CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of 1,2-dichloroethane. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

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

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

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

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

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into “less serious” or “serious” effects. “Serious” effects (SLOAELs) are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR

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

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

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

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

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

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

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

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

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

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

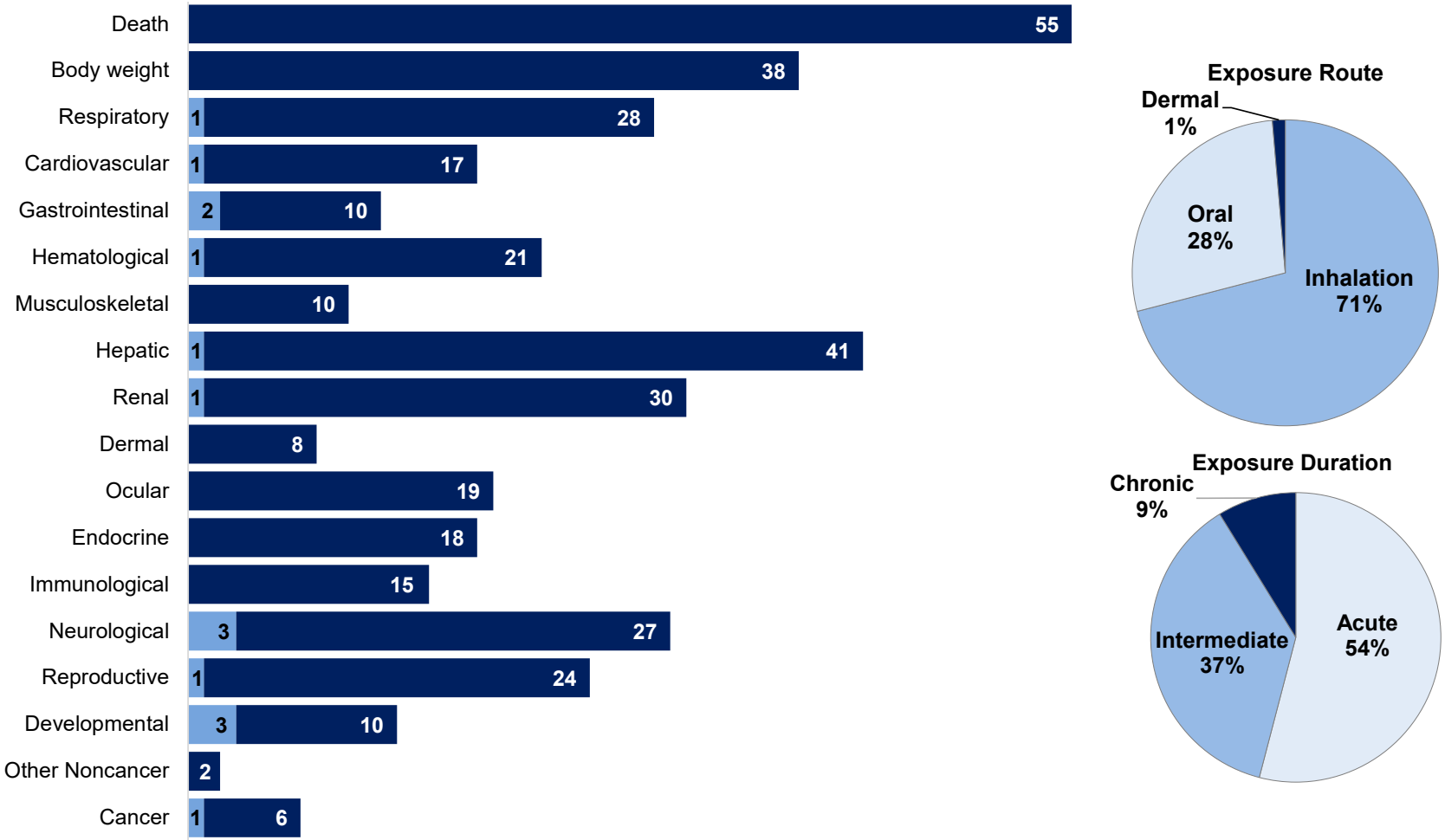
- ***Death:*** Mortality was observed in animals exposed by oral and inhalation routes. Administration by gavage results in death at much lower doses than administration in drinking water.

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Studies selected for derivation of inhalation MRLs.

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

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

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

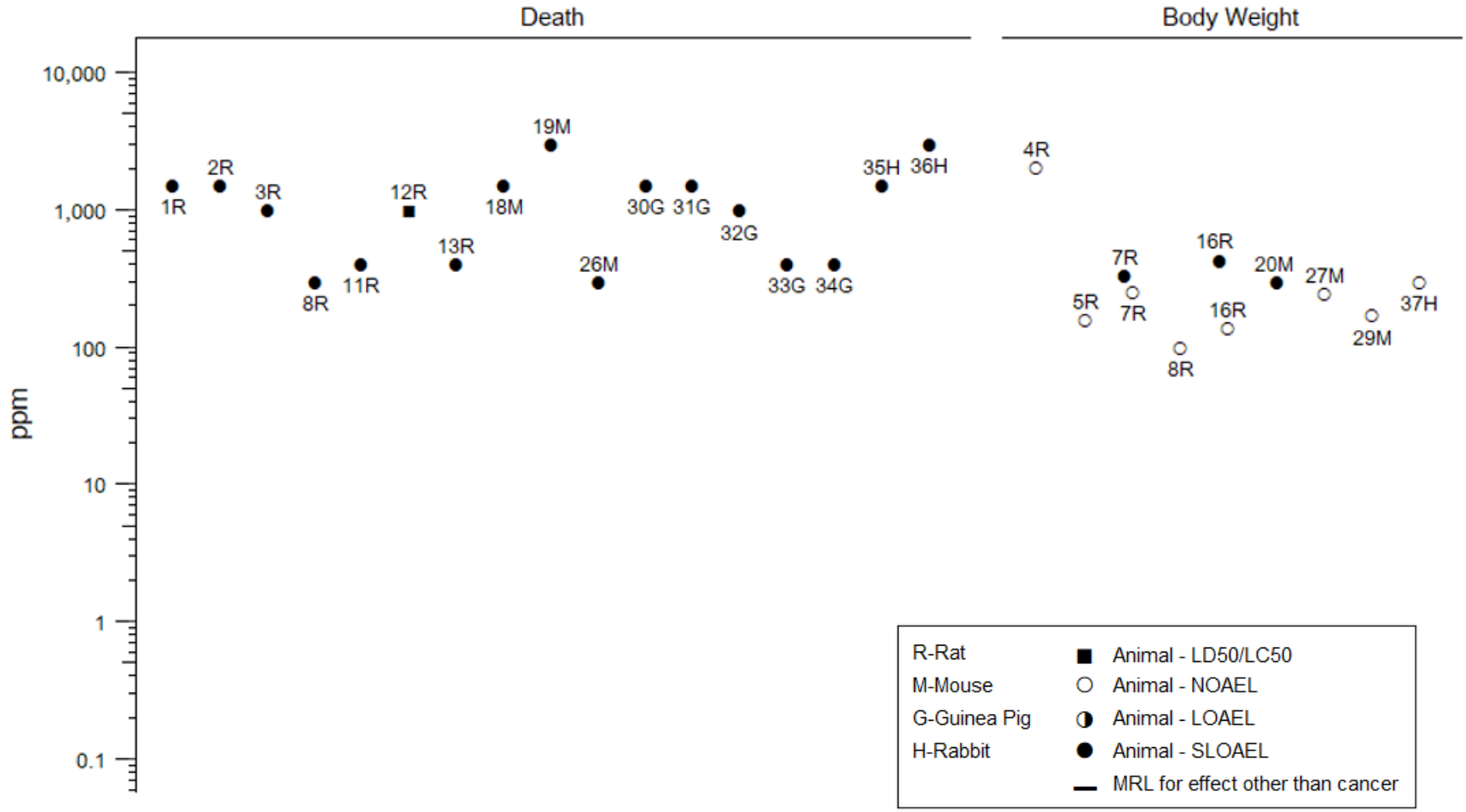


Figure 2-2. Levels of Significant Exposure to 1,2-Dichloroethane – Inhalation
Acute (≤14 days)

