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

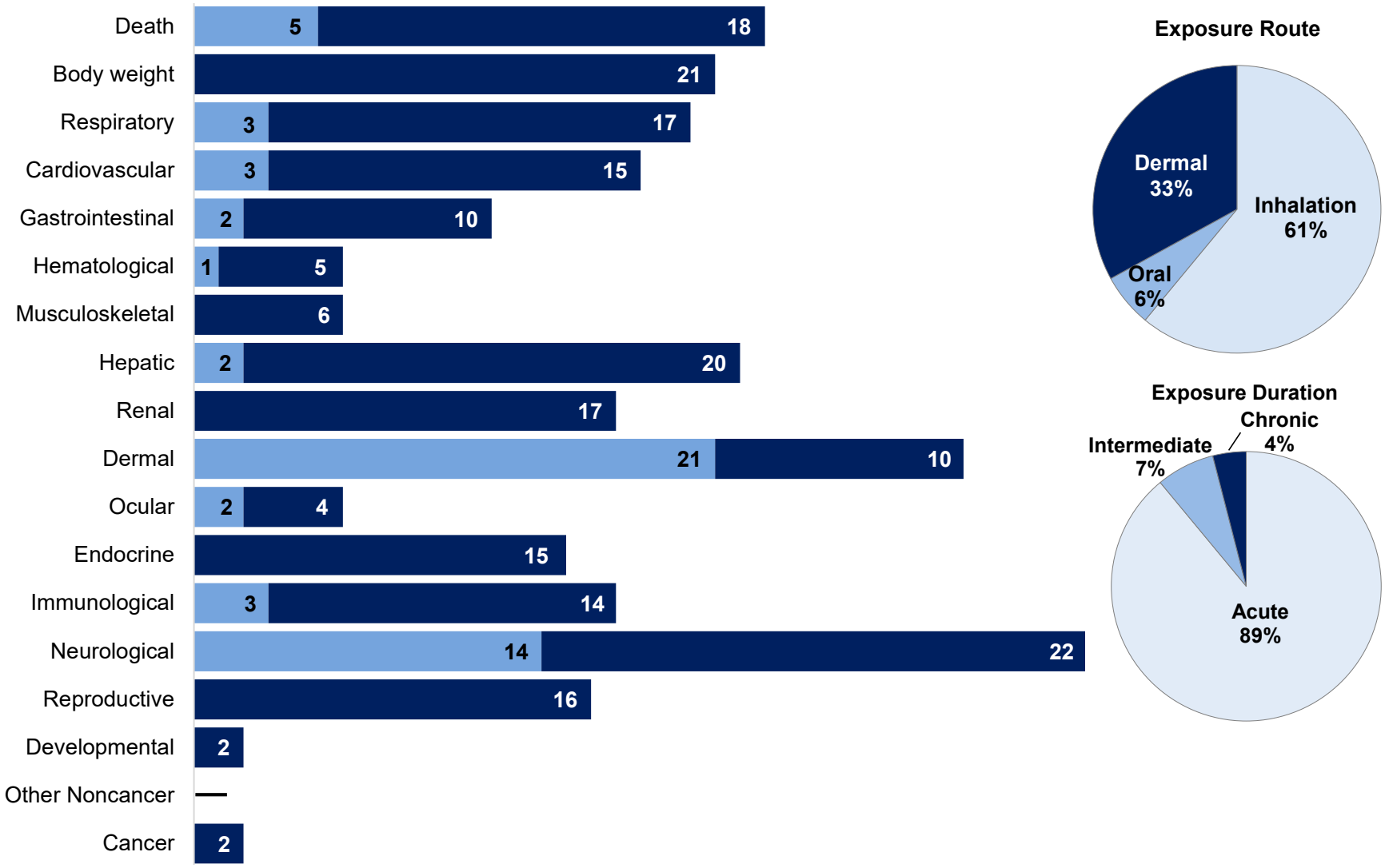
due to lack of quality studies. Dizziness, feeling of intoxication, increased reaction time, slurred speech, sleep and movement disorders, visual hallucination, tremor, and altered reflexes have been reported in people who voluntarily inhaled chloroethane. Animal studies have shown hyperactivity in mice 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 82 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,	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
			232,000, 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 an 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 an acute-duration MRL of 13 ppm. See Appendix A for more detailed information regarding the MRL.
[c]Used to derive an 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 an 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)

