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-dichloroethene. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

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

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figures 2-1, 2-2, and 2-3 provide an overview of the database of studies in humans or experimental animals for trans-1,2-dichloroethene, cis-1,2-dichloroethene, and mixtures of cis- and trans-1,2-dichloroethene, respectively, included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to cis- and trans-1,2-dichloroethene and mixtures of cis- and trans-1,2-dichloroethene, but may not be inclusive of the entire body of literature. A systematic review of the scientific evidence of the health effects associated with exposure to trans-1,2-dichloroethene was also conducted; the results of this review are presented in Appendix C.

Animal studies for trans-1,2-dichloroethene are presented in Table 2-1 and Figure 2-4 for inhalation exposure, Table 2-2 and Figure 2-5 for oral exposure, and Table 2-3 for dermal exposure. For cis-1,2-dichloroethene, oral studies are presented in Table 2-4 and Figure 2-6. For mixtures of cis-and trans-1,2-dichloroethene isomers, inhalation studies are presented in Table 2-5 and Figure 2-7. Note that only one study was identified for inhalation exposure to cis-1,2-dichloroethene and one study was identified for oral exposure to a mixture of the cis- and trans- isomers; therefore, summary tables and figures for these exposures were not developed.

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

For this profile, toxicity studies for 1,2-dichloroethene are categorized by isomer composition as follows: trans-1,2-dichloroethene; cis-1,2-dichloroethene; and mixtures of cis-and trans-1,2-dichloroethene.

trans-1,2-Dicloroethene. The toxicity of trans-1,2-dichloroethene has not been extensively studied. Only a few studies have evaluated toxicity to humans. Thus, available information regarding the health effects of trans-1,2-dichloroethene comes almost exclusively from studies in experimental animals. Studies include acute- and intermediate-duration inhalation and oral exposures. Studies have also assessed the effects of acute-duration dermal and ocular exposures. No chronic-duration studies were identified for any route of exposure. Available studies for trans-1,2-dichloroethene are depicted in Figure 2-1. Approximately half of the studies employed oral exposure. The most examined endpoints in inhalation and oral studies were lethality, hepatic, and immunological.

Based on this review, immunological effects are a presumed health effect for humans. Based on animal data, the following targets of trans-1,2-dichloroethene were identified as follows.

- ***Ocular Effects.*** Ocular effects are a suspected health effect based on limited acute-duration exposure of rats to 1,2-dichloroethene in air. Exposure to trans-1,2-dichloroethene in air and by instillation into the eye produces ocular irritation. A study in pregnant rats showed dose-related lacrimation during acute-duration, whole-body exposure to 1,2-dichloroethene vapor in air. Ocular irritation and damage to the eyes were also observed in rabbits following instillation of trans-1,2-dichloroethene to the eyes.

- ***Immunological Effects.*** Immunological effects of 1,2-dichloroethene are a presumed health effect for humans based on limited evidence in mice. Decreased humoral immunity, but not cellular immunity, was observed following intermediate-duration oral exposure. No changes in immune function were observed in animal studies following acute-duration oral exposure.

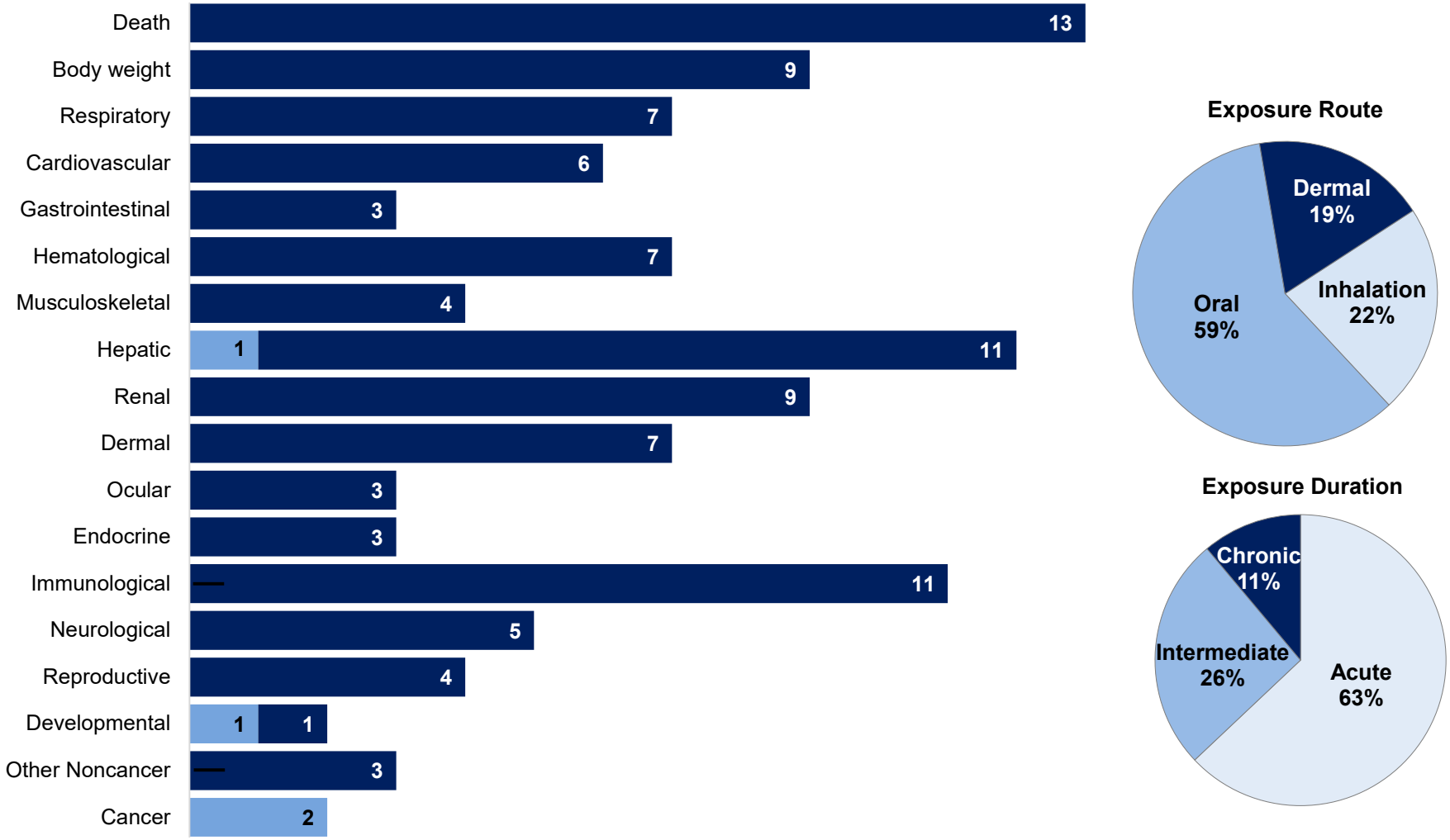
- ***Other Effects.*** Decreased body weight and hematological, developmental, and neurological effects have also been observed; however, these do not appear to be sensitive targets of trans-1,2-dichloroethene exposure. Dermal exposure was irritating and damaging to the skin.

cis-1,2-Dichloroethene. No studies investigating the toxicity of cis-1,2-dichloroethene in humans were identified. Available studies for trans-1,2-dichloroethene in laboratory animals are depicted in Figure 2-2. Studies on the toxicity of cis-1,2-dichloroethene are limited to two studies in rats: one study evaluating acute-duration lethality following a single dose inhalation exposure; and an oral exposure study evaluating comprehensive toxicological endpoints in animals exposed for acute- and intermediate-durations. No chronic-duration studies for cis-1,2-dichloroethene in laboratory animals were identified for any exposure route. No sensitive targets of cis-1,2-dichloroethene have been identified, as no biologically significant effects have been observed at sublethal levels.

Mixtures of cis- and trans-1,2-Dichloroethene. The toxicity of mixtures of the cis- and trans-isomers has been investigated in acute- and intermediate-duration studies, with most studies providing information on acute lethality. These studies are shown in Figure 2-3. No sensitive targets for mixtures of cis- and trans-1,2-dichloroethene were identified at sublethal exposures.

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

Most studies examined lethality and potential hepatic and immune effects of trans-1,2-dichloroethene
Fewer studies evaluated health effects in humans than animals (counts represent studies examining endpoint)

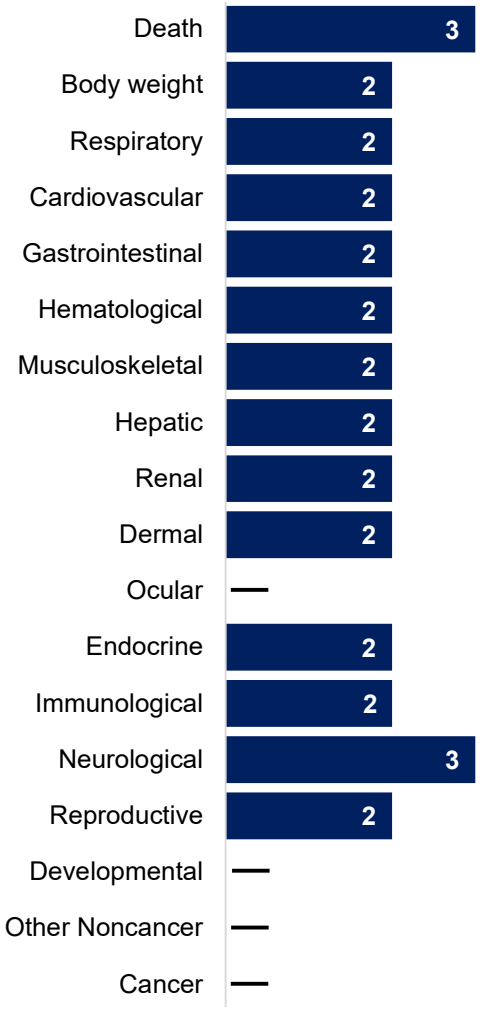


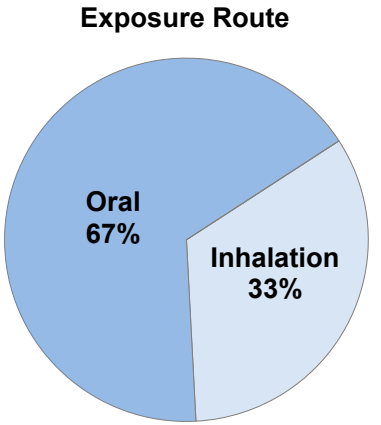
*Includes studies discussed in Chapter 2. A total of 27 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

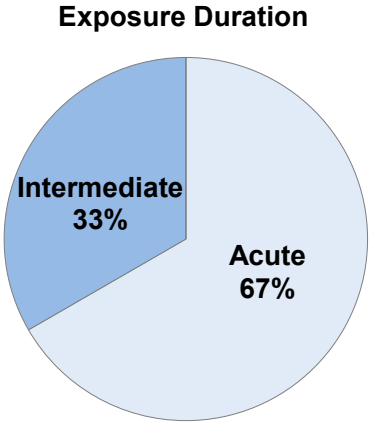
Figure 2-2. Overview of the Number of Studies Examining cis-1,2-Dichloroethene Health Effects*

Most studies examined lethality and potential hepatic and immune effects of cis-1,2-dichloroethene

The majority of the studies examined oral exposure in animals (counts represent studies examining endpoint); no data were identified for humans (counts represent studies examining endpoint)

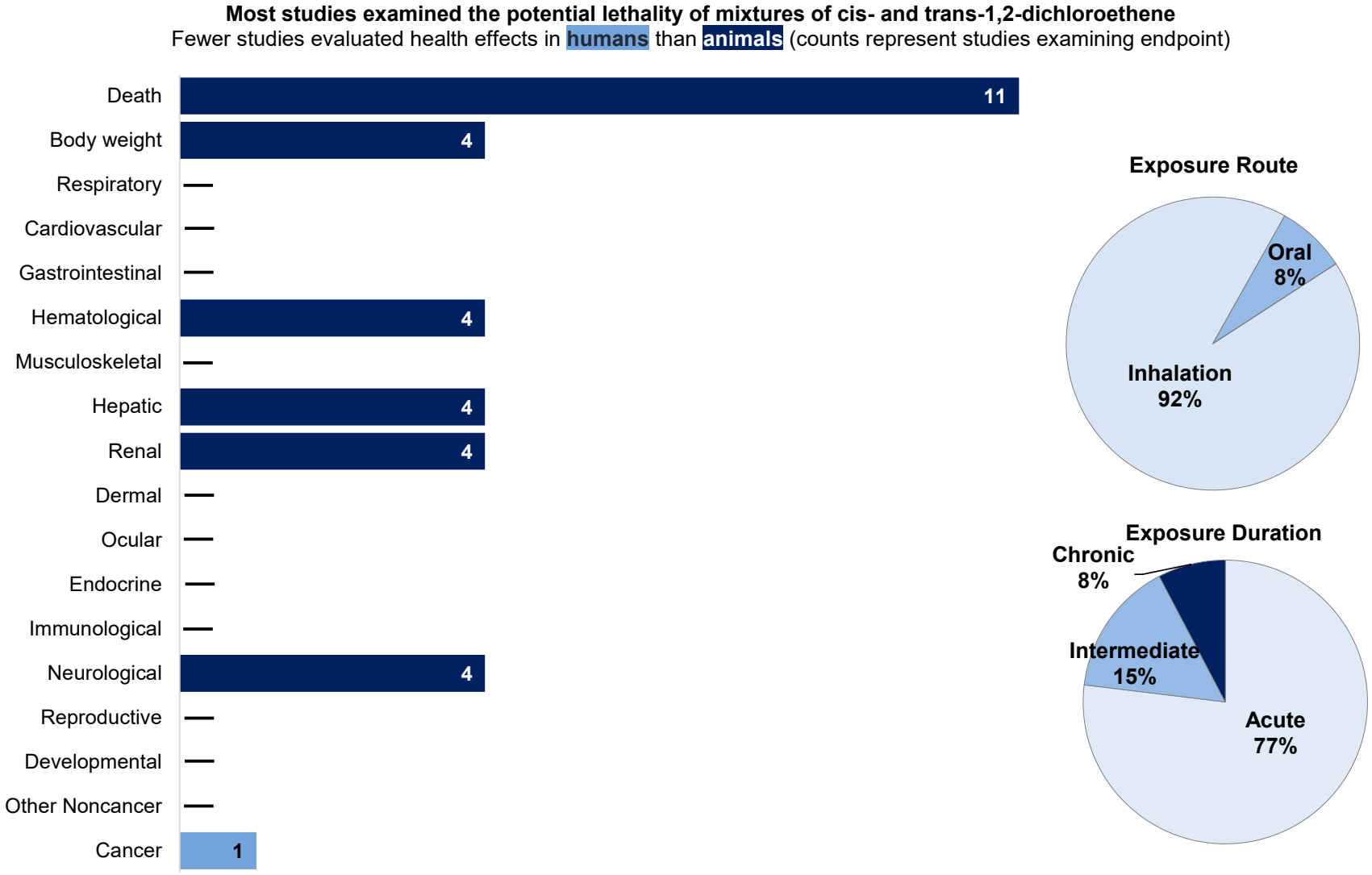






*Includes studies discussed in Chapter 2. A total of 3 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Figure 2-3. Overview of the Number of Studies Examining Mixtures of trans- and cis-1,2-Dichloroethene Health Effects*



*Includes studies discussed in Chapter 2. A total of 13 studies (including those finding no effect) have examined toxicity; studies examined multiple endpoints.

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Confidential 1999									
1	Rat (Sprague-Dawley) 5	4 hours	12,300, 22,500, 28,100, 34,100	LE, CS, BW, GN, HP	Death			24,100	LC_{50}
Hurtt et al. 1993									
2	Rat (CD BR) 24 F	6 hours/day 10 days GDs 7–16	0, 2000, 6,000, 12,000	BW, CS, DX, FI, GN, LE, OW	Bd wt	6,000	12,000		Maternal weight gain was decreased by 33.8% at the end of the exposure period; body weight at the end of gestation was similar to control
					Ocular		2,000[b]		Lacrimation ($BMCL_{10}$ = 256.47)
					Neuro	6,000	12,000		Lethargy
					Repro	2,000		6,000	Increased early resorptions
Gradiski et al. 1978									
3	Mouse (OF1, SPF) 20 F	6 hours		LE	Death			21,723	LC_{50}
INTERMEDIATE EXPOSURE									
DuPont 1998									
4	Rat (CD) 15 M, 15 F	6 hours/day 5 days/week 90 days	0, 200, 1,000, 4,000	BC, BW, CS, FI, GN, HE, HP, LE, NX, OP, UR	Bd wt	4,000			
					Resp	4,000			
					Cardio	4,000			
					Gastro	4,000			
					Hemato	4,000			
					Musc/skel	4,000			
					Hepatic	4,000			
					Renal	4,000			
					Dermal	4,000			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Ocular	4,000			
					Endocr	4,000			
					Immuno	1,000 M 4,000 F	4,000 M		Lymphocytes decreased by 26%
					Neuro	4,000			
					Repro	4,000			
					Other noncancer	1,000	4,000		Increased serum glucose

[a]The number corresponds to entries in Figure 2-4.
[b]Used to derive an acute-duration inhalation MRL. Using BMD modeling, BMC_{10} and $BMCL_{10}$ values of 740.28 and 256.47 ppm, respectively, were calculated for lacrimation. The $BMCL_{10}$ was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability), resulting in an acute-duration MRL of 3 ppm for trans-1,2-dichloroethene. See Appendix A for more detailed information regarding the MRL.

BC = blood chemistry; Bd wt or BW = body weight; BMC = benchmark concentration; BMCL = lower 95% confidence limit on the benchmark concentration; BMC = benchmark dose; Cardio = cardiological; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; F = female(s); FI = food intake; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LC_{50} = median lethal concentration; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NX = neurotoxicity; OP = ophthalmological; Repro = reproductive; Resp = respiratory; UR = urinalysis

Figure 2-4. Levels of Significant Exposure to trans-1,2-Dichloroethene – Inhalation
Acute (≤14 days)

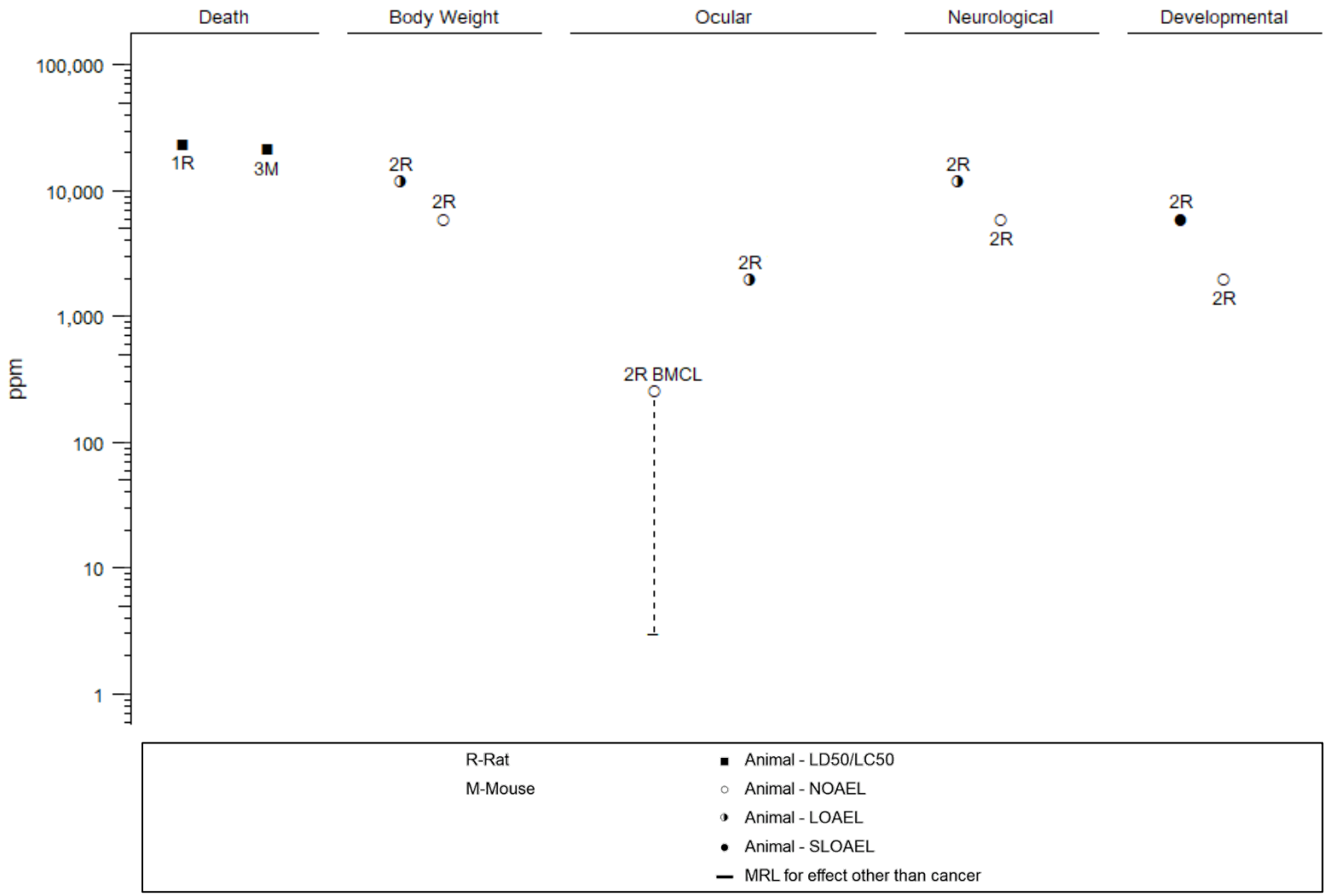


Figure 2-4. Levels of Significant Exposure to trans-1,2-Dichloroethene – Inhalation
Intermediate (15–364 days)