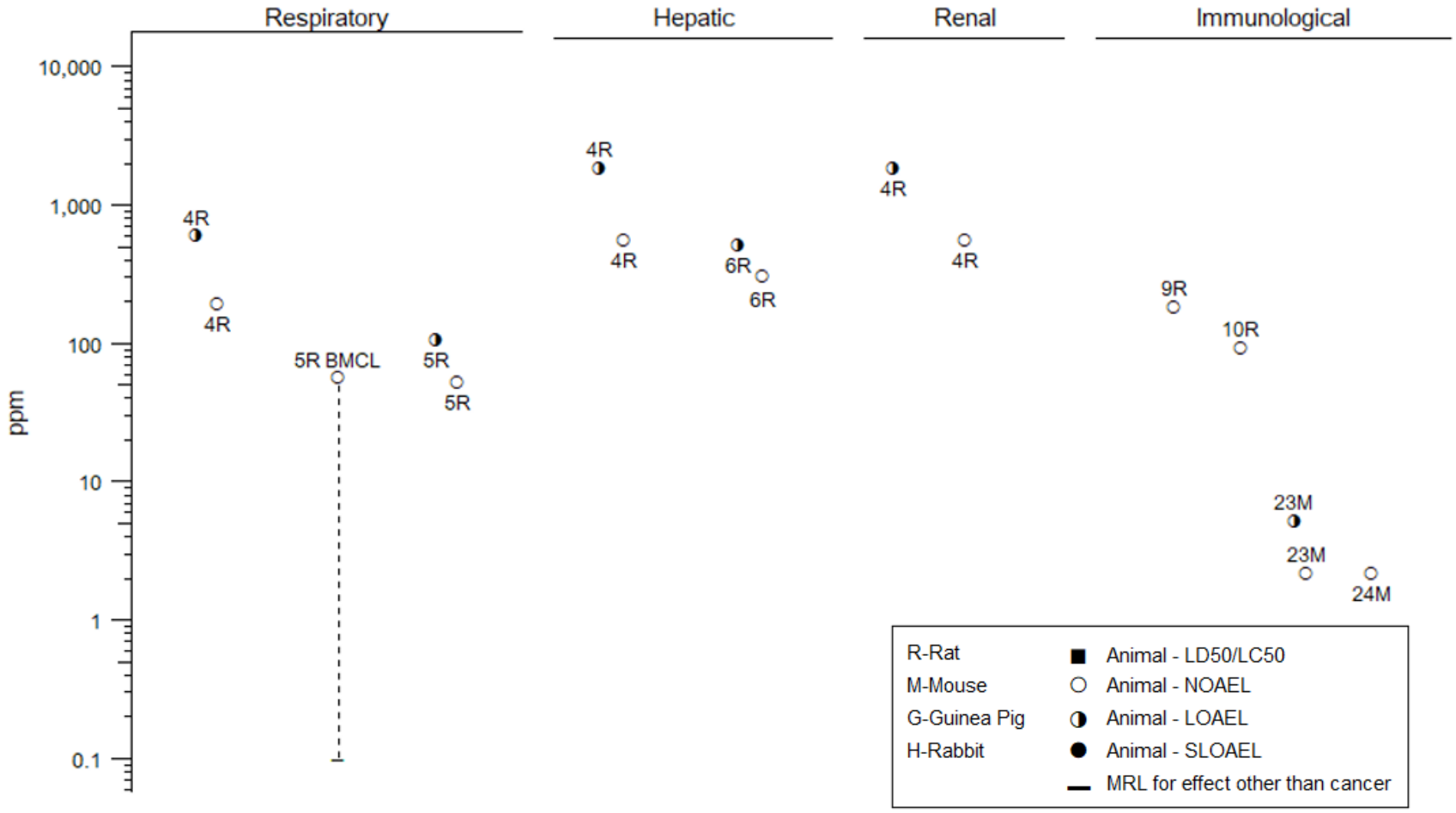


Figure 2-2. Levels of Significant Exposure to 1,2-Dichloroethane – Inhalation
Acute (≤14 days)

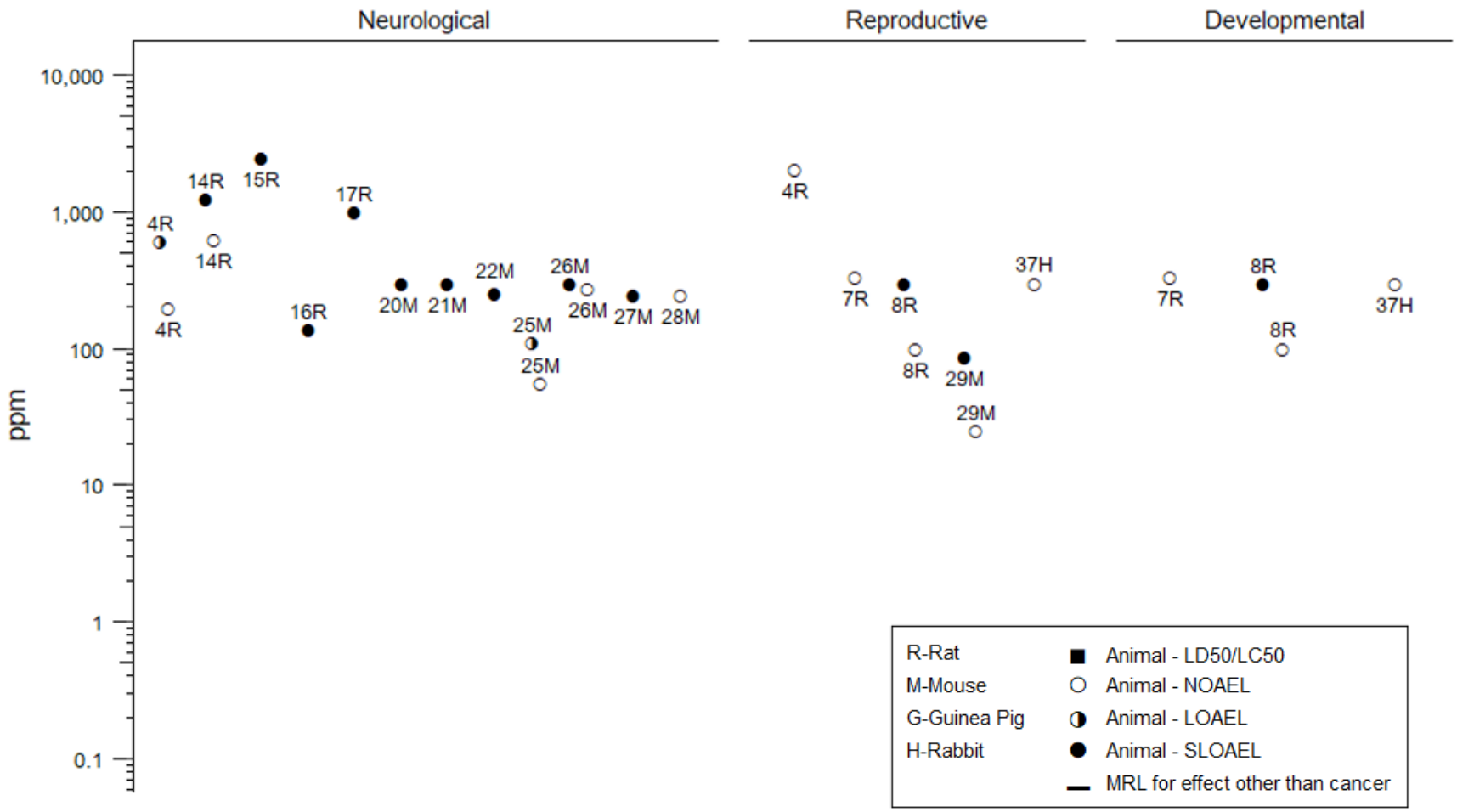


Figure 2-2. Levels of Significant Exposure to 1,2-Dichloroethane – Inhalation
Intermediate (15–364 days)

