CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

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

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

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

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

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

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

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

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

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

- **Body weight:** Depressed body weight or depressed body weight gain and actual body weight loss have been reported following inhalation or oral exposure of laboratory animals.

- **Respiratory endpoints:** Upper respiratory tract toxicity is a presumed health effect for humans based on strong evidence in animals. Increased lung weight, nasal lesions (e.g., hyperostosis, chronic active inflammation, metaplasia and atrophy in olfactory epithelium, hyperplasia in respiratory epithelium, turbinate atrophy), and laryngeal lesions (respiratory epithelial necrosis, metaplasia, and hyperplasia) have been associated with repeated inhalation exposure of rats and/or mice to 1,1-dichloroethene vapor. Clara cell (club cell) damage in the lungs was observed following oral exposure to 1,1-dichloroethene.

- **Hepatic endpoints:** Liver toxicity is a presumed health effect for humans based on strong evidence in animals. 1,1-Dichloroethene-induced liver effects, evidenced by biochemical changes (e.g., increases in serum liver enzyme levels, induction of hepatic enzymes) and marked histological changes (e.g., hepatocellular swelling, degeneration and necrosis of hepatocytes), have been reported in rats and mice for both inhalation and oral exposure routes. Fasting increases the hepatotoxicity of 1,1-dichloroethene.

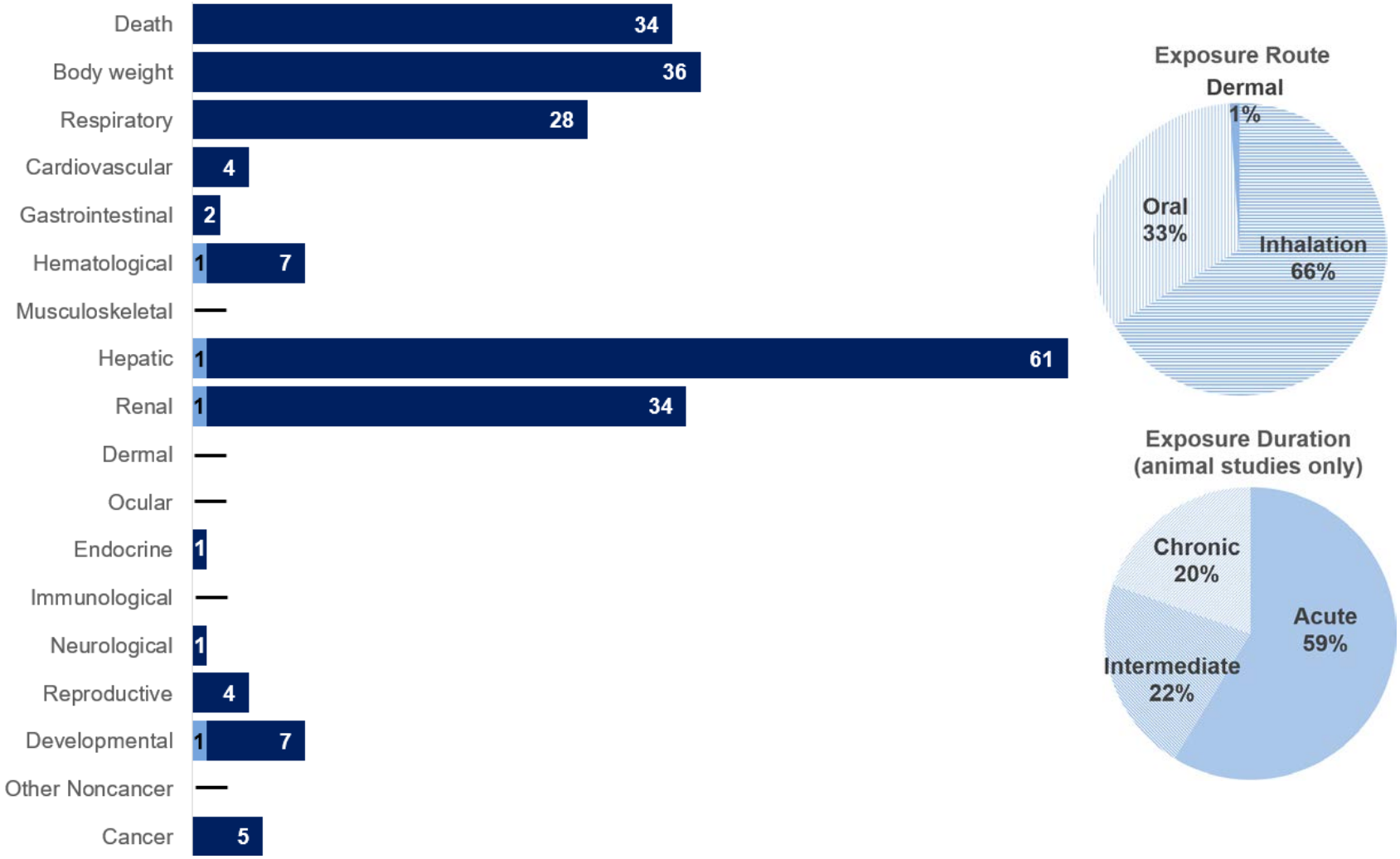
- **Renal endpoints:** Kidney toxicity is a presumed health effect for humans based on strong evidence in animals. 1,1-Dichloroethene-induced kidney effects, evidenced by increased kidney weight, enzyme changes (decreases in kidney monooxygenase and epoxide hydrolase levels), and histological changes (nephropathy and tubular swelling, degeneration, necrosis, and granular casts) were observed following repeated inhalation exposure; male mice appear to be most susceptible to 1,1-dichloroethene renal toxicity. Fasting increases renal toxicity.

- **Developmental endpoints:** Delayed ossification of selected bones was reported for fetuses from maternal mice exposed to 1,1-dichloroethene vapor during gestation.

- **Cancer:** Increased incidences of selected tumor types have been reported in some studies of rats or mice, most of which employed the inhalation exposure route. EPA (2002) considered available animal data to provide "*suggestive evidence* of carcinogenicity but not sufficient evidence to assess human carcinogenic potential following inhalation exposure" and "*inadequate* for an assessment of human carcinogenic potential by the oral route." IARC recently assigned 1,1-dichloroethene to Group 2B, based on "sufficient evidence of carcinogenicity in experimental animals" and no data or "inadequate evidence" in humans (Grosse et al. 2017).

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

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



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

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

Figure Key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
ACUTE EXPOSURE									
1	Rat (CD) 19–24 F	GDs 8–20 22–23 hours/day	0, 56, 283	BH, BW, FX, LE, MX	Bd wt			56	Maternal body weight loss
EPA 1977a									
2	Rat (CD) 18–58 F	GDs 6–16 22–23 hours/day	0, 15, 57, 300, 449	BW, DX, FI, MX	Death			15	2/18 maternal rats died
					Bd wt			15	Maternal body weight loss
EPA 1977a									
3	Rat (Sprague-Dawley) 4–22 M	Once 4 hours	0, 200, 250, 300, 375, 400	BC, BW, HP, LE, OW	Renal		250		At 250 ppm, swelling in renal cortex of fasted male rats At 300 ppm, cortical tubular necrosis of fasted male rats
Jackson and Conolly 1985									
4	Rat (Sprague-Dawley) 2–24 M	Once 4 hours	0, 250	BI	Hepatic		250		Decreased mitochondrial GSH
Jaeger 1977									
5	Rat (Holtzman) 5 M	Once 4 hours	0, 2,000	BI, CS, LE	Death			2,000	Death of 2/5 rats exposed during period of low GSH activity
					Hepatic		2,000		Increased serum alanine α-ketoglutarate transaminase activity
Jaeger et al. 1973a									
6	Rat (Holtzman) 5-6 M	Once 4 hours	Up to 20,000	EA, LE	Death			600	Fasted male rat LC_{50}
					Hepatic	100	150		Increased serum alanine α-ketoglutarate transaminase activity in fasted rats
Jaeger et al. 1974									