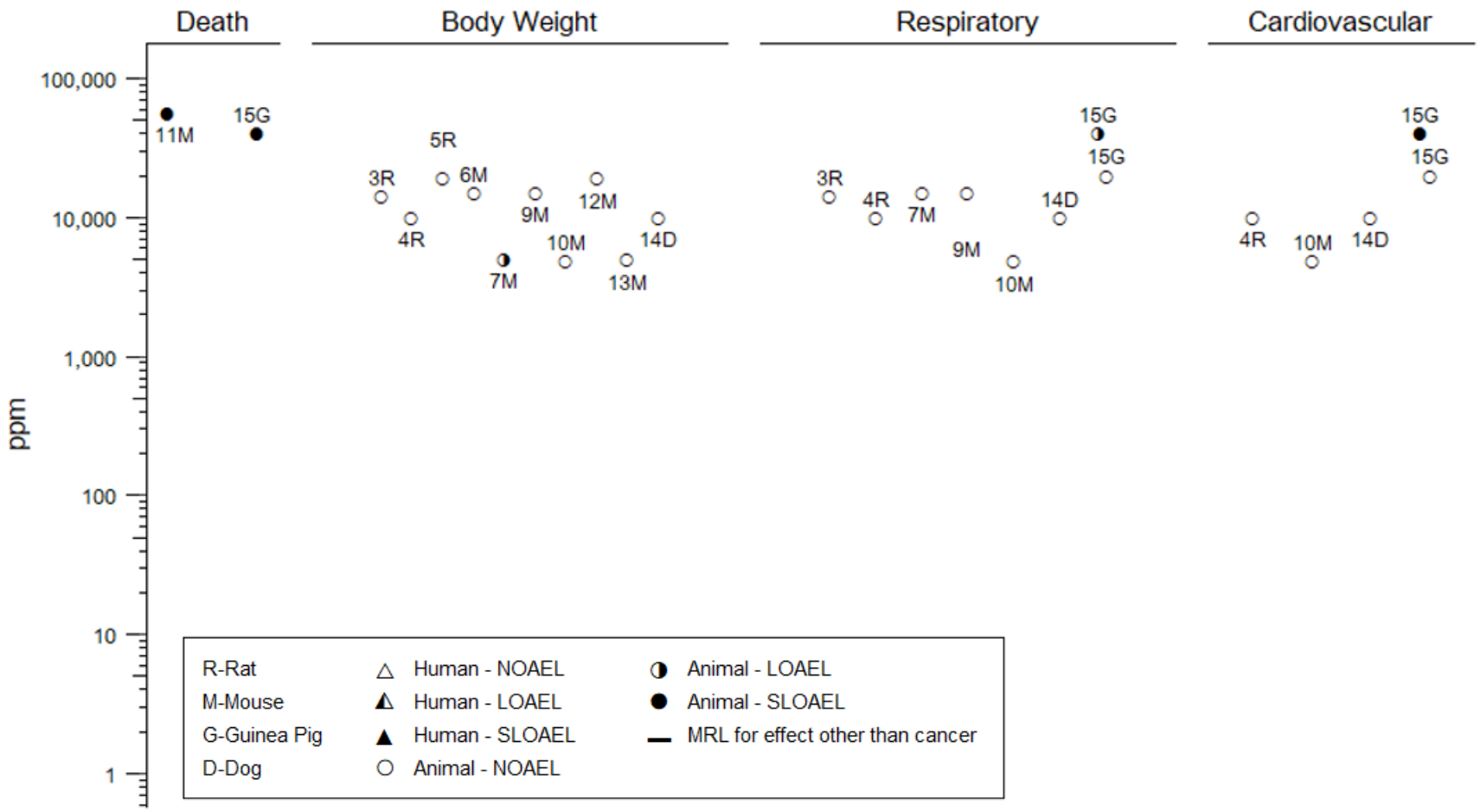


Figure 2-2. Levels of Significant Exposure to Chloroethane – Inhalation
Acute (≤14 days)

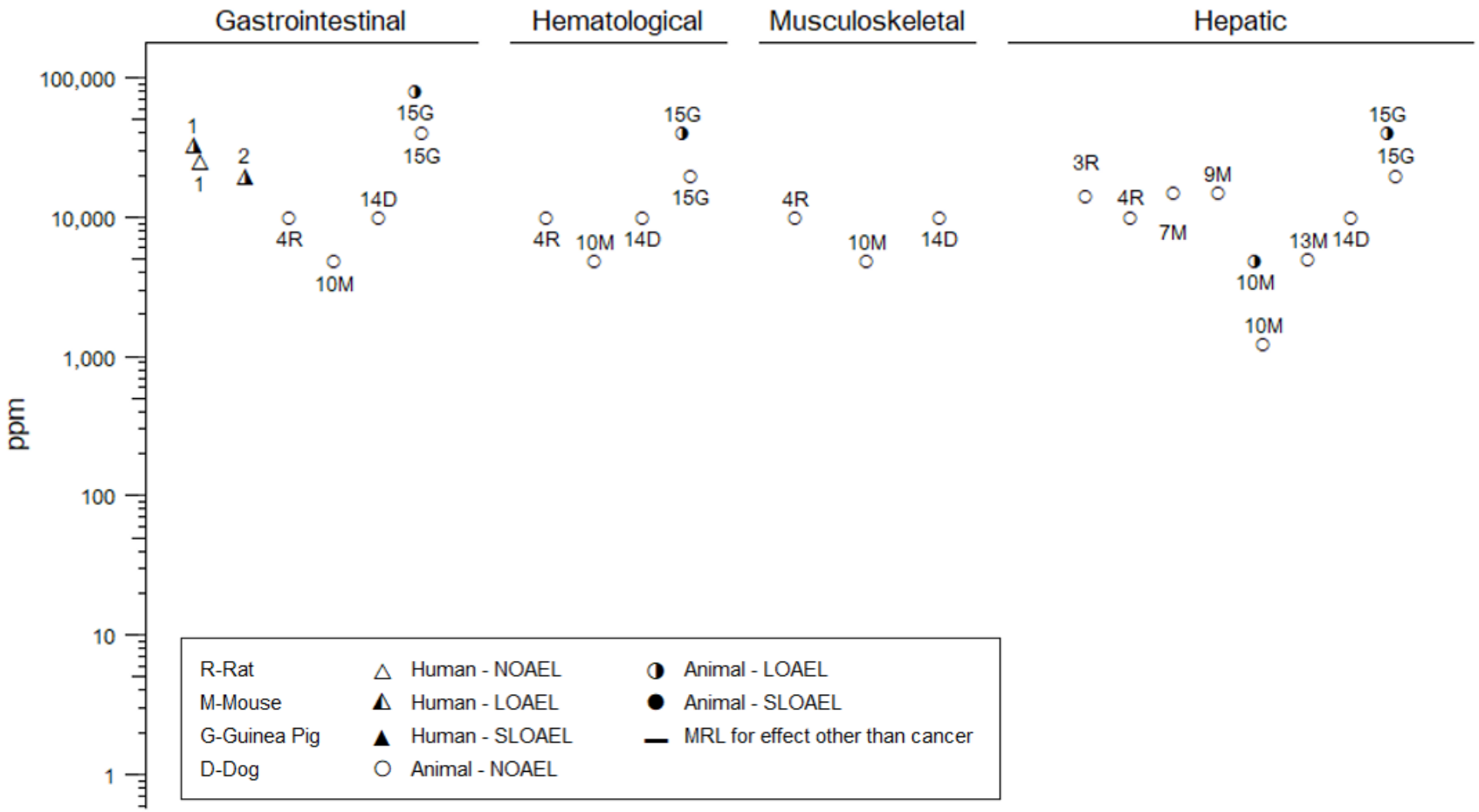


Figure 2-2. Levels of Significant Exposure to Chloroethane – Inhalation
Acute (≤14 days)

