty factor of 300:

- 10 for use of a LOAEL
- 3 for extrapolation from animals to humans after dosimetric adjustment
- 10 for human variability

$$MRL = LOAEL_{HEC} \div UFs$$
$$3{,}750\ ppm \div 300 = 12.5\ ppm \approx 13\ ppm$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: No supporting studies or pertinent information were available.

Agency Contacts (Chemical Managers): Carolyn Harper

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chloroethane
CAS Numbers: 75-00-3
Date: January 2024
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

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

Rationale for Not Deriving an MRL: Renal and neurological effects were observed in female mice exposed to 15,000 ppm chloroethane for 100 weeks (only concentration tested) (NTP 1989). However, this study also reported decreased survival in these exposed mice, attributed to carcinomas of the uterus. An MRL for renal and/or neurological effects was not derived since serious health effects were seen at the concentration level studied.

Agency Contacts (Chemical Managers): Carolyn Harper

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chloroethane
CAS Numbers: 75-00-3
Date: January 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

MRL Summary: The database was not considered adequate for derivation of an acute-duration oral MRL for chloroethane.

Rationale for Not Deriving an MRL: No acute-duration oral MRL was derived due to lack of adequate data regarding the potential effects of chloroethane. No toxicologically relevant effects were seen in rats exposed to chloroethane in drinking water at doses ranging from 297 to 662 mg/kg/day for 7 or 14 days (Dow 1995).

Agency Contacts (Chemical Managers): Carolyn Harper

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chloroethane
CAS Numbers: 75-00-3
Date: January 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

MRL Summary: The database was not considered adequate for derivation of an intermediate-duration oral MRL for chloroethane.

Rationale for Not Deriving an MRL: No intermediate-duration oral studies were located that met ATSDR quality inclusion criteria; therefore, no MRL could be derived.

Agency Contacts (Chemical Managers): Carolyn Harper

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Chloroethane
CAS Numbers: 75-00-3
Date: January 2024
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic

MRL Summary: The database was not considered adequate for derivation of a chronic-duration oral MRL for chloroethane.

Rationale for Not Deriving an MRL: No studies were located that describe the effects of chronic-duration oral exposure to chloroethane in humans or animals.

Agency Contacts (Chemical Managers): Carolyn Harper

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR CHLOROETHANE

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 chloroethane.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for chloroethane. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Foreign language studies are reviewed based on available English-language abstracts and/or tables (or summaries in regulatory assessments, such as International Agency for Research on Cancer [IARC] documents). If the study appears critical for hazard identification or MRL derivation, translation into English is requested. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of chloroethane 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 chloroethane 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

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

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

B.1.1 Literature Search

The current literature search was intended to update the 1998 Toxicological Profile for Chloroethane; thus, the literature search was restricted to studies published between January 1996 and May 2022. The following main databases were searched in May 2022:

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

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

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to chloroethane 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	
05/2022	("Ethyl Chloride"[mh] OR 75-00-3[rn] OR "Chloroethane"[tw] OR "Ethane, chloro-"[tw] OR "Ethyl chloride"[tw] OR "ethylchloride"[tw] OR "Freon 160"[tw] OR "Monochlorethane"[tw] OR "Monochloroethane"[tw] OR "chlorethane"[tw] OR "Aethylis"[tw] OR "Anodynon"[tw] OR "Chlorethan"[tw] OR "Chloryl anesthetic"[tw] OR "Chloryle anesthetic"[tw] OR "Cloretilo"[tw] OR "Dublofix"[tw] OR "Ether chloratus"[tw] OR "Ether chloridum"[tw] OR "Ether hydrochloric"[tw] OR "Ether muriatic"[tw] OR "Hydrochloric ether"[tw] OR "Kelene"[tw] OR "Muriatic ether"[tw] OR "Narcotile"[tw] OR "Chelen"[tw] OR "Chlorene"[tw] OR "Chloridum"[tw] OR "Chloryl"[tw] OR "Chlorethyl"[tw]) AND 1996:3000[dp]
NTRL	
05/2022	"Chloroethane" OR "Ethane, chloro-" OR "Ethyl chloride" OR "ethylchloride" OR "Freon 160" OR "Monochlorethane" OR "Monochloroethane" OR "chlorethane" OR "Aethylis" OR "Anodynon" OR "Chlorethan" OR "Chloryl anesthetic" OR "Chloryle anesthetic" OR "Cloretilo" OR "Dublofix" OR "Ether chloratus" OR "Ether chloridum" OR "Ether hydrochloric" OR "Ether muriatic" OR "Hydrochloric ether" OR "Kelene" OR "Muriatic ether" OR "Narcotile" OR "Chelen" OR "Chlorene" OR "Chloridum" OR "Chloryl" OR "Chlorethyl" Limited to 1996-2022
Toxcenter	
05/2022	FILE 'TOXCENTER' ENTERED AT 16:55:39 ON 16 MAY 2022 CHARGED TO COST=EH038.15.03.LB.04 L1 2227 SEA FILE=TOXCENTER 75-00-3 L2 2132 SEA FILE=TOXCENTER L1 NOT TSCATS/FS L3 1807 SEA FILE=TOXCENTER L2 NOT PATENT/DT L4 1040 SEA FILE=TOXCENTER L3 AND PY>1995 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 L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)