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Figure Key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
7	Rat (Holtzman) 5–6 M	Once 4 hours	Up to 20,000	EA, LE	Death			15,000	Nonfasted male rat LC_{50}
					Hepatic		2,000		Increased serum alanine α-ketoglutarate transaminase activity in nonfasted rats
Jaeger et al. 1974									
8	Rat (Sprague-Dawley) 4 M	Once 6 hours	10, 200	BM, EX, HP, TM, UM	Hepatic			200	Centrilobular degeneration and necrosis in fasted rats; no effect in nonfasted rats
					Renal			200	Hemoglobinuria; tubular degeneration in fasted rats; no effect in nonfasted rats
McKenna et al. 1978a									
9	Rat (Sprague-Dawley) 30 F treated 21 F control	GDs 6–15 7 hours/day	0 or 80	BW, CS, DX, FI, MX, OW, WI	Bd wt	80			
					Hepatic	80			
					Develop		80		Increased incidence of wavy ribs and delayed ossification of the skull
Murray et al. 1979									
10	Rat (Sprague-Dawley) 30 F treated 18 F control	GDs 6–15 7 hours/day	0 or 160	BW, CS, DX, FI, MX, OW, WI	Bd wt	160			
					Hepatic	160			
					Develop		160		Wavy ribs and delayed ossification of skull and cervical vertebrae
Murray et al. 1979									
11	Rat (Sprague-Dawley) 44 F treated 47 F control	GDs 6–15 7 hours/day	0 or 20	BW, CS, DX, FI, MX, OW, WI	Bd wt	20			
					Develop	20			
Murray et al. 1979									
12	Rat (CD) 5 or 10 M	1–3 days 22–23 hours/day	0, 60	BW, EA, HP, LE, OF	Hepatic		60		Mild to moderate centrilobular degeneration and/or necrosis, mild bile duct hyperplasia
					Renal	60			
Short et al. 1977a, 1977b									

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

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

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

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

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

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

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

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

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Figure Key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
38	Rat (Sprague-Dawley) 60–158 per sex	15 weeks 5 days/week, 4 hours/day (7 weeks) 7 hours/day (8 weeks)	0, 100	BW, CS, GN, HP, LE	Bd wt	100			
					Resp	100			
					Hepatic	100			
					Renal	100			
Maltoni et al. 1985									
39	Rat (F344/N) 5 M, 5 F	16 days 5 days/week 6 hours/day (+12 minutes)	0, 25, 50, 100, 200, 400	BW, CS, HP, LE, OW	Death			200	100% mortality by day 4
					Bd wt	100 M 50 F	100 F		15% depressed mean body weight gain in females
					Hepatic		25		Centrilobular cytoplasmic alterations in hepatocytes
					Renal		25		12–20% lower mean relative kidney weight
NTP 2015a									
40	Rat (F344/N) 10 M, 10 F	14 weeks 5 days/week 6 hours/day (+10 minutes)	0, 6.25, 12.5, 25, 50, 100	BC, BW, CS, HE, HP, LE, OF, OW	Bd wt	100			
					Resp		6.25[b,c]		Olfactory epithelium mineralization in males and females, olfactory epithelium atrophy in males ($BMCL_{10}$ = 1.59 ppm)
					Hepatic	6.25 M 25 F	12.5 M 50 F		Males: hepatic centrilobular cytoplasmic alterations Females: cytoplasmic vacuolization in hepatocytes
					Renal	100			
					Repro	50 M 100 F	100 M		5% decreased sperm motility, 15–16% decreased spermatid count
NTP 2015a									
41	Rat (black-hooded Wistar) 4 M	4 weeks continuous	0, 50	HP	Hepatic		50		Fatty changes and focal necrosis
Plummer et al. 1990									

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

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

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

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

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

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

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

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

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

Figure Key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
60	Hamster (Chinese) 30 M, 30 F (exposed) 17 M, 18 F (control)	52 weeks 4–5 days/week 4 hours/day	0, 25	BW, CS, GN, HP, LE	Bd wt	25			
					Resp	25			
					Hepatic	25			
					Renal	25			
Maltoni et al. 1985									

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[b]Used to derive an intermediate-duration inhalation minimal risk level (MRL) of 0.001 ppm for 1,1-dichloroethene; based on results from benchmark dose analysis ($BMCL_{10}$ of 1.59 ppm), adjustment for intermittent exposure, conversion to a human equivalent concentration ($BMCL_{HEC}$) of 0.036 ppm , and an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability); see Appendix A for more detailed information regarding the MRL.
[c]The intermediate-duration inhalation MRL of 0.001 ppm was adopted as the chronic-duration inhalation MRL; see Appendix A for more detailed information regarding the MRL.

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

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

Acute (≤14 days)

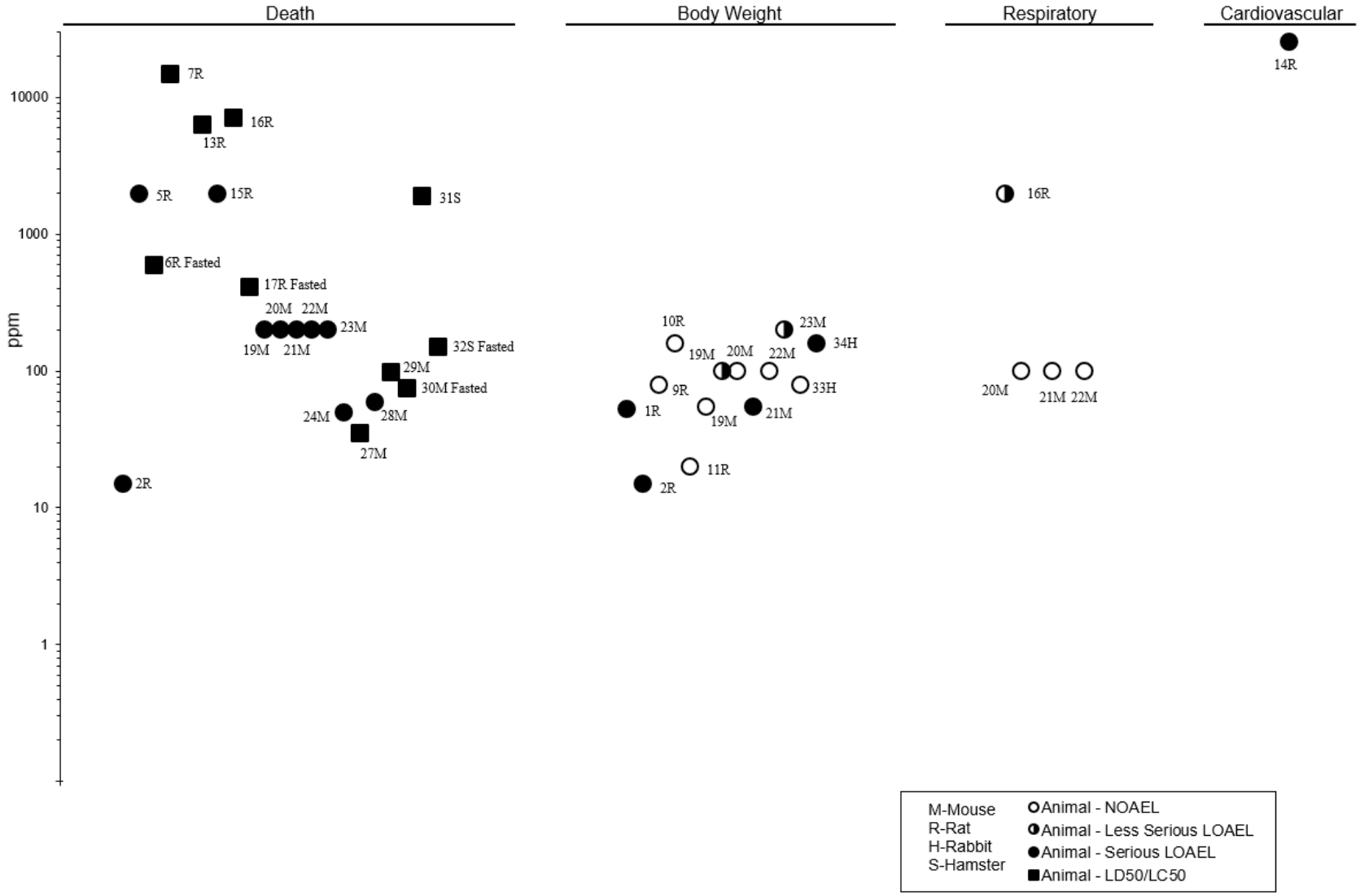


Figure 2-2. Levels of Significant Exposure to 1,1-Dichloroethene – Inhalation

Acute (≤14 days)