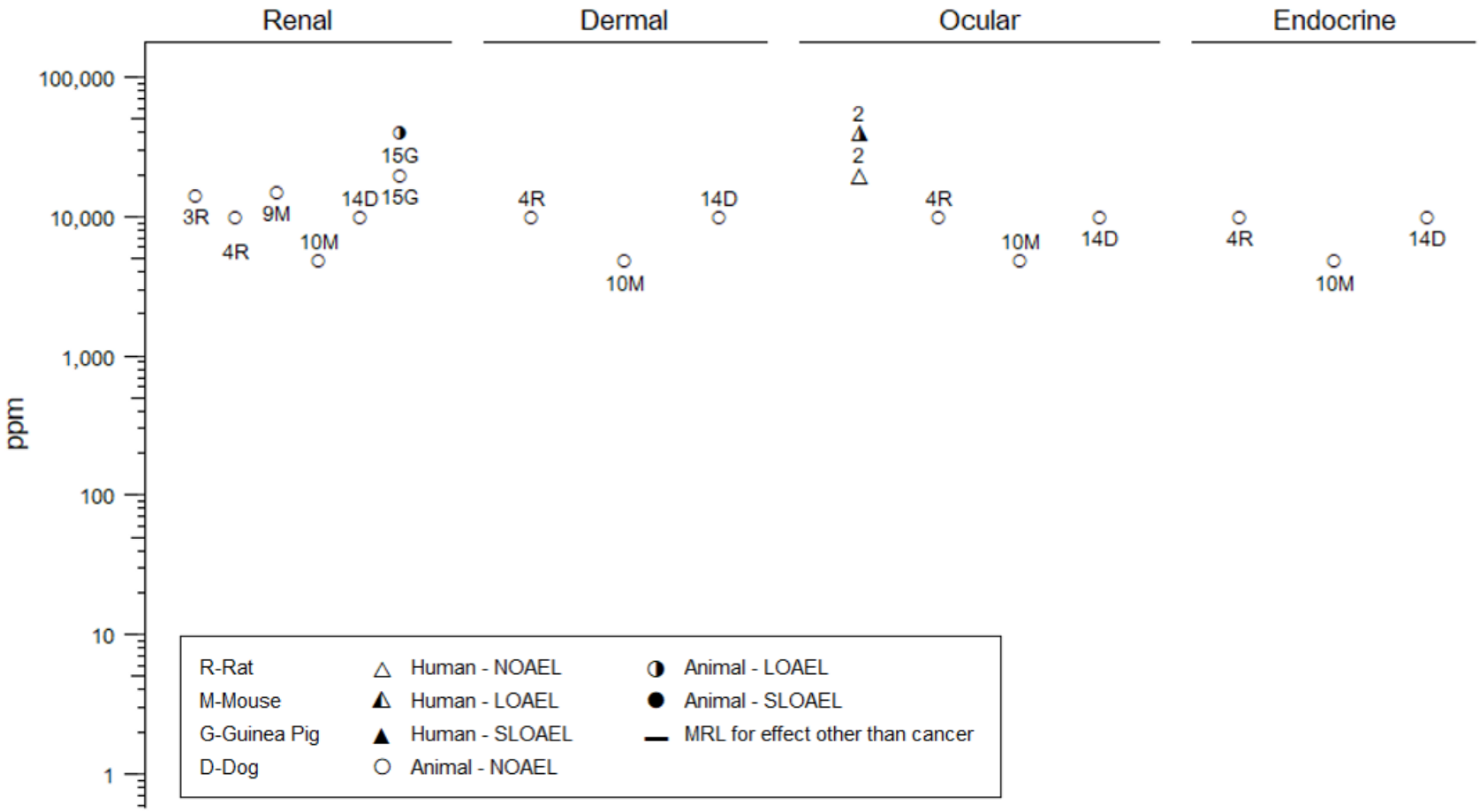


Figure 2-2. Levels of Significant Exposure to Chloroethane – Inhalation
Acute (≤14 days)

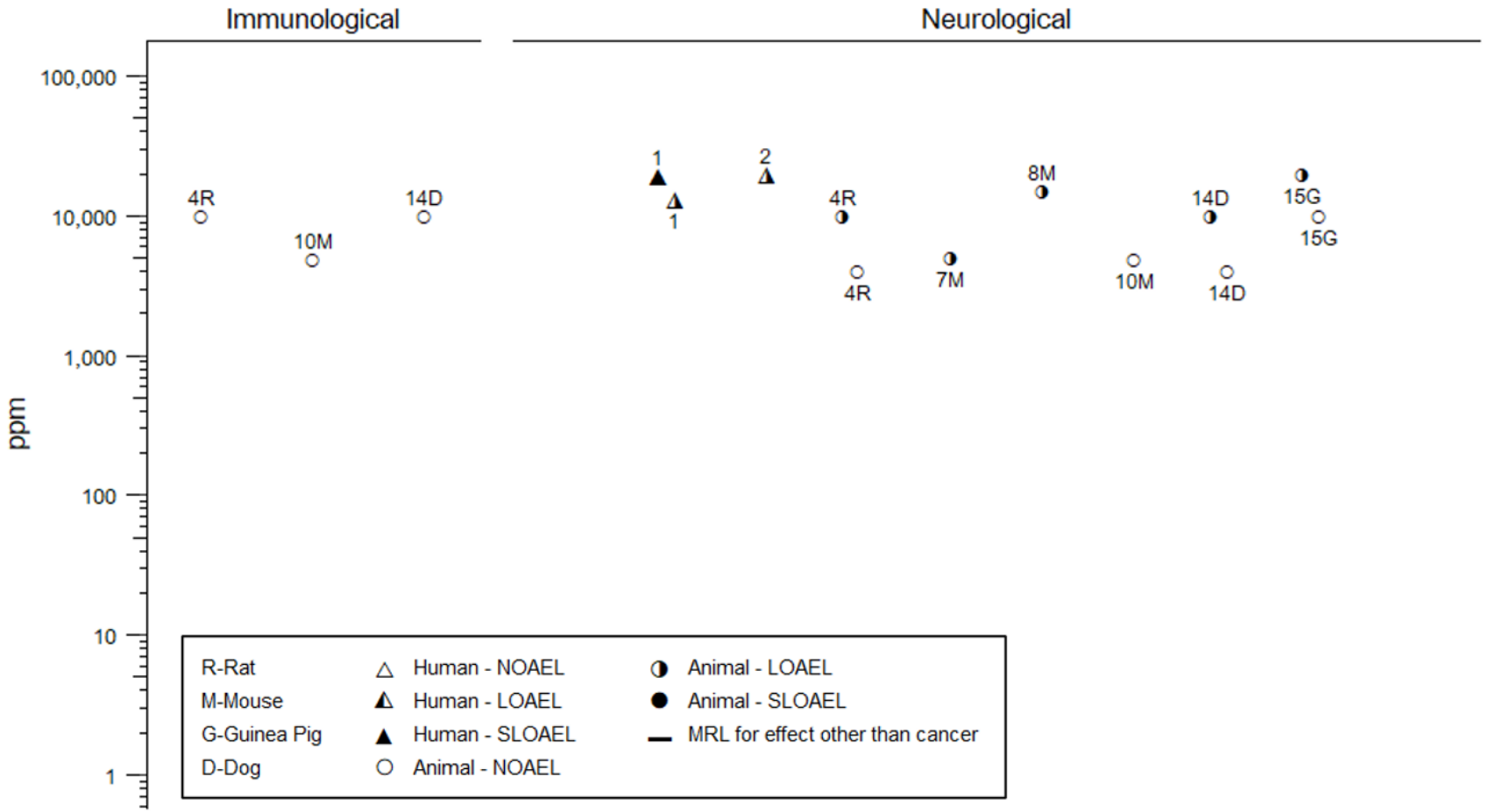


Figure 2-2. Levels of Significant Exposure to Chloroethane – Inhalation
Acute (≤14 days)