Table B-2. Database Query Strings

Database search date	Query string
	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 (CARCINOG? OR COCARCINOG? 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

Table B-2. Database Query Strings

Database search date	Query string
	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 414 SEA FILE=TOXCENTER L4 AND L37 L39 52 SEA FILE=TOXCENTER L38 AND MEDLINE/FS L41 362 SEA FILE=TOXCENTER L38 NOT MEDLINE/FS L42 393 DUP REM L39 L41 (21 DUPLICATES REMOVED) L*** DEL 52 S L38 AND MEDLINE/FS L*** DEL 52 S L38 AND MEDLINE/FS L43 52 SEA FILE=TOXCENTER L42 L*** DEL 362 S L38 NOT MEDLINE/FS L*** DEL 362 S L38 NOT MEDLINE/FS L44 341 SEA FILE=TOXCENTER L42 L45 341 SEA FILE=TOXCENTER (L43 OR L44) NOT MEDLINE/FS D SCAN L45

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
05/2022	Compounds searched: 75-00-3
NTP	
05/2022	75-00-3 chloroethane "ethyl chloride"
Regulations.gov	
05/2022	chloroethane 75-00-3 "ethyl chloride" Limited to EPA docket or notices
NIH RePORTER	
03/2023	Search Criteria Fiscal Year: Active Projects Text Search: "Chloroethane" OR "Ethane, chloro-" OR "Ethyl chloride" OR "ethylchloride" OR "Freon 160" OR "Monochlorethane" OR "Monochloroethane" OR "chlorethane" OR "Aethylis" OR "Anodynon" OR "Chlorethan" OR "Chloryl anesthetic" OR "Chloryle anesthetic" OR "Cloretilo" OR "Dublofix" OR "Ether chloratus" OR "Ether chloridum" OR "Ether hydrochloric" OR "Ether muriatic" OR "Hydrochloric ether" OR "Kelene" OR "Muriatic ether" OR "Narcotile" OR "Chelen" OR "Chlorene" OR "Chloryl" OR "Chlorethyl" (advanced)Limit to: Project Title, Project Terms, Project Abstracts Search Criteria Fiscal Year: Active Projects Text Search: "Chloridum" (advanced)Limit to: Project

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	Title, Project Terms, Project Abstracts
Other	Identified throughout the assessment process

The 2022 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 688
- Number of records identified from other strategies: 74
- Total number of records to undergo literature screening: 762

B.1.2 Literature Screening

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

- 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.

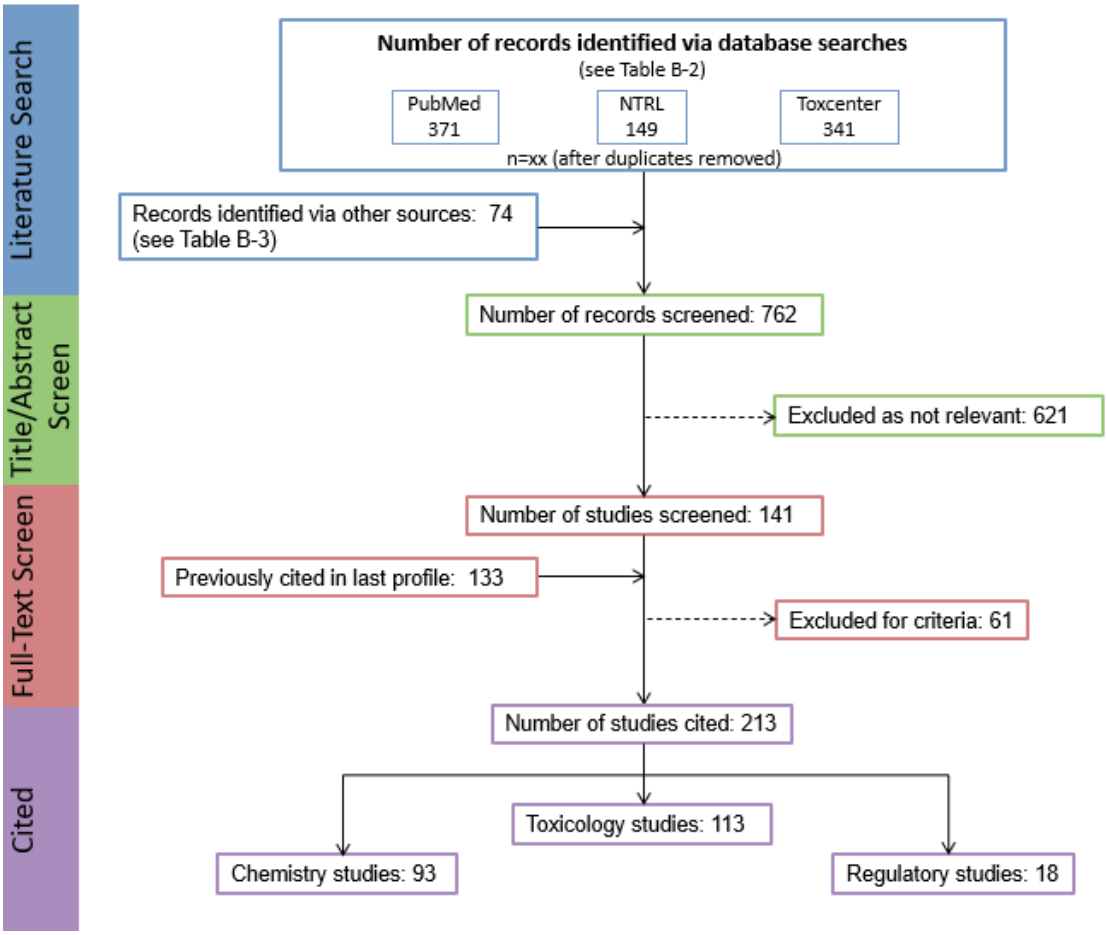
- Number of titles and abstracts screened: 762
- Number of studies considered relevant and moved to the next step: 141