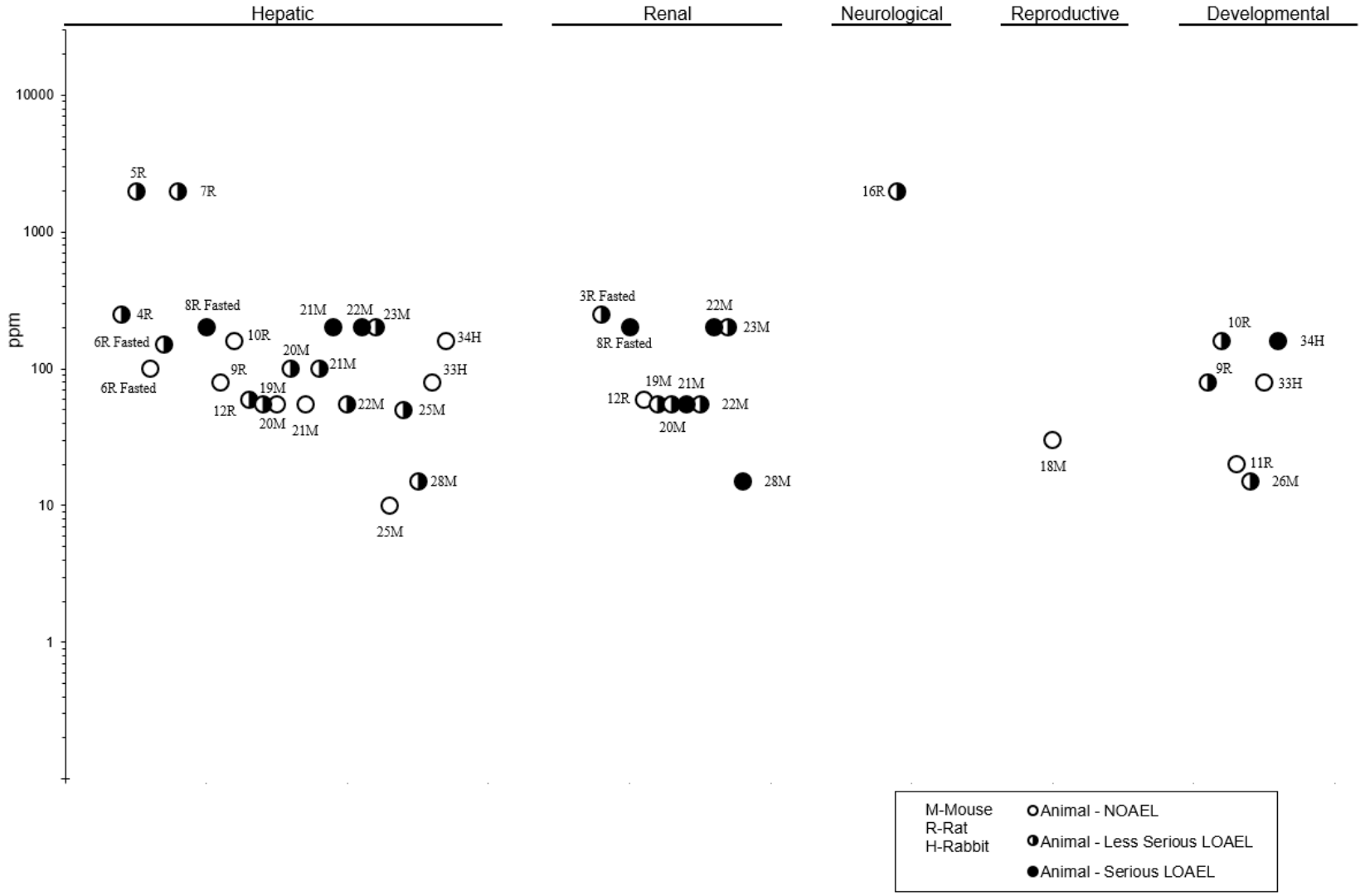


Figure 2-2. Levels of Significant Exposure to 1,1-Dichloroethene – Inhalation

Intermediate (15-364 days)

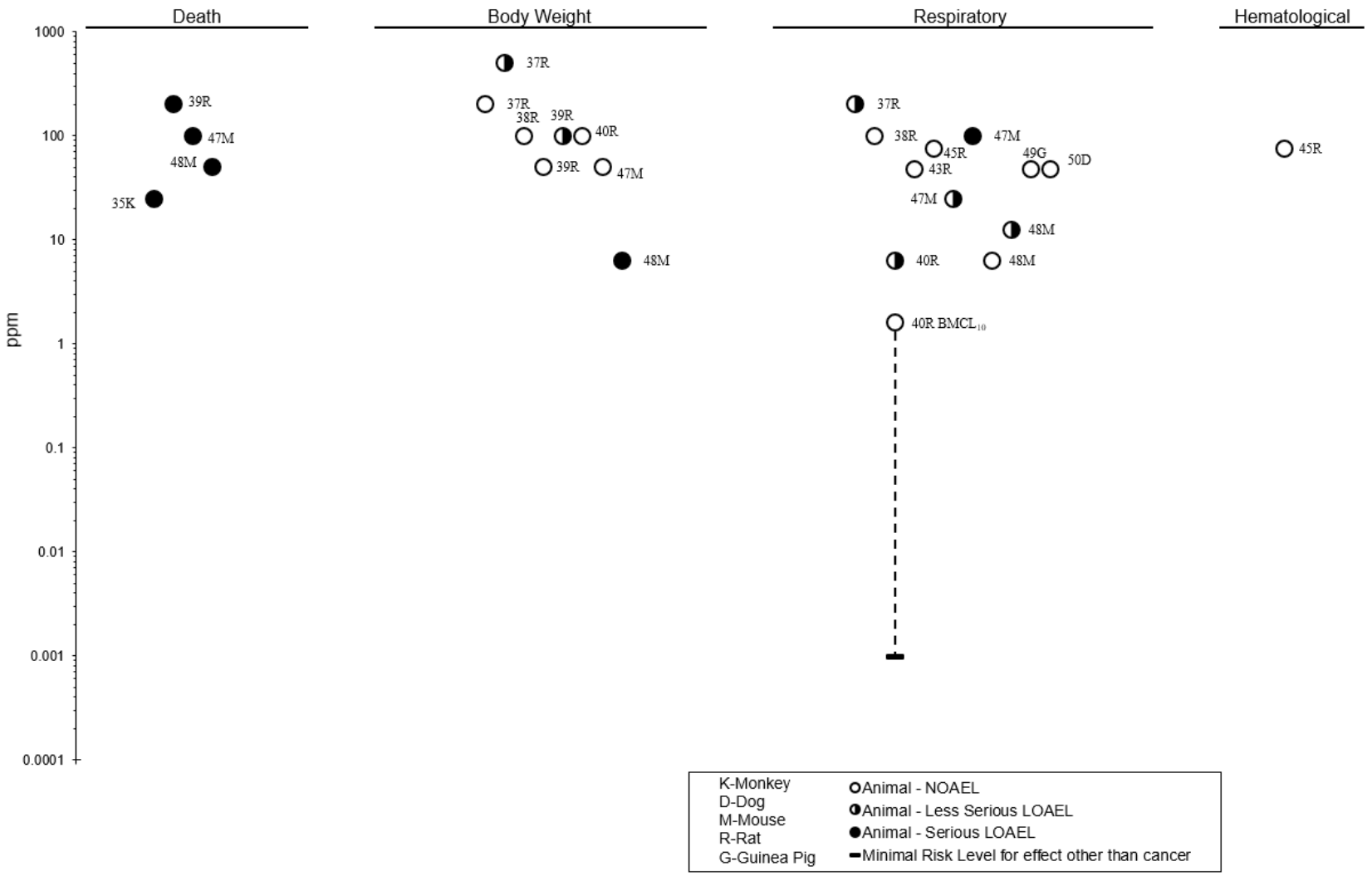


Figure 2-2. Levels of Significant Exposure to 1,1-Dichloroethene – Inhalation

Intermediate (15-364 days)