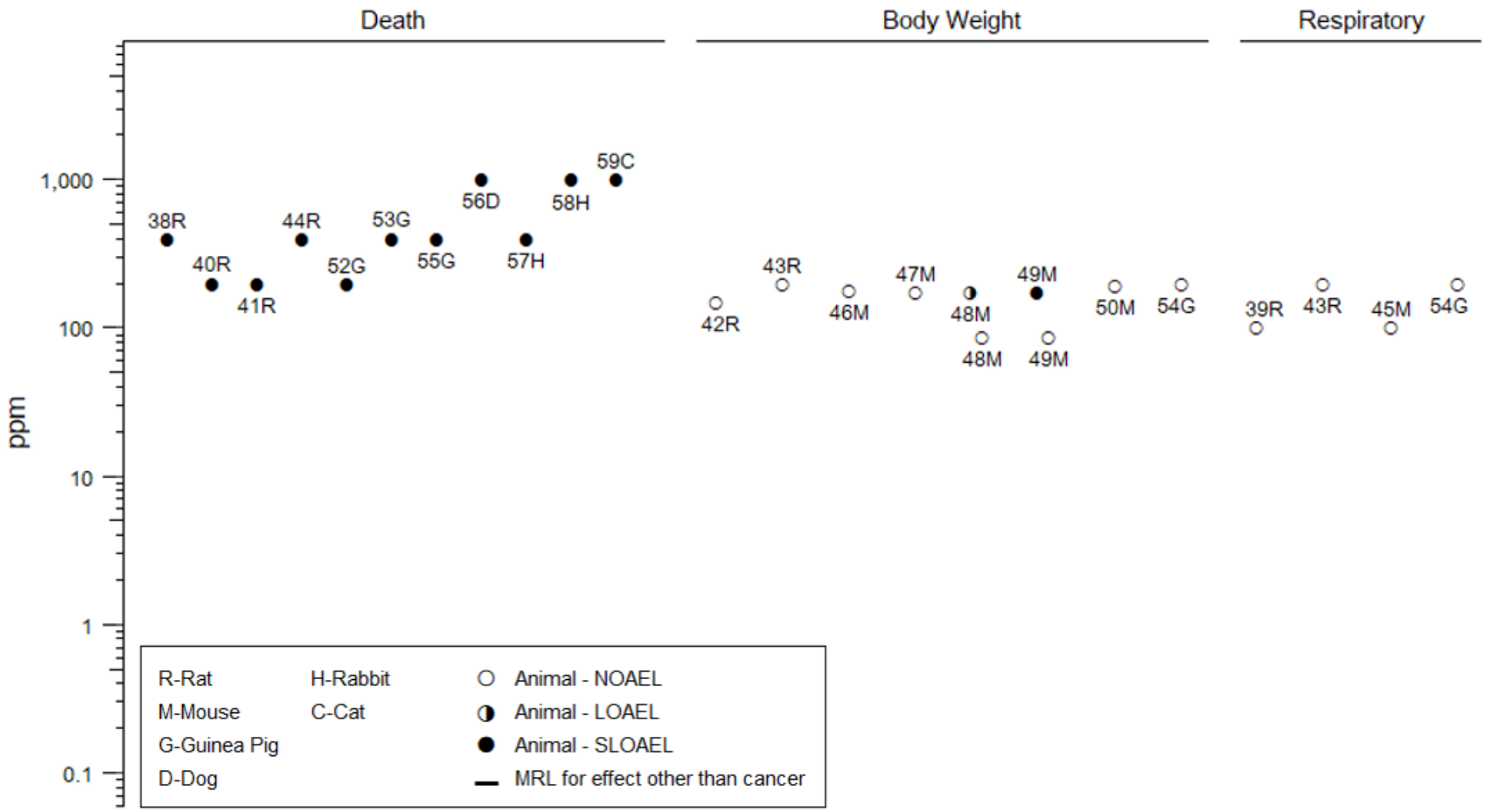


Figure 2-2. Levels of Significant Exposure to 1,2-Dichloroethane – Inhalation
Intermediate (15–364 days)

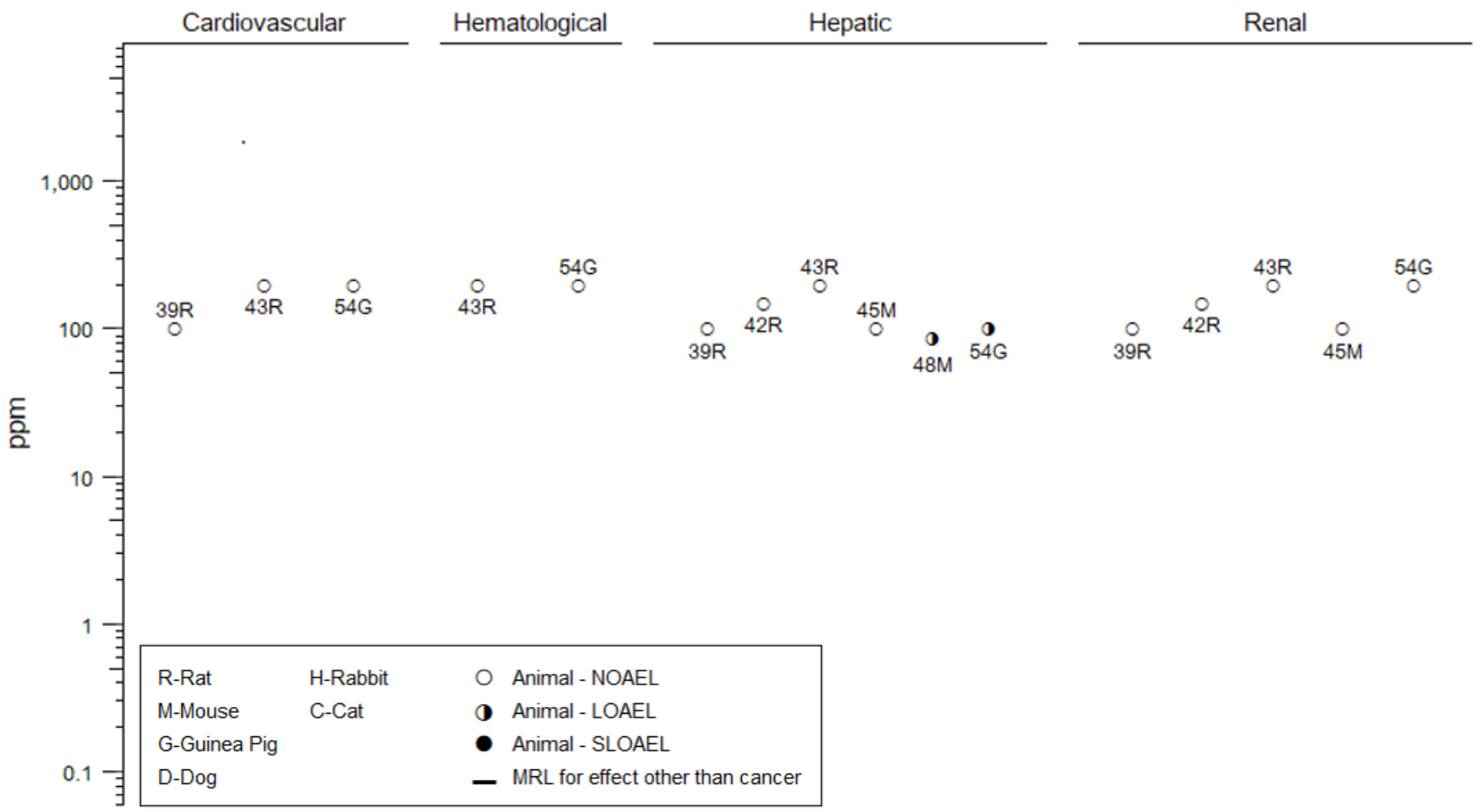


Figure 2-2. Levels of Significant Exposure to 1,2-Dichloroethane – Inhalation
Intermediate (15–364 days)