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: 141
- Number of studies cited in the previous toxicological profile: 133
- Total number of studies cited in the profile: 213

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

Figure B-1. May 2022 Literature Search Results and Screen for Chloroethane



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR CHLOROETHANE

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 chloroethane, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to chloroethane:

- 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 chloroethane. The inclusion criteria used to identify relevant studies examining the health effects of chloroethane are presented in Table C-1.

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

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

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

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

Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen were conducted to identify studies examining the health effects of chloroethane. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the current literature search was intended to update the 1998 toxicological profile for chloroethane; thus, the literature search was restricted to studies published between January 1996 and May 2022. See Appendix B for the databases searched and the search strategy.

See Appendix B for the databases searched and the search strategy.

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 chloroethane.

Title and Abstract Screen. In the Title and Abstract Screen step, 761 records were reviewed; 30 documents were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 62 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 62 documents (79 studies), 20 documents (33 studies) were included in the qualitative review.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

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

Table C-2. Data Extracted from Individual Studies

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

A summary of the extracted data for each study is presented in the Supplemental Document for Chloroethane and overviews of the results of the inhalation, oral, and dermal 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 chloroethane identified in human and animal studies are presented in Tables C-3 and C-4, respectively. Human inhalation studies examined a limited number of health outcomes, whereas animal inhalation and oral studies examined a comprehensive set of endpoints. Dermal exposure studies in humans were primarily interested in analgesic effects of chloroethane (discussed in Section 2.11). Both human and animal studies suggest the nervous system is the primary target of chloroethane exposure. Additionally, animal studies suggest the reproductive and developmental effects may also be sensitive targets. Although there are several case reports evaluating neurological effects in humans following inhalation, these studies were not included in this systematic review due to either a lack of estimated exposure or a comparison group (discussed in Section 2.15). The

remaining human (inhalation) and animal (inhalation and oral) studies related to neurological, reproductive and developmental outcomes were carried through to Steps 4–8 of the systematic review. There were 33 studies (published in 20 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review.

APPENDIX C

Table C-3. Overview of the Health Outcomes for Chloroethane Evaluated in Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Caner
Inhalation studies																	
Cohort																	
Case control																	
Population												1 1	1 1				
Case series		3 3	2 1	2 2	1 0		2 2						8 8				
Human controlled			1 1							1 1			3 3				
Oral studies																	
Cohort																	
Case control																	
Population																	
Case series																	
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series									3 1	1 1		3 3					
Human controlled									18 0				1 1				
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 Chloroethane Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration	11 0	12 1	13 6	6 1	3 0	3 0	12 2	10 1	5 0	3 0	7 0	8 1	15 10	10 1	2 0		
Intermediate-duration	6 1	5 1	3 1	2 0			7 2	5 1	2 0	1 0	5 0	6 2	4 2	4 2			
Chronic-duration	2 0	2 0	2 0	2 0		2 0	2 0	2 1	2 0		2 0	2 0	2 1	2 0			2 2
Oral studies																	
Acute-duration	2 0		1 0		1 0		1 0	1 0			1 0	1 0	3 1	1 0			
Intermediate-duration	1 0																
Chronic-duration																	
Dermal studies																	
Acute-duration						1 1			1 1				1 1				
Intermediate-duration																	
Chronic-duration																	

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The results of the risk of bias assessment for the different types of chloroethane health effects studies (human-controlled exposure and animal experimental studies) are presented in Tables C-8 and C-9, respectively.