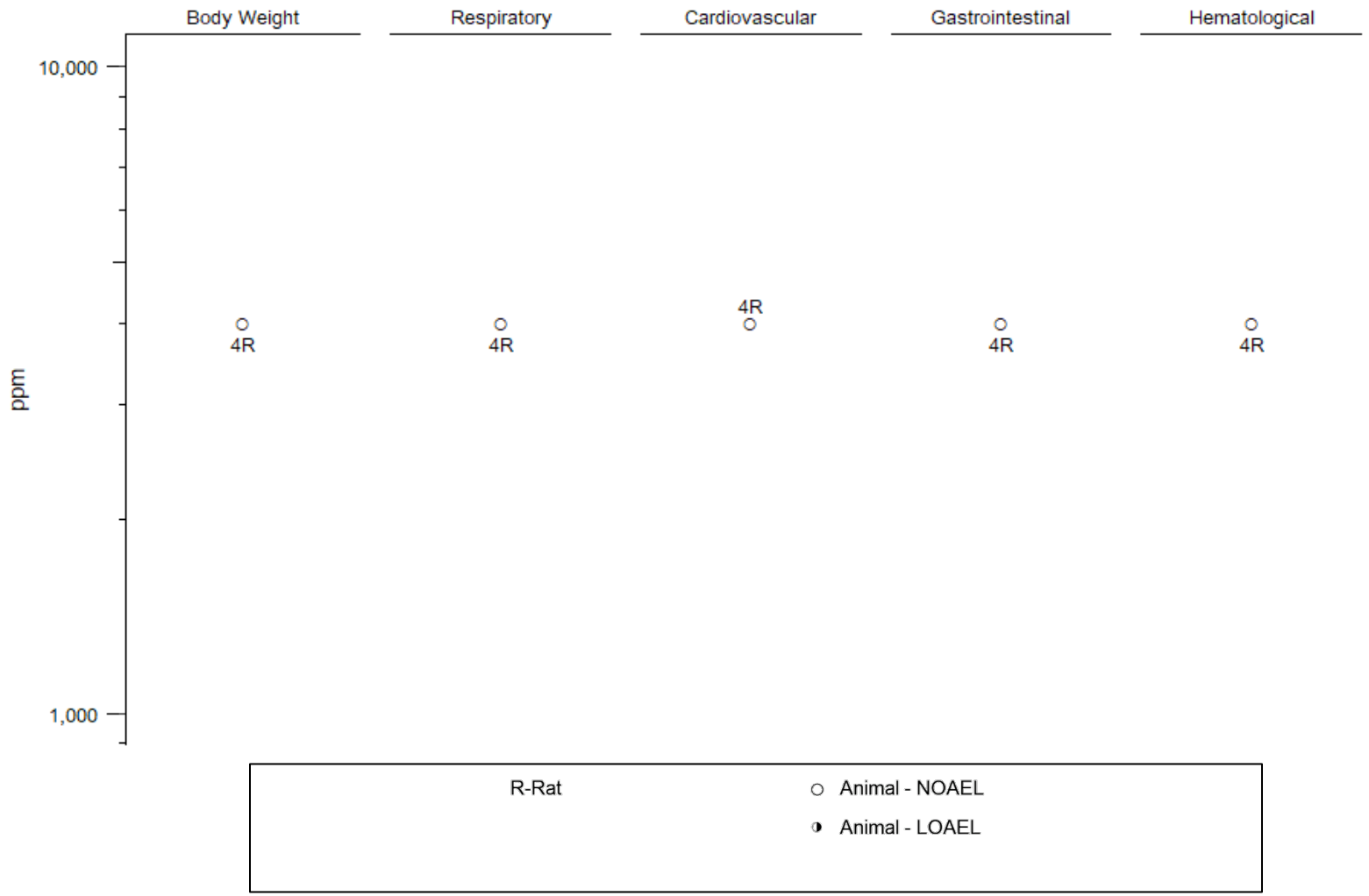


Figure 2-4. Levels of Significant Exposure to trans-1,2-Dichloroethene – Inhalation

Intermediate (15–364 days)

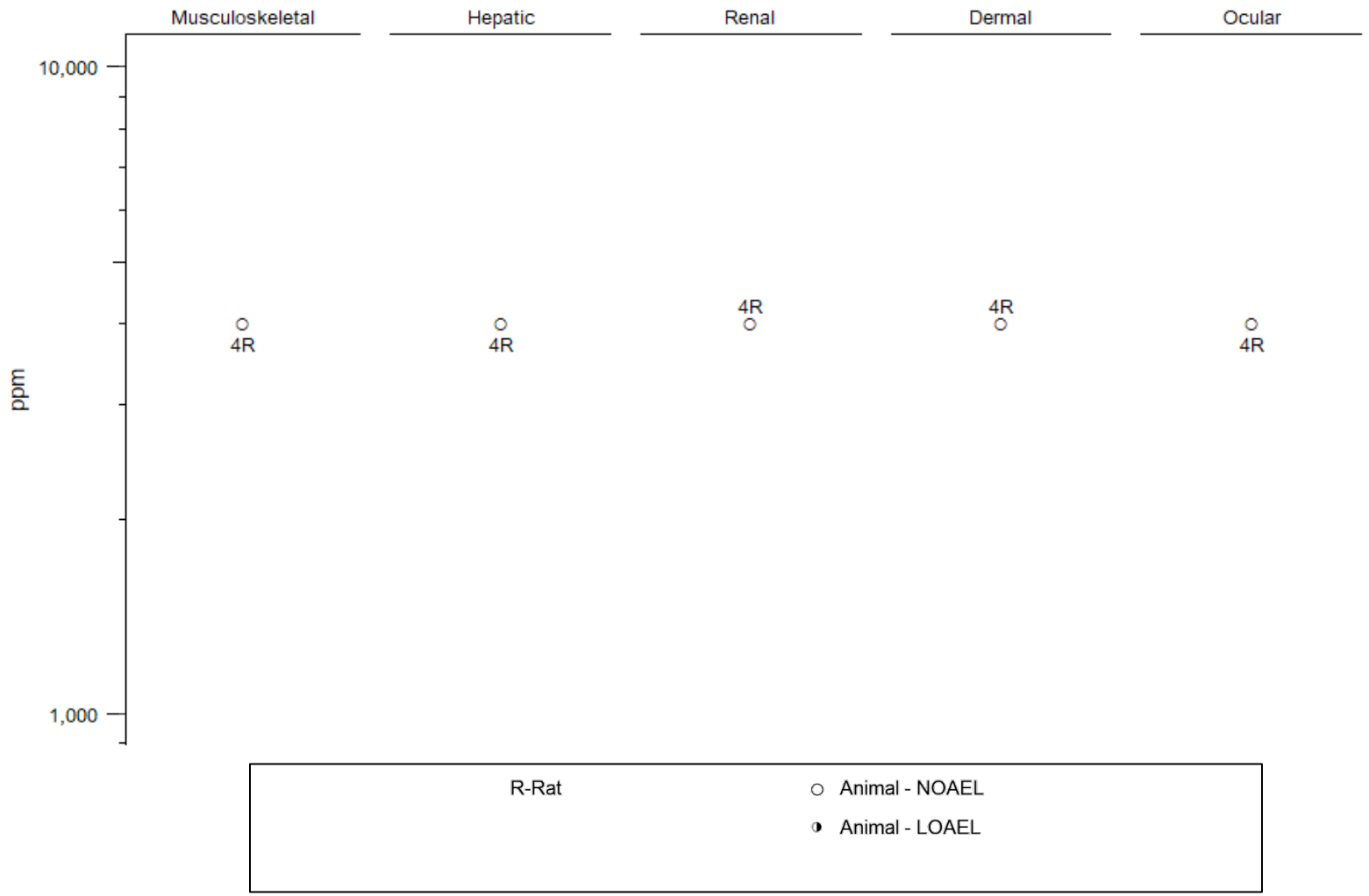


Figure 2-4. Levels of Significant Exposure to trans-1,2-Dichloroethene – Inhalation

Intermediate (15–364 days)

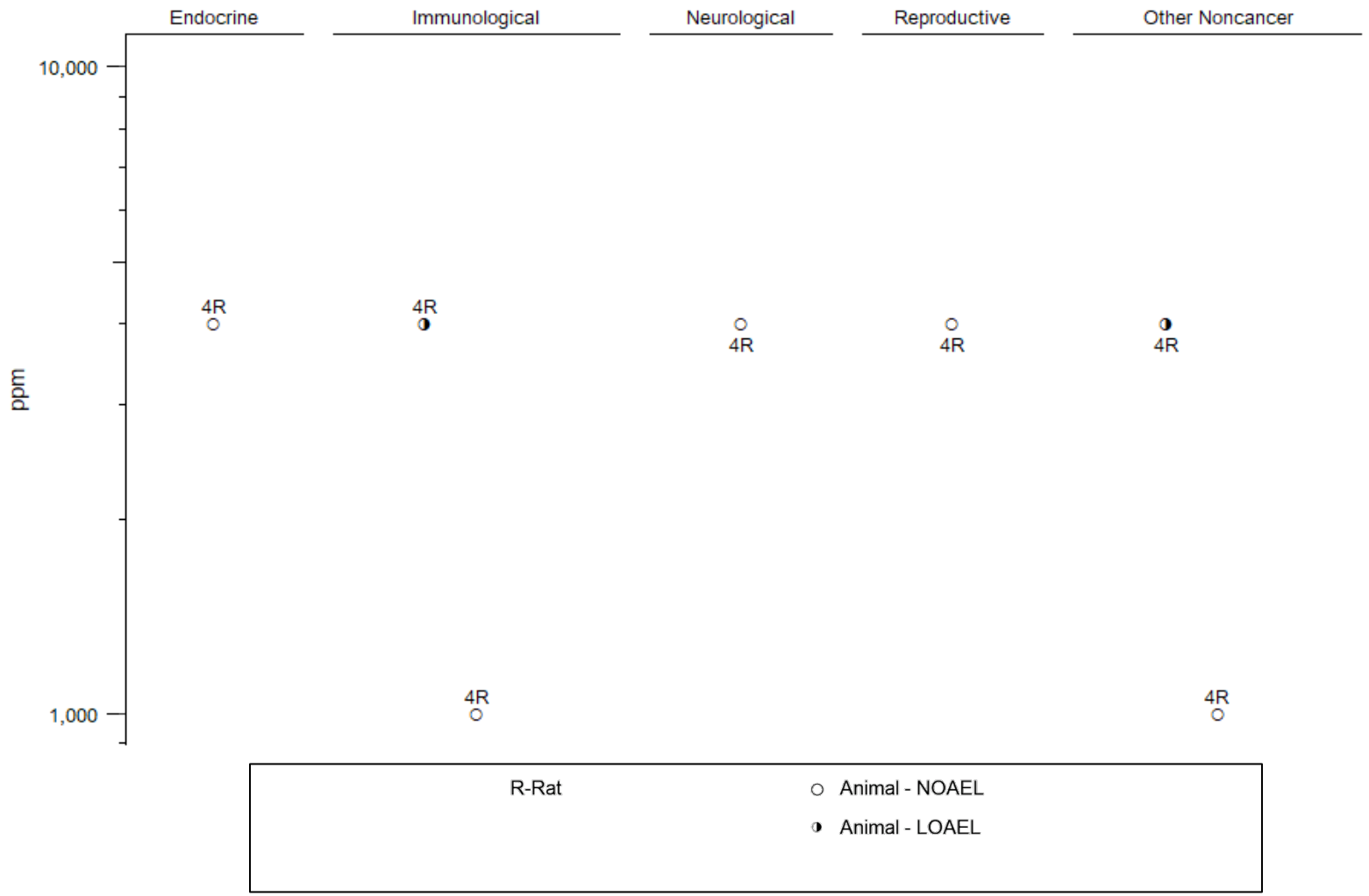


Table 2-2. Levels of Significant Exposure to trans-1,2-Dichloroethene – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Freundt et al. 1977									
1	Rat (Wistar SPF) 10 F	Once (GO)	630, 940, 1,130, 1,300, 1,400, 1,600	GN, HP, LE	Death			1,130	LD_{50}
Hayes et al. 1987									
2	Rat (Sprague-Dawley) 10 M, 10 F	Once (GO)	NS	CS, GN, LE	Death			9,932 F 7,902 M	LD_{50}
NTP 2002									
3	Rat (Fischer-344) 10 M, 10 F	5 days (F)	M: 0, 344, 708, 1,437, 2,793, 5,591; F: 0, 307, 597, 1,227, 2,227, 4,500	BC, FI, HE	Hemato	4,500 F 5,591 M			
					Hepatic	4,500 F 5,591 M			
Barnes et al. 1985									
4	Mouse (CD-1) NS B	Once (G)	800, 1,200, 1,600, 2,000, 2,400, 3,000, 3,500	CS, GN, LE	Death			2,391 F 2,122 M	LD_{50}
Barnes et al. 1985									
5	Mouse (CD-1) 9–10 M	14 days 1 time/day (G)	0, 21, 210	BC, BW, GN, HE, OW	Bd wt	210			
					Resp	210			
					Hemato	21	210		Decreased fibrinogen levels (12%) and prothrombin time (7%)
					Hepatic	21			
					Renal	210			
					Immuno	210			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Munson et al. 1982									
6	Mouse (CD-1) NS B	Once (G)	NS	CS, GN, LE	Death			2,391 F 2,221 M	LD_{50}
Munson et al. 1982									
7	Mouse (CD-1) 10–12 M	Once/day 14 days (G)	0, 22, 220	BC, BW, GN, HE, IX, OW	Bd wt	220			
					Hemato	220			
					Hepatic	220			
					Immuno	220			
Shopp et al. 1985									
8	Mouse (CD-1) 9–10 M	14 days 1 time/day (G)	0, 21, 210	BC, IX	Immuno	210			
INTERMEDIATE EXPOSURE									
Hayes et al. 1987									
9	Rat (Sprague-Dawley) 20 M, 20 F	90 days *ad libitum* (W)	M: 0, 402, 1,314, 3,114 F: 0, 353, 1,257, 2,809	BC, CS, GN, HE, HP, LE, OW, UR, WI	Bd wt	2,809 F 3,114 M			
					Hemato	2,809 F 3,114 M			
					Hepatic	2,809 F 3,114 M			
					Renal	2,809 F 3,114 M			
					Repro	2,809 F 3,114 M			
					Other noncancer	2,809 F 3,114 M			Serum glucose (no change)

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
NTP 2002									
10	Rat (Fischer-344) 10 M, 10 F	14 weeks (F)	M: 0, 190, 380, 770, 1,540, 3,210; F: 0 190, 395, 780, 1,580, 3,245	BC, BW, CS, FI, GN, HE, HP, NX, OW, RX	Bd wt	3,245 F 3,210 M			
					Resp	3,245 F 3,210 M			
					Cardio	3,245 F 3,210 M			
					Gastro	3,245 F 3,120 M			
					Hemato	780 F 190 M	1,580 F 380 M		Decreased erythrocyte count
					Hepatic	3,245 F 3,120 M			
					Renal	3,245 F 3,120 M			
					Dermal	3,245 F 3,120 M			
					Endocr	3,245 F 3,120 M			
					Immuno	3,245 F 3,120 M			
					Neuro	3,245 F 3,120 M			
					Repro	3,245 F 3,120 M			
					Other noncancer	3,245 F 3,210 M			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Barnes et al. 1985									
11	Mouse (CD-1) 140–260 M, 140–260 F	90 days *ad libitum* (W)	M: 0, 17, 175, 387 F: 0, 23, 224, 452	BC, BI, GN, HE, OW, WI	Bd wt	452 F			
						387 M			
					Hepatic	452 F			
						387 M			
					Renal	452 F			
						387 M			
					Immuno	452 F			
						387 M			
					Other noncancer		23 F 17 M		Serum glucose increased by 28% in females and 27% in males
NTP 2002									
12	Mouse (B6C3F1) 10 M, 10 F	14 weeks (F)	M: 0, 480, 920, 1,900, 3,850, 8,065; F: 0, 450, 915, 1,830, 3,760, 7,925	BW, CS, FI, GN, HP, NX, OW, RX	Bd wt	7,925 F 3,760 M	8,065 M		Terminal body weight decreased by 10.7%
					Resp	7,925 F			
						8,065 M			
					Cardio	7,925 F			
						8,065 M			
					Gastro	7,925 F			
						8,065 M			
					Hepatic	7,925 F			
						8,065 M			
					Renal	7,925 F			
						8,065 M			
					Dermal	7,925 F			
						8,065 M			
					Endocr	7,925 F			
						8,065 M			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Immuno	7,925 F 8,065 M			
					Neuro	7,925 F 8,065 M			
					Repro	7,925 F 8,065 M			
Shopp et al. 1985									
13	Mouse (CD-1) 6–23 B	90 days *ad libitum* (W)	M: 0, 17, 175, 387 F: 0, 23, 224, 452	IX, OW	Immuno	452 F 17 M	175 M[b]		Decreased humoral immunity (reduction in splenic AFCs against SRBCs) ($BMDL_{1SD}$=16.75)

[a]The number corresponds to entries in Figure 2-5.
[b]Used to derive an intermediate-duration oral MRL. Using BMD modeling, BMD_{10} and $BMDL_{1SD}$ values of 77.27 and 16.75 mg/kg/day, respectively, were calculated for humoral immune suppression. The $BMDL_{1SD}$ was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability), resulting in an acute-duration MRL of 0.2 mg/kg/day for trans-1,2-dichloroethene. See Appendix A for more detailed information regarding the MRL.