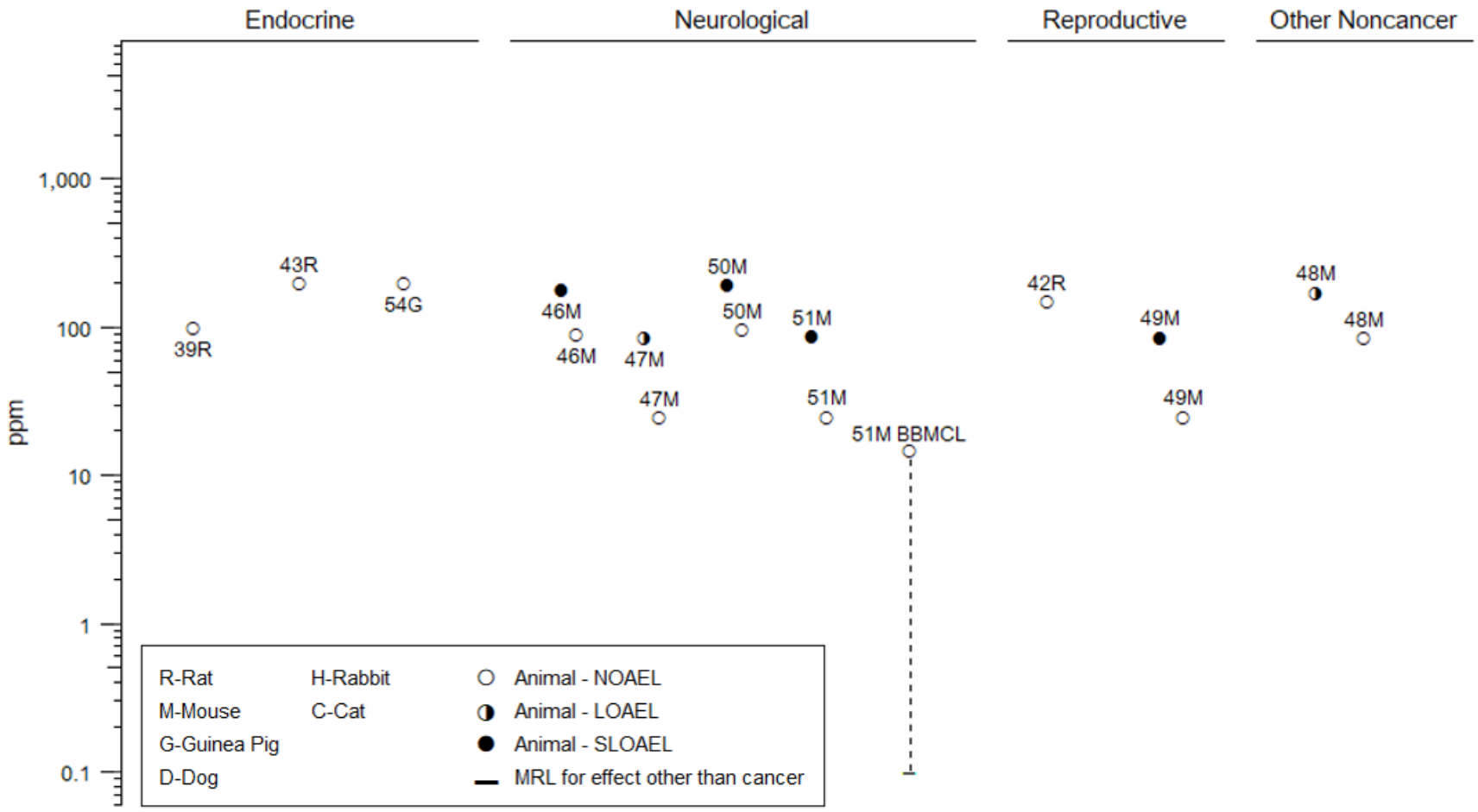


Figure 2-2. Levels of Significant Exposure to 1,2-Dichloroethane – Inhalation
Chronic (≥365 days)

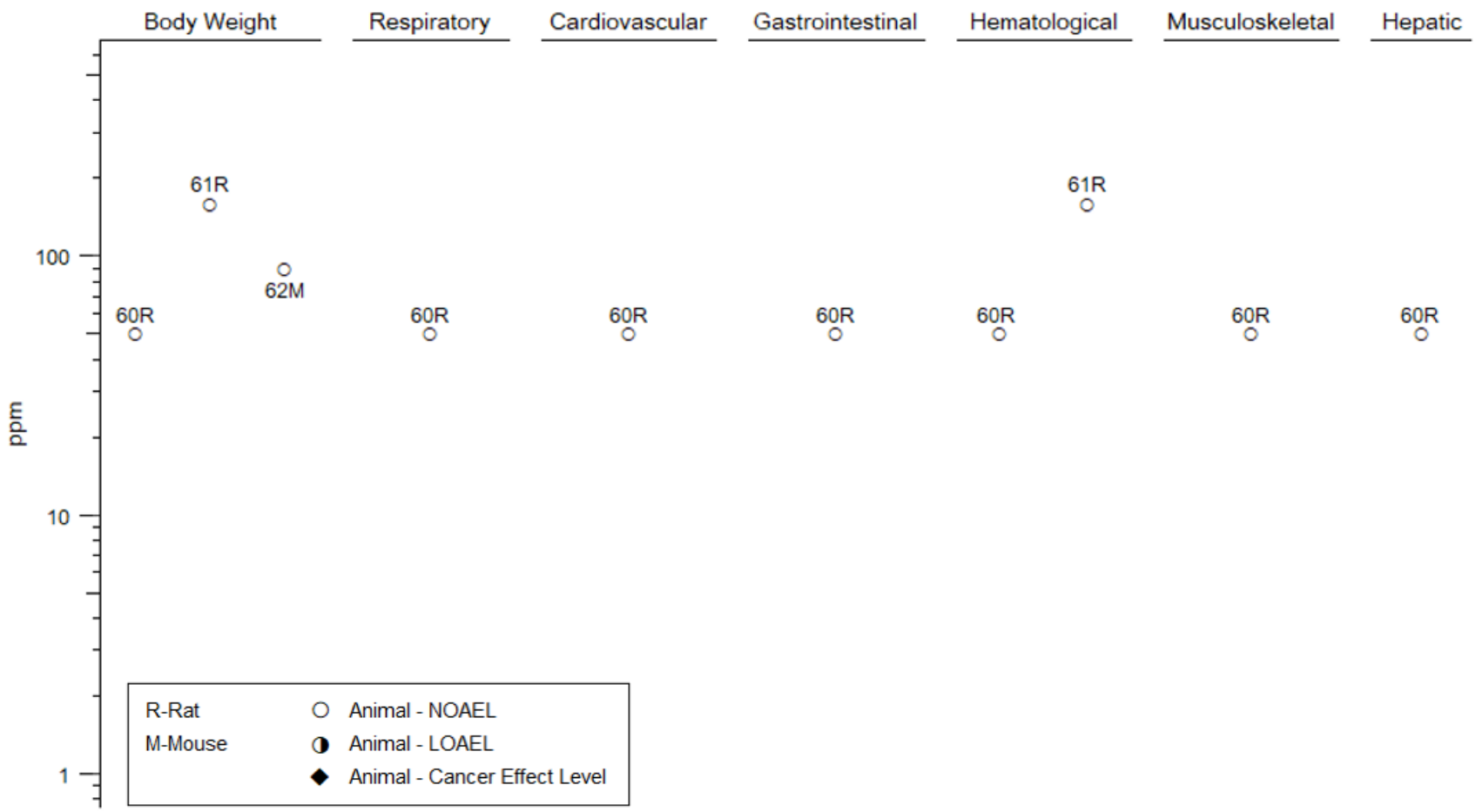
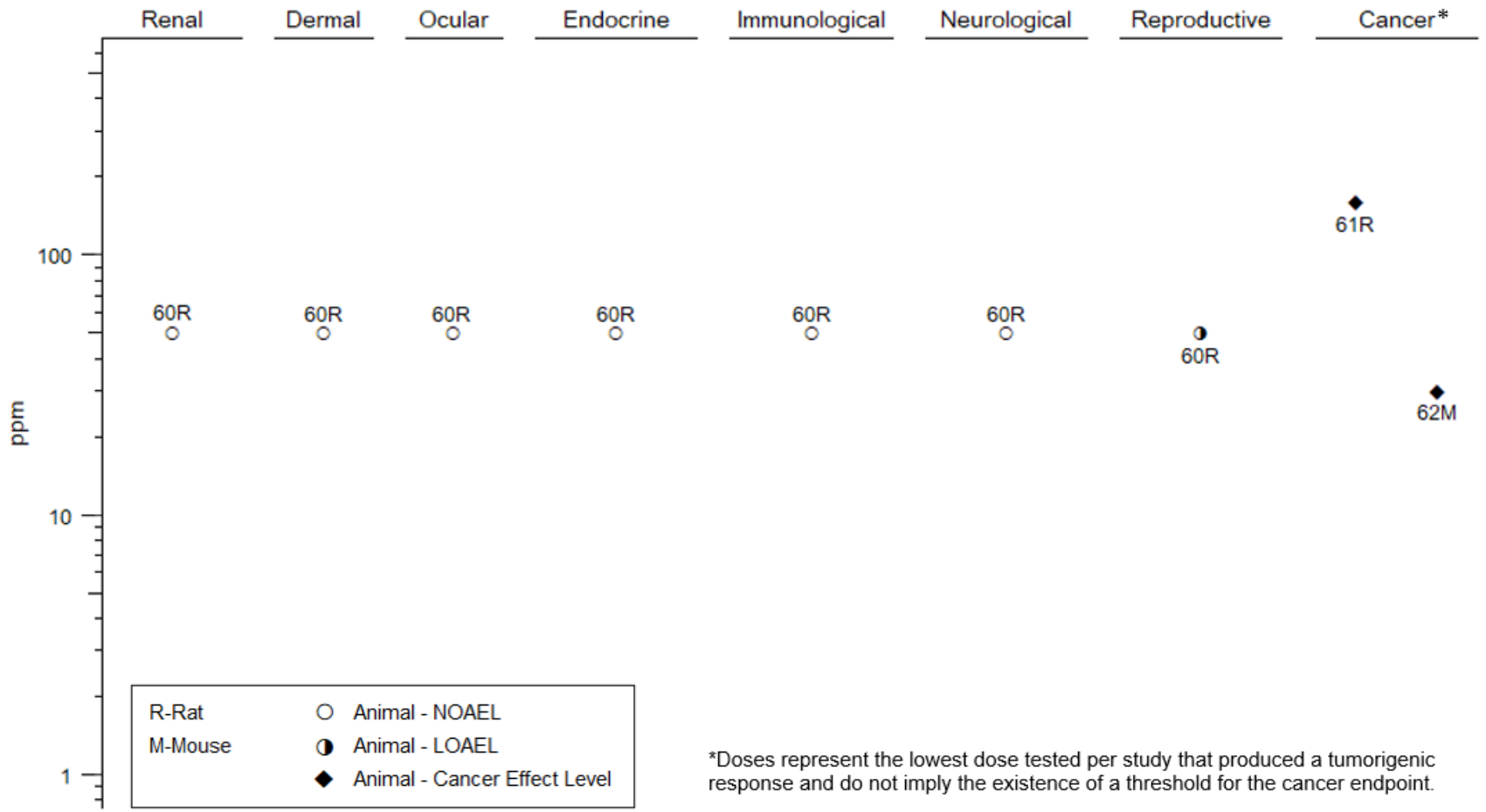