Table C-8. Summary of Risk of Bias Assessment for Chloroethane – Human-Controlled Exposure Studies

Reference	Risk of bias criteria and ratings: Selection bias – Was administered dose or exposure level adequately randomized?	Selection bias – Was the allocation to study groups adequately concealed?	Performance bias – Were 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?	Detection bias – **Is there confidence in the outcome assessment?***	Selective reporting bias – Were all measured outcomes reported?	Risk of bias tier
Outcome: Neurological effects								
Inhalation acute exposure								
USBM 1929	–	+	–	–	–	–	–	Third
Davidson 1925	–	+	–	+	–	+	–	Second
Bush et al. 1952	–	+	+	–	–	+	–	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias

*Key question used to assign risk of bias tier.

Table C-9. Summary of Risk of Bias Assessment for Chloroethane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is the confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Outcome: Neurological Effects									
Inhalation acute exposure									
Bush et al. 1952	–	+	–	+	–	– –	–	–	Third
Dow 1941 (monkey)	–	+	–	+	+	–	+	+	Second
Dow 1992 (mouse)	++	+	++	+	+	++	+	+	First
Dow 1992 (rat, ^{14}C-chloroethane)	++	+	++	+	+	++	+	+	First
Dow 1992 (mouse, ^{14}C-chloroethane)	++	+	++	+	+	++	+	+	First
Dow 1985	++	+	+	+	+	–	++	+	First
Gohlke and Schmidt 1972; Schmidt et al. 1972	–	+	–	+	–	–	+	+	Second
Landry et al. 1982 (rat)	++	+	+	+	+	++	+	+	First
Landry et al. 1982 (dog)	++	+	+	+	+	++	+	+	First
Landry et al. 1987, 1989	++	+	+	+	++	++	+	++	First
Lazarew 1929	–	+	–	+	–	–	+	+	Second
NTP 1989 (mouse, 2 weeks)	++	+	+	+	+	+	–	+	Second
NTP 1989 (rat, 2 weeks)	++	+	+	+	+	+	–	+	Second
Morris et al. 1953	–	+	–	+	+	– –	+	–	Second
USBM 1929 (810 minutes)	–	+	–	+	++	–	+	+	First

Table C-9. Summary of Risk of Bias Assessment for Chloroethane—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias: Was administered dose or exposure level adequately randomized?	Selection bias: Was the allocation to study groups adequately concealed?	Performance bias: Were experimental conditions identical across study groups?	Performance bias: Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias: Were outcome data complete without attrition or exclusion from analysis?	Detection bias: Is the confidence in the exposure characterization?	Detection bias: Is there confidence in the outcome assessment?*	Selective reporting bias: Were all measured outcomes reported?	Risk of bias tier
Inhalation intermediate exposure									
NTP 1989 (rat, 13 weeks)	++	+	+	+	++	+	+	+	First
NTP 1989 (mouse, 13 weeks)	++	+	+	+	++	+	+	+	First
Inhalation chronic exposure									
NTP 1989 (rat, 102 weeks)	++	+	+	+	++	+	+	+	First
NTP 1989 (mouse, 100 weeks)	++	+	+	+	++	+	+	+	First
Oral acute exposure									
Dow 1992 (mouse non-labelled)	++	+	–	+	+	++	+	+	First
Dow 1992 (rat, ^{14}C-chloroethane)	++	+	–	+	+	++	+	+	First
Dow 1992 (mouse, ^{14}C-chloroethane)	++	+	–	+	+	++	+	+	First
Dow 1995	++	+	+	+	++	++	+	++	First
Outcome: Reproductive Effects									
Inhalation acute exposure									
Breslin et al. 1988	++	+	+	+	+	+	+	+	First
Fedtke et al. 1994a, 1994b (rat)	–	+	–	+	+	+	+	–	First
Fedtke et al. 1994a, 1994b (mouse)	–	+	–	+	+	+	+	–	First

APPENDIX C

Table C-9. Summary of Risk of Bias Assessment for Chloroethane—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	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is the confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Gohlke and Schmidt 1972; Schmidt et al. 1972	–	+	–	+	–	–	+	+	Second
Landry et al. 1982 (rat)	++	+	+	+	+	++	+	+	First
Landry et al. 1982 (dog)	++	+	+	+	+	++	+	+	First
Landry et al. 1987, 1989	++	+	+	+	++	++	+	++	First
NTP 1989 (mouse, 2 weeks)	++	+	+	+	+	+	–	+	Second
NTP 1989 (rat, 2 weeks)	++	+	+	+	+	+	–	+	Second
van Liere et al. 1966	–	+	–	+	–	– –	+	–	Second
Inhalation intermediate exposure									
Bucher et al. 1995	+	+	+	+	++	+	+	+	First
NTP 1989 (rat, 13 weeks)	++	+	+	+	++	+	+	+	First
NTP 1989 (mouse, 13 weeks)	++	+	+	+	++	+	+	+	First
Inhalation chronic exposure									
NTP 1989 (rat, 102 weeks)	++	+	+	+	++	+	+	++	First
NTP 1989 (mouse, 100 weeks)	++	+	+	+	++	+	+	++	First
Oral acute exposure									
Dow 1995	++	+	+	+	++	++	+	++	First

Table C-9. Summary of Risk of Bias Assessment for Chloroethane—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	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is the confidence in the exposure characterization?	Is there confidence in the outcome assessment?*	Were all measured outcomes reported?	
Outcome: Developmental Effects									
Inhalation acute exposure									
Dow 1985	++	+	+	+	+	–	+	+	First
Scortichini et al. 1986	++	+	+	+	+	++	+	+	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias

*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 chloroethane 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 chloroethane and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure, and experimental animal studies are presented in Tables C-10, C-11, and C-12, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

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

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

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

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

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

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

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

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

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

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

The presence or absence of the key features and the initial confidence levels for studies examining neurological and reproductive outcomes observed in the human-controlled exposure and animal experimental studies are presented in Tables C-13 and C-14, respectively.