AFC = antibody-forming cell; B = both males and females; BC = blood chemistry; Bd wt or BW = body weight; BMD = benchmark dose; BMDL = lower 95% confidence limit on the benchmark dose; BI = biochemical changes; Cardio = cardiological; CS = clinical signs; Endocr = endocrine; (F) = feed; F = female(s); FI = food intake; (G) = gavage; (GO) = gavage in oil; Gastro = gastrointestinal; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; IX = immunotoxicity; LD_{50} = median lethal dose; 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 = neurotoxicity; OW = organ weight; Repro = reproductive; Resp = respiratory; RX = reproductive toxicity; SD = standard deviation; SRBCs = sheep red blood cells; UR = urinalysis; (W) = water; WI = water intake

Figure 2-5. Levels of Significant Exposure to trans-1,2-Dichloroethene – Oral

Acute (≤14 days)

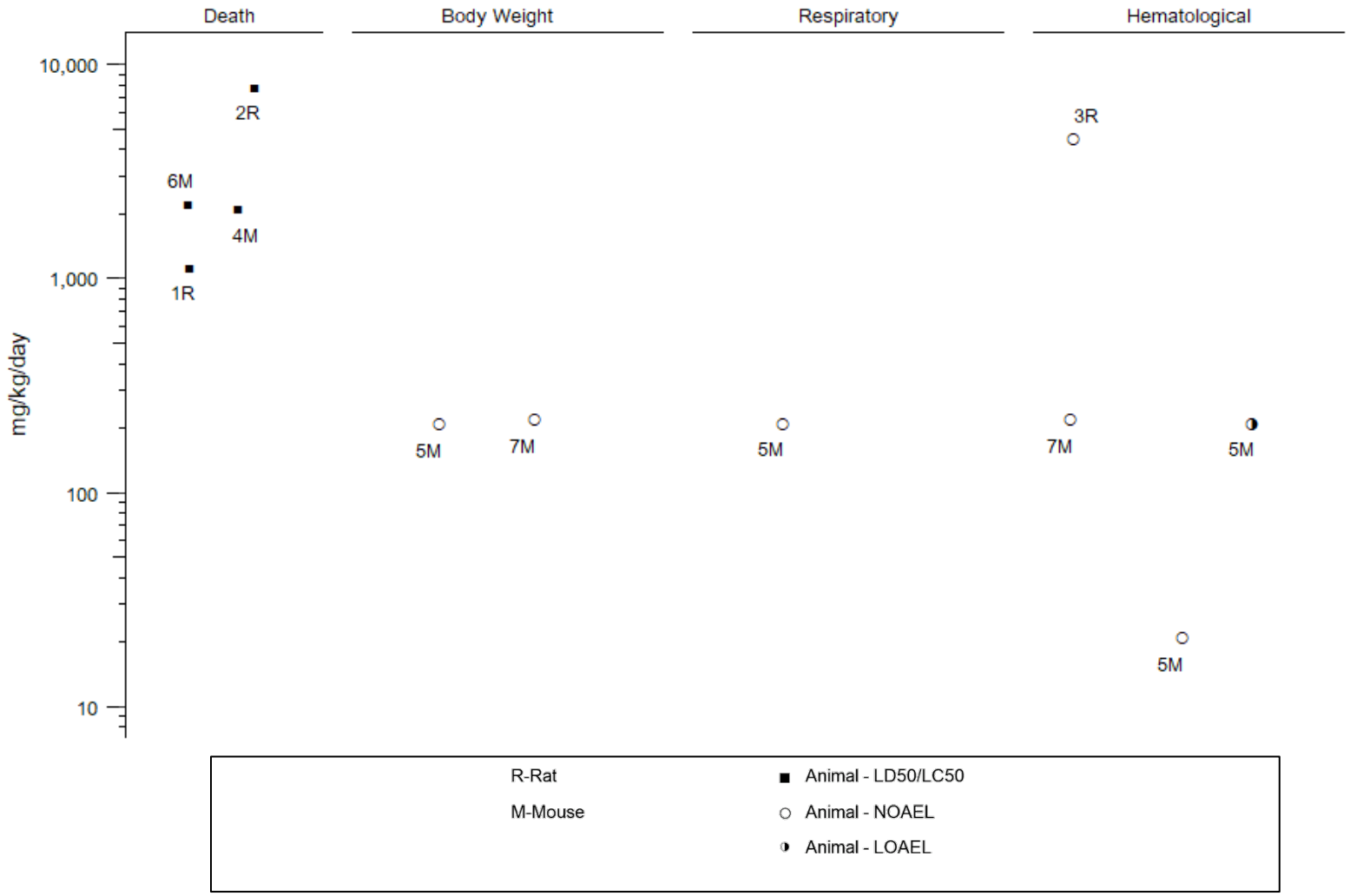


Figure 2-5. Levels of Significant Exposure to trans-1,2-Dichloroethene – Oral

Acute (≤14 days)

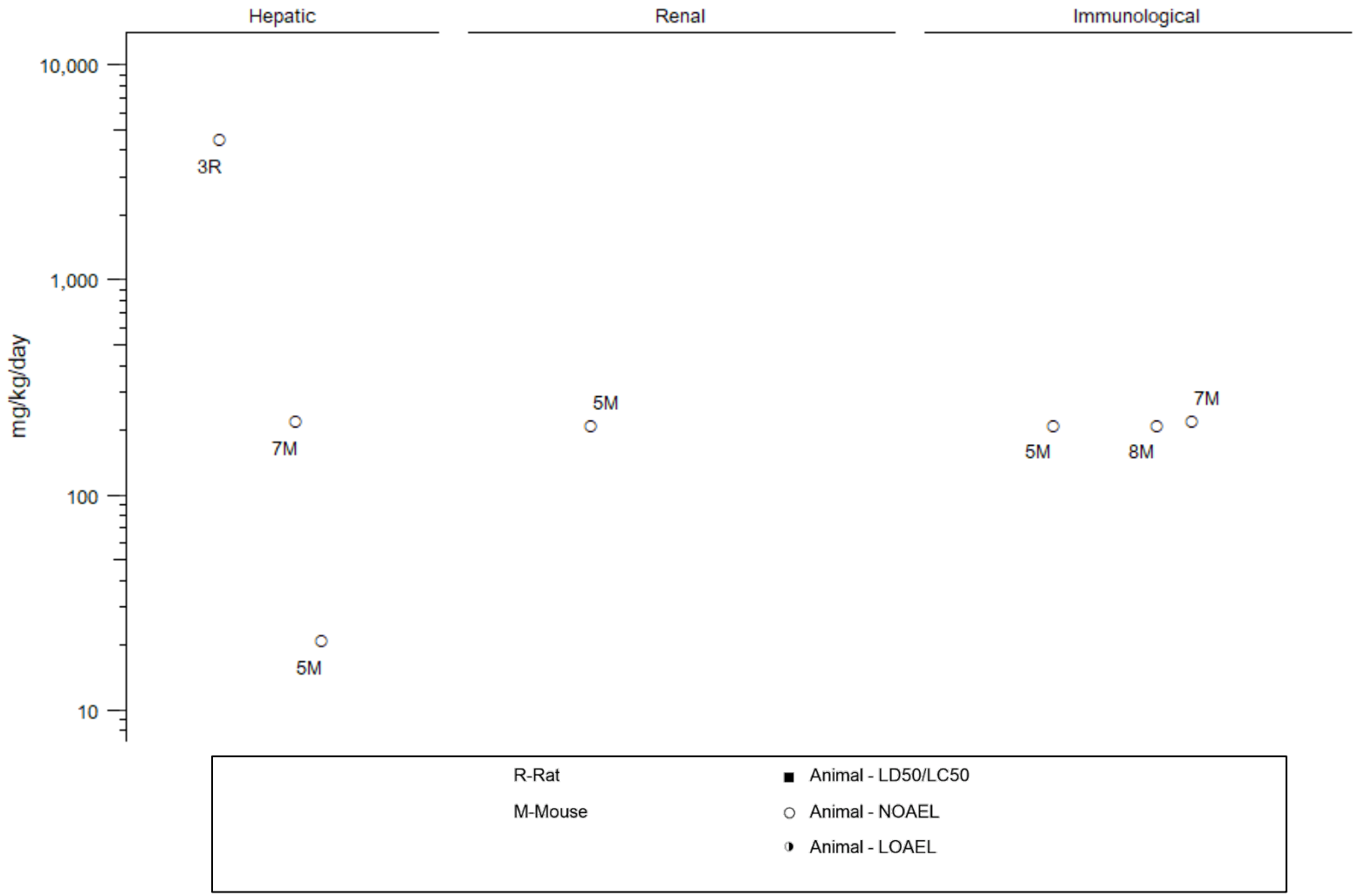


Figure 2-5. Levels of Significant Exposure to trans-1,2-Dichloroethene – Oral
Intermediate (15–364 days)

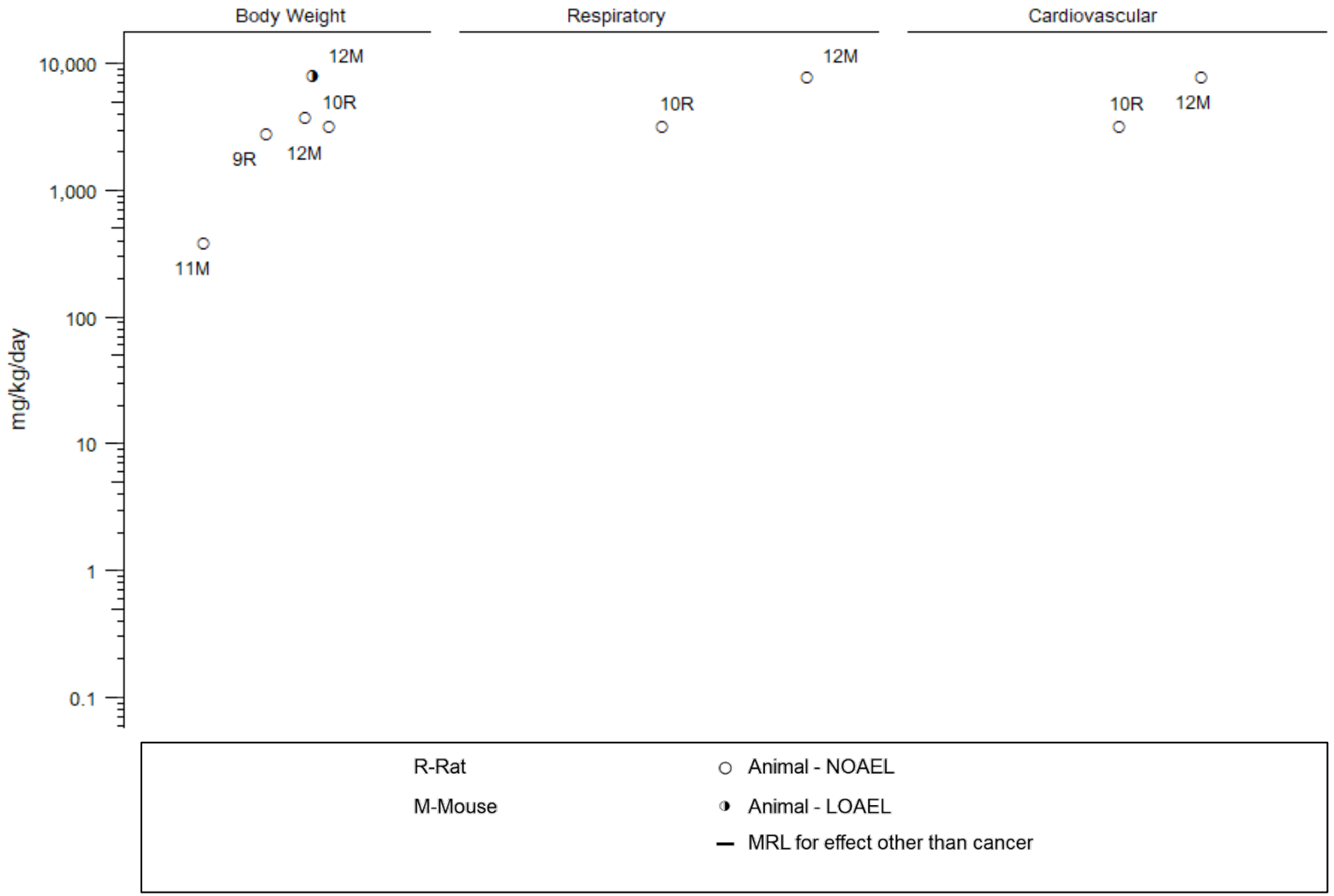


Figure 2-5. Levels of Significant Exposure to trans-1,2-Dichloroethene – Oral
Intermediate (15–364 days)

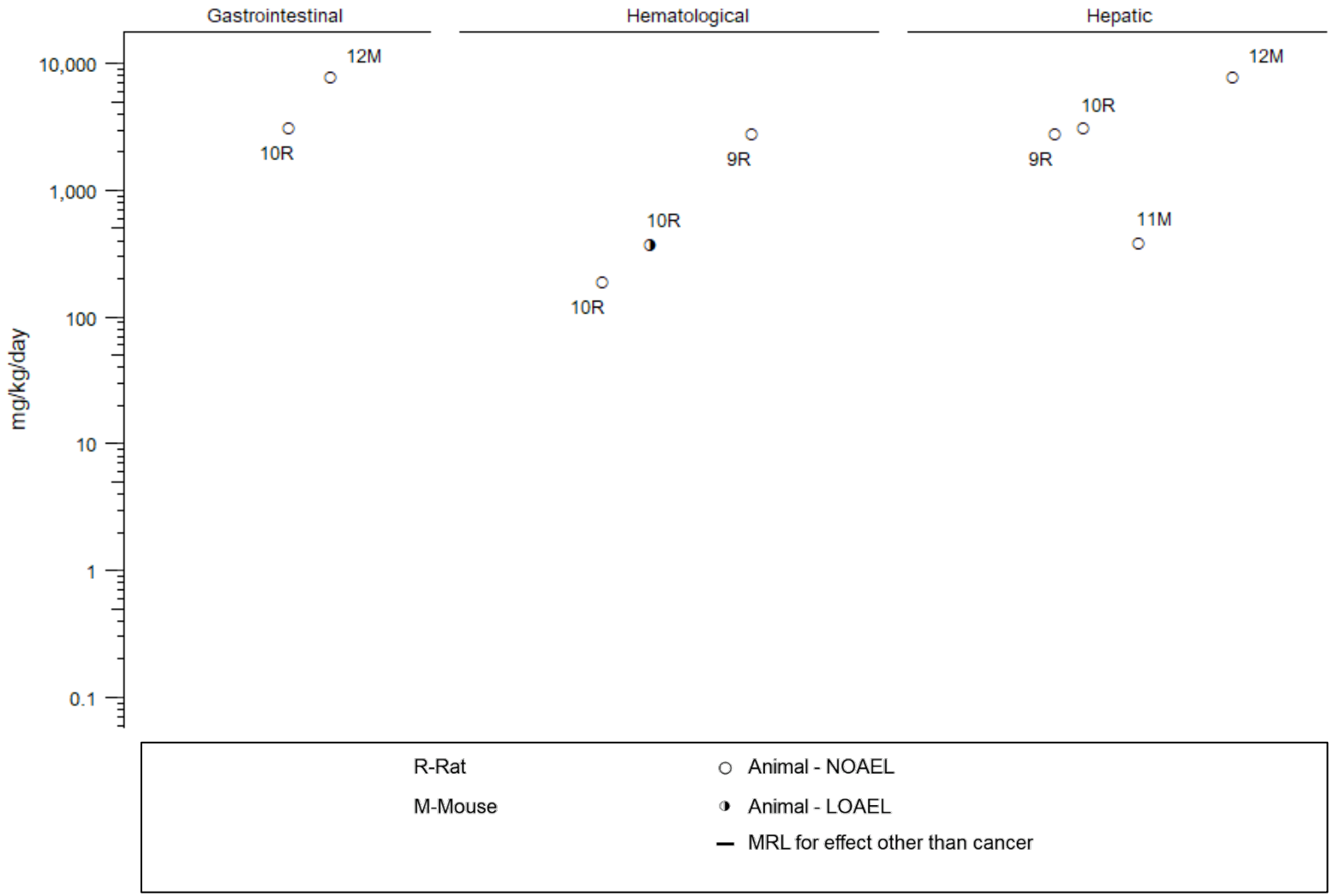


Figure 2-5. Levels of Significant Exposure to trans-1,2-Dichloroethene – Oral

Intermediate (15–364 days)

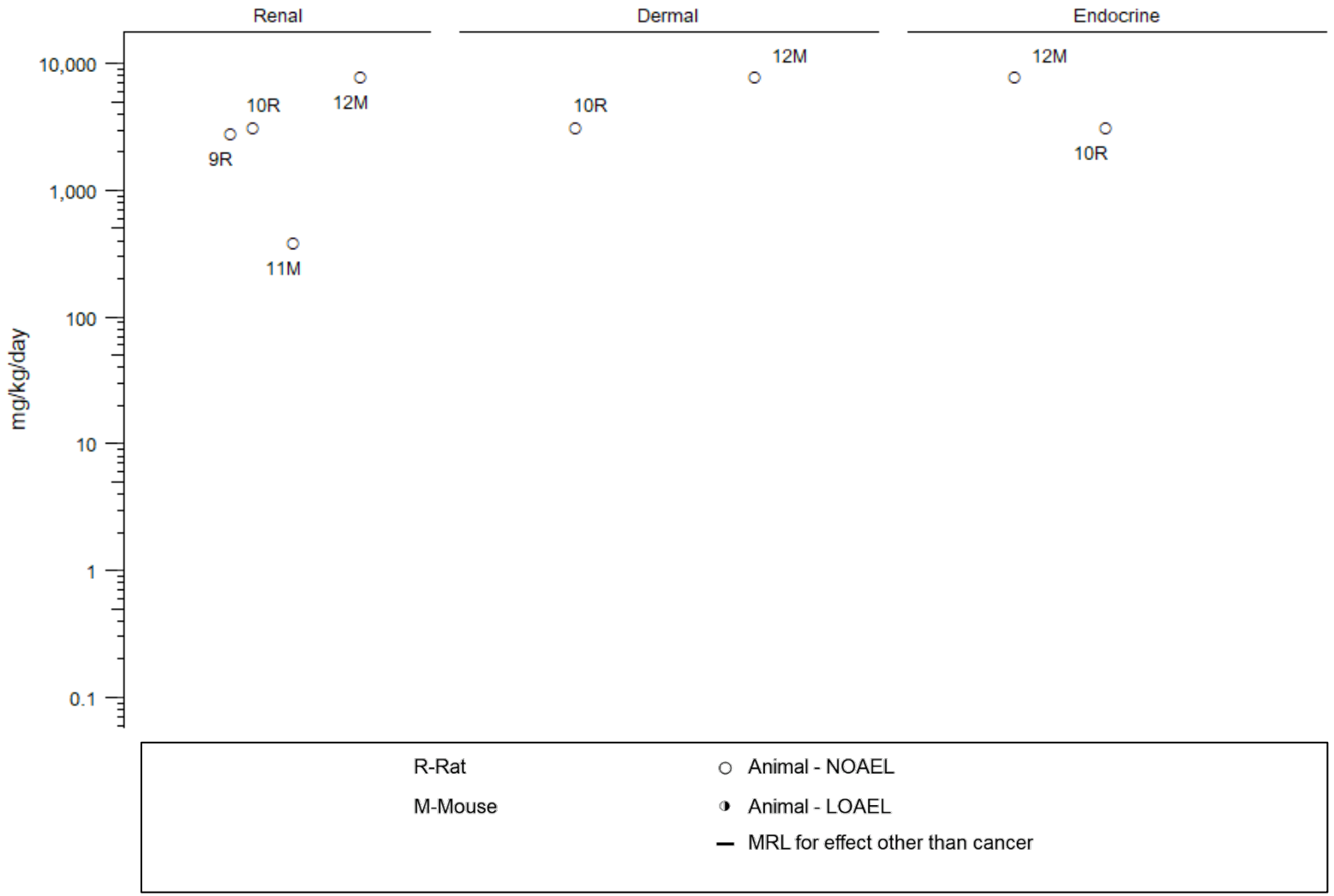


Figure 2-5. Levels of Significant Exposure to trans-1,2-Dichloroethene – Oral
Intermediate (15–364 days)

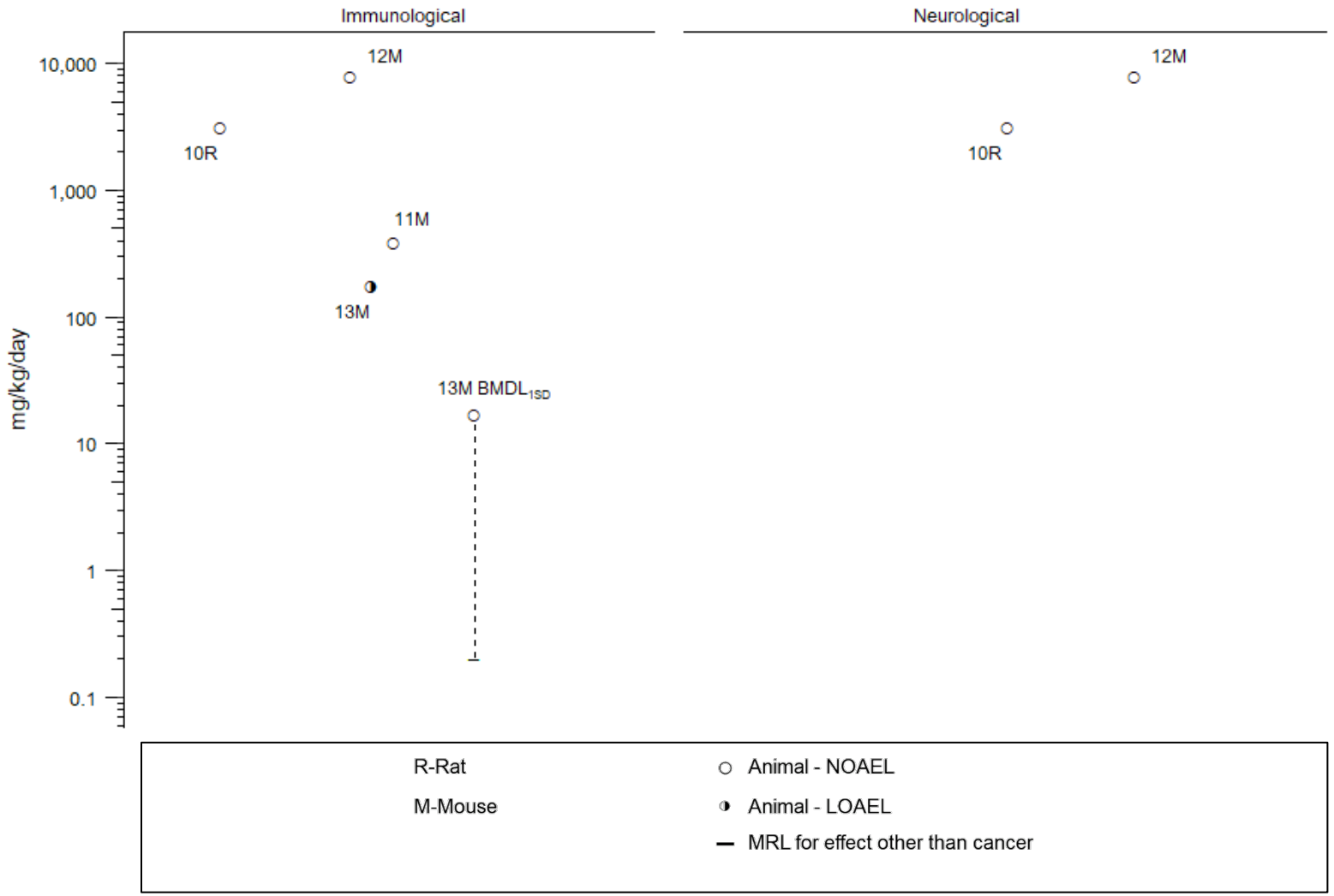


Figure 2-5. Levels of Significant Exposure to trans-1,2-Dichloroethene – Oral
Intermediate (15–364 days)