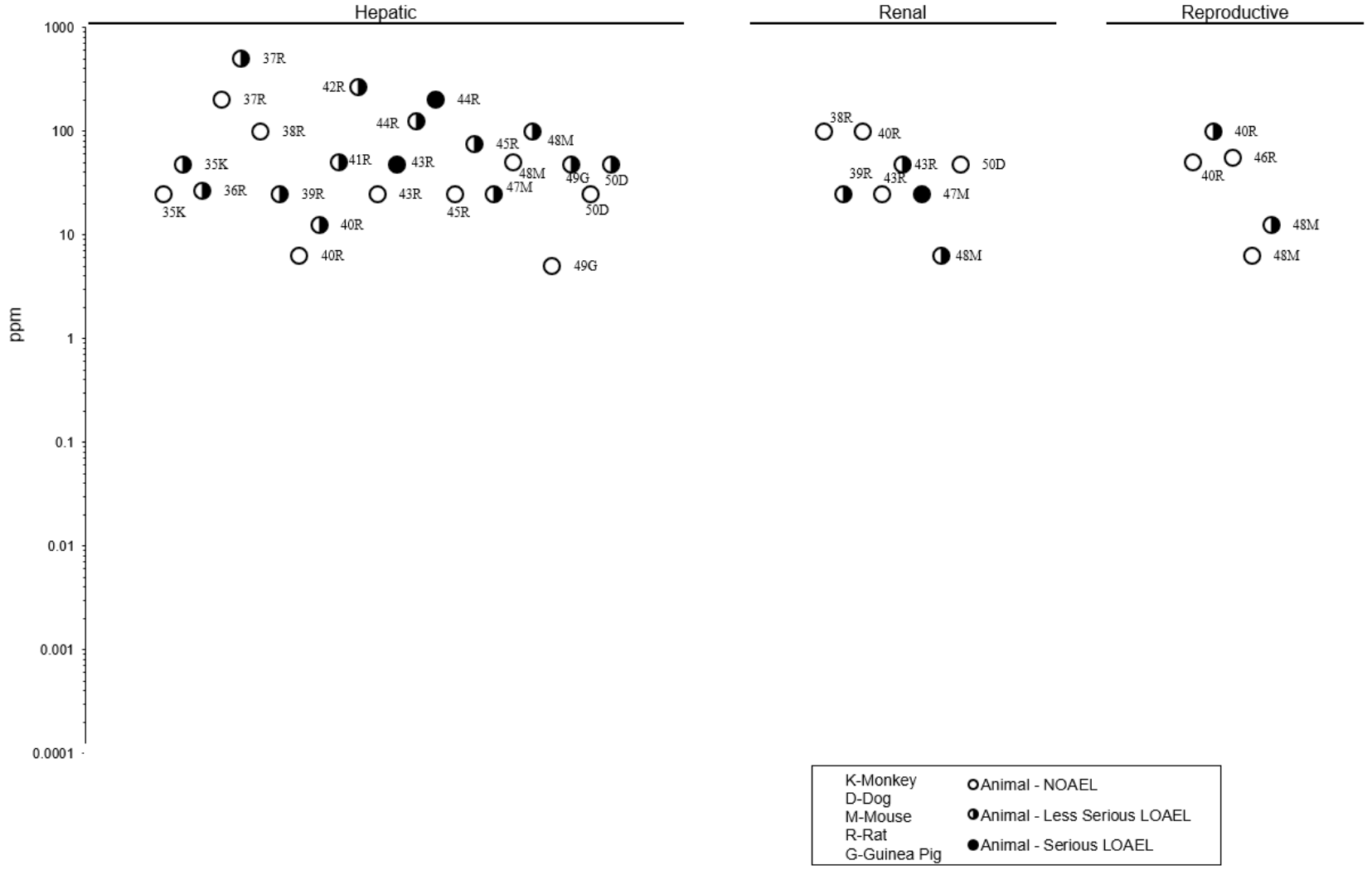


Figure 2-2. Levels of Significant Exposure to 1,1-Dichloroethene – Inhalation

Chronic (≥365 days)

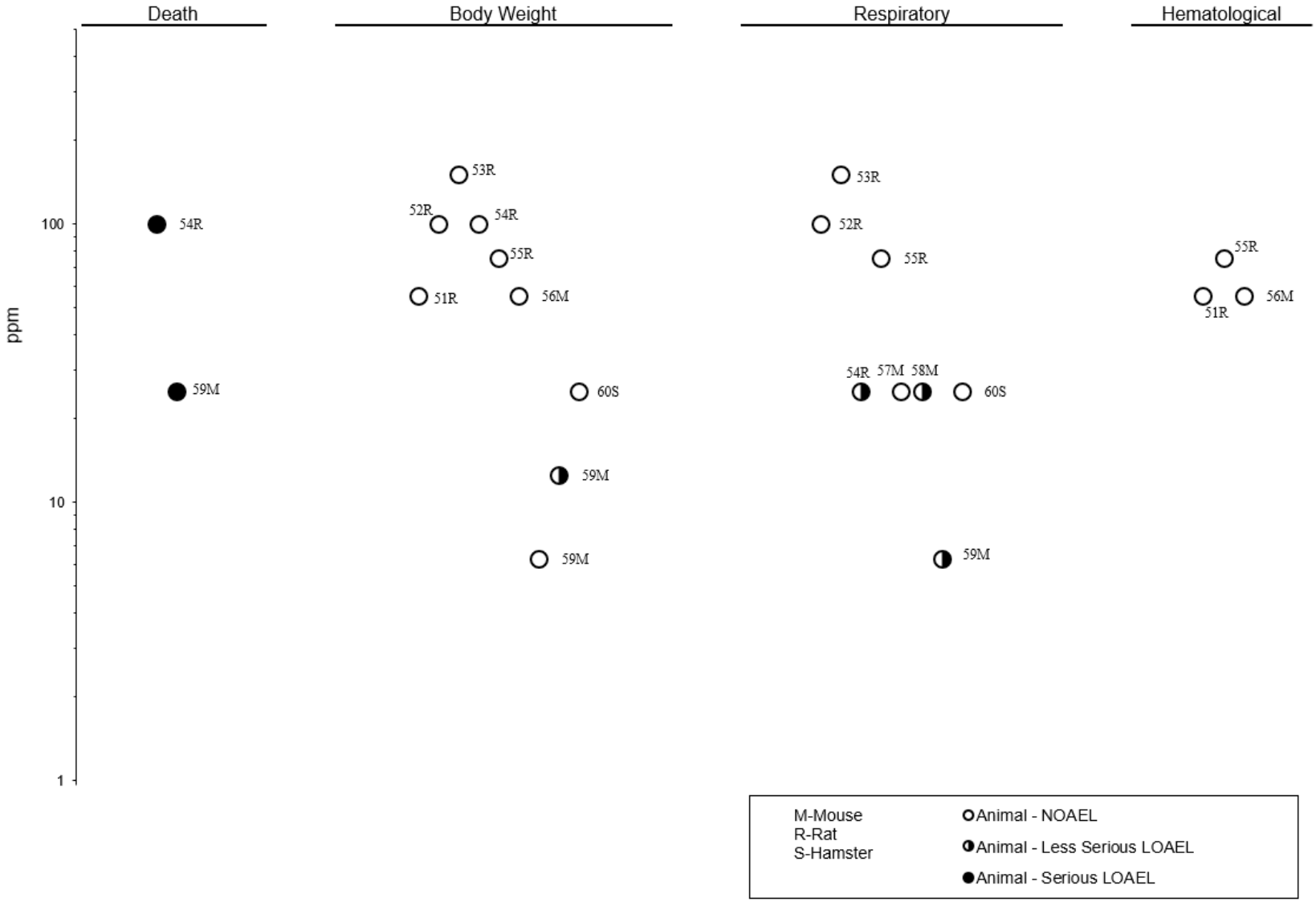


Figure 2-2. Levels of Significant Exposure to 1,1-Dichloroethene – Inhalation

Chronic (≥365 days)