Table C-13. Presence of Key Features of Study Design for Chloroethane—Human-Controlled Exposure

Reference	Key Features				
	Comparison group or served as own controls	Sufficient number of subjects tested	Appropriate outcome assessment	Appropriate statistical analysis	Initial study confidence
Outcome: Neurological Effects					
Inhalation acute exposure					
USBM 1929	No	No	No	No	Very Low
Davidson 1925	No	No	Yes	No	Very Low
Bush et al. 1952	No	Yes	Yes	No	Low

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

Reference	Key features				
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Neurological Effects					
Inhalation acute exposure					
Bush et al. 1952	No	Yes	Yes	No	Low
Dow 1941 (monkey)	No	No	No	No	Low
Dow 1992 (mouse)	Yes	No	Yes	No	Low
Dow 1992 (rat, ^{14}C-chloroethane)	No	Yes	Yes	Yes	Moderate
Dow 1992 (mouse, ^{14}C-chloroethane)	No	Yes	Yes	No	Low
Dow 1985 (10 days)	Yes	Yes	Yes	No	Moderate
Gohlke and Schmidt 1972; Schmidt et al. 1972	Yes	Yes	Yes	No	Moderate
Landry et al. 1982 (rat)	Yes	Yes	Yes	No	Moderate
Landry et al. 1982 (dog)	Yes	Yes	Yes	No	Moderate

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

Reference	Key features				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Landry et al. 1987, 1989	Yes	Yes	Yes	Yes	High
Lazarew 1929	No	No	Yes	No	Very Low
NTP 1989 (mouse, 2 weeks)	Yes	Yes	Yes	Yes	High
NTP 1989 (rat, 2 weeks)	Yes	Yes	Yes	Yes	High
Morris et al. 1953	No	Yes	Yes	No	Low
USBM 1929 (540 minutes)	Yes	Yes	Yes	No	Moderate
Inhalation intermediate exposure					
NTP 1989 (rat, 13 weeks)	Yes	Yes	Yes	Yes	High
NTP 1989 (mouse, 13 weeks)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
NTP 1989 (rat, 102 weeks)	Yes	Yes	Yes	No	Moderate
NTP 1989 (mouse, 100 weeks)	Yes	Yes	Yes	No	Moderate
Oral acute exposure					
Dow 1992 (mouse)	No	No	Yes	Yes	Low
Dow 1992 (rat, ^{14}C-chloroethane)	No	Yes	Yes	Yes	Moderate
Dow 1992 (mouse, ^{14}C-chloroethane)	No	Yes	Yes	Yes	Moderate
Dow 1995	Yes	Yes	Yes	Yes	High
Outcome: Reproductive Effects					
Inhalation acute exposure					
Breslin et al. 1988	Yes	Yes	Yes	Yes	High
Fedtke et al. 1994a (rat)	Yes	Yes	No	No	Low
Fedtke et al. 1994a (mouse)	Yes	Yes	No	No	Low
Gohlke and Schmidt 1972; Schmidt et al. 1972	Yes	Yes	Yes	No	Moderate
Landry et al. 1982 (rat)	Yes	Yes	Yes	No	Moderate
Landry et al. 1982 (dog)	Yes	Yes	Yes	No	Moderate
Landry et al. 1987, 1989	Yes	Yes	Yes	Yes	High
NTP 1989 (mouse, 2 weeks)	Yes	Yes	Yes	Yes	High
NTP 1989 (rat, 2 weeks)	Yes	Yes	Yes	Yes	High
van Liere et al. 1966	No	Yes	Yes	No	Low

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

Reference	Key features: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Inhalation intermediate exposure					
Bucher et al. 1995	Yes	Yes	Yes	Yes	High
NTP 1989 (rat, 13 weeks)	Yes	Yes	Yes	Yes	High
NTP 1989 (mouse, 13 weeks)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
NTP 1989 (rat, 102 weeks)	Yes	Yes	Yes	Yes	High
NTP 1989 (mouse, 100 weeks)	Yes	Yes	Yes	Yes	High
Oral acute exposure					
Dow 1995	Yes	Yes	No	Yes	Moderate
Outcome: Developmental Effects					
Inhalation acute exposure					
Dow 1985	Yes	Yes	Yes	No	Moderate
Scortichini et al. 1986	Yes	Yes	Yes	Yes	High