Figure 2-2. Levels of Significant Exposure to 1,2-Dichloroethane – Inhalation
Chronic (≥365 days)



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Studies selected for derivation of oral MRLs.

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

B = both males and females; BC = serum (blood) chemistry; Bd wt or BW = body weight; BI = biochemical changes; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; F = female(s); FI = food intake; (G) = gavage; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; (GO) = gavage in oil; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; IX = immune function; LD_{50} = median lethal dose; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OW = organ weight; Repro = reproductive; Resp = respiratory; RX = reproductive function; UR = urinalysis; (W) = drinking water; WI = water intake

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

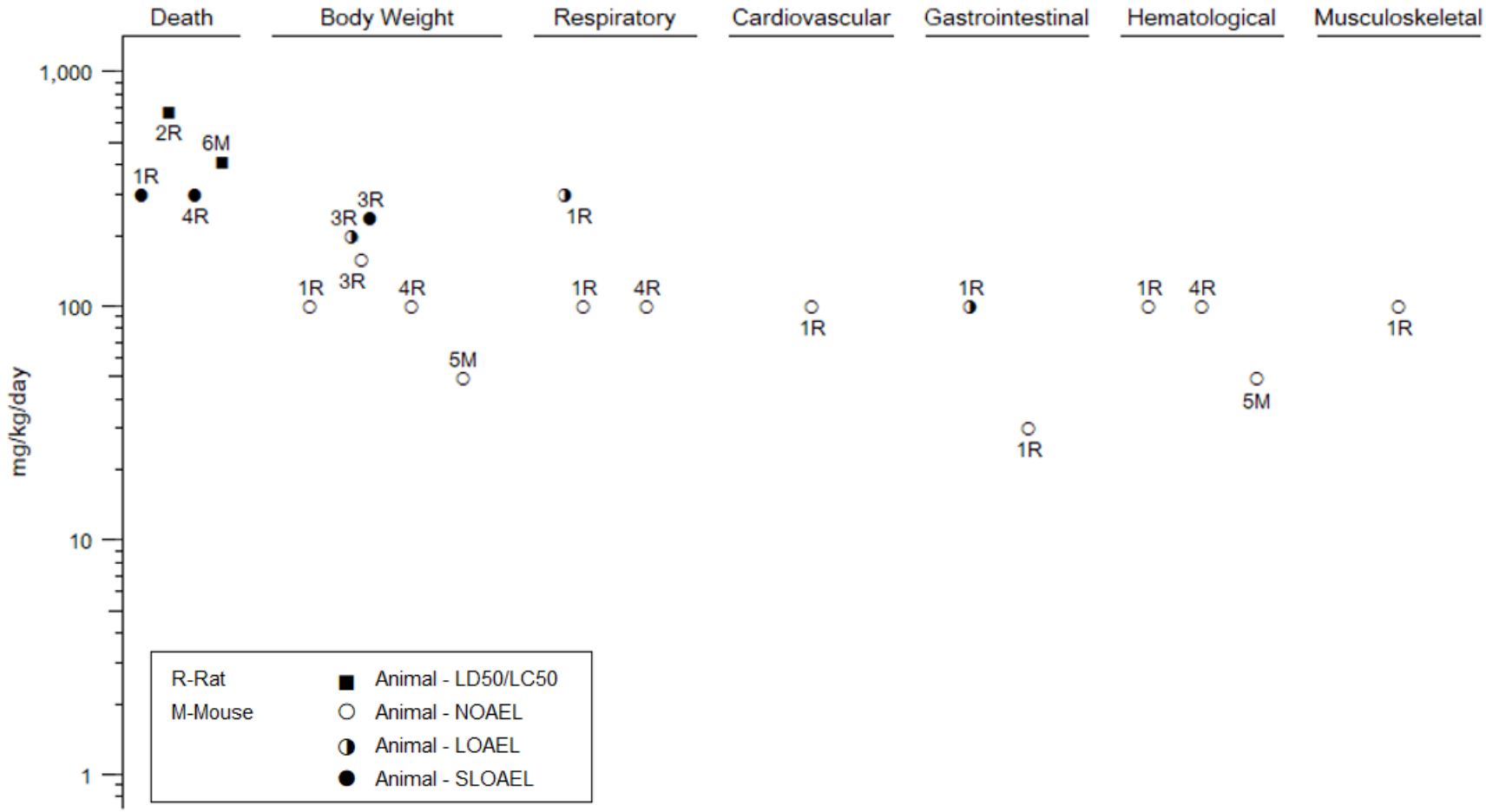


Figure 2-3. Levels of Significant Exposure to 1,2-Dichloroethane – Oral
Acute (≤14 days)