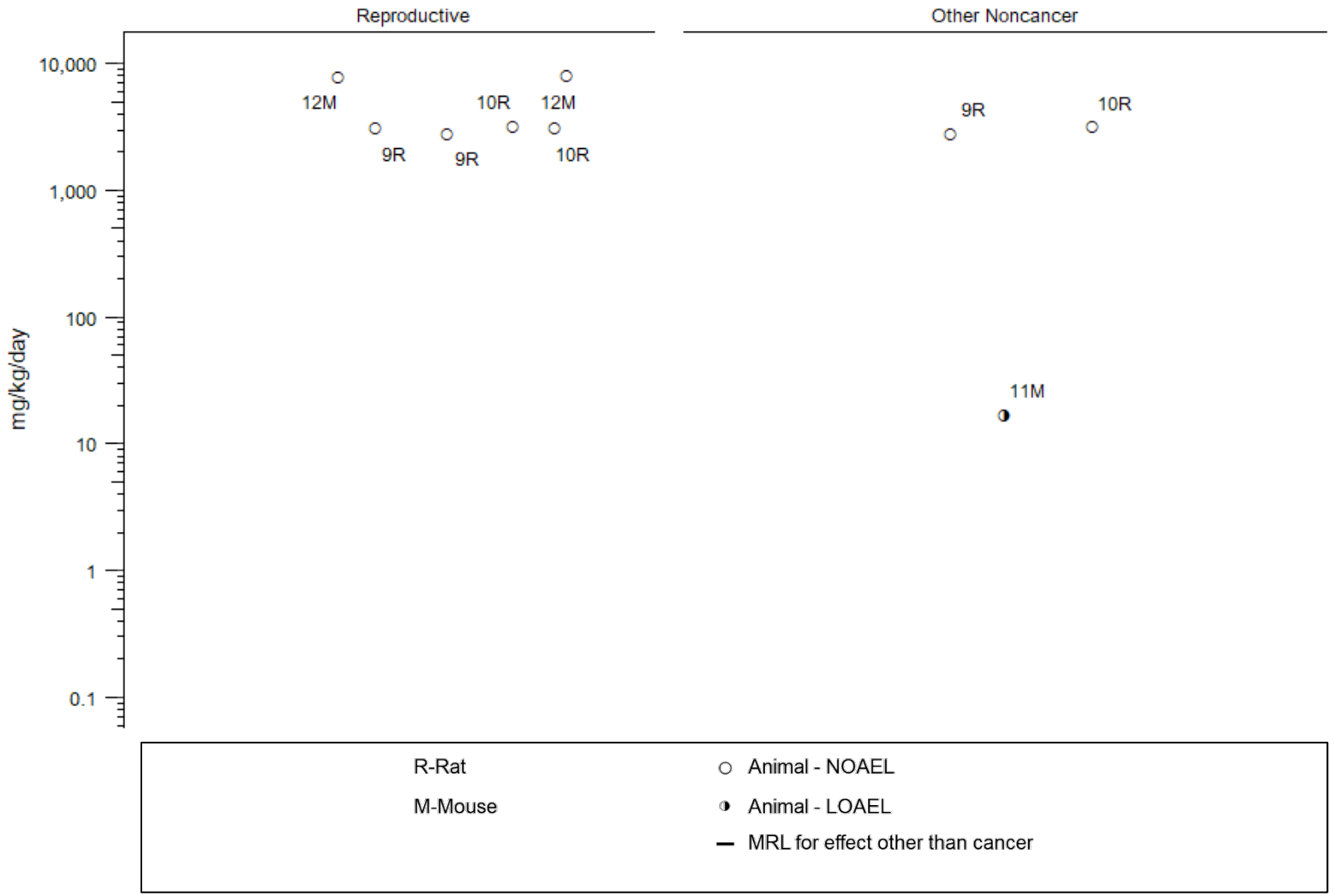


Table 2-3. Levels of Significant Exposure to trans-1,2-Dichloroethene – Dermal

Figure key	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Brock 1990									
	Rabbit (NS) 5 M, 1 F	24 hours	170 mg/kg	CS	Dermal		170		Mild-to-moderate erythema
Brock 1990									
	Rabbit (NS) 2 M, 3 F	24 hours	5,000 mg/kg	BW, CS, LE	Bd wt		5,000		Body weight loss (magnitude not reported)
					Dermal			5,000	Severe dermal irritation
DuPont 1988a									
	Rabbit (New Zealand) 2M, 2F	24 hours	5,000 mg/kg	BW, CS, LE	Dermal			5,000	Dermal irritation, erythema, edema, necrosis, fissuring of the skin, epidermal scaling
DuPont 1988b									
	Rabbit (New Zealand) 5 M, 1 F	48 hours	630 mg/kg	CS	Dermal		630		Mild-to-moderate erythema
DuPont 1988c									
	Rabbit (New Zealand White) 2 F	20 seconds (eyes)	0.01 mL	CS	Ocular			0.01 mL	Transient severe corneal opacity, moderate iritis, and conjunctivitis

Bd wt or BW = body weight; CS = clinical signs; F = female(s); LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level

Table 2-4. Levels of Significant Exposure to cis-1,2-Dichloroethene – 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									
EPA/AMRL 1990; McCauley et al. 1995									
1	Rat (Sprague-Dawley) 10 M, 10 F	14 days 1 time/day (GO)	0, 97, 290, 970, 1,900	BW, BC, CS, FI, HE, HP, OW, WI	Bd wt	1,900			
					Resp	1,900			
					Cardio	1,900			
					Gastro	1,900			
					Hemato	97 F	290 F		Decreased hematocrit
						1,900 M			
					Musc/skel	1,900			
					Hepatic	970 F	1,900 F		Increased serum cholesterol
						1,900 M			
					Renal	1,900			
					Dermal	1,900			
					Endocr	1,900			
					Immuno	1,900			
					Repro	1,900			
INTERMEDIATE EXPOSURE									
EPA/AMRL 1990; McCauley et al. 1995									
2	Rat (Sprague-Dawley) 10 M, 10 F	90 days 1 time/day (GO)	0, 32, 97, 290, 870	BC, BW, FI, GN, HE, HP, OW, WI	Bd wt	870 F 290 M		870 M	Body weight gain decreased by 37%
					Resp	870			
					Cardio	870			
					Gastro	870			
					Hemato	97 F	290 F		Decreased hematocrit
						32 M	97 M		Decreased hematocrit
					Musc/skel	870			
					Hepatic	870			
					Renal	870			
					Dermal	870			

Table 2-4. Levels of Significant Exposure to cis-1,2-Dichloroethene – 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	870			
					Immuno	870			
					Neuro	870			
					Repro	870			

[a]The number corresponds to entries in Figure 2-6.

BC = blood chemistry; Bd wt or BW = body weight; Cardio = cardiological; CS = clinical signs; Endocr = endocrine; F = female(s); FI = food intake; (GO) = gavage in oil; Gastro = gastrointestinal; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; OW = organ weight; Repro = reproductive; Resp = respiratory; WI = water intake

Figure 2-6. Levels of Significant Exposure to cis-1,2-Dichloroethene – Oral

Acute (≤14 days)

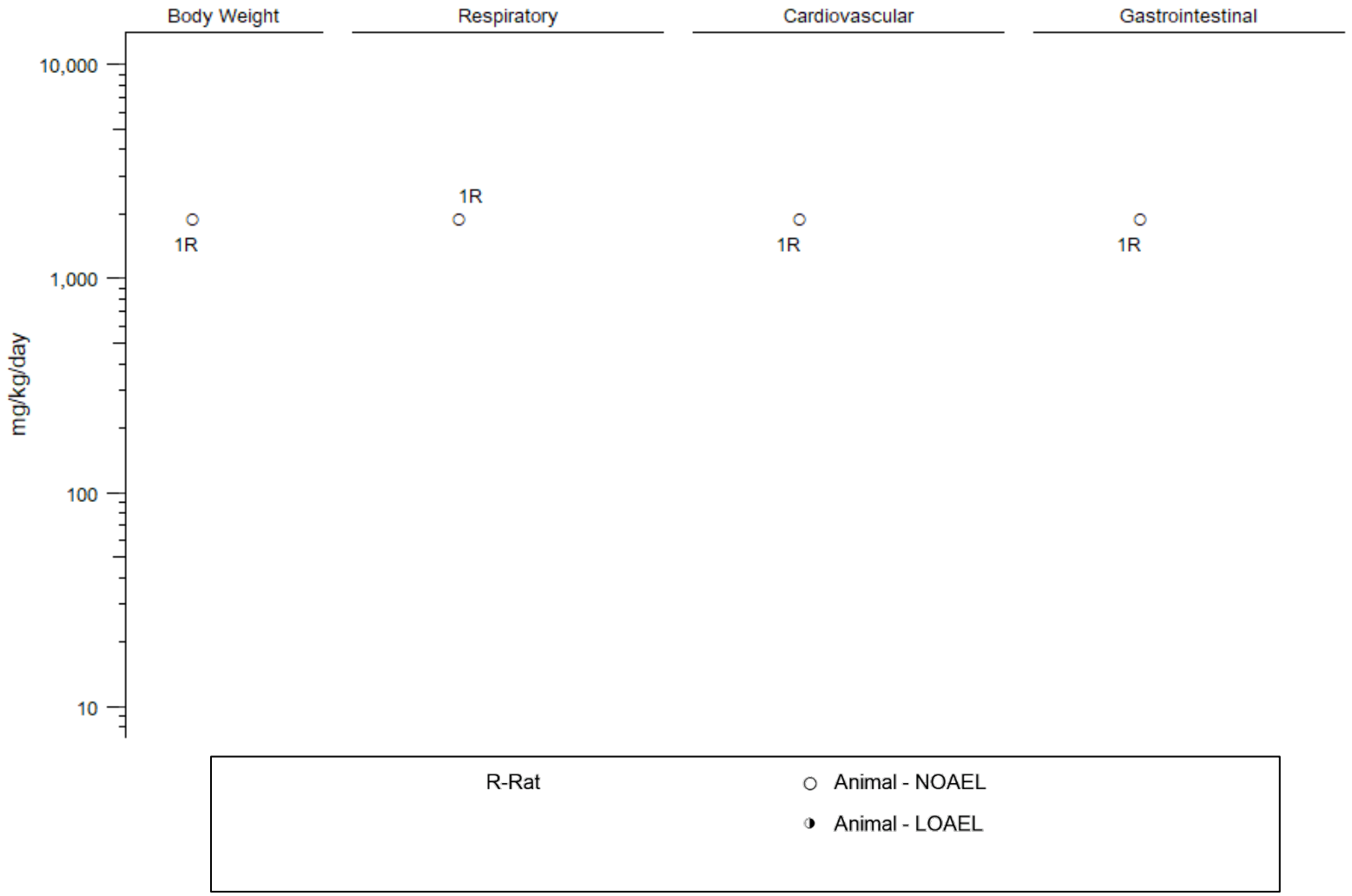


Figure 2-6. Levels of Significant Exposure to cis-1,2-Dichloroethene – Oral

Acute (≤14 days)

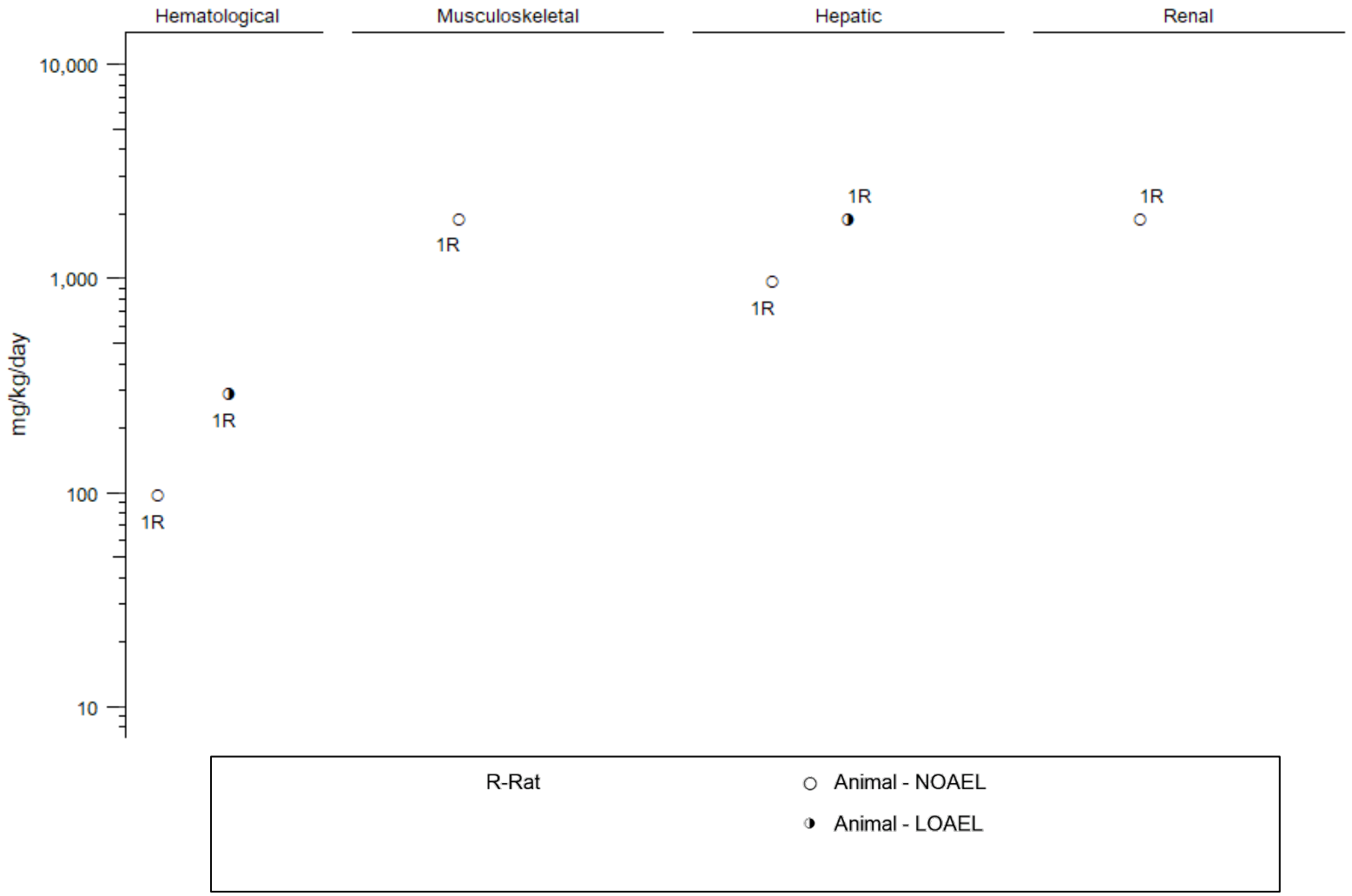


Figure 2-6. Levels of Significant Exposure to cis-1,2-Dichloroethene – Oral

Acute (≤14 days)

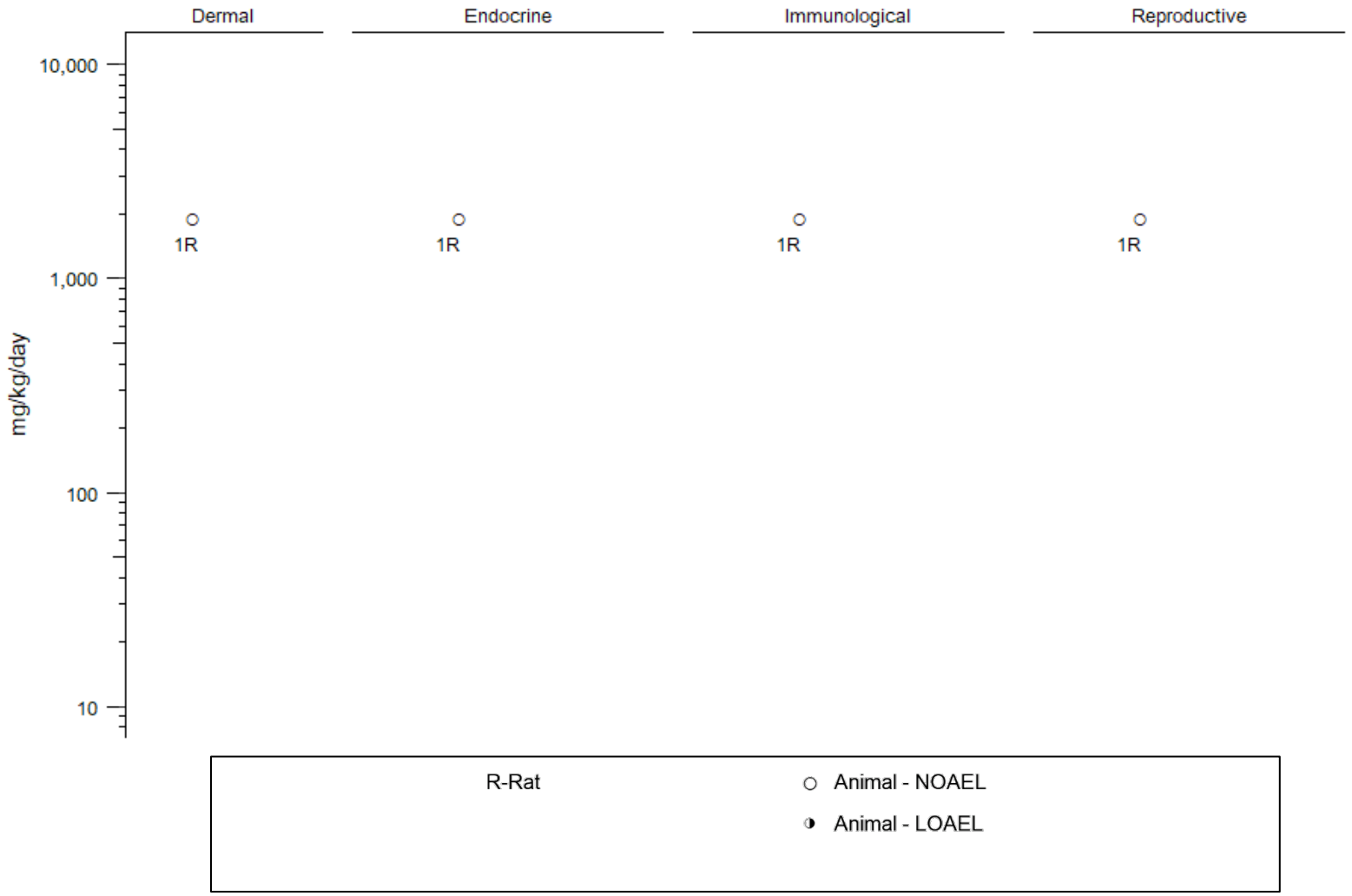


Figure 2-6. Levels of Significant Exposure to cis-1,2-Dichloroethene – Oral
Intermediate (15–364 days)

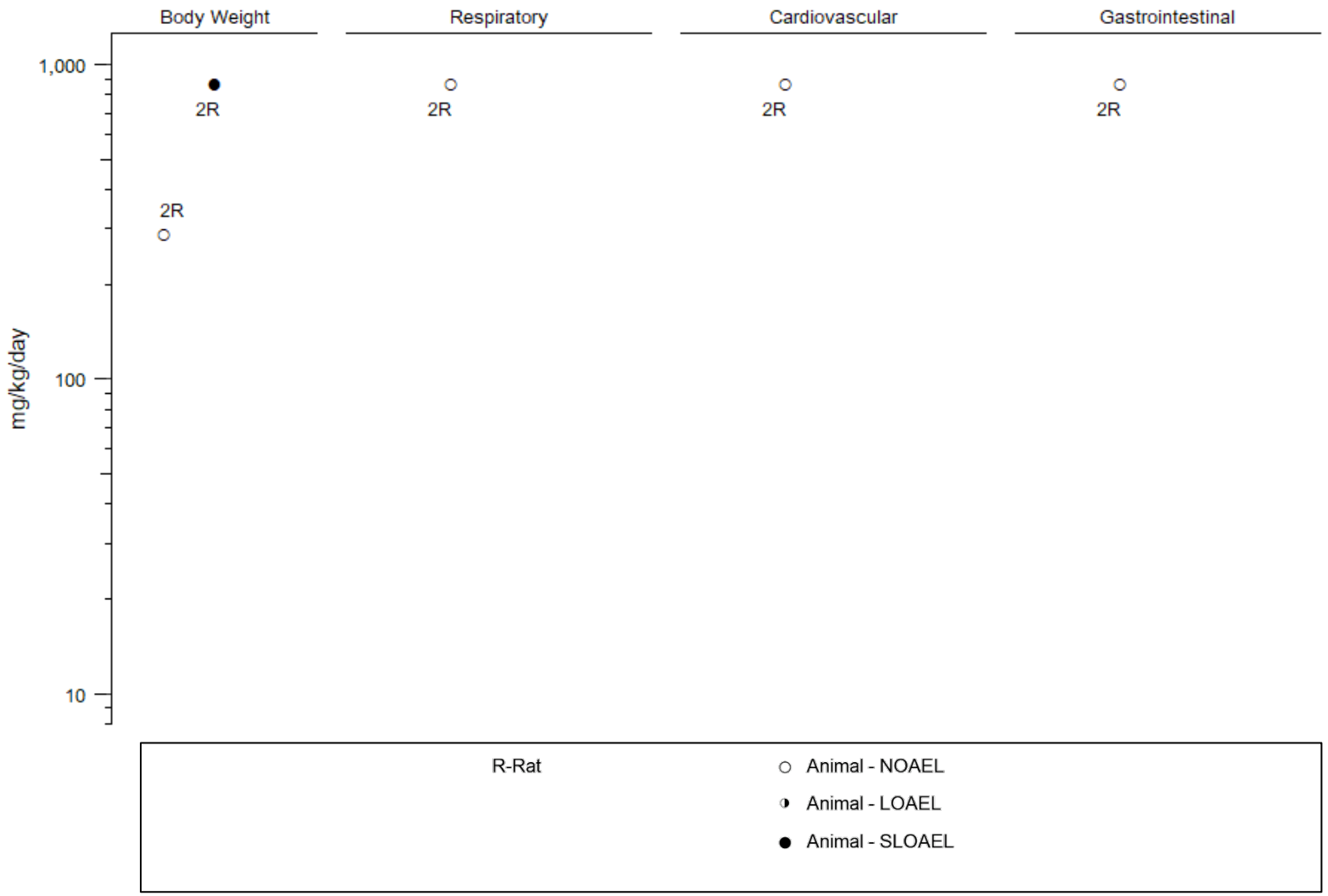


Figure 2-6. Levels of Significant Exposure to cis-1,2-Dichloroethene – Oral
Intermediate (15–364 days)