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

Table C-15. Initial Confidence Rating for Chloroethane Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Neurological Effects		
Inhalation acute exposure		
Human studies		
USBM 1929	Very Low	Low
Davidson 1925	Very Low	
Bush et al. 1952	Low	
Animal studies		
Bush et al. 1952	Low	
Dow 1941 (monkey)	Low	

Table C-15. Initial Confidence Rating for Chloroethane Health Effects Studies

	Initial study confidence	Initial confidence rating
Dow 1992 (mouse)	Low	High
Dow 1992 (rat, ^{14}C-chloroethane)	Moderate	
Dow 1992 (mouse, ^{14}C-chloroethane)	Low	
Dow 1985 (10 days)	Moderate	
Gohlke and Schmidt 1972; Schmidt et al. 1972	Moderate	
Landry et al. 1982 (rat)	Moderate	
Landry et al. 1982 (dog)	Moderate	
Landry et al. 1987, 1989	High	
Lazarew 1929	Very Low	
NTP 1989 (mouse, 2 weeks)	High	
NTP 1989 (rat, 2 weeks)	High	
Morris et al. 1953	Low	
USBM 1929 (540 minutes)	Moderate	
Inhalation intermediate exposure		
Animal studies		
NTP 1989 (rat, 13 weeks)	High	High
NTP 1989 (mouse, 13 weeks)	High	
Inhalation chronic exposure		
Animal studies		
NTP 1989 (rat, 102 weeks)	Moderate	Moderate
NTP 1989 (mouse, 100 weeks)	Moderate	
Oral acute exposure		
Animal studies		
Dow 1992 (mouse)	Low	High
Dow 1992 (rat, ^{14}C-chloroethane)	Moderate	
Dow 1992 (mouse, ^{14}C-chloroethane)	Moderate	
Dow 1995	High	
Outcome: Reproductive Effects		
Inhalation acute exposure		
Animal studies		
Breslin et al. 1988	High	High
Fedtke et al. 1994a, 1994b (rat)	Low	
Fedtke et al. 1994a, 1994b (mouse)	Low	
Gohlke and Schmidt 1972; Schmidt et al. 1972	Moderate	
Landry et al. 1982 (rat)	Moderate	
Landry et al. 1982 (dog)	Moderate	
Landry et al. 1987, 1989	High	
NTP 1989 (mouse, 2 weeks	High	
NTP 1989 (rat, 2 weeks)	High	
van Liere et al. 1966	Low	High

Table C-15. Initial Confidence Rating for Chloroethane Health Effects Studies

	Initial study confidence	Initial confidence rating
Inhalation intermediate exposure		
Animal studies		
Bucher et al. 1995	High	High
NTP 1989 (rat, 13 weeks)	High	
NTP 1989 (mouse, 13 weeks)	High	
Inhalation chronic exposure		
Animal studies		
NTP 1989 (rat, 102 weeks)	High	High
NTP 1989 (mouse, 100 weeks)	High	
Oral acute exposure		
Animal studies		
Dow 1995	Moderate	Moderate
Outcome: Developmental Effects		
Inhalation acute exposure		
Animal studies		
Dow 1985	Moderate	High
Scortichini et al. 1986	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 neurological and reproductive 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 chloroethane 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: Neurological Effects			
Human studies	Low	-1 risk of bias +1 consistency	Low
Animal studies	High	+1 consistency -1 indirectness	High
Outcome: Reproductive Effects			
Animal studies	High	-1 inconsistency -1 indirectness	Low

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

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Developmental Effects			
Animal studies	High	-1 inconsistency -1 indirectness -1 imprecision	Low

Table C-17. Confidence in the Body of Evidence for Chloroethane

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Neurological effects	Low	High
Reproductive effects	No data	Low
Developmental effects	No data	Low

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

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

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

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
    - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
    - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects

- Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
- Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:

- No downgrade if none of the factors are considered indirect
- Downgrade one confidence level if one of the factors is considered indirect
- Downgrade two confidence levels if two or more of the factors are considered indirect

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

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

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

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

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

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the

null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:

- Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

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

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

In the seventh step of the systematic review of the health effects data for chloroethane, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome OR very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for chloroethane is presented in Table C-18.

Table C-18. Level of Evidence of Health Effects for Chloroethane

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Neurological	Low	Health effect	Low
Animal studies			
Neurological	High	Health effect	High
Reproductive	Low	Health effect	Low
Developmental	Low	Health effect	Low