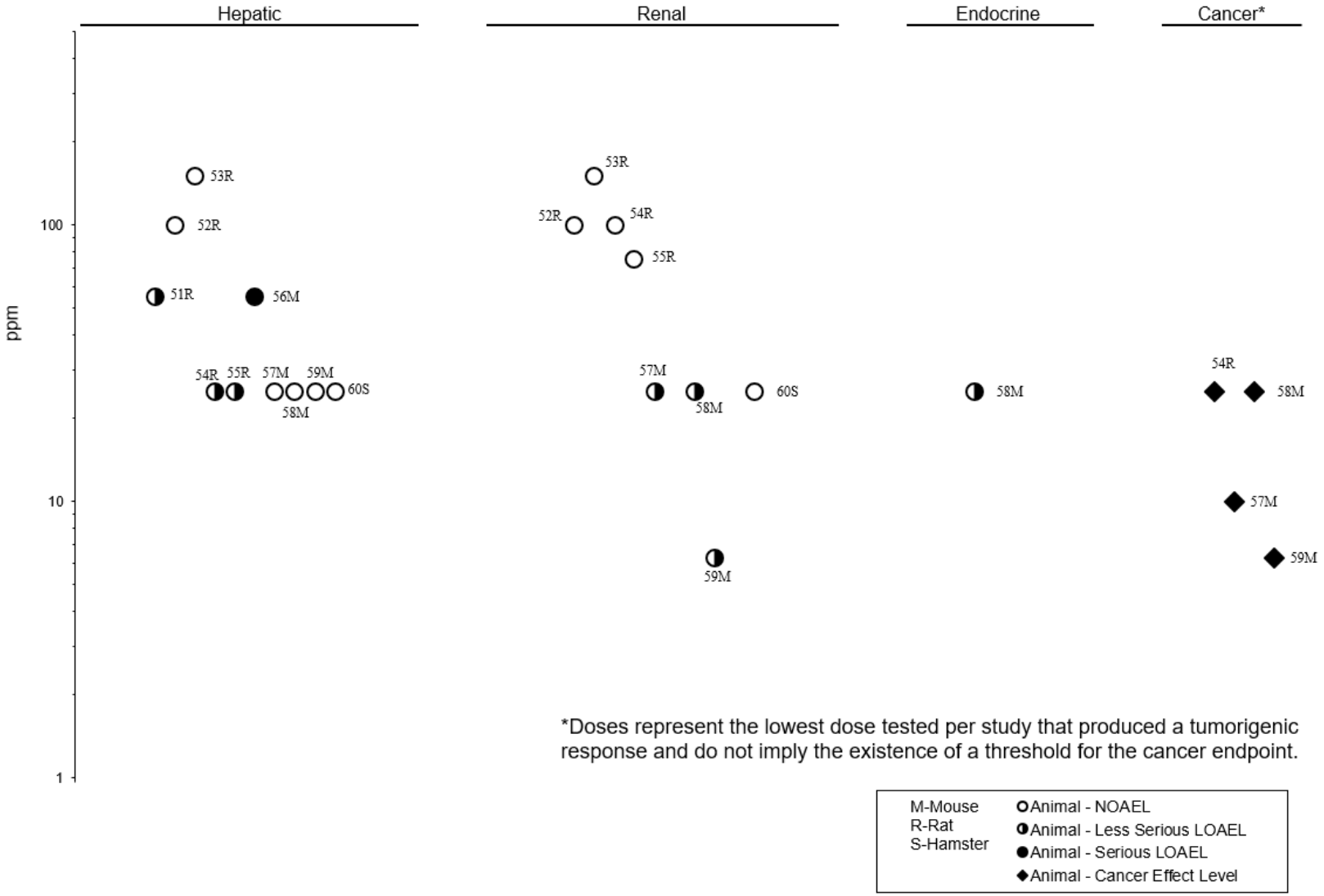


Table 2-2. Levels of Significant Exposure to 1,1-Dichloroethene – Oral

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

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

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

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

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

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
16	Mouse (C57BL/6) 5 or 7 M	Once (GO)	0, 100, 200	HP, OF	Resp		100		Reversible cellular changes in Clara cells (club cells) of bronchiolar epithelium
Forkert and Reynolds 1982									
17	Mouse (C57BL/6) 6 M	Once (GO)	0, 200	BW, HP, OW	Bd wt			200	26% depressed mean body weight at 5 days posttreatment
					Resp		200		Reversible damage and disruption of Clara cells (club cells); increased lung weight
Forkert et al. 1985									
18	Mouse (Alderley Park) 6 M, 6 F	Once (GO)	5 unspecified dose levels	LE	Death			217 M 194 F	LD_{50}
Jones and Hathway 1978a									
19	Mouse (B6C3F1) 5 M, 5 F	Once (GO)	0, 10, 50, 100, 500, 1,000	LE	Death			500	5/5 males died; 3/5 females died
NTP 1982									
20	Mouse (B6C3F1) 5 M, 5 F	14 days 1 time/day (GO)	0, 5, 10, 50, 100, 500	BW, CS, GN	Death			500	100% mortality
					Hepatic			500	Liver necrosis
NTP 1982									
INTERMEDIATE EXPOSURE									
21	Rat (Sprague-Dawley) NS F	61–82 days (premating or premating + gestation) (W)	0, 0.02, 18	BW, CS, FX, HP, MX	Bd wt	18			
Dawson et al. 1993									

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

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

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
26	Rat (Sprague-Dawley) 50 M, 50 F (treated) 100 M, 100 F (control)	52 weeks 4–5 days/week 1 time/day (GO)	0, 5, 10, 20	BW, CS, GN, HP, LE	Bd wt	20			
					Resp	20			
					Hepatic	20			
					Renal	20			
Maltoni et al. 1985									
27	Rat (F344) 50 M, 50 F	104 weeks 5 days/week 1 time/day (GO)	0, 1, 5	BW, CS, GN, HP	Bd wt	5			
					Resp	5			
					Cardio	5			
					Gastro	5			
					Hepatic	5			
					Renal	5			
NTP 1982									
28	Rat (Sprague-Dawley) 48 M, 48 F (treated) 80 M, 80 F (control)	2 years *ad libitum* (W)	M: 0, 7, 10, 20; F: 0, 9, 14, 30	BC, BW, CS, FI, OW	Hemato	20 M 30 F			
					Hepatic	10 M	20 M 9[b] F		Hepatocellular swelling with midzonal fatty changes in males and females ($BMDL_{10}$ = 4.51 mg/kg/day)
					Renal	20 M 30 F			
Quast et al. 1983									

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

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

NTP 1982

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[b]Used to derive a chronic-duration oral minimal risk level (MRL) of 0.05 mg/kg/day for 1,1-dichloroethene; based on a $BMDL_{10}$ of 4.51 mg/kg/day for hepatic midzonal fatty change and an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability); see Appendix A for more detailed information regarding the MRL.