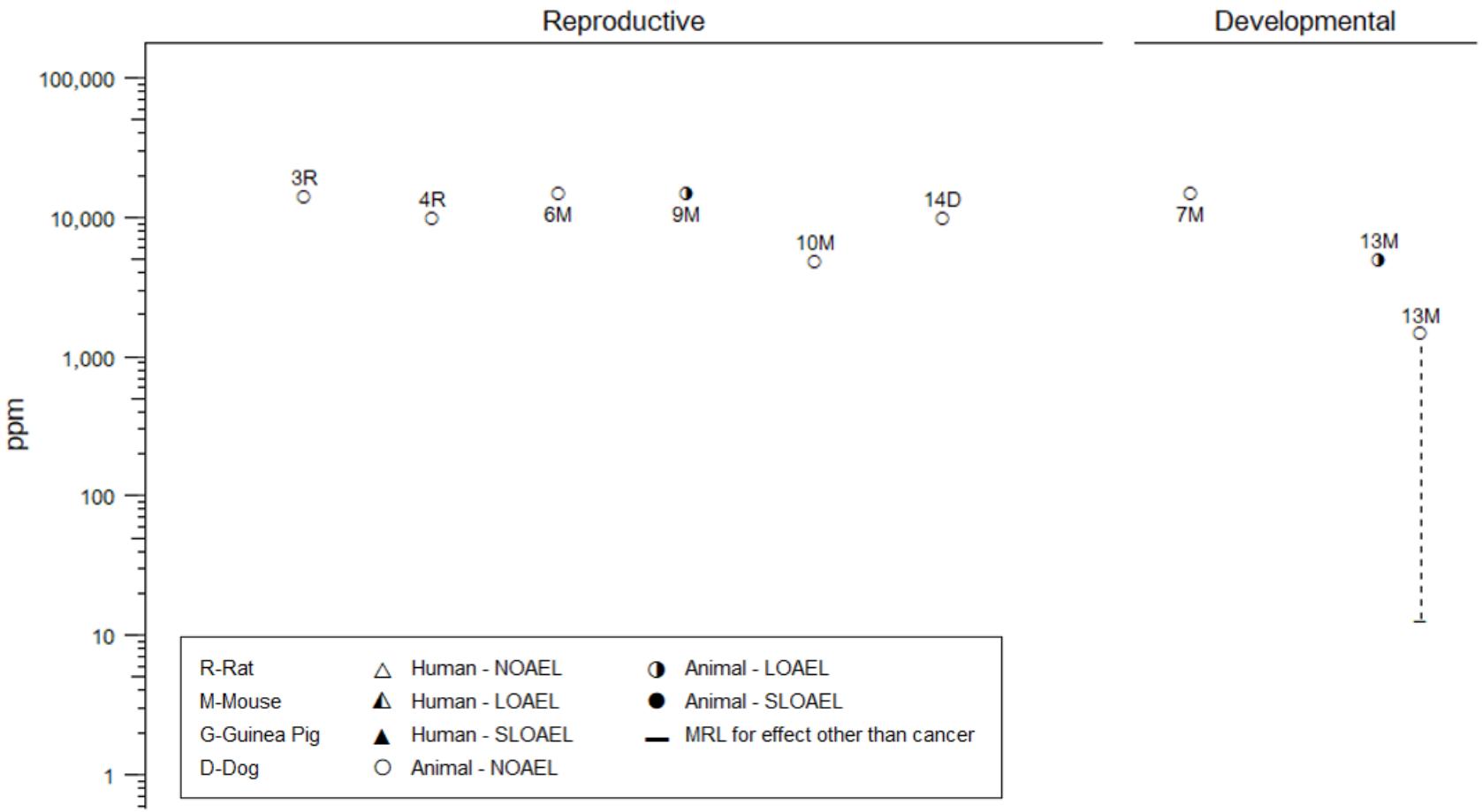


Figure 2-2. Levels of Significant Exposure to Chloroethane – Inhalation
Intermediate (15–364 days)

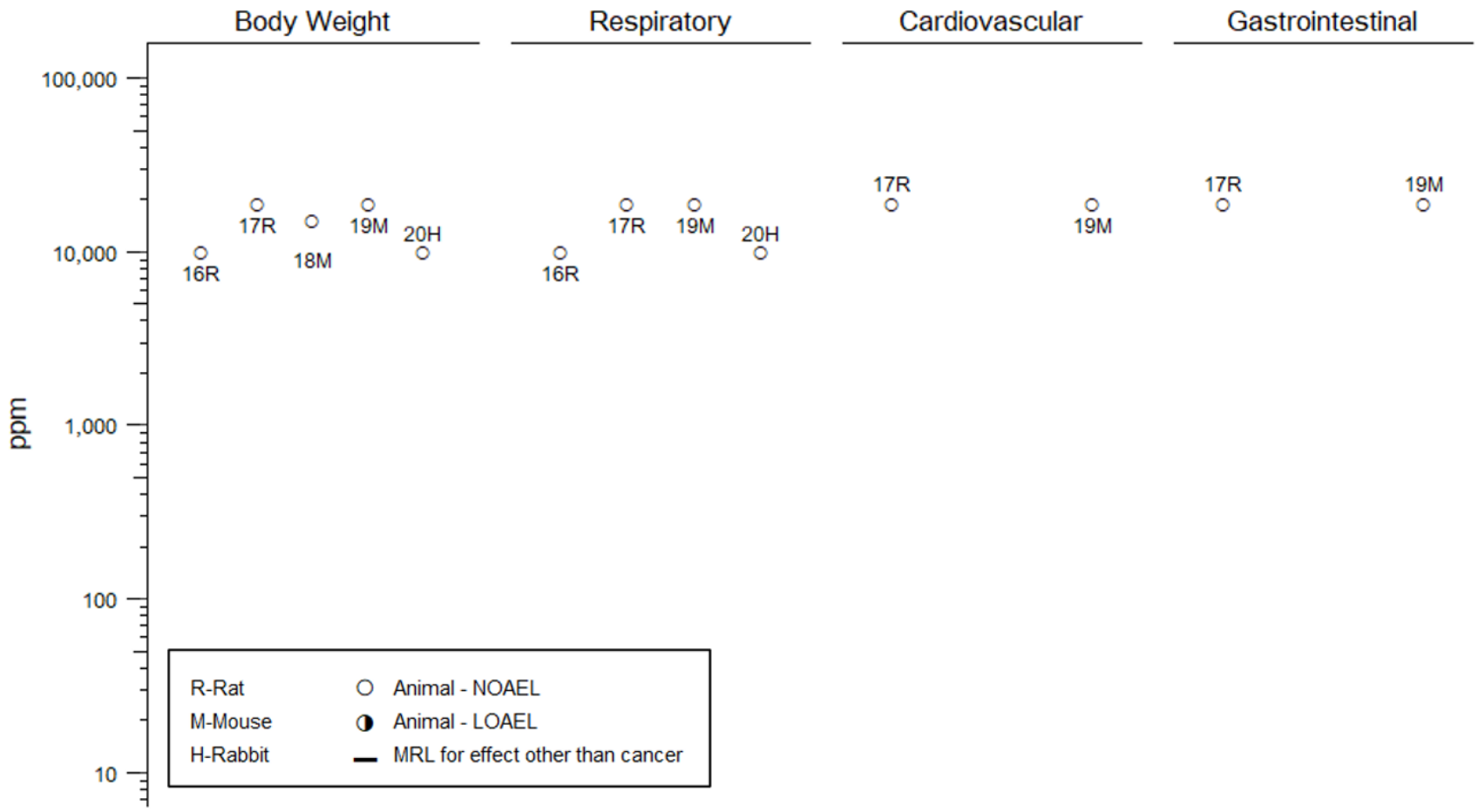


Figure 2-2. Levels of Significant Exposure to Chloroethane – Inhalation
Intermediate (15–364 days)