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

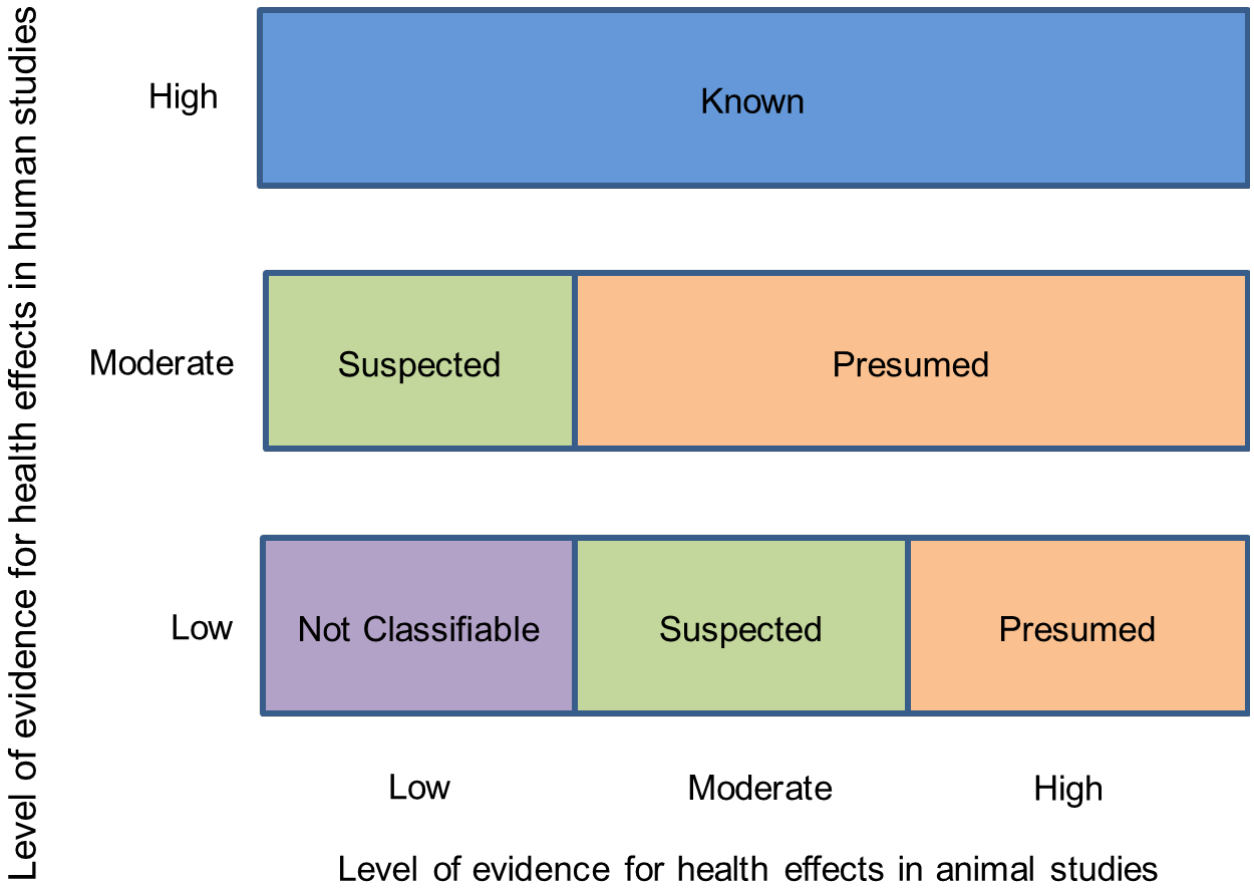
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **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

Figure C-1. Hazard Identification Scheme



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

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

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

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

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

Presumed Health Effects

- Neurological
  - Low level of evidence from human studies: several case reports described neurological symptoms after inhaling chloroethane; however, exposure levels are not known (Al-Ajmi et al. 2018; Demarest et al. 2011; Finch and Lobo 2005; Hager et al. 2021; Hes et al. 1979; Kuthiah and Er 2019; Nordin et al. 1988; Senussi and Chalise 2015). Volunteers who inhaled chloroethane reported feeling dizzy and slightly intoxicated and had increased reaction times (Davidson 1925; USBM 1929); however, these studies were poor quality with high risk of bias.
  - High level of evidence from animal studies: neurological effects have been reported in several species following inhalation (Bush et al. 1952; Dow 1985, 1992, 1995; Landry et al. 1982; Lazarew 1929; Morris et al. 1953; NTP 1989; USBM 1929;) and gavage (Dow 1992) exposure.

Not Classifiable Health Effects

- Reproductive
  - Low level of evidence from animal studies: inhalation studies have reported effects on the length of the estrous cycle (Bucher et al. 1995), uterine weight (Fedtke et al. 1994a), and uterine glutathione levels (Fedtke et al. 1994b), although no histopathological and/or hormonal changes have been reported after exposure (Bucher et al. 1995; Landry et al. 1982, 1987, 1989; NTP 1989). Breslin et al. (1988) reported that inhalation did not affect the estrous cycle of mice.
- Developmental
  - Low level of confidence from animal studies: one inhalation study reported increased incidence of delayed fetal foramina closure (DFFC) of the skull bones in pups exposed *in utero* on GDs 6–15 (Scortichini et al. 1986), whereas another study of pups exposed *in utero* on GDs 6–15 did not report any fetal abnormalities (Dow 1985).