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

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

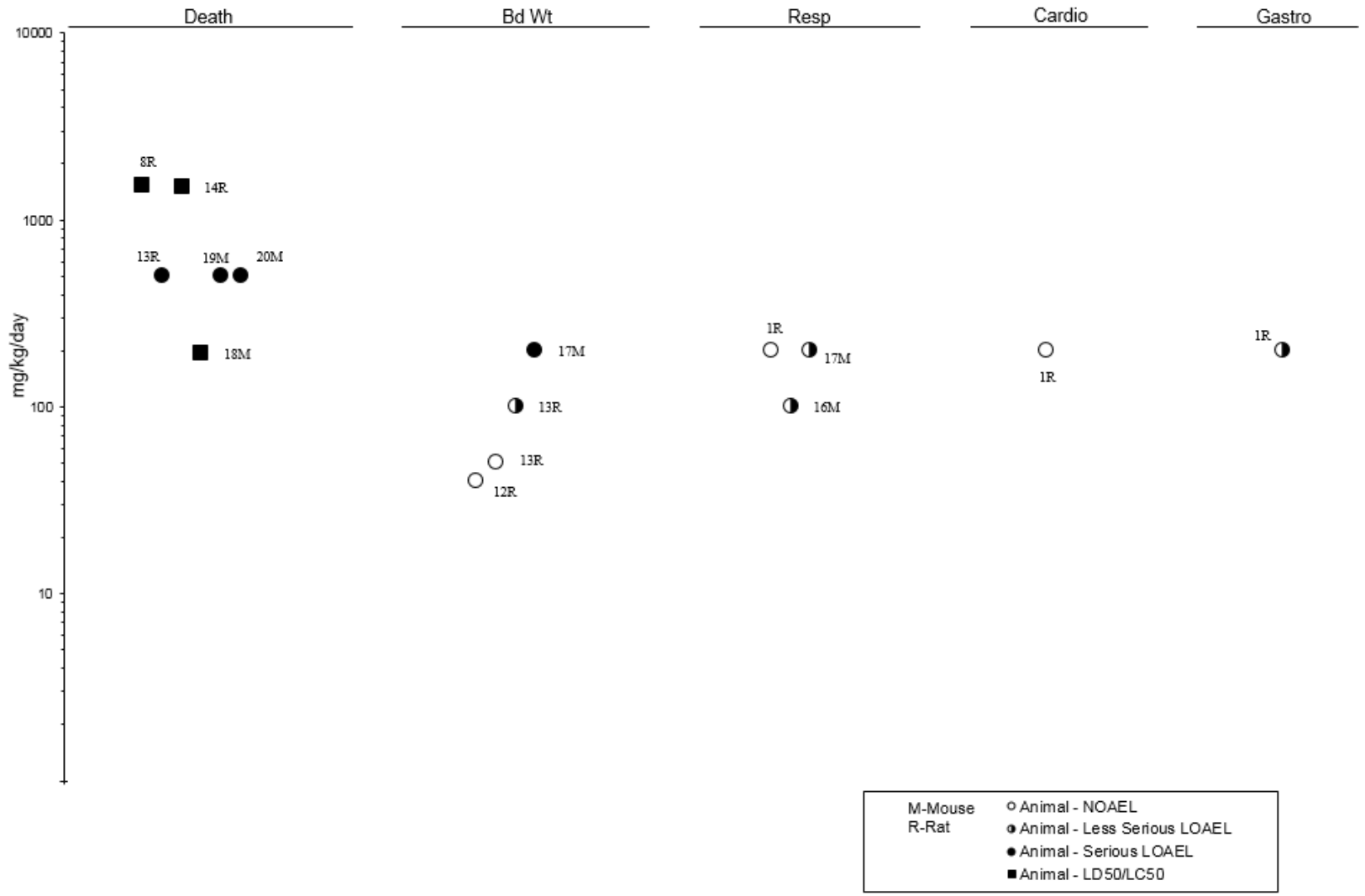


Figure 2-3. Levels of Significant Exposure to 1,1-Dichloroethene – Oral
Acute (≤14 days)

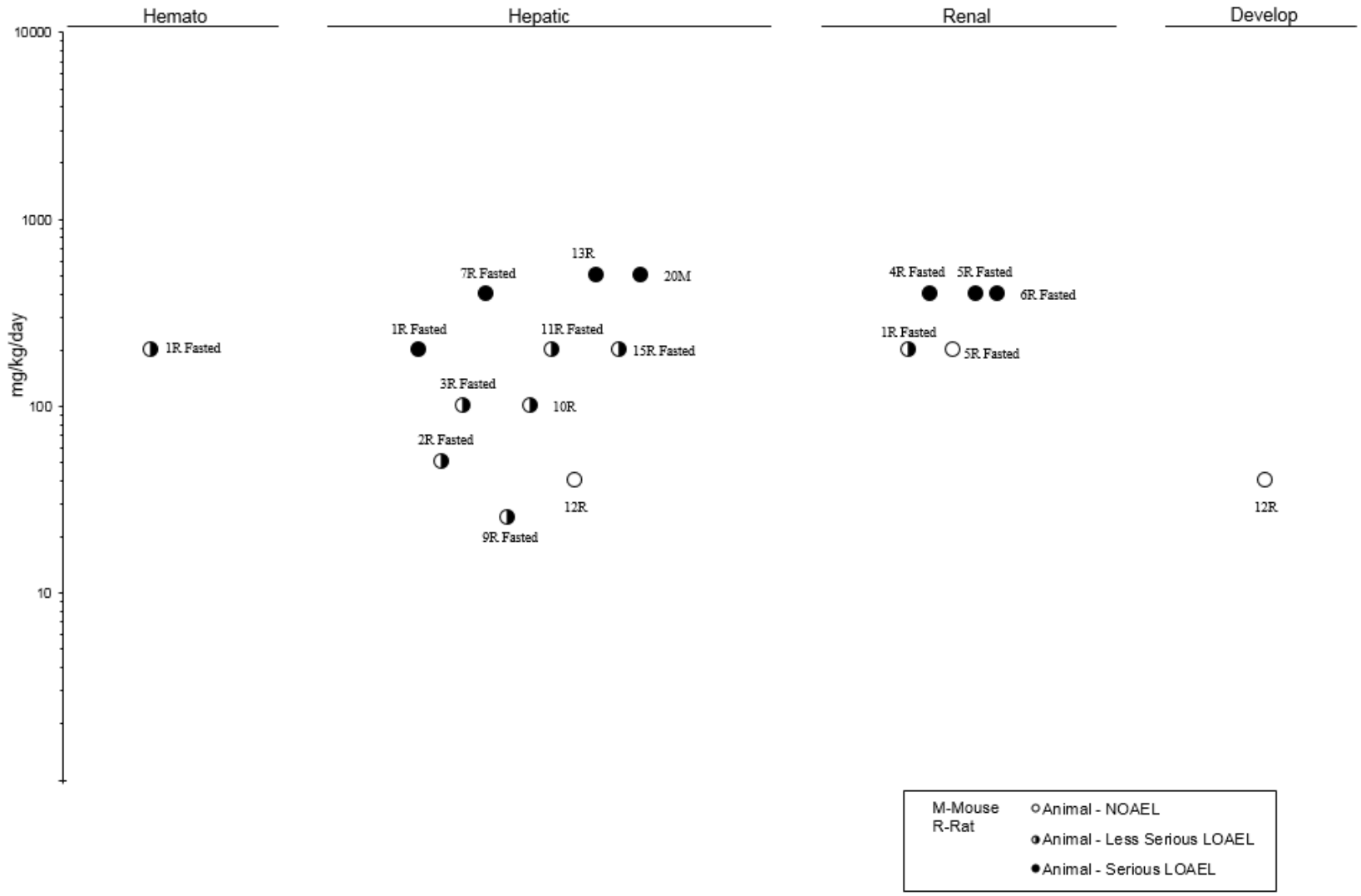


Figure 2-3. Levels of Significant Exposure to 1,1-Dichloroethene – Oral
Intermediate (15-364 days)