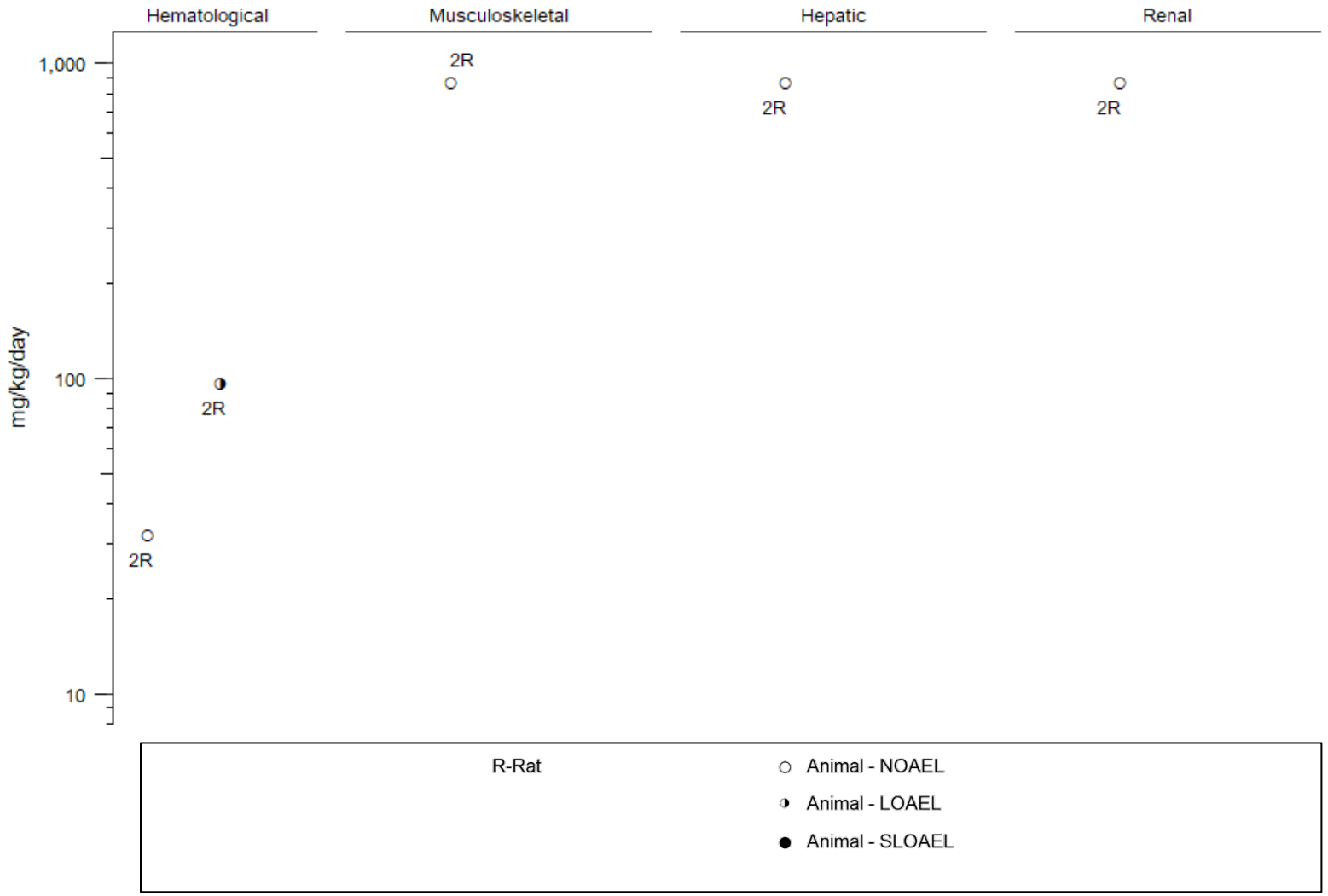


Figure 2-6. Levels of Significant Exposure to cis-1,2-Dichloroethene – Oral

Intermediate (15–364 days)

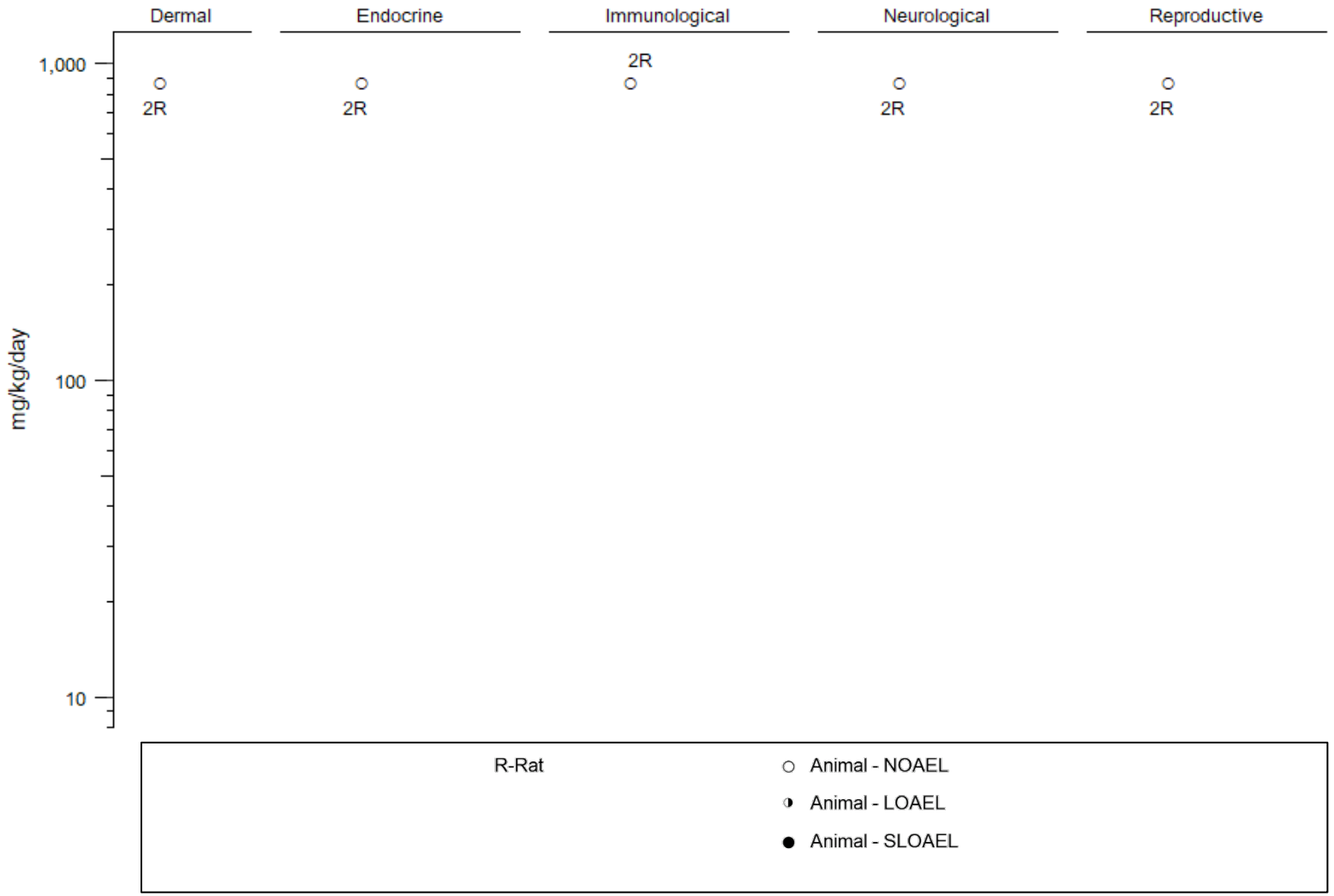


Table 2-5. Levels of Significant Exposure to Mixtures of cis- and trans-1,2-Dichloroethene – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Dow Chemical Company 1960									
1	Rat (NS) 9 M	Once 0.1, 0.2, or 0.35 hours	50,123	CS, LE	Death			50,123	100% lethality after 19 minutes of exposure
					Neuro			50,123	Tremors during exposure for 0.1 and 0.2 hours
Dow Chemical Company 1960									
2	Rat (NS) 9 M	Once 0.2, 0.5, or 1.5 hours	29,035	CS, LE	Death			29,035	100% lethality in rats exposed for 1.5 hours
					Neuro			29,035	Unconsciousness and tremors for all exposure durations
Dow Chemical Company 1960									
3	Rat (NS) 9 M	Once 4 or 7 hours	16,810	CS, LE	Death			16,810	Death in 6/9 rats exposed for 4 and 7 hours
					Neuro			16,810	Tremors and prone position in rats exposed for 7 hours
Dow Chemical Company 1960									
4	Rat (NS) 9 M	Once 1 hour	14,814	CS, LE					
Dow Chemical Company 1960									
5	Rat (NS) 9 M	Once 2, 4, or 7 hours	7,297	CS, LE	Neuro			7,297	Tremors and staggering in rats exposed for 7 hours
Dow Chemical Company 1994									
6	Rat (NS) 10 M, 10 F	7 hours/day 5 days/week 2 weeks	1,000	BC, BW, CS, HE, LE, OW	Bd wt	1,000			
					Hemato	1,000			
					Hepatic	1,000			
					Renal	1,000			

Table 2-5. Levels of Significant Exposure to Mixtures of cis- and trans-1,2-Dichloroethene – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Dow Chemical Company 1994									
7	Rabbit (NS) 3 M, 3 F	7 hours/day 5 days/week 2 weeks	1,000	BC, BW, CS, HE, LE, OW	Bd wt	1,000			
					Hemato	1,000			
					Hepatic	1,000			
					Renal	1,000			
INTERMEDIATE EXPOSURE									
Dow Chemical Company 1994									
8	Rat (NS) 12 M, 12 F	7 hours/day 5 days/week 6 months	0, 500, 1,000	BC, BW, CS, HE, LE, OW	Bd wt	1,000			
					Hemato	1,000			
					Hepatic	1,000			
					Renal	1,000			
Dow Chemical Company 1994									
9	Rabbit (NS) 3 M, 3 F	7 hours/day 5 days/week 6 months	0, 500, 1,000	BC, BW, CS, HE, LE, OW	Bd wt	1,000			
					Hemato	1,000			
					Hepatic	1,000			
					Renal	1,000			

[a]The number corresponds to entries in Figure 2-7.

BC = blood chemistry; Bd wt or BW = body weight; CS = clinical signs; F = female(s); HE = hematology; Hemato = hematological; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OW = organ weight

Figure 2-7. Levels of Significant Exposure to Mixtures of cis- and trans-1,2-Dichloroethene – Inhalation

Acute (≤14 days)

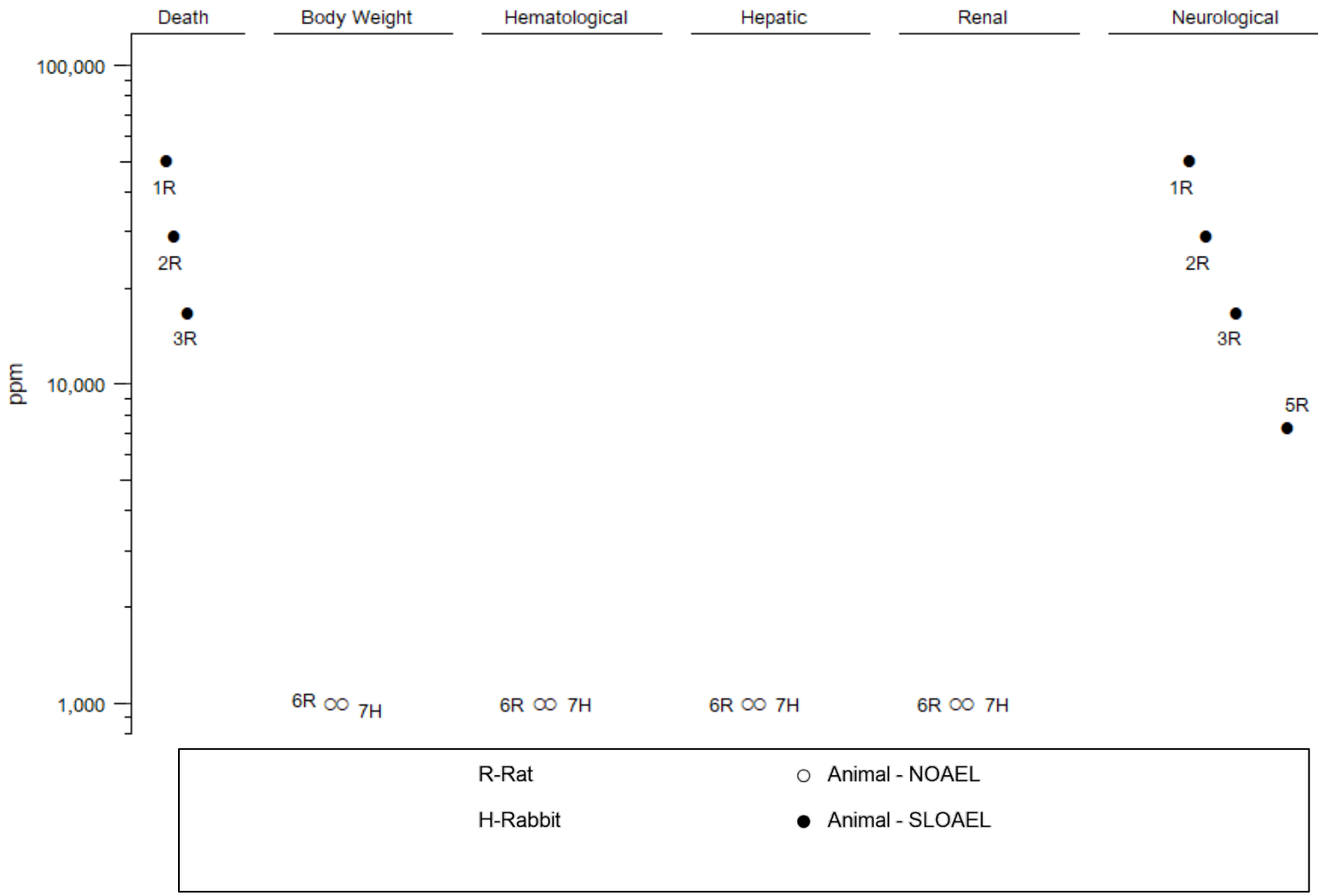
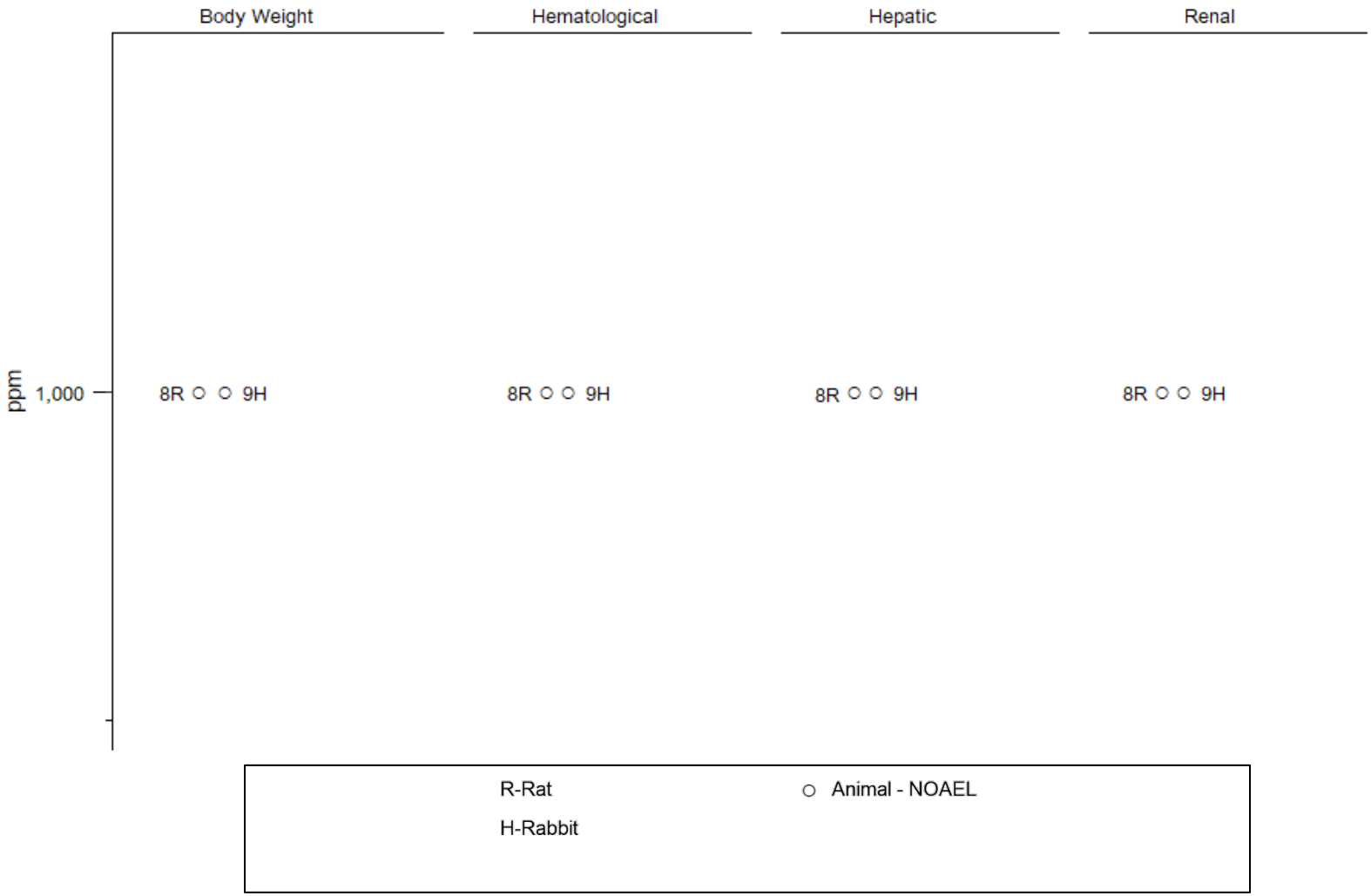


Figure 2-7. Levels of Significant Exposure to Mixtures of cis- and trans-1,2-Dichloroethene – Inhalation

Intermediate (15–364 days)



2.2 DEATH

trans-1,2-Dichloroethene. No studies were located regarding lethality in humans from inhalation, oral, or dermal exposure to trans-1,2-dichloroethene. In laboratory animals, acute- and intermediate-duration studies have evaluated lethality of trans-1,2-dichloroethene by inhalation, oral, and dermal exposure. Inhalation studies show that lethality occurs at high exposure levels.

In rats (5/sex/group) whole-body exposed to trans-1,2-dichloroethene vapor for 4 hours, 0/10, 4/10, 7/10, and 10/10 deaths occurred at 12,300, 22,500, 28,100, and 34,100 ppm, respectively (Confidential 1999). The LC_{50} for male and female rats was 24,100 ppm.