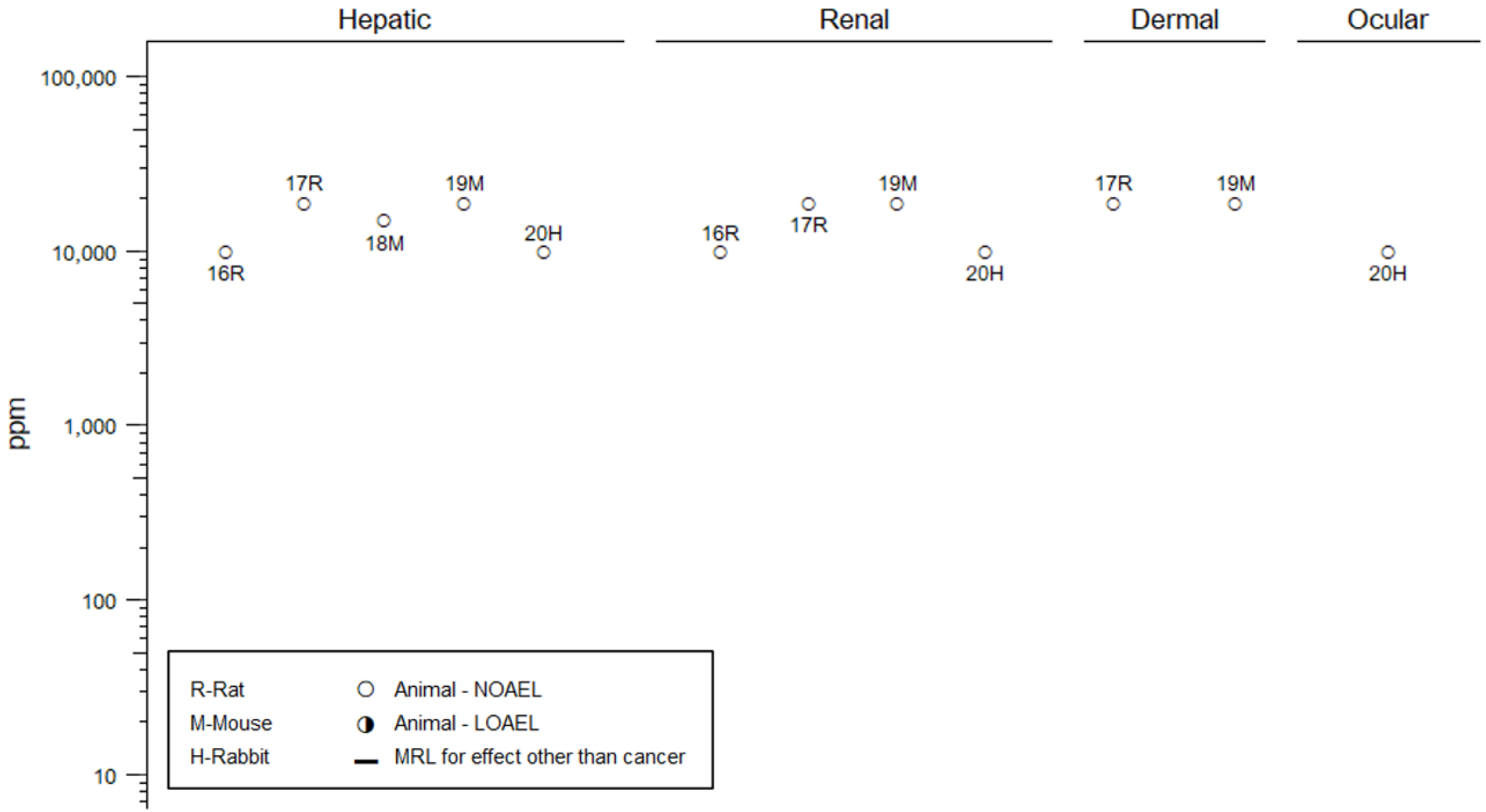


Figure 2-2. Levels of Significant Exposure to Chloroethane – Inhalation
Intermediate (15–364 days)

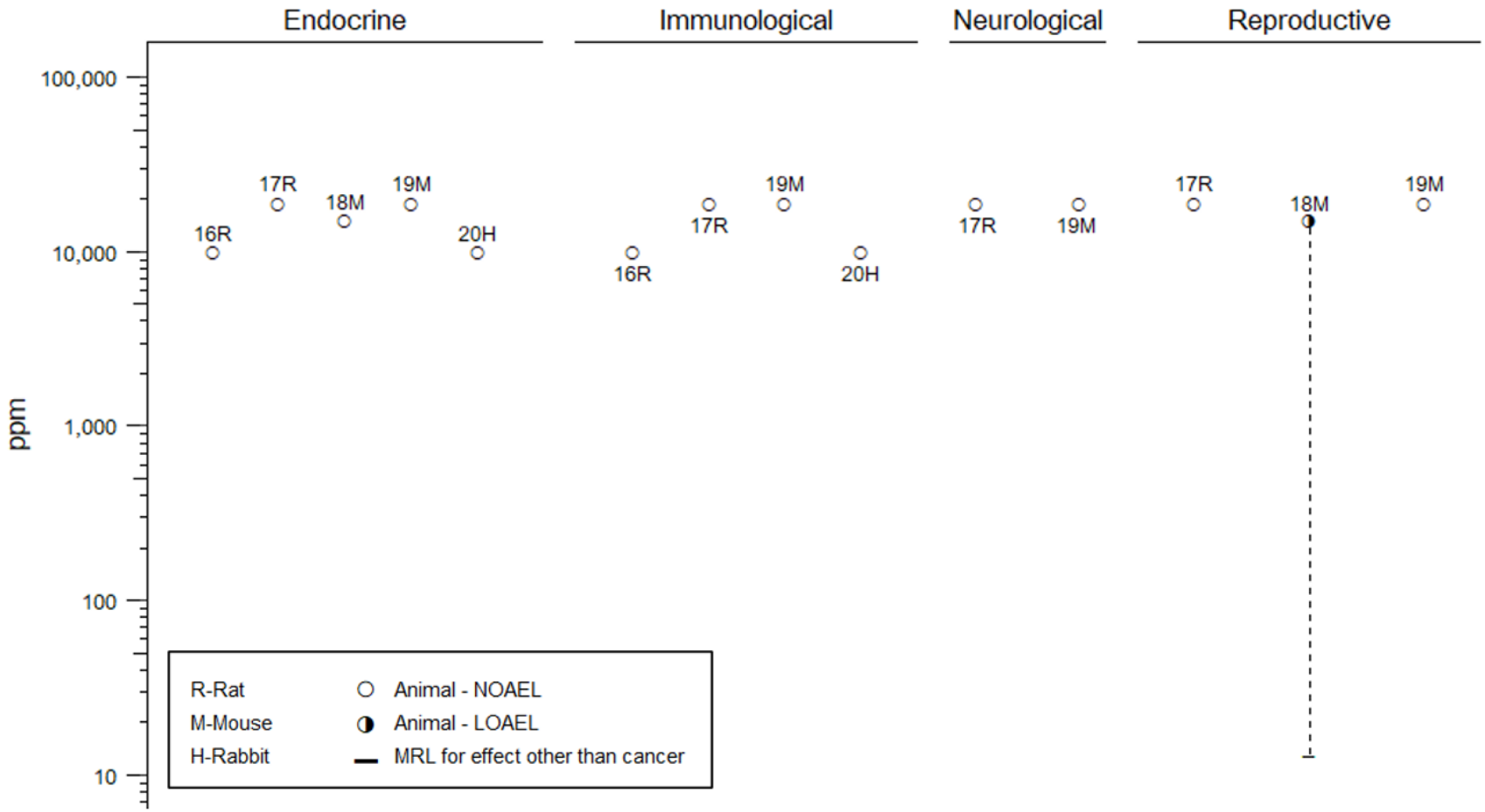


Figure 2-2. Levels of Significant Exposure to Chloroethane – Inhalation
Chronic (≥365 days)