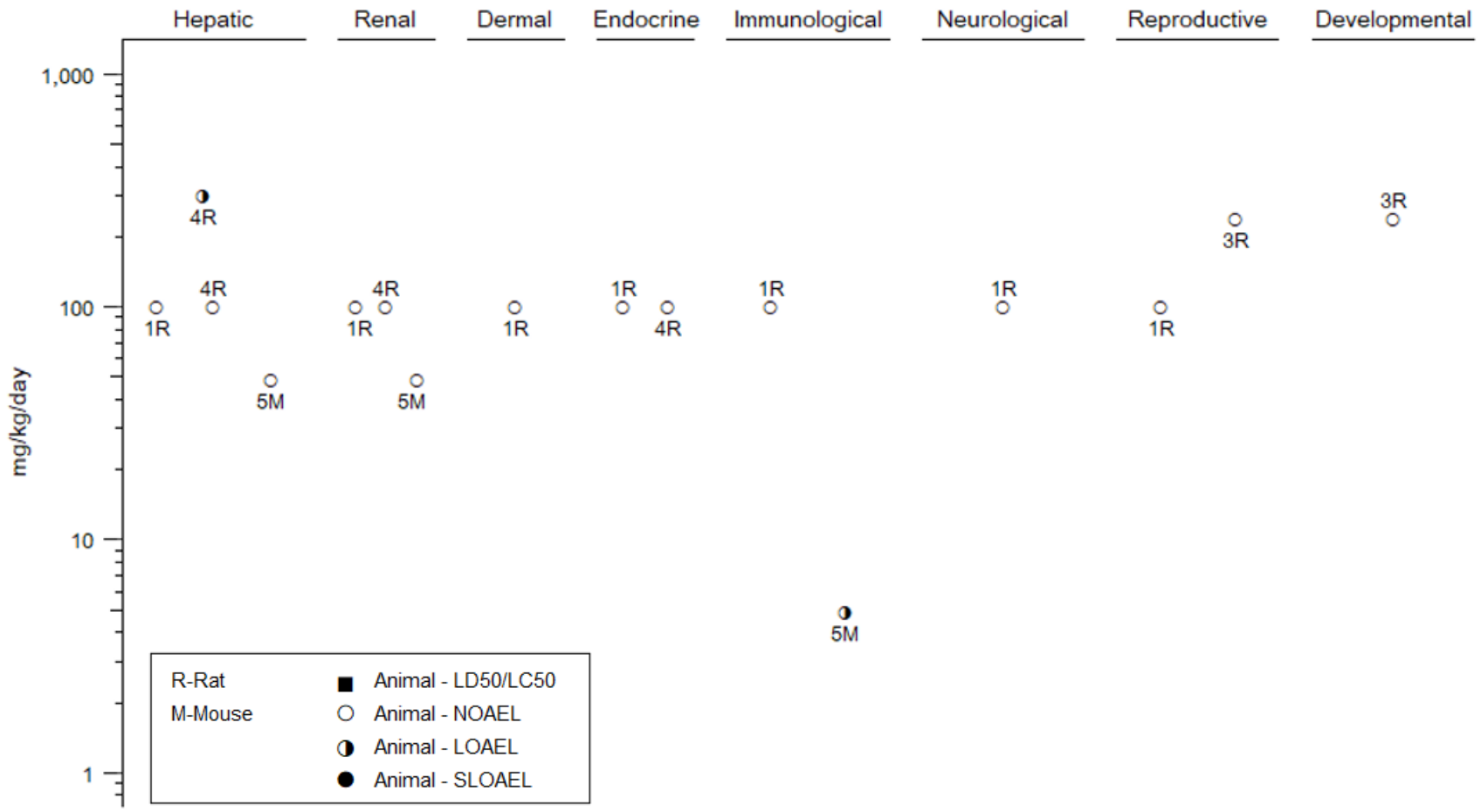


Figure 2-3. Levels of Significant Exposure to 1,2-Dichloroethane – Oral
Intermediate (15–364 days)

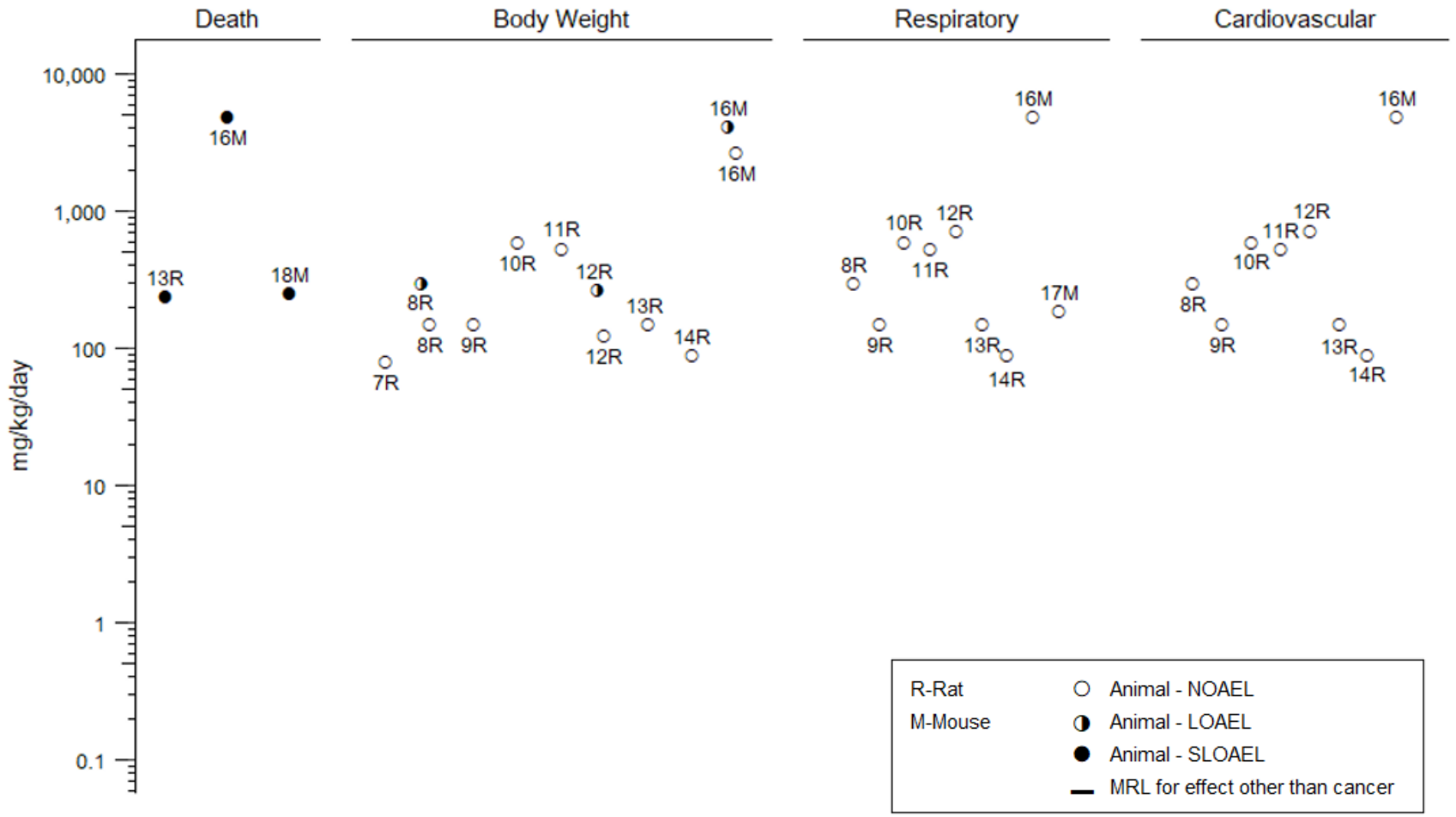


Figure 2-3. Levels of Significant Exposure to 1,2-Dichloroethane – Oral
Intermediate (15–364 days)