In mice, a 6-hour LC_{50} value of 21,723 ppm was determined; the cause of death was not reported (Gradiski et al. 1978). No maternal mortality was observed in rats in a gestational exposure study of inhaled trans-1,2-dichloroethene at up to the highest concentrations tested of 12,000 ppm (Hurtt et al. 1993). In a 90-day inhalation study in rats, no treatment-related deaths occurred at concentrations up to 4,000 ppm, the highest concentration tested (DuPont 1998). For oral exposure, LD_{50} values of 7,902 and 9,938 mg/kg were determined in male and female rats, respectively (Hayes et al. 1987), and the range of LD_{50} values in mice was 2,122–2,391 mg/kg (Barnes et al. 1985; Munson et al. 1982). The cause of death was not reported; however, neurological symptoms associated with lethal oral doses included decreased activity, ataxia, suppressed or total loss of righting reflex, and depressed respiration (Barnes et al. 1985; Hayes et al. 1987). No treatment-related deaths were observed in intermediate-duration oral studies in rats and mice. The highest doses of trans-1,2-dichloroethene tested in these studies were as follows: 3,114 mg/kg/day in male rats and 2,809 mg/kg/day in female rats in a 90-day drinking water study (Hayes et al. 1987); 3,210 and 3,245 mg/kg/day in male and female rats, respectively, in a 14-week dietary exposure study (NTP 2002); and 8,065 and 7,925 mg/kg/day in male and female mice, respectively, in a 14-week dietary exposure study (NTP 2002). Dermal exposure studies in rabbits did not observe any lethality following a 24-hour exposure to 5,000 mg/kg trans-1,2-dichloroethene (Brock 1990; DuPont 1988a).

cis-1,2-Dichloroethene. No studies were located regarding lethality in humans from inhalation, oral, or dermal exposure to cis-1,2-dichloroethene, and few studies have evaluated lethality in laboratory animals. Mortality in rats exhibited dose-dependence, with no deaths at 12,100 ppm, 4/10 deaths at 13,500 ppm, and 100% mortality at 15,700 and 23,200 ppm (Dupont 1999). The cause of death was not specifically reported, although neurological effects (unresponsive to stimuli) were reported. No additional studies

evaluating lethality of inhaled cis-1,2-dichloroethene were identified. A 14-day gavage study in rats did not observe any treatment-related lethality. The study authors stated that deaths in the two highest dose groups (970 mg/kg/day: 2/20 deaths; 1,900 mg/kg/day: 5/20 deaths) were due to gavage errors, although no deaths were observed in lower dose groups (≤290 mg/kg/day). In a 90-day gavage study in rats, no treatment-related mortality was observed at doses up to 870 mg/kg/day, the highest dose tested (EPA/AMRL 1990, McCauley et al. 1995). No studies evaluating mortality following dermal exposure to cis-1,2-dichloroethene were identified.

Mixed Isomers or Isomeric Composition Not Reported. In humans, a single fatality was reported after inhalation of 1,2-dichloroethene vapor in a small enclosure (Hamilton 1934). No information regarding level or duration of exposure or isomeric composition of the vapor was reported. No additional information regarding lethal effects in humans following inhalation of 1,2-dichloroethene was identified.

Information on lethality of mixed cis- and trans-1,2-dichloroethene in laboratory animals is available for acute- and intermediate-duration inhalation exposures and acute-duration oral exposure. A series of single exposure inhalation studies in rats examined lethality of a mixture of trans- and cis-1,2-dichloroethene; the percentage of each isomer in the mixture was not reported (Dow Chemical Company 1960). Lethality was 100% in rats exposed to 50,123 ppm for 19 minutes and 29,035 ppm for 1.5 hours. Results of this study show that lethality of the mixed isomer exposure exhibited dose-dependence. For example, no lethality was observed in rats exposed to 7,297 ppm for 4 or 7 hours, compared to mortality in 6/9 rats exposed to 16,810 ppm for 4 or 7 hours. The cause of death was not reported, although signs of neurotoxicity were observed. No mortality was observed in rats or rabbits exposed to 1,000 ppm of a mixture of 58% cis- and 42% trans-1,2-dichloroethene for 2 weeks (Dow Chemical Company 1994). In a 6-month inhalation study of a mixture of 58% cis- and 42% trans-1,2-dichloroethene in rats and rabbits, no mortality was observed at the highest concentration tested of 1,000 ppm (Dow Chemical Company 1994). For oral exposure, a 7-day gavage study in mice evaluated lethality for a dose-range of 30–2,000 mg/kg/day of a mixture of the cis- and trans- isomers; the composition of the mixture was not reported (Kallman et al. 1983). No lethality was observed at doses ≤300 mg/kg/day. At a dose of 1,000 mg/kg/day, 4/7 mice died, and 100% lethality was observed in mice administered 3,000 mg/kg/day. The cause of death was not reported.

2.3 BODY WEIGHT

No studies evaluating body weight effects of inhalation, oral, or dermal exposure of humans to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located.

trans-1,2-Dichloroethene. In laboratory animals, body weight effects have been evaluated for acute- and intermediate-duration inhalation and oral exposures. A developmental study evaluated maternal body weight in rats exposed to inhaled trans-1,2-dichloroethene on GDs 7–16 (Hurtt et al. 1993). In dams exposed to 12,000 ppm, maternal body weight gain was decreased by 33.8% at the end of the exposure period on GD 16, with no effects on body weight gain observed in rats exposed to 2,000 or 6,000 ppm. The decrease in body weight gain at 12,000 ppm was accompanied by 16% decreased food intake during the exposure period, which was most likely secondary to 1,2-dichloroethene-induced narcosis. At the end of gestation (GD 22), body weight of dams in all treatment groups was similar to controls. A 90-day inhalation study in rats did not observe any effects on body weight at exposure concentrations up to 4,000 ppm, the highest concentration tested (DuPont 1998). No effects on body weight were observed in 14-day gavage studies in mice at the highest doses tested of 210 mg/kg/day (Barnes et al. 1985) and 220 mg/kg/day (Munson et al. 1982). Intermediate-duration oral studies have reported conflicting results regarding effects of exposure to trans-1,2-dichloroethene on body weight. A 14-week dietary study in mice reported a 10.7% decrease in terminal body weight in females exposed to 7,925 mg/kg/day, without an accompanying decrease in feed consumption; <10% decreases in terminal body weight were observed in males at doses up to 8,065 mg/kg/day (NTP 2002). Decreases of <10% body weight were observed in other intermediate-duration oral studies in rats or mice, although these studies examined lower doses as follows (highest doses tested): 90-day drinking water study in rats (3,114 mg/kg/day in males and 2,809 mg/kg/day in females) (Hayes et al. 1987); 14-week dietary study in rats (3,245 mg/kg/day in males and 3,210 mg/kg/day in females) (NTP 2002); and 90-day drinking water study in mice (452 mg/kg/day in males and 387 mg/kg/day in females) (Barnes et al. 1985). Body weight loss was observed following a single 24-hour dermal exposure of rabbits to 5,000 mg/kg trans-1,2-dichloroethene (Brock 1990); however, the magnitude of loss and statistical significance were not reported.

cis-1,2-Dichloroethene. No studies were located regarding body weight effects in animals from inhalation or dermal exposure. No consistent or dose-related effects on terminal body weight or body weight gain were observed in a 14-day gavage study in rats. In male rats, terminal body weight in the 1,900 mg/kg/day group (highest dose tested) was decreased by 8.4% compared to controls; however, changes in body weight of <10% are not considered adverse. Terminal body weights in female rats were

similar to control for all treatment groups (EPA/AMRL 1990, McCauley et al. 1995). For intermediate-duration oral exposure, a 90-day gavage study found a 37% decrease in body weight gain in male rats in the highest dose group (870 mg/kg/day), although terminal body weight was not statistically different from controls (EPA/AMRL 1990; McCauley et al. 1995). In female rats, terminal body weight and body weight gain were similar to controls in all treatment groups.

Mixed Isomers or Isomeric Composition Not Reported. No effects on body weight in rats or rabbits were observed following inhalation exposure for 2 weeks or 6 months of rats and rabbits to up to 1,000 ppm (highest concentration tested) of a mixture of 58% cis-1,2-dichloroethene and 42% trans-1,2-dichloroethene (Dow Chemical Company 1994).

2.4 RESPIRATORY

No studies evaluating respiratory effects of inhalation, oral, or dermal exposure of humans to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located.

trans-1,2-Dichloroethene. Inhalation and oral exposures to trans-1,2-dichloroethene did not result in any adverse respiratory effects at the highest exposure concentrations tested: 90-day inhalation exposure of rats at concentrations up to 4,000 ppm, purity 99.86% (DuPont 1998); 14-day gavage exposure of rats to 210 mg/kg/day, purity 98% (Barnes et al. 1985); 14-week dietary exposure at doses up to 3,245 and 3,210 mg/kg/day in male and female rats, respectively, and 7,925 and 8,065 mg/kg/day in male and female mice, respectively, purity 99% (NTP 2002). A series of inhalation exposure studies in rats by Freundt et al. (1977) identified adverse respiratory effects (slight capillary hyperemia of the lung with alveolar septal distention) following a single 8-hour exposure to 200 ppm and repeated 8-hour exposures to 200 ppm for up to 16 weeks; however, these finding have not been corroborated in other studies at higher exposure levels and pulmonary capillary hyperemia and alveolar septal distention were observed in some control rats (0, 17, or 33% in the different control groups). The Freundt et al. (1977) study had several weaknesses: purity of the test substance was not reported so that potential for contaminants in the test substance was not assessed; a small number of animals (n=6) were examined; and statistical evaluation of the histological data was not presented. Given these weaknesses and lack of corroborating data, reliable NOAELs and LOAELs cannot be determined.

cis-1,2-Dichloroethene. No studies were located regarding respiratory effects of cis-1,2-dichloroethene in animals from inhalation or dermal exposure. No adverse respiratory effects were observed in rats

administered cis-1,2-dichloroethene by gavage at doses of up to 1,900 mg/kg/day for 14 days or up to 870 mg/kg/day for 90 days (EPA/AMRL 1990, McCauley et al. 1995).

Mixed Isomers or Isomeric Composition Not Reported. No studies of respiratory effects of mixed cis- and trans-1,2-dichloroethene in animals were identified.

2.5 CARDIOVASCULAR

No studies evaluating cardiovascular effects of inhalation, oral, or dermal exposure of humans to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located.

trans-1,2-Dichloroethene. No cardiovascular effects were observed in the following intermediate-duration inhalation or oral exposure studies of trans-1,2-dichloroethene: rats after a 90-day inhalation exposure at concentrations up to 4,000 ppm trans-1,2-dichloroethene (DuPont 1998); rats in a 14-week feeding study at doses up to 3,245 and 3,210 mg/kg/day in males and females, respectively (NTP 2002); and mice in a 14-week feeding study at doses up to 7,925 and 8,065 mg/kg/day in males and females, respectively. Freundt et al. (1977) reported histological effects in the heart (severe fibrous swelling of the myocardium and hyperemia) in rats following a single 8-hour exposure to 3,000 ppm and a single gavage dose of 1,130 mg/kg. However, given the study weaknesses, as described in Section 2.4 (Respiratory), reliable NOAELs and LOAELs cannot be determined.

cis-1,2-Dichloroethene. No studies were located regarding cardiovascular effects of inhalation or dermal exposure of animals to cis-1,2-dichloroethene. In acute- and intermediate-duration oral studies in male and female rats, no adverse cardiovascular effects were observed (EPA/AMRL 1990; McCauley et al. 1995). The highest doses tested in the studies were 1,900 mg/kg/day in the 14-day gavage study and 870 mg/kg/day in the 90-day gavage study. No additional studies evaluating cardiovascular effects of cis-1,2-dichloroethene were located.

Mixed Isomers or Isomeric Composition Not Reported. No studies of cardiovascular effects of mixed cis- and trans-1,2-dichloroethene in animals were identified.

2.6 GASTROINTESTINAL

No studies evaluating gastrointestinal effects of inhalation, oral, or dermal exposure of humans to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located. Note that effects on the gallbladder are discussed under hepatic effects (Section 2.9).

trans-1,2-Dichloroethene. Little information is available regarding gastrointestinal effects of trans-1,2-dichloroethene in laboratory animals. No gastrointestinal effects were found in 90-day inhalation studies in male and female rats at concentrations up to 4,000 ppm based on histopathological assessments (DuPont 1998). In a single dose, gavage study in rats, hyperemia of the mucosal surface of the stomach and small intestine was observed in all animals that died (Barnes et al. 1985). The range of lethal doses was 1,600–3,500 mg/kg. Due to the lack of incidence data for death and gastrointestinal effects, reliable NOAEL and LOAEL values could not be identified. Intermediate-duration oral dietary exposure to trans-1,2-dichloroethene did not observe histopathological changes to the gastrointestinal tract in rats (3,245 and 3,210 mg/kg/day in males and females, respectively) or mice (7,925 and 8,065 in males and females, respectively) (NTP 2002).

cis-1,2-Dichloroethene. No studies were located regarding gastrointestinal effects of inhalation or dermal exposure to cis-1,2-dichloroethene in animals. No gastrointestinal effects were noted in rats exposed by gavage to 1,900 mg/kg/day cis-1,2-dichloroethene for 14 days or 870 mg/kg/day cis-1,2-dichloroethene for 90 days based on histopathology (EPA/AMRL 1990; McCauley et al. 1995).

Mixed Isomers or Isomeric Composition Not Reported. No studies of gastrointestinal effects of mixed cis- and trans-1,2-dichloroethene in animals were identified.

2.7 HEMATOLOGICAL

No studies evaluating hematological effects of inhalation, oral, or dermal exposure of humans to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located.

trans-1,2-Dichloroethene. Little information is available on hematological effects of inhaled trans-1,2-dichloroethene. No effects on erythrocyte count, hematocrit, or hemoglobin were observed in rats exposed to inhaled trans-1,2-dichloroethene at concentrations of 1,000 or 4,000 ppm for 90 days (DuPont 1998). A statistically significant decrease (26%) in lymphocyte count was reported after 90 days of exposure to 4,000 ppm in male rats, but not female rats (DuPont 1998). The toxicological significance of

this finding is uncertain due to the small magnitude of change. Freundt et al. (1977) observed a 9% decrease in erythrocyte count, compared to controls, in rats exposed to 1,000 ppm for 8 hours (highest dose tested), with no effects observed at 200 ppm. In addition, leukocyte counts were decreased by 23% in female rats after 8 hours at 200 and 1,000 ppm. Given the weaknesses of this study (see discussion in Section 2.4), reliable NOAEL and LOAEL values cannot be determined.

Acute-duration oral exposure studies did not observe effects on erythrocyte counts or related hematological parameters. No changes to hematological parameters (hematocrit, hemoglobin concentrations, erythrocyte counts, reticulocyte count, mean cell volume, mean cell hemoglobin concentration, platelets, white blood cell count or differentiation) were observed following dietary exposure of male and female rats for 5 days at the highest doses tested of 5,591 and 4,500 mg/kg/day in males and females, respectively (NTP 2002). At lower doses (≤240 mg/kg/day), no effects on hematocrit or blood hemoglobin were observed in male mice exposed daily by gavage for 14 days (Munson et al. 1982). No effects on leukocyte counts were observed in a 14-day gavage study in mice at 240 mg/kg/day (Munson et al. 1982). Intermediate-duration studies did not observe biologically relevant changes to hematological parameters. Barnes et al. (1985) reported a 23% increase in leukocyte counts in female mice after a 90-day exposure to 224 mg/kg/day, but not 452 mg/kg/day; differential analysis showed that the increase was primarily due to a 3-fold increase in eosinophils. This finding is not considered to be biologically significant as changes were not observed at a higher dose. Fibrinogen levels and prothrombin time were decreased by 12 and 7%, respectively, compared to controls, in mice administered 210 mg/kg/day by gavage for 14 days (Barnes et al. 1985). Results are clinically inconsistent. Decreased fibrinogen would be expected to increase prothrombin time (e.g., longer time to fibrinogen clot formation); however, prothrombin time was decreased. Munson et al. (1982) did not observe any changes to fibrinogen levels or prothrombin time in mice exposed by gavage to trans-1,2-dichloroethene for 14 days at the highest dose tested (220 mg/kg/day).

Results of intermediate-duration oral studies on erythrocyte counts and related hematological parameters are inconsistent. Hayes et al. (1987) did not observe effects on hematological parameters, including erythrocyte counts, hematocrit, and hemoglobin, in Sprague-Dawley-derived CD rats exposed to trans-1,2-dichloroethene in drinking water for 90 days at doses up to 2,809 and 3,114 mg/kg/day in males and females, respectively. In contrast, small, dose-related decreases in erythrocyte counts were observed in a 14-week dietary exposure study in F344/N rats at similar and lower doses (NTP 2002). Erythrocyte count was significantly decreased in male rats by 2.5, 3.6, 4.2, and 7.1%, relative to controls, at doses of 380, 770, 1,540, and 3,210 mg/kg/day, respectively; no decreases were observed at a dose of 189 mg/kg/day.

Decreases in erythrocyte counts were accompanied by dose-related decreases in hematocrit and blood hemoglobin concentrations at doses ≥770 mg/kg/day. In female rats, erythrocyte counts were decreased by 3.3 and 5.1% in the 1,580 and 3,245 mg/kg/day groups, respectively; no decreases were observed at doses ≤780 mg/kg/day. Hematocrit and blood hemoglobin concentrations were decreased in the 1,580 and 3,245 mg/kg/day groups. The basis for different results of the Hayes et al. (1987) and NTP (2002) studies is not apparent but could be due to the different rat strains utilized. No changes in leukocyte counts were observed in intermediate-duration oral studies as follows: male and female rats exposed to 3,210 and 3,245 mg/kg/day, respectively, in the diet (NTP 2002); male mice exposed to 387 mg/kg/day for 90 days in drinking water (Barnes et al. 1985); and male and female mice exposed to 8,065 and 7,925 mg/kg/day, respectively in the diet (NTP 2002).

cis-1,2-Dichloroethene. No studies were located regarding hematological effects of inhalation or dermal exposure to cis-1,2-dichloroethene in animals. EPA/AMRL (1990) and McCauley et al. (1995) evaluated hematological effects of gavage administration of cis-1,2-dichloroethene in rats exposed for 14 and 90 days. In the 14-day study, hematocrit was decreased by 11% at doses of 290, 970, and 1,900 mg/kg/day, relative to controls, in females; however, no effects were observed for erythrocyte count or hemoglobin concentration. No hematological effects were observed in males administered up to 1,900 mg/kg/day for 14 days. In the 90-day study in female rats, hematocrit was decreased by 9.9 and 6.5% at doses of 290 and 870 mg/kg/day, respectively. Erythrocyte count and hemoglobin concentration were decreased by 5.9% and 3.9%, respectively, in the 290 mg/kg/day group, but not in the 870 mg/kg/day group, indicating that these changes were not related to treatment with cis-1,2-dichloroethene. In male rats, no treatment-related effects were observed for erythrocyte count. However, hematocrit was decreased by 5.8, 8.9, and 8.9% at doses of 290, 970, and 1,900 mg/kg/day, respectively, and hemoglobin concentration was decreased by 6.0% at doses of 970 and 1,900 mg/kg/day. The toxicological significance of decreased hematocrit and hemoglobin concentration in the absence of decreased erythrocyte count is uncertain.

Mixed Isomers or Isomeric Composition Not Reported. Dow Chemical Company (1994) did not observe effects on hematocrit or hemoglobin in rats and rabbits exposed to a mixture of 1,2-dichloroethene isomers (42% trans and 58% cis) following inhalation exposure to 1,000 ppm for 2 weeks or 6 months. No information on erythrocyte count was reported.

2.8 MUSCULOSKELETAL

No studies evaluating musculoskeletal effects of inhalation, oral, or dermal exposure of humans to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located.

trans-1,2-Dichloroethene. Musculoskeletal effects of trans-1,2-dichloroethene have not been well-investigated. However, no histopathological effects in rats were observed in muscle tissue following inhalation at concentrations up to 4,000 ppm for 90 days (DuPont 1998).

cis-1,2-Dichloroethene. Acute- and intermediate-duration studies did not observe musculoskeletal effects of cis-1,2-dichloroethene based on histopathological assessments in rats exposed by gavage at doses up to 1,900 mg/kg/day for 14 days or up to 870 mg/kg/day for 90 days (EPA/AMRL 1990; McCauley et al. 1995).

Mixed Isomers or Isomeric Composition Not Reported. No studies evaluating musculoskeletal effects of mixed cis- and trans-1,2-dichloroethene in animals were identified.

2.9 HEPATIC

trans-1,2-Dichloroethene. In a case-control study of the general population (e.g., non-occupational), the risk of gallstone disease was positively associated with trans-1,2-dichloroethene levels in adipose tissue (Ji et al. 2016). The study population included 194 patients with and 190 patients without cholesterol gallstone disease. Results were stratified by quartiles (Q) based on the concentration of trans-1,2-dichloroethene in adipose tissue (ng/g lipid weight): Q1 12.82–721.7; Q2 721.7–1,351; Q3 1,351–2,558; and Q4 2,558–18,135. Odds ratios (ORs) were increased ($p \leq 0.05$) in Q2 (3.49; 95% confidence interval [CI] 1.93, 6.33), Q3 (2.38; 95% CI 1.32, 4.27), and Q4 (2.48; 95% CI 1.38, 4.46), respectively, relative to Q1. In addition, the concentration of trans-1,2-dichloroethene in adipose tissue of patients with gallstone disease (mean of 1,542 ng/g lipid weight) was significantly higher ($p=0.008$) compared to patients without gallstone disease (mean of 1,213 ng/g lipid weight).