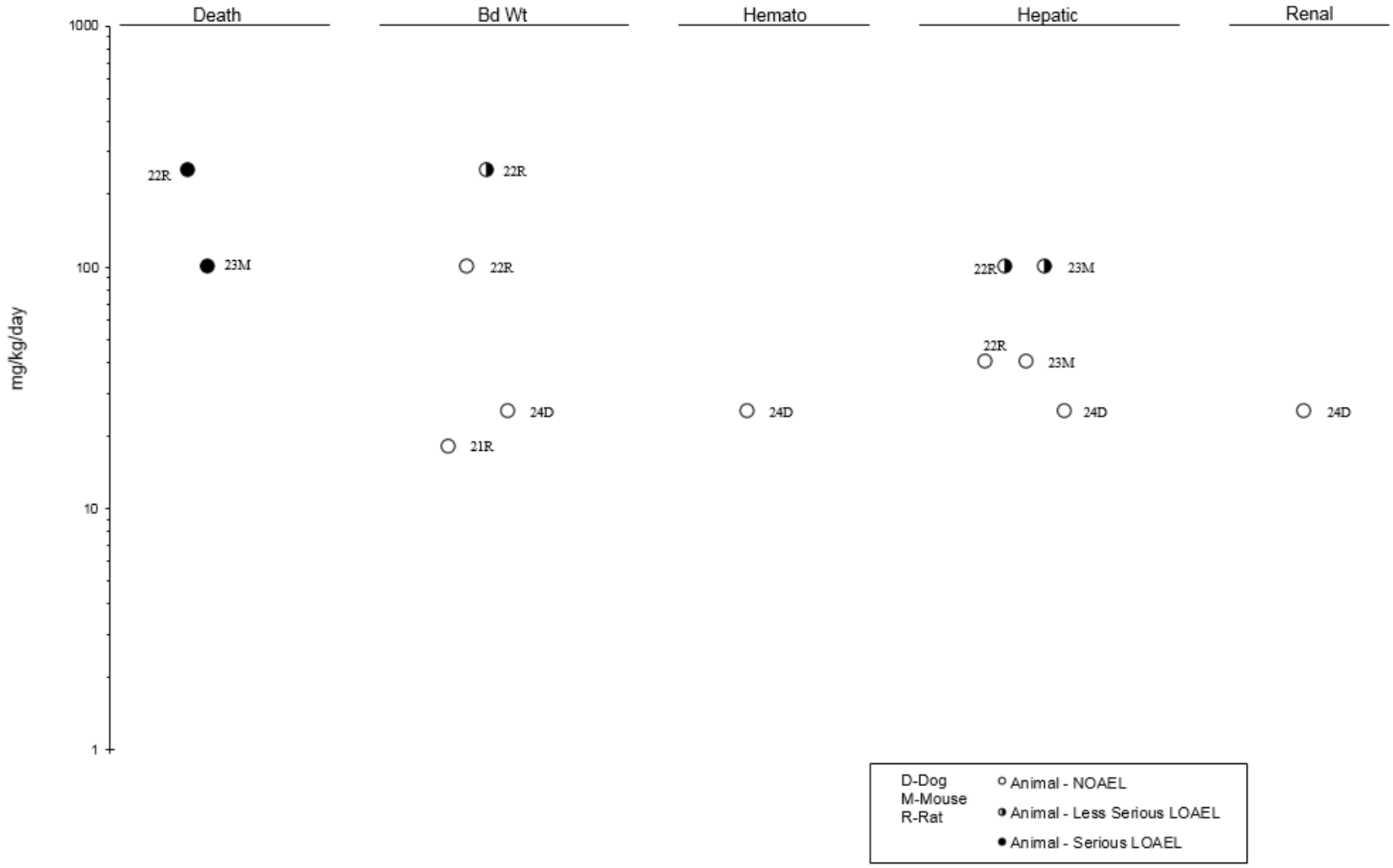
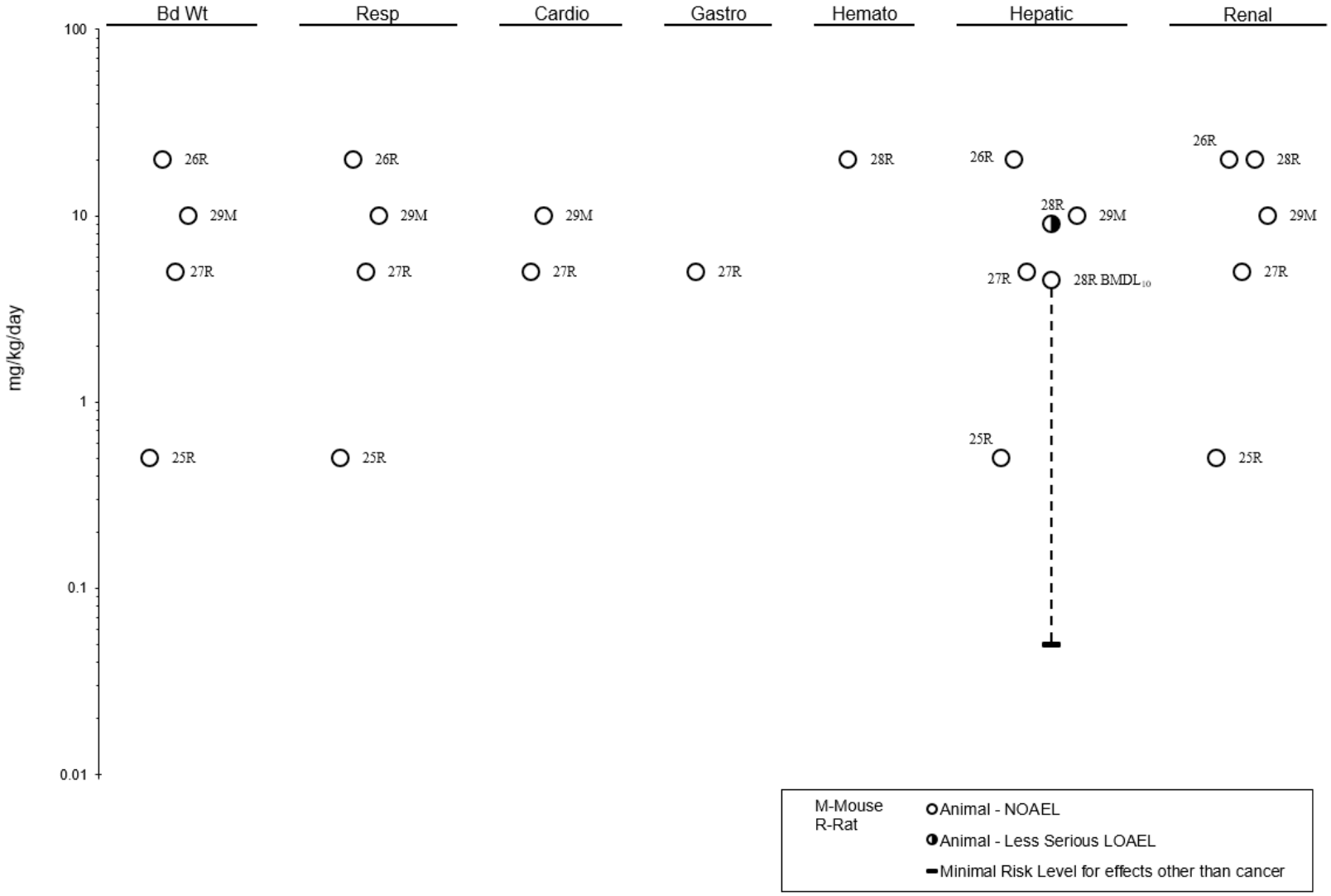


Figure 2-3. Levels of Significant Exposure to 1,1-Dichloroethene – Oral

Chronic (≥365 days)



2.2 DEATH

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

The lethality of 1,1-dichloroethene in animals following inhalation exposure varies considerably and is influenced by such factors as species, strain, sex, and food intake. LC_{50} values for laboratory animals acutely exposed to 1,1-dichloroethene vapor are presented in Table 2-3. Fasted laboratory animals were much more susceptible to the lethal effects of inhaled 1,1-dichloroethene than animals maintained on normal diet, mice were more susceptible than rats, and males were more susceptible than females. Single 4-hour exposure of Sprague-Dawley rats maintained on normal diet resulted in LC_{50} values of 7,145 ppm for males and 10,275 ppm for females (Zeller et al. 1979a); among similarly-exposed Sprague-Dawley rats fasted for 16 hours prior to exposure, 4-hour LC_{50} values were 415 ppm for males and 6,545 ppm for females. Jaeger et al. (1974) reported respective LC_{50} values of 15,000 and 600 ppm for nonfasted and fasted male Holtzman rats exposed to 1,1-dichloroethene vapor for 4 hours. Similar exposures of fed and fasted Chinese hamsters resulted in 4-hour LC_{50} values of 1,915 and 2,945 ppm for fed males and females, respectively, and 150 ppm and 455 ppm for fasted males and females, respectively (Klimisch and Freisberg 1979a, 1979b). Although the effects of fasting on the acute lethality of inhaled 1,1-dichloroethene among fed and fasted mice have not been compared in a single strain, available results indicate that mice are markedly more sensitive than rats. For example, 4-hour LC_{50} values of 98 and 105 ppm were calculated for fed male and female CD-1 mice (Short et al. 1977a, 1977b). Fasting of mice does not appear to significantly affect acute lethality, as indicated by 4-hour LC_{50} values of 75 and 125 ppm for fasted NMRI male and female mice, respectively (Zeller et al. 1979c). The proposed mechanism by which fasting increases the toxicity of 1,1-dichloroethene is discussed in Section 2.21.