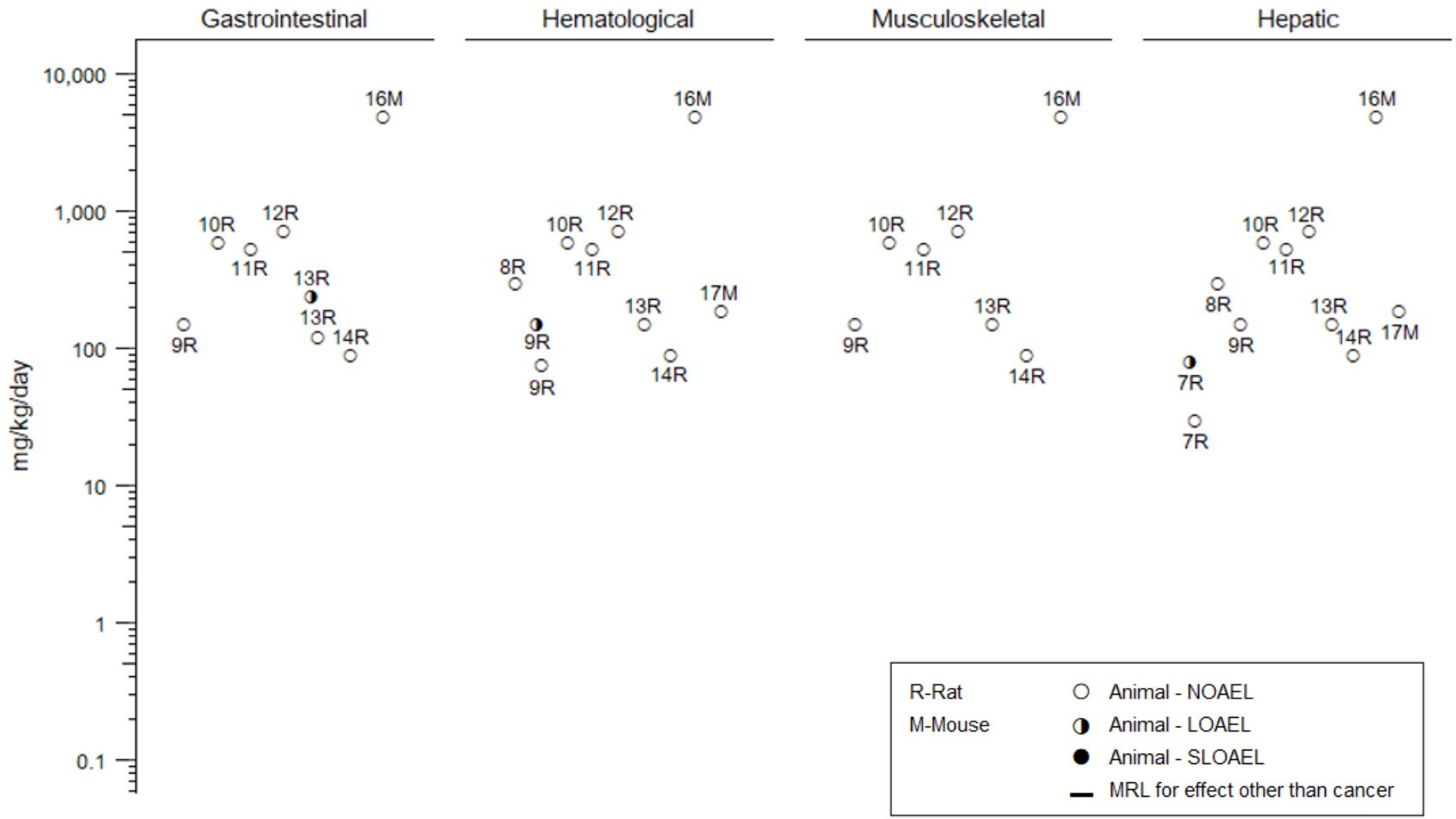


Figure 2-3. Levels of Significant Exposure to 1,2-Dichloroethane – Oral
Intermediate (15–364 days)

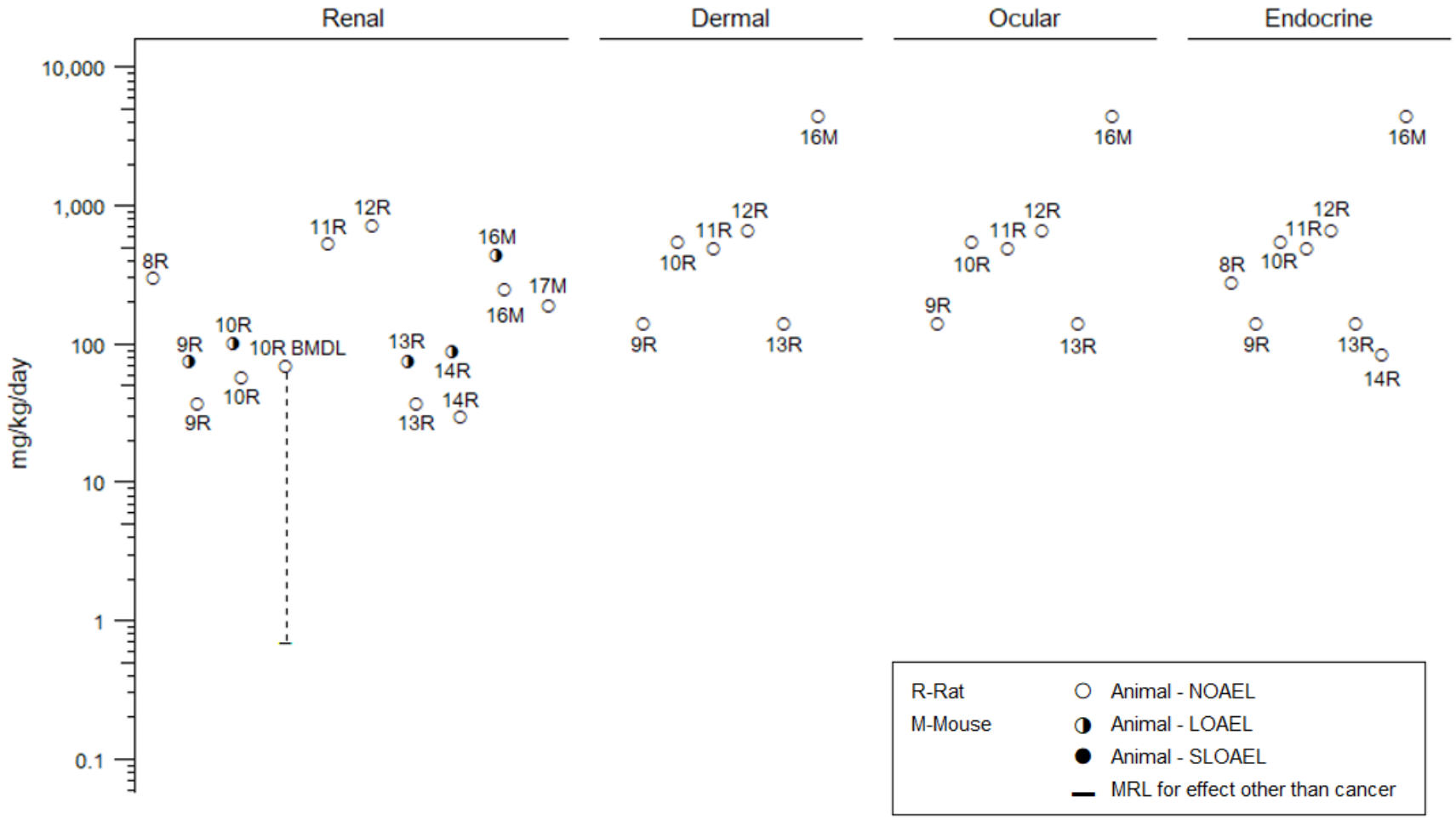


Figure 2-3. Levels of Significant Exposure to 1,2-Dichloroethane – Oral
Intermediate (15–364 days)