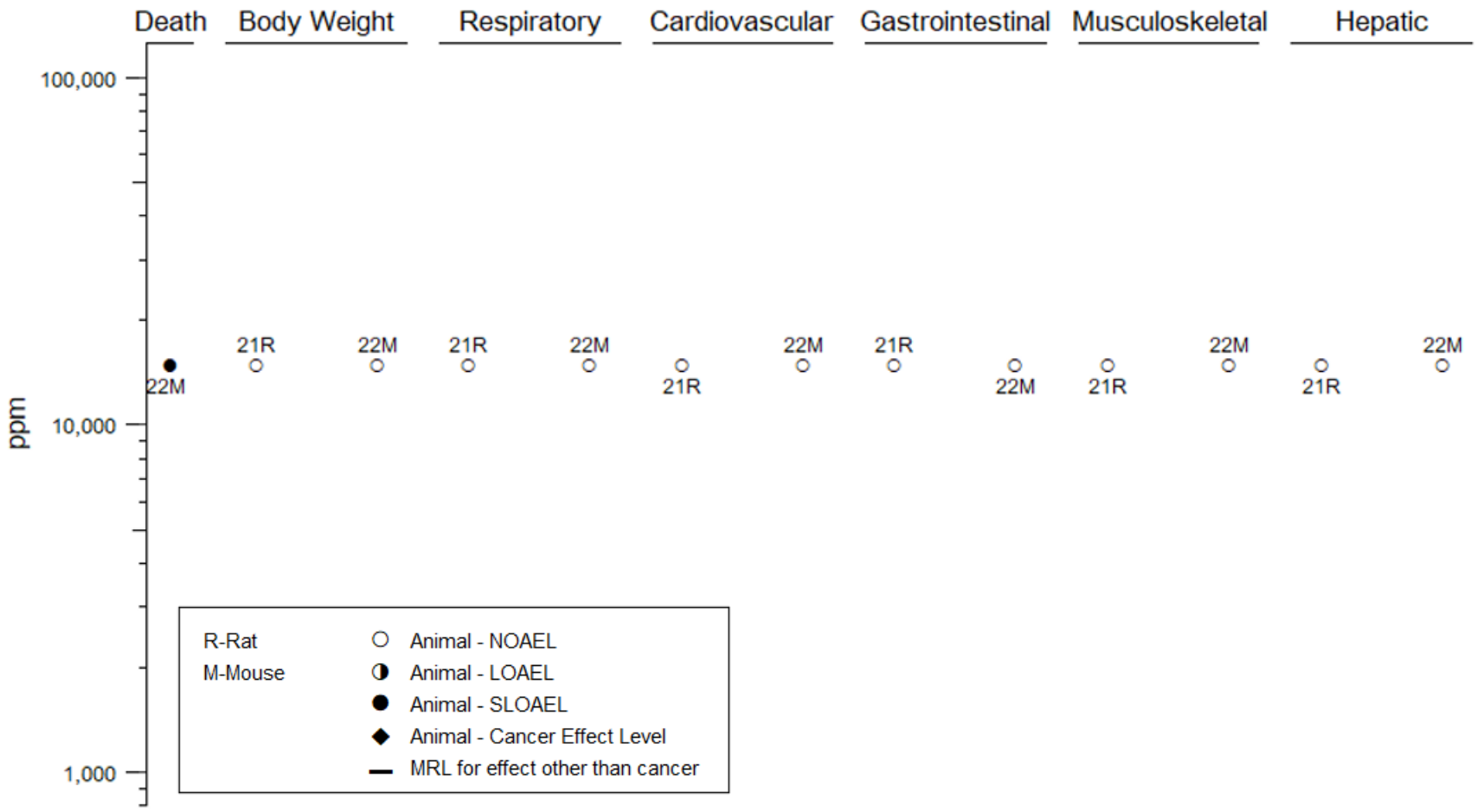


Figure 2-2. Levels of Significant Exposure to Chloroethane – Inhalation
Chronic (≥365 days)

