CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

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

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

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

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to 1,2-dichloropropane, 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 1,2-dichloropropane 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, animal oral studies are presented in Table 2-2 and Figure 2-3, and animal dermal studies are presented in Table 2-3. Summaries of human observational cancer studies are presented in Table 2-4 in Section 2.19 (Cancer).

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

dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of 1,2-dichloropropane are indicated in Tables 2-1 and 2-2 and Figures 2-2 and 2-3.

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

The health effects of 1,2-dichloropropane have been evaluated in a limited number of epidemiology studies and several animal studies. As illustrated in Figure 2-1, the most widely examined endpoints were hepatic, renal, hematological, and body weight effects. Most available health effects data come from oral and inhalation exposure studies in animals. Animal data are available for each health effect category and exposure duration category. The small number of available observational epidemiology studies were predominantly focused on cancer, with one case-control study evaluating potential associations with atopic dermatitis. Additional information comes from several case reports of acute oral or inhalation poisoning.

The human and animal studies suggest several sensitive targets of 1,2-dichloropropane toxicity:

- **Respiratory Endpoints.** Respiratory effects are a presumed health effect for humans based on limited evidence of respiratory tract irritation in humans and strong evidence of nasal lesions in laboratory animals following acute-, intermediate-, and chronic-duration inhalation exposure. Acute exposures resulted in degeneration of the olfactory mucosa and inflammatory and exudative changes in rats, with mice and rabbits showing nasal mucosal degeneration to a lesser degree. Nasal lesions observed after intermediate-duration exposure included inflammation and hyperplasia of the respiratory epithelium, degeneration and atrophy of the olfactory epithelium, and submucosal inflammation in rats; metaplasia, atrophy, necrosis, and desquamation of the respiratory epithelium in mice; and slight degeneration of the olfactory epithelium in rabbits. Following chronic-duration exposure, nasal lesions observed in rats and mice included inflammation and metaplasia of the respiratory epithelium, hyperplasia of the transitional

epithelium, atrophy of the olfactory epithelium, and squamous cell hyperplasia of the submucosal glands.

- **Hematological Endpoints.** Hematological effects are a presumed health effect for humans based on limited evidence in humans and strong evidence of hemolytic anemia in laboratory animals following inhalation and oral exposure. Human findings include case reports of hemolytic anemia and disseminated intravascular coagulation following acute inhalation, oral, or dermal exposure. Hemolytic anemia in animals was characterized by increased serum bilirubin levels, bone marrow congestion, hemosiderosis in the spleen, and/or increased hematopoiesis in the spleen and bone marrow following acute- or intermediate-duration inhalation and oral exposures. However, only mild anemia was observed following chronic-duration inhalation exposure. Hematological blood parameters were not assessed following chronic-duration oral exposure.

- **Hepatic Endpoints.** Hepatic effects are a presumed health effect for humans based on limited evidence in humans and strong evidence from inhalation and oral studies in animals. Numerous human cases studies report hepatic effects, including altered serum liver enzymes, impaired liver function, toxic hepatitis, hepatic necrosis, and liver failure, following acute inhalation, oral, or dermal exposure to high exposure levels of 1,2-dichloropropane. Hepatic lesions, primarily fatty degeneration and necrosis, were consistently observed in inhalation and oral studies in laboratory animals.

- **Neurological Endpoints.** CNS depression is a presumed health effect for humans based on limited evidence in humans, limited evidence in laboratory animals following acute inhalation exposure, and strong evidence in laboratory animals following acute oral exposure.