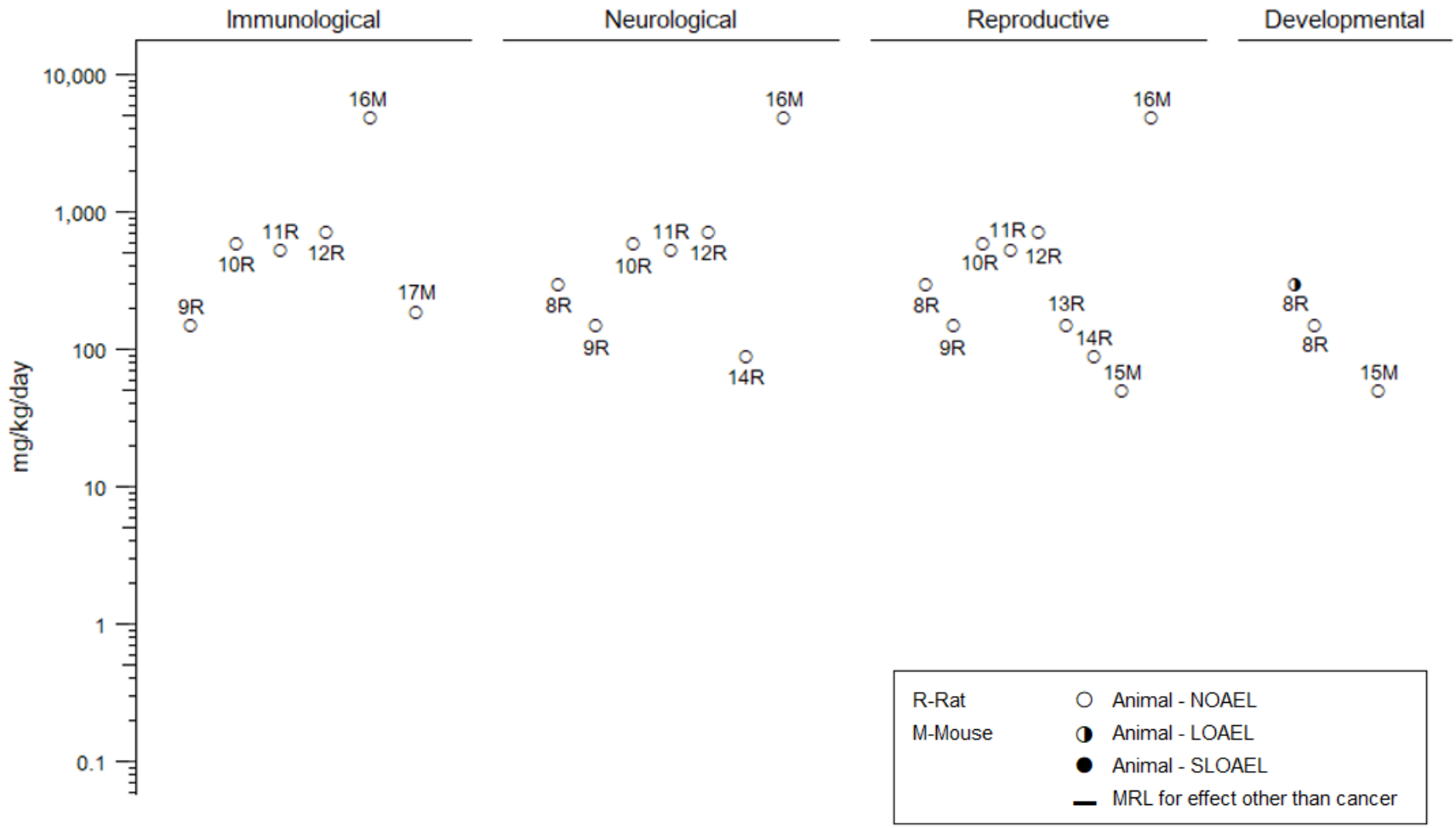
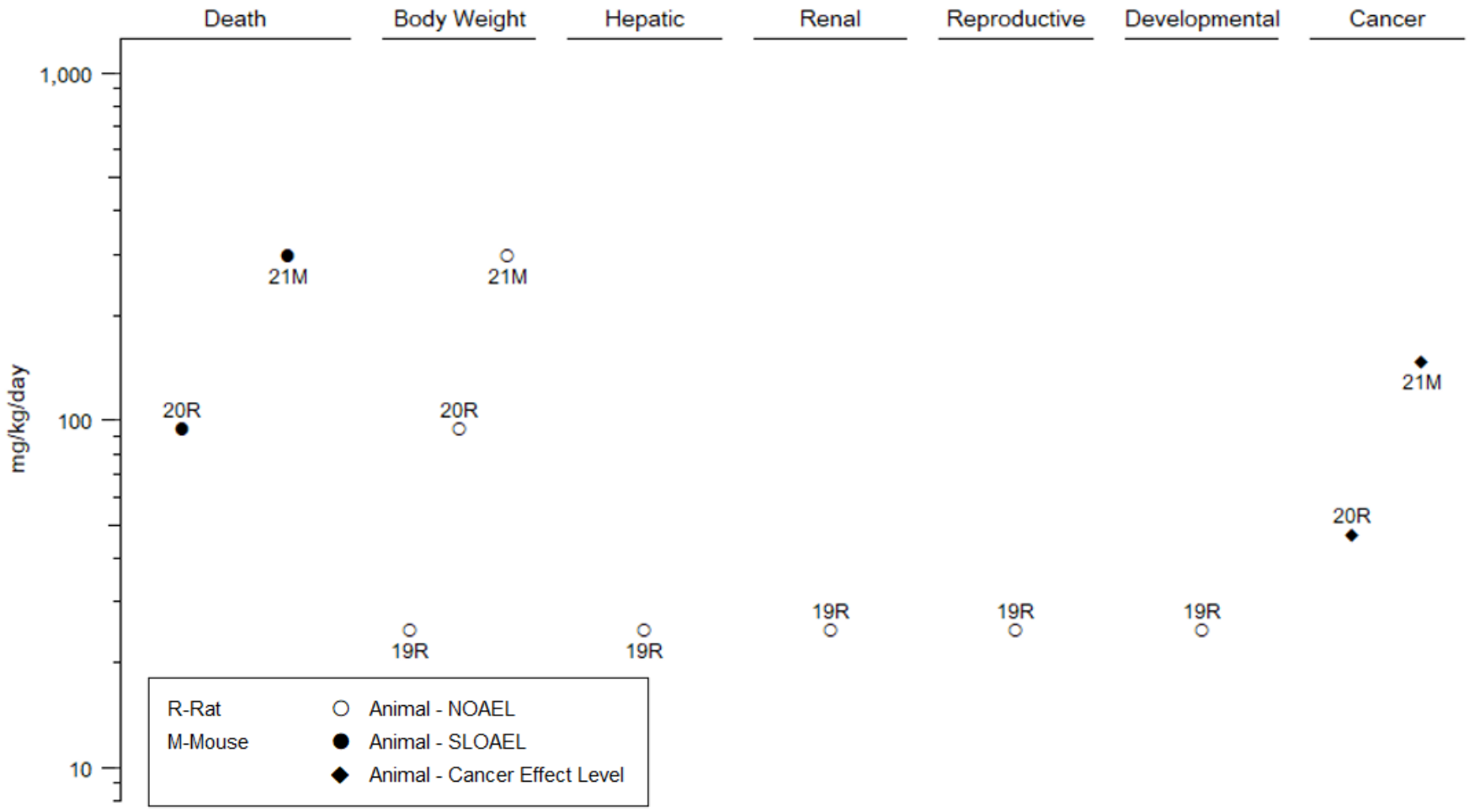


Figure 2-3. Levels of Significant Exposure to 1,2-Dichloroethane – Oral
Chronic (≥365 days)



2.2 DEATH

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

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

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

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

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

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

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

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

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

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

2.3 BODY WEIGHT

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

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

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

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

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

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

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

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

2.4 RESPIRATORY

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

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

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

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

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

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

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

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

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

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

2.5 CARDIOVASCULAR

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

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

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

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

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

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

2.6 HEMATOLOGICAL

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

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

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

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

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

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

2.7 MUSCULOSKELETAL

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

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

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

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

2.8 HEPATIC

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

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

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

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

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

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

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

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

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

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

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

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

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

2.9 RENAL

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

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

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

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

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

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

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

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

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

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

2.10 DERMAL

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

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

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

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

2.11 OCULAR

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

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

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

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

2.12 GASTROINTESTINAL

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

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

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

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

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

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

2.13 ENDOCRINE

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

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

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

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

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

2.14 IMMUNOLOGICAL

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

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

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

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

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

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

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

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

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

2.15 NEUROLOGICAL

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

2.16 REPRODUCTIVE

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

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

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

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

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

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

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

2.17 DEVELOPMENTAL

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

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

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

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

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

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

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

2.18 OTHER NONCANCER

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

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

2.19 CANCER

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

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

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

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

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

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

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

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

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

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

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

2.20 GENOTOXICITY

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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