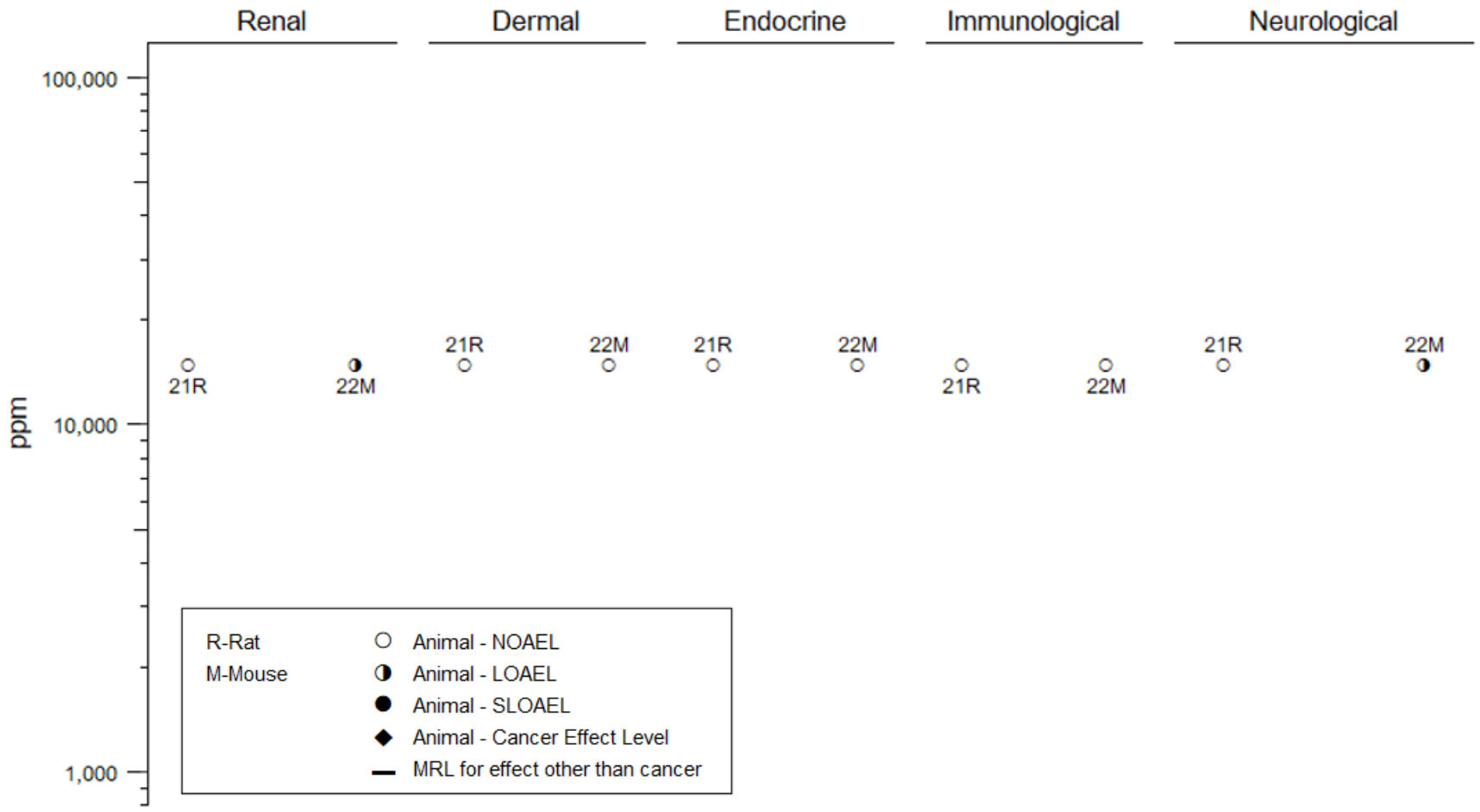


Figure 2-2. Levels of Significant Exposure to Chloroethane – Inhalation
Chronic (≥365 days)

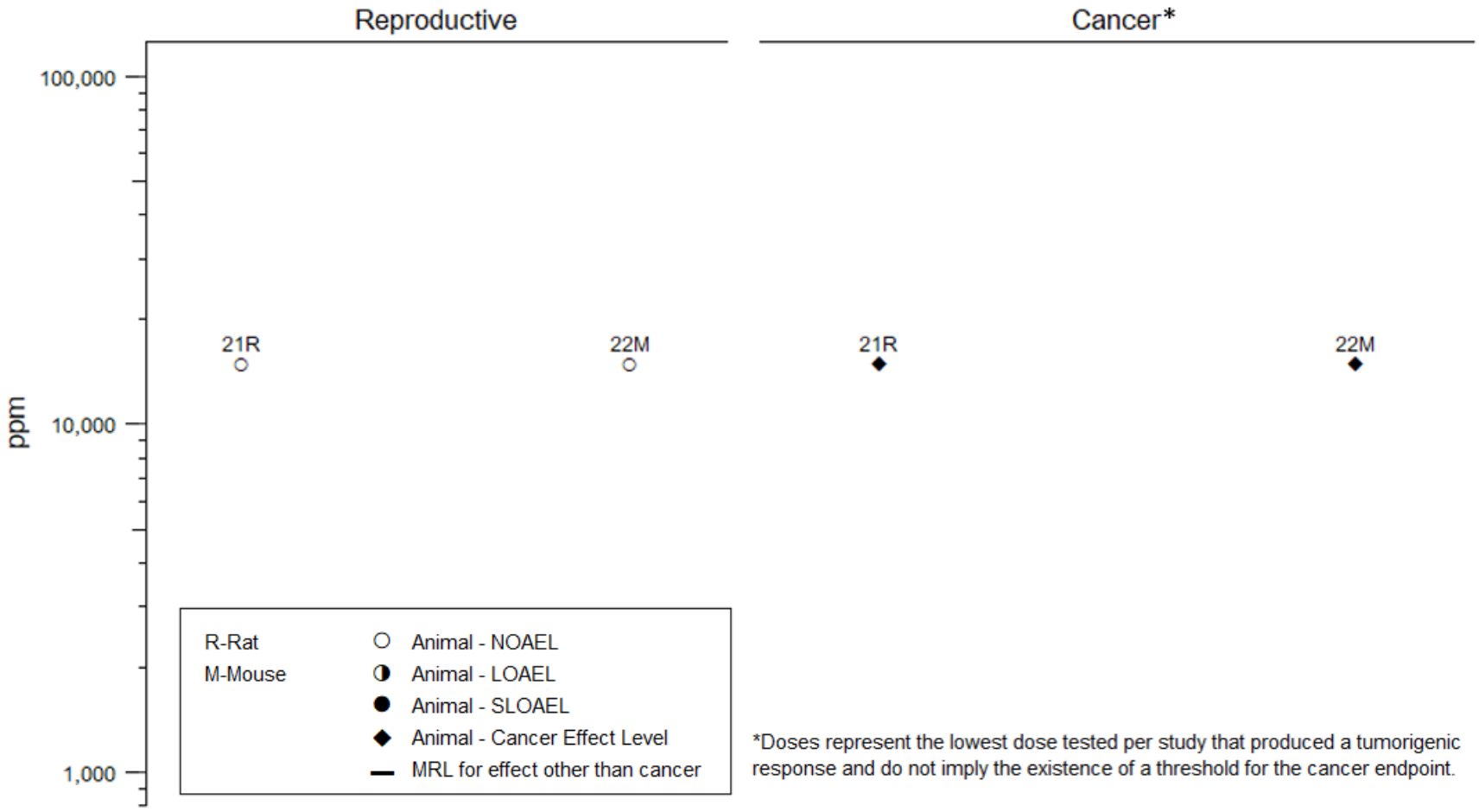


Table 2-2. Levels of Significant Exposure to Chloroethane – Oral (mg/kg/day)

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)