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

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

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

[a]Deaths occurred in rats exposed during a period of low glutathione (GSH) activity.
[b]No deaths in female mice similarly exposed for 3 or 8 days.
[c]No deaths in similarly-exposed female Swiss, Balb/c, or C57Bl mice.

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

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

Reported single-dose oral LD_{50} values were 1,800 and 1,500 mg/kg in male and female rats, respectively (Ponomarkov and Tomatis 1980), and 217 and 194 mg/kg in male and female mice, respectively (Jones and Hathaway 1978a). In repeated-dose studies of rats and mice, high rates of mortality were observed at doses ≥500 mg/kg/day (rats) and ≥250 mg/kg/day (mice) (NTP 1982).

2.3 BODY WEIGHT

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

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

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

2.4 RESPIRATORY

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

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

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

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

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

2.5 CARDIOVASCULAR

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

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

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

2.6 GASTROINTESTINAL

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

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

2.7 HEMATOLOGICAL

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

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

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

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

2.8 MUSCULOSKELETAL

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

2.9 HEPATIC

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

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

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

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

Hepatotoxicity was reported in rats and mice repeatedly exposed to 1,1-dichloroethene vapor. In a series of studies (NTP 2015a), centrilobular cytoplasmic alterations in hepatocytes were observed in rats exposed for 16 days at the lowest exposure level tested (25 ppm). Similar exposure of mice at 25 ppm resulted in 10–14% increased liver weight; centrilobular necrosis was noted at 100 ppm. In 14-week repeated-exposure studies, hepatic cytoplasmic alterations were observed in male and female rats at exposure levels as low as 12.5 and 50 ppm, respectively (NOAELs of 6.25 and 25 ppm, respectively). At 50 and 100 ppm, all male and female rats exhibited hepatic cytoplasmic alterations. Similar exposures of mice resulted in hepatocellular hypertrophy and necrosis in females at 100 ppm (highest exposure level tested; NOAEL of 50 ppm) and a NOAEL of 50 ppm for males (highest exposure level tested). The male rats appeared to be more susceptible than the female rats to 1,1-dichloroethene hepatotoxicity, and the rats appeared to be more susceptible than the mice. In the chronic-duration (104-week) studies, the lowest exposure level tested in rats (25 ppm) resulted in chronic inflammation and diffuse fatty changes in the liver; exposure levels ≥50 ppm resulted in hepatic necrosis and/or cystic degeneration in males and females. There were no signs of exposure-related hepatic effects in mice similarly exposed at up to 25 ppm (the highest exposure level tested). Differences in the ranges of exposure levels (25–100 ppm for rats and 6.25–25 ppm for mice) preclude drawing conclusions regarding the relative susceptibility of the rats and mice to 1,1-dichloroethene hepatotoxicity under the conditions of the chronic studies. 1,1-Dichloroethene exposure-related hepatic effects such as cytoplasmic alterations, fatty changes, and/or focal necrosis were reported in other intermediate- and chronic-duration inhalation studies of laboratory animals exposed at 25–75 ppm (Balmer et al. 1976; Lee et al. 1977, 1978; Plummer et al. 1990; Prendergast et al. 1967; Quast et al. 1986).

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

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

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

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

2.10 RENAL

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

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

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

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

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

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

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

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

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

2.11 DERMAL

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

2.12 OCULAR

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

2.13 ENDOCRINE

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

2.14 IMMUNOLOGICAL

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

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

2.15 NEUROLOGICAL

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

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

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

2.16 REPRODUCTIVE

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

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

2.17 DEVELOPMENTAL

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

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

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

In a series of studies that employed gestational exposure of laboratory animals to 1,1-dichloroethene vapor for up to 23 hours/day (EPA 1977a, Short et al. 1977c), most developmental effects (skeletal anomalies, soft tissue anomalies, decreased pup weight, fetal resorptions) occurred at exposure levels that induced maternal toxicity (e.g., decreased maternal body weight, death). However, increased incidences of unossified incus and incompletely ossified sternebrae were observed in fetuses from maternal mice exposed to 1,1-dichloroethene vapor at 15 ppm (an exposure level not resulting in maternal toxicity) for up to 23 hours/day (EPA 1977a). No evidence of exposure-related developmental neurotoxicity was observed among surviving pups subjected to a battery of behavioral tasks when tested at various lactational days (postnatal days 1–21) following gestational exposure via their mothers exposed to 1,1-dichloroethene vapor at concentrations as high as 283 ppm during gestation (Short 1977a).

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

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

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

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

2.18 OTHER NONCANCER

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

2.19 CANCER

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

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

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

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

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

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

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

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

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

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

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

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

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

2.20 GENOTOXICITY

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

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

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

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

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

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

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

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

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

1,1-Dichloroethene has also been tested in several *in vivo* studies in animals; results are summarized in Table 2-5. In general, 1,1-dichloroethene did not demonstrate genotoxicity in mammalian studies *in vivo*. 1,1-Dichloroethene did not induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* exposed by feeding or injection (Foureman et al. 1994; also reported in NTP 2015a). 1,1-Dichloroethene did not induce chromosomal aberrations in rats intermittently exposed by inhalation at up to 75 ppm for up to 2 years (Rampy et al. 1977). 1,1-Dichloroethene did not induce micronuclei in bone marrow of mice following gavage administration or in fetal liver or blood following intraperitoneal administration to pregnant mice (Sawada et al. 1987). 1,1-Dichloroethene inhalation was associated with low rates of DNA alkylation in the livers and kidneys of mice and rats (Reitz et al. 1980). DNA repair mechanisms were induced in the kidney cells of mice in which normal replicative DNA synthesis had

been inhibited, but apparently not in mouse liver nor kidneys or liver of rats (Reitz et al. 1980). Negative results were reported in assays for dominant lethal mutations in mice (Andersen et al. 1977) and rats (Short et al. 1977c). In a mouse host-mediated assay system, 1,1-dichloroethene induced gene mutation and gene conversion in yeast (Bronzetti et al. 1981).

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

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

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

2.21 MECHANISMS OF ACTION

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

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

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

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

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

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

Possible mechanisms responsible for increased susceptibility to 1,1-dichloroethene toxicity in fasted animals have been studied. Jaeger et al. (1973a) demonstrated that fasted rats exhibited depleted hepatic GSH and increased susceptibility to 1,1-dichloroethene hepatotoxicity. Hepatic GSH levels diminished during the inactive/sleep cycle (lack of food intake), making them more susceptible to 1,1-dichloroethene hepatotoxicity. GSH acts by detoxifying electrophilic 1,1-dichloroethene metabolites. Bruckner et al. (2002) evaluated the diurnal rhythm in rats and its relationship to metabolism of the chlorinated hydrocarbon, carbon tetrachloride, and found that lack of food intake during the inactive/sleep cycle not only depressed GSH levels, but also resulted in CYP2E1 induction. Depletion of GSH in concert with CYP2E1 induction significantly increased metabolic activation and suppressed its inactivation.