Results of studies in laboratory animals indicate that the liver is not a sensitive target for trans-1,2-dichloroethene. No histopathological liver effects or increases in serum liver enzymes (alkaline phosphatase [AP], alanine transaminase [ALT], and aspartate transaminase [AST]) were observed in rats exposed by inhalation at concentrations up to 4,000 ppm for 90 days (DuPont 1998). Small increases in relative liver weights were observed in male and female rats at concentrations ≥200 ppm. However, the

magnitude of increases was small (4–6% in males and 4–8%; in females) and increases were not dose-dependent. In the absence of histopathological changes or increased serum liver enzymes, increases in relative liver weights are not considered adverse and could be an adaptive response due to increased enzyme expression following exposure to a xenobiotic. Freundt et al. (1977) reported fatty degeneration of liver lobules in rats exposed to 200–3,000 ppm for 8 hours and 200 ppm for up to 2 weeks. However, a statistical analysis conducted for this report showed that the incidence of lesions was not significantly different from controls. In addition, the Freundt et al. 1977 study has several weaknesses, as discussed in Section 2.4 (Respiratory).

In addition to inhalation studies conducting histopathological assessments of the liver, potential effects on the mixed function oxidase system were examined in rats (Freundt and Macholz 1978). A single 8-hour inhalation exposure to trans-1,2-dichloroethene at 200 ppm increased hexobarbital sleeping time and zoxazolamine paralysis time in rats. These effects indicate possible inhibition of the mixed function oxidase system. Additional details on metabolism of trans-1,2-dichloroethene are provided in Section 3.1.3 (Toxicokinetics, Metabolism).

Acute- and intermediate-duration oral studies consistently show no adverse hepatic effects from exposure to trans-1,2-dichloroethene. Acute-duration studies with 14-day exposures did not find adverse liver effects in rats based on gross examination of livers in rats exposed to single doses up to 210 mg/kg/day (Barnes et al. 1985) and to 220 mg/kg/day (Munson et al. 1982). No evidence of hepatotoxicity was observed in intermediate-duration studies as follows (maximum doses tested): 3,114 and 2,809 mg/kg/day in male and female rats, respectively, in a 90-day drinking water study based on histopathology (Hayes et al. 1987); 3,210 and 3,245 mg/kg/day in male and female rats, respectively, in a 90-day dietary study based on histopathological examination (NTP 2002); 387 and 452 mg/kg/day in male and female rats, respectively, in a 90-day drinking water study based on gross necropsy (Barnes et al. 1985); and 8,065 and 7,925 mg/kg/day in male and female mice, respectively, in a 90-day dietary study based on histopathology (NTP 2002).

Other hepatic effects observed following oral exposure to trans-1,2-dichloroethene are not considered to be toxicologically significant. NTP (2002) reported increased relative liver weights (5.5–9.6% above control) in female rats at doses ≥395 mg/kg/day, although increases did not exhibit dose-dependence; no change in relative liver weight was observed in male rats. In mice, increased relative liver weights were observed in males (8.9–14% above control) and females (11% above control) at doses ≥1,900 and ≥3,760 mg/kg/day, respectively (NTP 2002). However, in the absence of gross and histopathological

findings, increases in relative liver weights are not considered toxicologically significant. Other oral exposure studies did not observe increased relative liver weight in rats or mice (Barnes et al. 1985; Hayes et al. 1987). Barnes et al. (1985) observed increases in serum AP of 62 and 33% above controls at doses of 175 and 387 mg/kg/day, respectively, in male mice following a 90-day exposure to trans-1,2-dichloroethene in drinking water. The increases did not exhibit dose-dependence and no changes were observed for other serum liver enzymes (lactate dehydrogenase, ALT, and AST). Therefore, the increases in serum AP activity also are not considered toxicologically significant.

cis-1,2-Dichloroethene. No studies evaluating hepatic effects of inhalation, oral, or dermal exposure of humans to cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located. In rats, histopathological assessments of the liver did not identify adverse effects of gavage exposure of rats to cis-1,2-dichloroethene following exposure to 1,900 mg/kg/day for 14 days or 870 mg/kg/day for 90 days (EPA/AMRL 1990; McCauley et al. 1995). Dose-related increases in relative liver weights were observed in male and female rats exposed for 14 and 90 days. In the 14-day study, increases ranged from 15% at 97 mg/kg/day to 38% at 1,900 mg/kg/day. In the 90-day study, relative liver weights were increased by 15% at 32 mg/kg/day and 39% at 870 mg/kg/day (EPA/AMRL 1990; McCauley et al. 1995). Similar dose-dependent increases were observed in male rats, with increases of 16 and 38% at doses of 32 and 870 mg/kg/day, respectively (EPA/AMRL 1990; McCauley et al. 1995). However, given the absence of histopathological changes or changes in serum liver enzymes (AP, ALT, AST), the toxicological significance of increases in relative liver weights is uncertain. In rats exposed to 1,900 mg/kg/day for 14 days, but not to 870 mg/kg/day for 90 days, blood cholesterol increased by 40% compared to controls (EPA/AMRL 1990; McCauley et al. 1995). The toxicological significance of this transient effect is not established.

A single 8-hour inhalation exposure to cis-1,2-dichloroethene at 200 ppm increased hexobarbital sleeping time and zoxazolamine paralysis time in rats, indicating possible inhibition of the mixed function oxidase system (Freundt and Macholz 1978). See Section 3.1.3 (Toxicokinetics, Metabolism) for additional information on the metabolism of cis-1,2-dichloroethene.

Mixed Isomers or Isomeric Composition Not Reported. No hepatic effects were observed in rats or rabbits exposed to a mixture of 1,2-dichloroethene isomers (42% trans and 58% cis) by inhalation for 2 weeks or 6 months based on serum liver enzymes (Dow Chemical Company 1994).

2.10 RENAL

No studies evaluating renal effects of inhalation, oral, or dermal exposure of humans to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located.

trans-1,2-Dichloroethene. Results of inhalation and oral exposure studies on trans-1,2-dichloroethene in animals have not identified toxicologically significant renal effects. No histopathological findings or increases in markers of decreased renal function (serum creatinine and blood urea nitrogen [BUN] levels) were observed in male or female rats following inhalation exposure of 200–4,000 ppm for 90 days (DuPont 1998). Similarly, no renal effects were observed following oral exposure, with maximum doses tested as follows: 14-day gavage at doses up to 210 mg/kg/day in mice, based on BUN (Barnes et al. 1985); 3,114 and 2,809 mg/kg/day in male and female rats, respectively, in a 90-day drinking water study based on creatinine, BUN, and gross necropsy (Hayes et al. 1987); 3,210 and 3,245 in male and female rats, respectively, in a 90-day dietary study based on histopathology and creatinine levels (NTP 2002); 387 and 452 in male and female rats, respectively, in a 90-day drinking water study based on gross necropsy and BUN (Barnes et al. 1985); and 8,065 and 7,925 in male and female mice, respectively, in a 90-day dietary study based on histopathology (NTP 2002).

cis-1,2-Dichloroethene. No histopathological effects were observed in the kidneys following gavage exposure of rats to cis-1,2-dichloroethene at doses up to 1,900 mg/kg/day for 14 days or 870 mg/kg/day for 90 days (EPA/AMRL 1990; McCauley et al. 1995). In addition, no changes in serum creatinine were observed in male or female rats at doses up to 870 mg/kg/day for 90 days (EPA/AMRL 1990; McCauley et al. 1995). EPA/AMRL (1990) and McCauley et al. (1995) observed increased relative kidney weights in male rats, but not female rats, exposed to cis-1,2-dichloroethene for 90 days, with increases ranging from 14% at 32 mg/kg/day to 27% at 870 mg/kg/day. Given the absence of histopathological and functional findings in the kidney, changes in relative kidney weights are not considered adverse.

Mixed Isomers or Isomeric Composition Not Reported. No increase in BUN was observed in rats or rabbits exposed to 1,000 ppm to a mixture of 58% cis-1,2-dichloroethene and 42% trans-1,2-dichloroethene for 14 or 90 days (Dow Chemical Company 1994).

2.11 DERMAL

No studies evaluating dermal effects of inhalation, oral, or dermal exposure of humans to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located.

trans-1,2-Dichloroethene. Studies on dermal exposure of rabbits to trans-1,2-dichloroethene provide evidence of dose-dependent damage to skin. In rabbits exposed for 24 hours to 170 mg/kg trans-1,2-dichloroethene, mild-to-moderate erythema was observed; severe dermal irritation was observed at 5,000 mg/kg (Brock 1990). Following a 48-hour dermal exposure to 630 mg/kg trans-1,2-dichloroethene, mild-to-moderate erythema was observed (DuPont 1988b). DuPont (1988a) reported more severe dermal effects, including edema, necrosis, fissuring, and epidermal scaling, in rabbits exposed to 5,000 mg/kg for 24 hours. No dermal effects have been observed in inhalation or oral exposure studies of trans-1,2-dichloroethene, based on histological examinations. The highest concentrations tested are as follows: 4,000 ppm in rats in a 90-day inhalation study (DuPont 1998); 3,210 and 3,245 mg/kg/day in male and female rats, respectively, in a 90-day dietary study (NTP 2002); and 8,065 and 7,925 mg/kg/day in male and female mice, respectively, in a 90-day dietary study (NTP 2002).

cis-1,2-Dichloroethene. No dermal exposure studies of cis-1,2-dichloroethene were identified. No histopathological effects were observed in skin following gavage exposure of rats to cis-1,2-dichloroethene at doses up to 1,900 mg/kg/day for 14 days or 870 mg/kg/day for 90 days (EPA/AMRL 1990; McCauley et al. 1995).

Mixed Isomers or Isomeric Composition Not Reported. No studies evaluating dermal effects of mixed cis- and trans-1,2-dichloroethene in animals were identified.

2.12 OCULAR

trans-1,2-Dichloroethene. An experimental study in two human subjects exposed to trans-1,2-dichloroethene concentrations of 830–2,220 ppm for 30 minutes reported slight burning of the eyes (Lehmann and Schmidt-Kehl 1936). The purity of the test substance was not reported, and accurate measurement of exposure concentrations is uncertain. No additional information on exposure conditions was reported.

Exposure of laboratory animals to trans-1,2-dichloroethene vapor in air and by instillation into the eye produces lacrimation and ocular irritation, respectively. In pregnant rats exposed by whole-body inhalation at 2,000, 6,000, or 12,000 ppm for 10 days on GDs 7–16, lacrimation was observed in 13/24, 22/24, and 24/24 rats, respectively, compared to 0/24 in controls (Hurtt et al. 1993). Lacrimation was not observed during the post-exposure period on GDs 17–22. Brown, periocular staining, due to excessive lacrimation, was observed in the 6,000 ppm (18/24) and 12,000 ppm (22/24) exposure groups. Instillation

of 0.01 mL trans-1,2-dichloroethene to the eyes of rabbits for 20 seconds resulted in transient severe corneal opacity, moderate iritis, and conjunctivitis (DuPont 1988c). No additional studies on potential ocular irritant effects of trans-1,2-dichloroethene were identified. Histopathological assessment did not show ocular effects in rats exposed by inhalation to concentrations up to 4,000 ppm for 90 days (DuPont 1998).

cis-1,2-Dichloroethene. No studies examining ocular effects of inhalation, oral, or ocular exposure of humans or animals to cis-1,2-dichloroethene were identified.

Mixed Isomers or Isomeric Composition Not Reported. No studies examining ocular effects of inhalation, oral, or ocular exposure of humans or animals to mixed cis- and trans-1,2-dichloroethene were identified.

2.13 ENDOCRINE

No studies evaluating endocrine effects of inhalation, oral, or dermal exposure of humans to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located.

trans-1,2-Dichloroethene. No studies evaluating endocrine effects following acute-duration inhalation or oral exposure of laboratory animals were identified. No histopathological effects to the adrenal gland or thyroid were observed in rats exposed to inhaled trans-1,2-dichloroethene at concentrations up to 4,000 ppm for 90 days (DuPont 1998). Similarly, no adrenal or thyroid effects were observed in a 14-week dietary study in male and female rats at maximum doses of 3,210 and 3,245 mg/kg/day, respectively, or in male and female mice at 8,065 and 7,925 mg/kg/day, respectively (NTP 2002). trans-1,2-Dichloroethene did not inhibit aromatase activity in human recombinant microsomes in an EPA Office of Prevention, Pesticides, and Toxic Substances (OPPTS) 890.1200 test (Confidential 2015a) and did not adversely affect estradiol or testosterone production in H295R human adrenocortical carcinoma cells (Confidential 2015b).

cis-1,2-Dichloroethene. Histological examination revealed no compound-related effects in the thyroid in rats exposed to cis-1,2-dichloroethene by gavage at doses up to 1,900 or 870 mg/kg/day for 14 or 90 days, respectively (EPA/AMRL 1990; McCauley et al. 1995).

Mixed Isomers or Isomeric Composition Not Reported. No studies examining endocrine effects of inhalation, oral, or dermal exposure of animals to mixed cis- and trans-1,2-dichloroethene were identified.

2.14 IMMUNOLOGICAL

No studies evaluating immunological effects of inhalation, oral, or dermal exposure of humans to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located.

trans-1,2-Dichloroethene. Little information is available regarding immunological effects of inhaled trans-1,2-dichloroethene. No histological changes to the spleen, thymus, or lymph nodes were observed in rats exposed in a 90-day inhalation study at concentrations up to 4,000 ppm (DuPont 1998). Slight to severe fatty degeneration of Kupffer cells was seen after 8 hours (200, 1,000 and 3,000 ppm) and up to 16 weeks (200 ppm) of exposure to trans-1,2-dichloroethene (Freundt et al. 1977). However, an analysis conducted by ATSDR for this document shows that the incidence in treatment groups is not statistically significant compared to controls. In addition, as described in Section 2.4 (Respiratory), the study has several weaknesses; therefore, it is difficult to make conclusions on immunological effects based on these findings.

The effects of orally administered trans-1,2-dichloroethene on the immune system have been investigated in rats and mice. Endpoints examined include weights of immune organs (spleen and thymus), histopathology of immune tissues (spleen, thymus, and lymph nodes), and functional tests of cell-mediated and humoral immunity. In general, most studies do not show effects on weights of immune organs. No effects were observed on absolute and/or relative spleen or thymus weights in 14-day gavage studies at doses up to 220 mg/kg/day (Barnes et al. 1985; Munson et al. 1982; Shopp et al. 1985). For intermediate-duration exposure, no effects on absolute spleen weight were observed in 90-day drinking water studies in male mice exposed to 210 mg/kg/day (Shopp et al. 1985) or relative spleen and thymus weights in male and female mice exposed to 387 and 452 mg/kg/day respectively (Barnes et al. 1985). In the NTP (2002) 14-week dietary studies, no effects were observed on relative thymus weight in rats at doses of 3,210 and 3,245 mg/kg/day in males and females, respectively, or in mice at doses of 8,065 and 7,925 mg/kg/day in males and females, respectively. In addition, no histopathological changes in spleen, thymus, or lymph nodes were observed in rats or mice in the NTP (2002) study.

Studies assessing effects of acute-duration oral exposure to trans-1,2-dichloroethene on humoral or cell-mediated immunity have been conducted in mice. No effects on humoral immunity were observed in

mice following 14-day gavage exposure to doses up 210 mg/kg/day (Shopp et al. 1985) or 220 mg/kg/day (Munson et al. 1982). In these studies, humoral immunity was assessed by measurement of the number of spleen IgM AFCs directed against sRBCs, serum antibody titers to sRBC, and spleen cell response to the B cell mitogen lipopolysaccharide. Cell-mediated immunity was assessed by delayed-type hypersensitivity response to sRBCs, popliteal lymph node proliferation responses to sRBC, and spleen cell response to the T-lymphocyte mitogen concanavalin A. Intermediate-duration exposure of mice to trans-1,2-dichloroethene in drinking water for 90 days decreased humoral immune function in males, but not females (Shopp et al. 1985). Suppression in humoral immunity in male mice, as measured by reductions in spleen AFCs directed against sRBCs, was observed at 175 and 387 mg/kg/day when expressed as AFC/10^6 spleen cells; the magnitude of the decrease was 26% in both groups. Other tests of immune function (spleen cell response to B cell mitogen lipopolysaccharide and hemagglutination titers) did not show suppression of humoral immunity. However, the sRBC AFC response is considered the "gold standard" for evaluating T-cell-dependent antibody responses and is considered one of the best predictors of immunotoxicity in mice (Ladics 2007). Shopp et al. (1985) did not observe any effects on cell-mediated immunity, as assessed by delayed-type hypersensitivity response to sRBC, popliteal lymph node proliferation responses to sRBC, and spleen cell response to the T-lymphocyte mitogen concanavalin A.

cis-1,2-Dichloroethene. No histopathological effects were observed in the spleen, thymus or lymph nodes of rats following gavage exposure to cis-1,2-dichloroethene at doses up to 1,900 mg/kg/day for 14 days or 870 mg/kg/day for 90 days (EPA/AMRL 1990; McCauley et al. 1995). In the same study, a slight increase in female relative thymus weight (11%) at 90 days in the highest dose group was not considered adverse given the lack of histological changes (EPA/AMRL 1990; McCauley et al. 1995).

Mixed Isomers or Isomeric Composition Not Reported. No studies examining immunological effects of inhalation, oral, or dermal exposure of animals to mixed cis- and trans-1,2-dichloroethene were identified.

2.15 NEUROLOGICAL

No reliable studies evaluating neurological effects of inhalation, oral, or dermal exposure of humans to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located.

trans-1,2-Dichloroethene. Little information on neurological effects of trans-1,2-dichloroethene is available. In an acute-duration inhalation toxicity test, male and female rats displayed decreased

responses to alerting stimuli during the 4-hour exposure period (incidence not provided) (Confidential 1999). At sublethal levels, narcosis (incidence data not reported) was observed in rats exposed by inhalation on GDs 7–16 at concentrations of 6,000 and 12,000 ppm, but not at 2,000 ppm (Hurtt et al. 1993). Lethargy was reported in 10/24 in rats exposed to 12,000 ppm but was not observed in any rats at 2,000 or 6,000 ppm (Hurtt et al. 1993). No clinical signs of neurotoxicity or histopathological effects on brain or spinal cord tissues were observed in rats exposed by inhalation for 90 days to concentrations up to 4,000 ppm (DuPont 1998). In single-dose oral lethality studies in rats, clinical signs of neurotoxicity have been observed (Barnes et al. 1985; Hayes et al. 1987); however, due to the lack of incidence data, reliable NOAEL and LOAEL values could not be identified. Hayes et al. (1987) observed clinical signs of neurotoxicity, including central nervous system depression, ataxia, and depressed respiration, at all doses (doses not reported), with dose-dependent severity. Barnes et al. (1985) observed decreased activity, ataxia, and suppressed or total lack of righting reflex in rats following doses of 1,600–3,500 mg/kg. No treatment-related effects were observed in rats or mice based on functional observational batteries, cage-side evaluations for clinical signs, or histopathological changes in neurological tissues in a 14-week dietary study in male and female rats at maximum doses of 3,210 and 3,245 mg/kg/day, respectively, or in male and female mice at 8,065 and 7,925 mg/kg/day, respectively (NTP 2002).

cis-1,2-Dichloroethene. No studies evaluating neurological effects of cis-1,2-dichloroethene in humans were located. EPA/AMRL (1990) evaluated clinical signs of neurotoxicity and histopathology of brain tissue in rats exposed to cis-1,2-dichlorethene by gavage for 14 (0, 97, 290, 970, and 1,900 mg/kg/day) or 90 (0, 32, 290, and 870 mg/kg/day) days. In the 14-day study, signs of nervous system depression (lethargy and ataxia) were observed in the "high dose groups" in exposed rats. However, incidence data were not reported; therefore, NOAEL and LOAEL values could not be identified. No histopathological effects in brain tissue were observed. In rats exposed by inhalation for 90 days concentrations up to 870 ppm, no clinical signs of neurotoxicity or histopathological effects in nervous system tissues were observed (EPA/AMRL 1990; McCauley et al. 1995).

Mixed Isomers or Isomeric Composition Not Reported. Clinical signs of neurotoxicity were observed in a series of acute-duration inhalation studies of a mixture of trans- and cis-1,2-dichloroethene; the percentage of each isomer in the mixture was not reported (Dow Chemical Company 1960). Clinical signs included tremors, prone position, and/or unconsciousness, and were observed at the following exposures: 16,810 ppm for 7 hours; 29,035 ppm for 0.2, 0.5, and 1.5 hours; and 50,123 ppm for 0.1 and 0.2 hours.