Table C-19. Hazard Identification Conclusions for Chloroethane

Outcome	Hazard identification
Neurological	Presumed
Reproductive	Not classifiable
Developmental	Not classifiable

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

Minimal Risk Levels (MRLs)

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

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

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

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

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

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

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

TABLE LEGEND

See Sample LSE Table (page D-5)

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

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

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

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

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

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

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

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

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

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

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

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

FIGURE LEGEND

See Sample LSE Figure (page D-6)

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

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

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

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

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

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

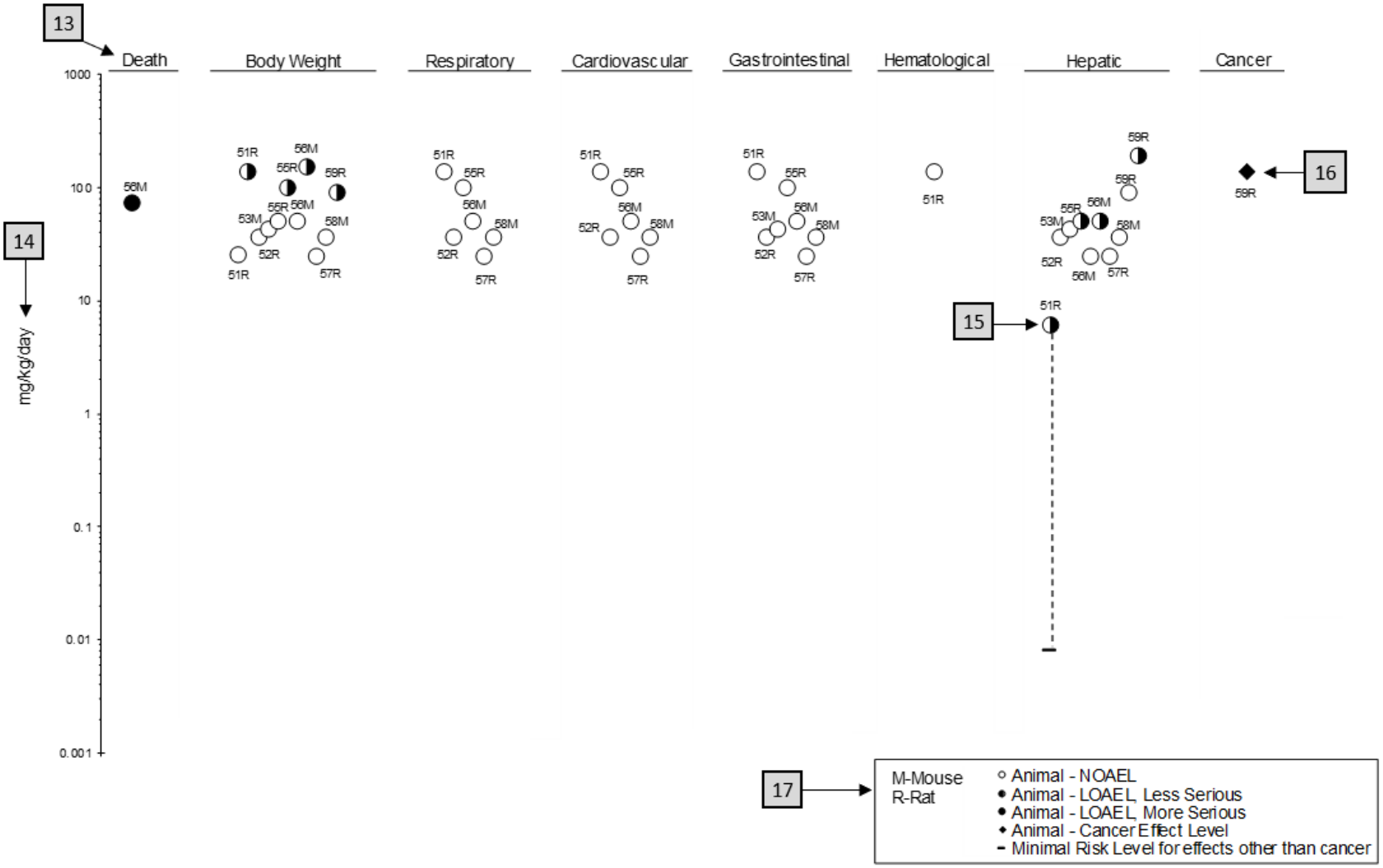
(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

Table 2-X. Levels of Significant Exposure to [Chemical X] – 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)	Effect
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	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

[a]The number corresponds to entries in Figure 2-x.
[b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

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



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

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

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

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

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

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

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

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

APPENDIX F. GLOSSARY

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

Ceiling Value—A concentration that must not be exceeded.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Minimal LOAEL—Indicates a minimal adverse effect or a reduced capacity of an organ or system to absorb additional toxic stress that does not necessarily lead to the inability of the organ or system to function normally.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Serious LOAEL—A dose that evokes failure in a biological system and can lead to morbidity or mortality.

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

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

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

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

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

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

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

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

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

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

USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result