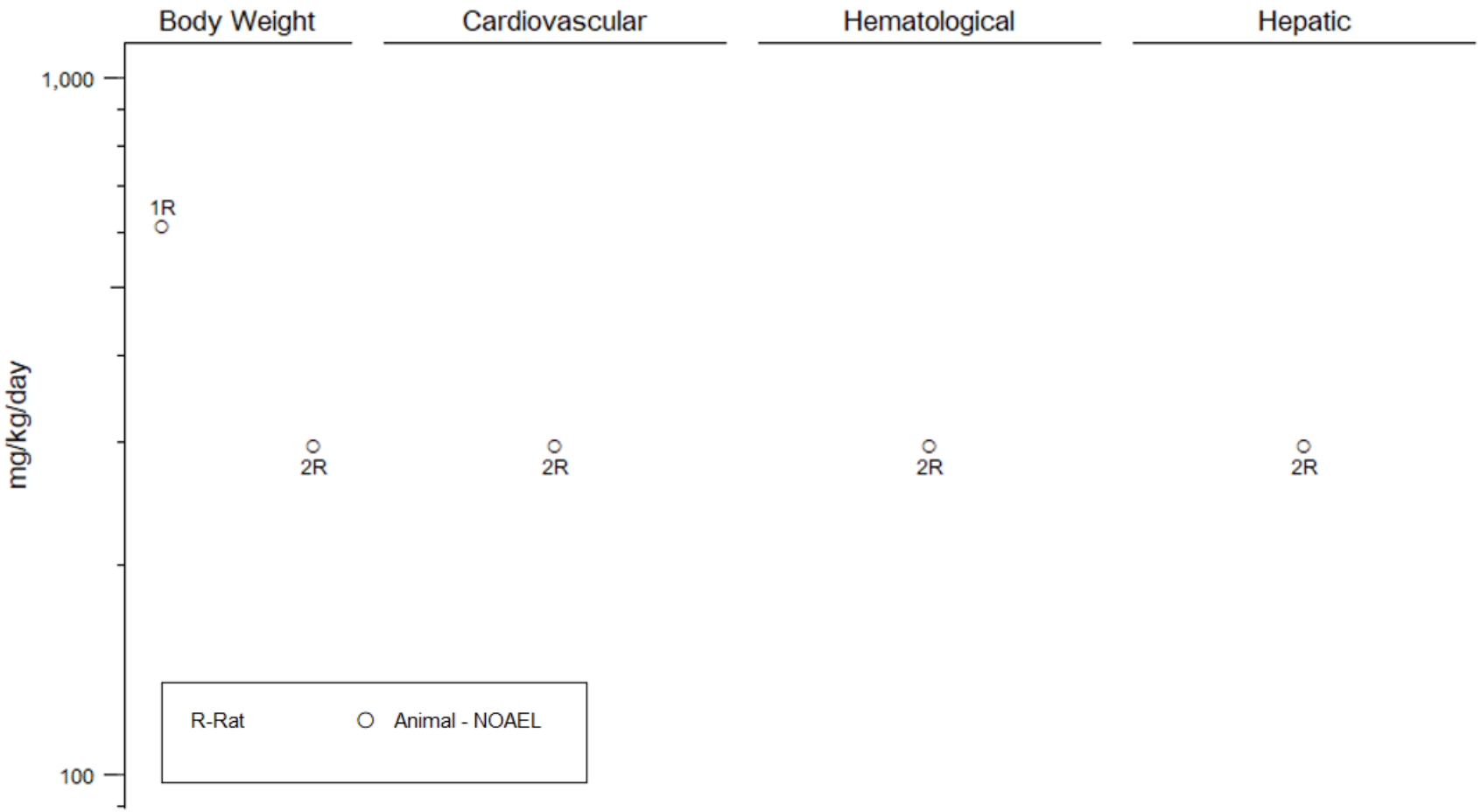
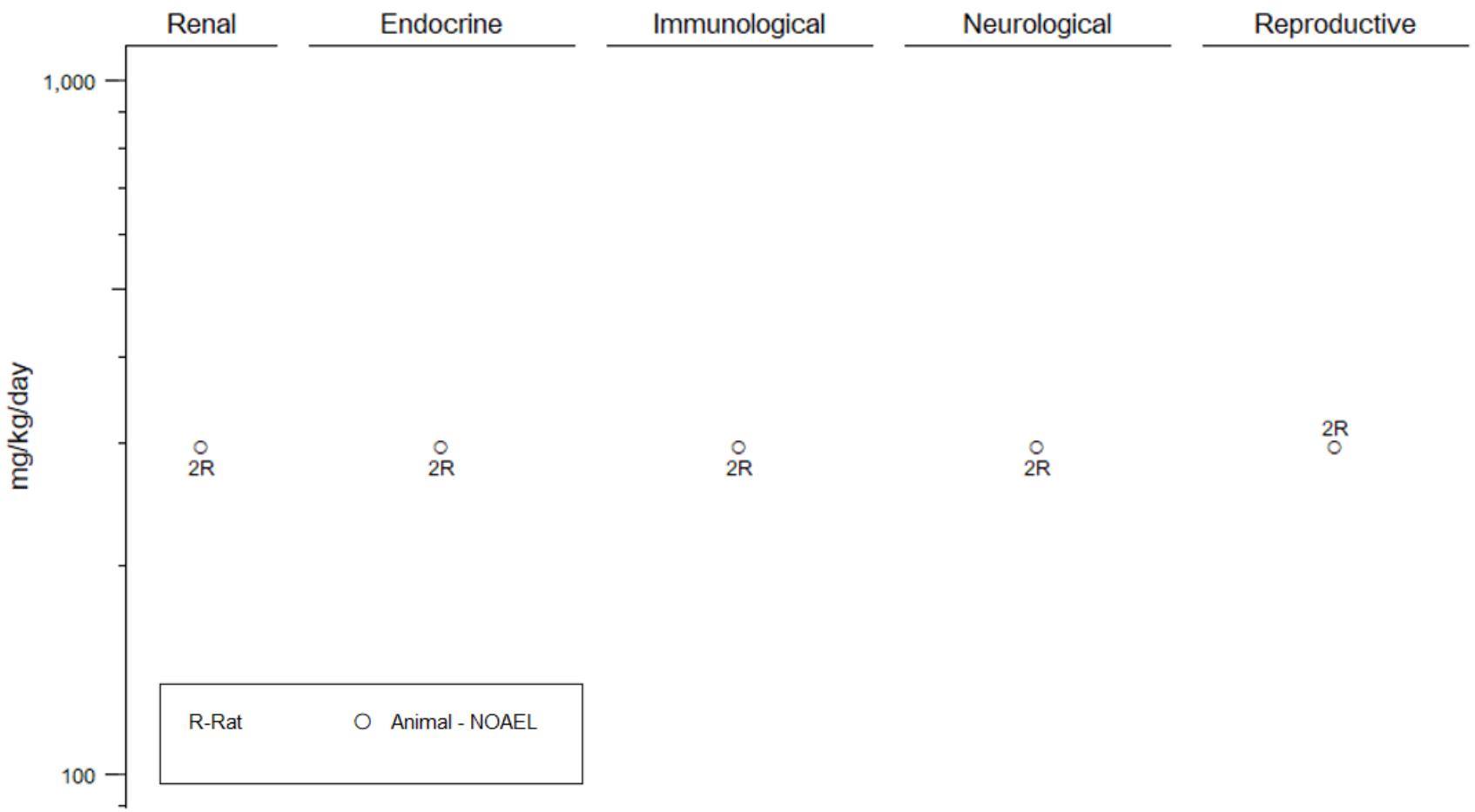


Figure 2-3. Levels of Significant Exposure to Chloroethane – Oral
Acute (≤14 days)



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). Several deaths have also been attributed to chloroethane following intentional misuse of chloroethane as a recreational inhalant (Broussard et al. 2000; Hong and Ponampalam 2022; Schwark et al. 2022; Yacoub et al. 1993). In these cases, blood concentrations measured at autopsy or upon hospital admission ranged from <1 to 65 mg/dL; chloroethane was also detected in urine, lung, and brain tissues. Other drugs were also reported in the toxicology screen in some cases (Broussard et al. 2000; Hong and Ponampalam 2022). 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 et 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 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). As reviewed by Marbach (1996), chloroethane 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). It also 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; Winkler et al. 2023; Young et al. 2023). 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; Young et al. 2023). 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). 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.

Several additional acute-duration inhalation studies evaluated neurological effects in animals. While discussed below, these studies are not included in the Table 2-1 or plotted in Figure 2-2 due to lack of a concurrent control group (Dow 1992; Lazarew 1929) or inadequate reporting (Bush et al. 1952; Morris et al. 1952). Loss of reflexes was seen in mice after 2 hours of exposure to 53,053 ppm (Lazarew 1929). 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). In dogs, unspecified 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; concentrations were not reported (Morris et al. 1953).

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).

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 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 (desiccator test for exposure to gases)	Gene mutation	–	–	NTP 1989
Strains TA1535, TA100	Gene mutation	+	+	Milman et al. 1988
Eukaryotic 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.