Behavioral changes have been observed in mice exposed by inhalation for 4 hours to an unspecified form of 1,2-dichloroethene (De Ceaurriz et al. 1983). The reported changes consisted of a dose-related decrease in the duration of immobility in the "behavioral despair" swimming test. A 45% decrease in the total duration of immobility occurred at a concentration of 1,720 ppm. The toxicological significance of changes in the duration of swimming immobility is not known. Frantik et al. (1994) studied effects of inhalation exposure to 1,2-dichloroethene on the propagation and maintenance of the electrically evoked seizure discharge in rats and mice. The isomeric composition of 1,2-dichloroethene was not reported. The concentration of 1,2-dichloroethene evoking a 30% depression in the duration of hindlimb tonic extension in rats was 1,810 ppm and velocity of tonic extension in mice was 3,400 ppm.

2.16 REPRODUCTIVE

No studies evaluating reproductive effects of inhalation, oral, or dermal exposure of humans to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located.

trans-1,2-Dichloroethene. No effects on reproductive function or tissues have been found following intermediate-duration oral exposure to trans-1,2-dichloroethene. Following inhalation exposure of pregnant rats to trans-1,2-dichloroethene on GDs 7–15 (Hurtt et al. 1993), the total number of early resorptions per litter significantly increased from 0.3 in controls to 0.8 in the 6,000-ppm group and 1.1 in the 12,000-ppm group; the number of resorptions per litter in the 2,000-ppm group was 0.6 and was not statistically significantly different from controls. The study authors did not consider the increase in resorptions to be biologically significant because resorption rate in controls was below historical controls from the previous 2 years (0.6–1.5/litter), and the resorption rates in treatment groups were within historical controls for control animals. However, given the dose-dependent increase, resorptions appear to be treatment-related. No histopathological changes to male or female reproductive organs were observed in rats exposed by inhalation to 4,000 ppm for 90 days (DuPont 1998). No effects on sperm counts, sperm motility, vaginal cytology, or estrous stages or cycle length were observed in male and female rats and mice a 14-week dietary study (NTP 2002). In addition, no histopathological changes were observed in male and female reproductive tissues. The maximum doses tested were 3,210 and 3,245 mg/kg/day in male and female rats, respectively, and 8,065 and 7,925 mg/kg/day in male and female mice, respectively (NTP 2002). No treatment-related histopathological lesions in the reproductive organs were seen in male and female rats exposed to 3,114 and 2,809 mg/kg/day, respectively, of trans-1,2-dichloroethene in drinking water for 90 days (Hayes et al. 1987).

cis-1,2-Dichloroethene. No studies evaluating reproductive effects of inhalation exposure to cis-1,2-dichloroethene were identified. No treatment-related histopathological lesions in male and female reproductive organs were observed in rats administered cis-1,2-dichloroethene by gavage at maximum doses of 1,900 mg/kg/day for 14 days or 870 mg/kg/day for 90 days (EPA/AMRL 1990; McCauley et al. 1995).

Mixed Isomers or Isomeric Composition Not Reported. No studies examining reproductive effects of inhalation, oral, or dermal exposure of animals to mixed cis- and trans-1,2-dichloroethene were identified.

2.17 DEVELOPMENTAL

trans-1,2-Dichloroethene. No association between exposure to trans-1,2-dichloroethene and birth defects (neural tube defect or oral cleft defects) in children born to mothers exposed during pregnancy to trans-1,2-dichloroethene in drinking water at Marine Corps Base Camp Lejeune in North Carolina was found (Ruckart et al. 2013). Birth defects were diagnosed before 20 years of age. The study population evaluated for neural tube defects consisted of 541 children, including 15 cases of neural tube defects. The OR was 1.1 (95% CI 0.4, 3.1; p=0.85). For oral cleft defects, the study population included 550 children, with 24 cases of oral cleft defects. The OR was 0.3 (95% CI 0.2, 1.3; p=0.19). Although Ruckart et al. (2013) stated that exposure was to trans-1,2-dichlorethene, no information was reported to confirm that the trans- form was the only isomer present in drinking water. This study also assessed childhood hematopoietic cancers; these results are described in Section 2.19 (Cancer).

Developmental effects were observed in rats following inhalation exposure of dams to trans-1,2-dichloroethene on GDs 7–15 (Hurtt et al. 1993). Mean female fetal weight was decreased by 5.9%, compared to controls, at 12,000 ppm; no effect on mean male fetal weight was observed. No external, internal, or skeletal anomalies or variations were observed.

cis-1,2-Dichloroethene. No studies examining developmental effects of inhalation, oral, or dermal exposure of humans or animals to cis-1,2-dichloroethene were identified.

Mixed Isomers or Isomeric Composition Not Reported. No studies examining reproductive effects of inhalation, oral, or dermal exposure of humans or animals to mixed cis- and trans-1,2-dichloroethene were identified.

2.18 OTHER NONCANCER

trans-1,2-Dichloroethene. Increased serum glucose levels have been observed following inhalation and oral exposure to trans-1,2-dichloroethene. DuPont (1998) observed small increases in serum glucose in male and female rats exposed to 4,000 ppm for 90 days. Serum glucose was increased by 19 and 17% in males and females, respectively, compared to controls. The study authors suggest that increased serum glucose may have been related to a stress response and did not consider the increase to be toxicologically significant. An increase in serum glucose was observed in male and female mice exposed to trans-1,2-dichloroethene in drinking water for 90 days (Barnes et al. 1985); the increases did not exhibit dose-dependence. In male mice exposed to 17, 175, and 387 mg/kg/day, glucose was increased by 27, 20, and 24%, respectively, compared to controls; in females, increases in the 23, 224, and 452 mg/kg/day groups were 28, 20, and 28%, respectively. In contrast, no effects on glucose levels were observed in male or female rats at oral doses via drinking water up to 3,114 and 2,809 mg/kg/day, respectively (Hayes et al. 1987). Given that no effects on glucose levels were observed at much higher oral doses in the study by Hayes et al. (1987), the possible relationship between exposure to trans-1,2-dichloroethene and serum glucose levels is uncertain.

cis-1,2-Dichloroethene. No studies examining effects on blood or serum glucose following inhalation, oral, or dermal exposure to cis-1,2-dichloroethene were identified.

Mixed Isomers or Isomeric Composition Not Reported. No studies examining effects on blood or serum glucose following inhalation, oral, or dermal exposure to mixed cis- and trans-1,2-dichloroethene were identified.

2.19 CANCER

No studies evaluating potential carcinogenic effects of inhalation, oral, or dermal exposure of laboratory animals to trans-1,2-dichloroethene, cis-1,2-dichloroethene, or mixtures of cis- and trans-1,2-dichloroethene were located.

trans-1,2-Dichloroethene. A case-control study evaluating children born to mothers exposed during pregnancy to trans-1,2-dichloroethene in drinking water at Marine Corps Base Camp Lejeune in North Carolina did not find associations between exposure and childhood cancer (Ruckart et al. 2013). Childhood hematopoietic cancers (leukemia and non-Hodgkin’s lymphoma) were diagnosed before

20 years of age. The study population included 539 children, with 13 cases of hematopoietic cancers diagnosed before 20 years of age. The OR for combined leukemia and non-Hodgkin's lymphoma was 1.5 (95% CI 0.5, 4.7; p=0.44). Ruckart et al. (2015) also did not find associations between exposure to trans-1,2-dichloroethene in drinking water at Camp Lejeune and male breast cancer. The study population consisted of 444 males, with 71 cases of breast cancer. Odds ratios for low cumulative exposure (>0–<472 ppb-months) and high cumulative exposure (≥472 ppb-months) were 0.67 (95% CI 0.03, 4.25) and 1.99 (95% CI 0.42, 7.47), respectively. Although Ruckart et al. (2013, 2015) stated that exposure was to trans-1,2-dichlorethene, no information was reported to confirm that the trans- form was the only isomer present in drinking water.

cis-1,2-Dichloroethene. No studies examining the carcinogenicity of inhalation, oral, or dermal exposure of humans or animals to cis-1,2-dichloroethene were identified.

Mixed Isomers or Isomeric Composition Not Reported. No association between occupational exposure to 1,2-dichlorethene and pancreatic cancer was observed in a population-based, case-control study of 63,097 cases and 252,386 controls (Kernan et al. 1999). Exposures were qualitatively stratified by intensity as low, medium, and high, but no quantitative exposure data were reported. For the high-intensity exposure group, ORs (95% CI) were 0.5 (0.5, 1.1) for black females, 0.8 (0.5, 1.2) for black males, 0.8 (0.5, 1.1) for white females, and 0.8 (0.7, 1.0) for white males.

No studies examining the carcinogenicity of inhalation, oral, or dermal exposure of animals to mixed cis- and trans-1,2-dichloroethene were identified.

Cancer Classifications. 1,2-Dichloroethene is not listed by the HHS NTP in the 15th Report on Carcinogens (NTP 2021). EPA has not classified the carcinogenicity of 1,2-dichloroethene due to inadequate information (IRIS 2010a, 2010b). IARC has not evaluated the carcinogenicity of 1,2-dichloroethene (IARC 2024).

2.20 GENOTOXICITY

Genotoxic effects of cis- and trans-1,2-dichloroethene in humans are unknown. Several studies have investigated the potential genotoxicity of trans-1,2-dichloroethene, cis-1,2-dichloroethene, and mixtures of cis- and trans-1,2-dichloroethene using *in vivo* mouse models and *in vitro* test systems (Tables 2-6 and 2-7, respectively).

Table 2-6. Genotoxicity of cis- and trans-1,2-Dichloroethene *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
trans-1,2-Dichloroethene			
Mammalian systems:			
Mouse bone marrow	Chromosomal aberrations	–	Cerna and Kypenova 1977
Mouse bone marrow	Chromosomal aberrations	–	NTP 2002
Mouse bone marrow	Sister chromatid exchange	–	NTP 2002
Peripheral blood erythrocytes (mouse)	Micronuclei frequency	–	NTP 2002
Host-mediated assays:			
Salmonella typhimurium TA1950, TA1951, TA1952 (mouse host-mediated assay)	Gene mutation	–	Cerna and Kypenova 1977
Saccharomyces cerevisiae D7 (mouse host-mediated assay)	Gene mutation	–	Cantelli-Forti and Bronzetti 1988
S. cerevisiae D7 (mouse host-mediated assay)	Gene mutation	–	Bronzetti et al. 1984
S. cerevisiae D7 (mouse host-mediated assay)	Gene conversion	–	Bronzetti et al. 1984
S. cerevisiae D7 (mouse host-mediated assay)	Gene conversion	–	Cantelli-Forti and Bronzetti 1988
cis-1,2-Dichloroethene			
Mammalian systems:			
Mouse bone marrow	Chromosomal aberrations	+	Cerna and Kypenova 1977
Mouse bone marrow	Chromosomal aberrations	–	NTP 2002
Mouse bone marrow	Sister chromatid exchange	–	NTP 2002
Host-mediated assays:			
S. typhimurium TA1950, TA1951, TA1952 (mouse host-mediated assay)	Gene mutation	+	Cerna and Kypenova 1977
S. cerevisiae D7 (mouse host-mediated assay)	Gene mutation	+	Cantelli-Forti and Bronzetti 1988
S. cerevisiae D7 (mouse host-mediated assay)	Gene mutation	+	Bronzetti et al. 1984
S. cerevisiae D7 (mouse host-mediated assay)	Gene conversion	+	Bronzetti et al. 1984
S. cerevisiae D7 (mouse host-mediated assay)	Gene conversion	–	Cantelli-Forti and Bronzetti 1988
Mixed isomers or isomeric composition not reported[a]			
Mammalian systems:			
Mouse bone	Chromosomal aberrations	–	Crebelli et al. 1999

[a]Mixture consisted of trans- and cis-1,2-dichloroethene isomers, the percentage of each isomer was not reported.

– = negative result; + = positive result

Table 2-7. Genotoxicity of cis- and trans-1,2-Dichloroethene *In Vitro*

Species (test system)	Endpoint	Results: Activation With	Results: Activation Without	Reference
trans-1,2-Dichloroethene				
Prokaryotic organisms:				
Escherichia coli K12	Gene mutation	–	–	Greim et al. 1975
E. coli K12	Gene mutation	–	–	Cantelli-Forti and Bronzetti 1988
Salmonella typhimurium TA1950, TA1951, TA1952	Gene mutation	ND	–	Cerna and Kypenova 1977
S. typhimurium TA100,TA 1535, TA1537, TA98	Gene mutation	–	–	NTP 2002
S. typhimurium TA98, TA100, TA1535, TA1537 and *E. coli WP2 uvrA*	Gene mutation	–	–	Confidential 2015c
Eukaryotic organisms:				
Fungi:				
Saccharomyces cerevisiae D7	Gene mutation	–	–	Bronzetti et al. 1984
S. cerevisiae D7	Gene mutation	–	–	Galli et al. 1982
S. cerevisiae D7	Gene conversion	–	–	Bronzetti et al. 1984
S. cerevisiae D7	Gene conversion	–	–	Galli et al. 1982
S. cerevisiae D7	Gene mutation	–	–	Koch et al. 1988
S. cerevisiae D61.M	Aneuploidy	+	+	Koch et al. 1988
Mammalian cells:				
CHL cells	Chromosomal aberrations	–	–	Sawada et al. 1987
CHO cells	Chromosomal aberrations	–	–	NTP 2002
CHL cells	Sister chromatid exchange	–	–	Sawada et al. 1987
CHO cells	Sister chromatid exchange	+/–	–	NTP 2002
CHO cells	Gene mutation	–	–	Confidential 2014
Rat hepatocytes	Unscheduled DNA synthesis	NA	–	Costa and Ivanetich 1984
cis-1,2-Dichloroethene				
Prokaryotic organisms:				
E. coli K12	Gene mutation	–	–	Greim et al. 1975
E. coli K12	Gene mutation	–	–	Cantelli-Forti and Bronzetti 1988
S. typhimurium TA1950, TA1951, TAA1952	Gene mutation	ND	–	Cerna and Kypenova 1977

Table 2-7. Genotoxicity of cis- and trans-1,2-Dichloroethene *In Vitro*

Species (test system)	Endpoint	Results: Activation With	Results: Activation Without	Reference
S. typhimurium TA97, TA98, TA100, TA1535, TA1537	Gene mutation	–	–	NTP 2002
S. typhimurium TA100, TA1535, TA97, TA 98	Gene mutation	–	–	NTP 2024
S. typhimurium TA97, TA98, TA100, TA1535, TA1537	Gene mutation	–	–	Zeiger et al. 1988
Eukaryotic organisms:				
Fungi:				
S. cerevisiae D7	Gene mutation	+	–	Bronzetti et al. 1984
S. cerevisiae D7	Gene mutation	–	–	Galli et al. 1982
S. cerevisiae D7	Gene conversion	–	–	Galli et al. 1982
Mammalian cells:				
CHL cells	Chromosomal aberrations	–	–	Sawada et al. 1987
CHO cells	Chromosomal aberrations	–	–	NTP 2002
CHL cells	Sister chromatid exchange	–	–	Sawada et al. 1987
CHO cells	Sister chromatid exchange	+/–	+	NTP 2002
Rat hepatocytes	Unscheduled DNA synthesis	NA	–	Costa and Ivanetich 1984
Mixed isomers or isomeric composition not reported[a]				
Prokaryotic organisms:				
S. typhimurium TA98, TA100, TA1535, TA1537	Gene mutation	–	–	NTP 2002
S. typhimurium TA98, TA100, TA1535, TA1537	Gene mutation	–	–	Mortelmans et al. 1986
Eukaryotic organisms				
Fungi:				
Aspergillus nidulans	Aneuploidy	ND	–	Crebelli et al. 1995
Mammalian cells:				
CHO cells	Chromosomal aberrations	–	–	NTP 2002
CHO cells	Sister chromatid exchange	+	+	NTP 2002

Table 2-7. Genotoxicity of cis- and trans-1,2-Dichloroethene *In Vitro*

Species (test system)	Endpoint	Results: Activation: With	Results: Activation: Without	Reference
Peripheral blood lymphocytes (human)	Micronuclei frequency	+	+	Tafazoli and Kirsch-Volders 1996
Peripheral blood lymphocytes (human)	DNA damage	+	+	Tafazoli and Kirsch-Volders 1996

[a]Mixture consisted of both trans- and cis-1,2-dichloroethene, the percentage of each isomer was not reported.

+ = positive result; – = negative result; +/– = equivocal result; CHL = Chinese hamster lung fibroblast; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; NA = not applicable; ND = not determined; NR = not reported

trans-1,2-Dichloroethene. trans-1,2-Dichloroethene did not produce genotoxic effects when tested *in vivo* or *in vitro*. No increases in chromosome aberrations or sister chromatid exchanges were observed in bone marrow cells of mice following an intraperitoneal (i.p.) injection of up to 2,000 mg/kg trans-1,2-dichloroethene (Cerna and Kypenova 1977; NTP 2002). Peripheral blood from mice fed up to 50,000 ppm of trans-1,2-dichloroethene for 14 weeks showed no increase in micronuclei frequency (NTP 2002). No alterations in the occurrence of gene mutations or gene conversions were observed in bacterial systems (Cantelli-Forti and Bronzetti 1988; Cerna and Kypenova 1977; Greim et al. 1975; NTP 2002; Confidential 2015c), mammalian cells (Confidential 2014), or fungi (Bronzetti et al. 1984; Galli et al. 1982; Koch et al. 1988), except for one study that reported increased aneuploidy in *Saccharomyces cerevisiae* D61.M with and without activation (Koch et al. 1988). In mammalian cells, no increases in chromosomal aberrations or sister chromatid exchanges were seen in Chinese hamster cell lines with or without activation (Sawada et al. 1987 and NTP 2002), or in unscheduled deoxyribonucleic acid (DNA) synthesis in rat hepatocytes (Costa and Ivanetich 1984).

cis-1,2-Dichloroethene. Reports on the genotoxic effects of cis-1,2-dichlorethene have been inconsistent. Repeated i.p. injections of cis-1,2-dichloroethene (1/6 LD_{50}) produced chromosomal aberrations in mouse bone marrow cells (Cerna and Kypenova 1977), whereas a single i.p. injection up to 2,000 mg/kg did not result in an increase in chromosomal aberrations or sister chromatid exchanges in mouse bone marrow (NTP 2002). cis-1,2-Dichloroethene was found to be mutagenic in the host-mediated assay using a series of *Salmonella* tester strains and *S. cerevisiae* D7 in mice (Bronzetti et al. 1984; Cantelli-Forti and Bronzetti 1988; Cerna and Kypenova 1977). Results of most *in vitro* studies show that cis-1,2-dichloro-ethene is not genotoxic. No increase in gene mutations were seen in *Escherichia coli* (Cantelli-Forti and Bronzetti 1988; Greim et al. 1975), *Salmonella* (Cerna and Kypenova 1977; NTP 2002, 2024; Zeiger et

al. 1988) or *Saccharomyces* (Galli et al. 1982) with or without activation. The one exception was the Bronzetti et al. (1984) study, which reported increased mutations in *Saccharomyces* in the presence of metabolic activators. In Chinese hamster cells, cis-1,2-dichloroethene, with or without activation, did not increase the number of chromosomal aberrations (NTP 2002; Sawada et al. 1987). Sawada et al. (1987) reported no increase in sister chromatid exchanges in Chinese hamster lung fibroblast cells in the presence or absence of activation, whereas NTP (2002) showed increased exchanges in Chinese hamster ovary cells in the absence of activation. cis-1,2-Dichloroethene did not induce unscheduled DNA synthesis in rat hepatocytes *in vitro* (Costa and Ivanetich 1984).

Mixed Isomers or Isomeric Composition Not Reported. Limited *in vivo* data are available regarding genotoxicity of mixtures of cis- and trans-1,2-dichloroethene. For all studies cited below, the mixture investigated consisted of both trans- and cis-1,2-dichloroethene; however, the percentage of each isomer was not reported. No increase in chromosomal aberrations was seen in the bone marrow of CD-1 mice following an i.p. injection of a mixture of cis- and trans-1,2-dichloroethene (Crebelli et al. 1999). Results from studies investigating genotoxic effects *in vitro* are inconsistent. Mixed isomers were shown not to be mutagenic in *Salmonella* (Mortelmans et al. 1986; NTP 2002) and did not increase aneuploidy in *Aspergillus* (Crebelli et al. 1995). However, in Chinese hamster ovary cells, an increase in sister chromatid exchanges was observed following exposure to a mixture of cis- and trans-1,2-dichloroethene, although chromosomal aberrations were not increased (NTP 2002). In isolated human peripheral blood lymphocytes, DNA damage and micronuclei frequency were increased after exposure to mixed isomers of 1,2-dichloroethene (Tafazoli and Kirsch-Volders 1996).

2.21 MECHANISM OF TOXICITY

The mechanism of toxicity of 1,2-dichloroethene has not been determined. As reviewed in Section 3.1.3 (Toxicokinetics, Metabolism), studies conducted in rats have shown that 1,2-dichloroethene can alter cytochrome P450 (CYP) levels and mixed-function oxidase activities. Inhibition of CYP2E1 activity has been attributed to formation of reactive metabolites of 1,2-dichloroethene (Lilly et al. 1998). Metabolites that could possibly contribute to health effects include epoxides, dichloroacetaldehyde, dichloroethanol, and dichloroacetic acid. The Integrated Risk Information System (IRIS 2010a, 2010b) noted that metabolites could possibly bind to cell components.