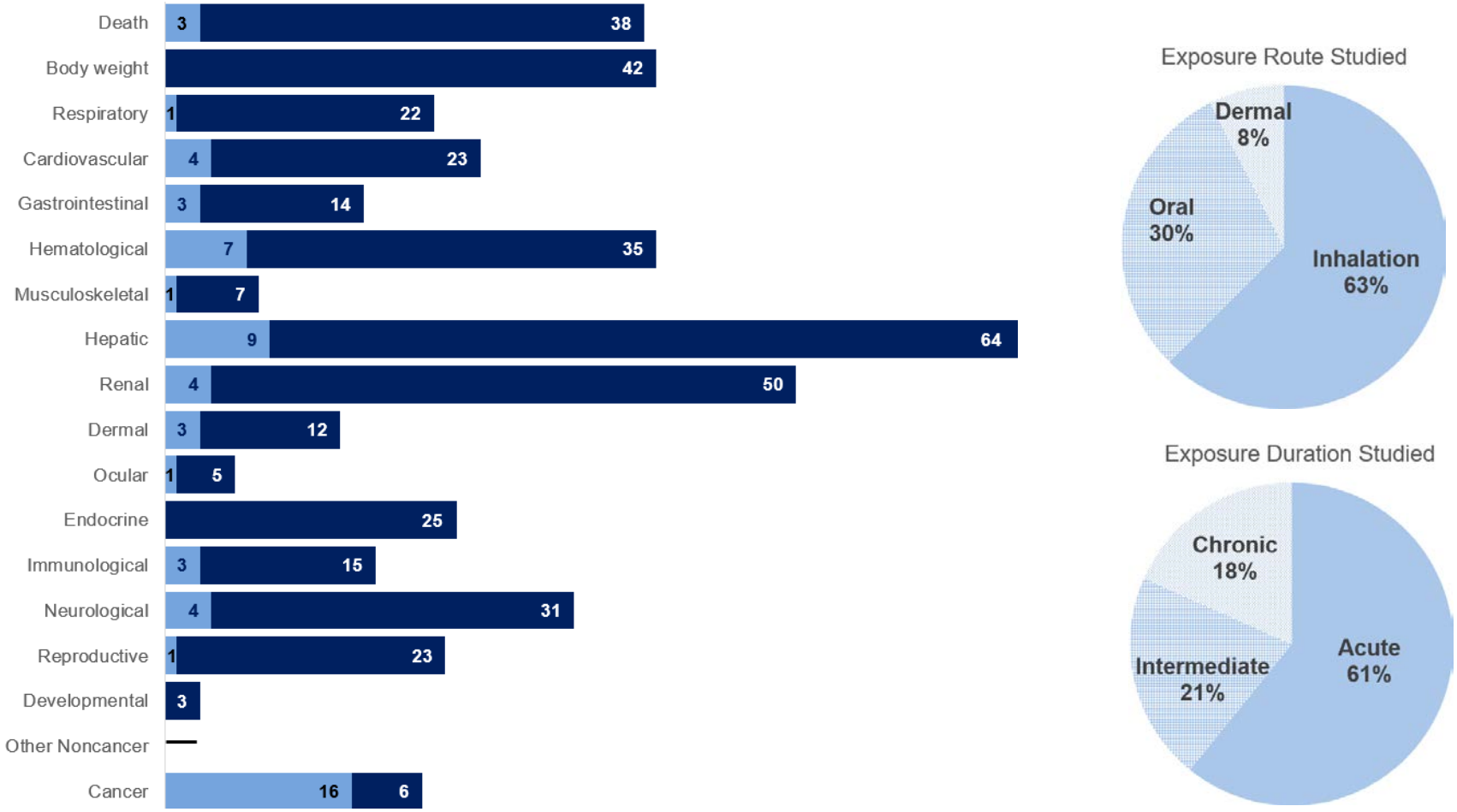
- **Developmental Endpoints.** Developmental toxicity is a presumed effect for humans based on high evidence of developmental effects (delayed skeletal development, decreased neonatal weight and survival) in laboratory animals at high oral doses. Maternal toxicity (decreased maternal body weight, maternal CNS depression) was observed at similar doses.

- **Renal Endpoints.** Available data are inadequate to determine if renal effects will occur in humans following exposure to 1,2-dichloropropane. A few human case reports indicate renal failure following oral or inhalation exposure to high levels of 1,2-dichloropropane. In laboratory animals, there is inconsistent evidence for renal lesions following inhalation exposure and no evidence of renal toxicity following oral exposure.

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

Hepatic, renal, hematological, and body weight effects of 1,2-dichloropropane were the most widely examined potential toxicity outcomes

More studies evaluated health effects in **animals** than **humans** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 113 studies (including those finding no effect) have examined toxicity; most animal studies examined multiple endpoints.

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
ACUTE EXPOSURE									
1	Rat (Sherman) 6 NS	4 hours (WB)	2,000	LE	Death			2,000	2–4/6 died (exact number not reported)
Carpenter et al. 1949									
2	Rat (NS) 12 B	7 hours (WB)	1,600	CS, LE	Death			1,600	3/12 died
					Neuro		1,600		Mild incoordination
Heppel et al. 1946a									
3	Rat (NS) 13–20 B	5–8 days 7 hours/day (WB)	1,600, 2,200	CS, LE	Death			2,200	8/20 died
					Bd wt		1,600		Body weight loss
					Resp		2,200		Lung congestion
					Cardio	2,200			
					Hepatic		2,200		Fatty degeneration, centrilobular congestion, necrosis
					Endocr		2,200		Lipoid depletion in adrenal cortex
					Neuro		1,600	2,200	Mild incoordination at 1,600 ppm, with gross incoordination and prostration at 2,200 ppm
Heppel et al. 1946b [Histology assessed at 2,200 ppm only]									
4	Rat (NS) 3–8 NS	3–12 days 7 hours/day (WB)	0, 400	LE, HP	Cardio	400			
					Hepatic	400			
					Renal	400			
Heppel et al. 1948									
5	Rat (Sprague-Dawley) 33 NS; 3 controls	7 hours (WB)	0, 2,200	GN, HP, CS	Death			2,200	2/33 died
					Hepatic		2,200		Fatty degeneration, centrilobular necrosis
					Renal		2,200		Fatty degeneration
					Endocr		2,200		Depletion of the lipoid material of the adrenal cortex
Highman and Heppel 1946									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
6	Rat (Sprague-Dawley) 36 NS, 6 controls	1–5 days 7 hours/day (WB)	0, 2,200	GN, HP, CS	Death			2,200	9/36 died
					Hepatic		2,200		Fatty degeneration, centrilobular necrosis
					Renal		2,200		Fatty degeneration
					Endocr		2,200		Depletion of the lipoid material of the adrenal cortex
Highman and Heppel 1946									
7	Rat (NS) NS	4 hours (NS)	2,000	LE	Death			2,000	Approximate lethal concentration (ALC)
Kennedy and Graepel 1991									
8	Rat (Fischer-344) 5 M	6 hours (WB)	0, 500, 1,500	CS, HP	Hepatic	1,500			
					Renal	1,500			
					Neuro	500		1,500	Anesthesia
Nitschke and Johnson 1983									
9	Rat (Fischer-344) 5 M, 5 F	2 weeks 4–5 days/week 6 hours/day (WB)	0, 100, 300, 1,000	BC, BI, BW, CS, GN, HE, HP, OW, UR	Resp		100[b]		Olfactory mucosal degeneration
					Hemato	1,000			
					Hepatic	300	1,000		Increased liver weight, hepatocellular hypertrophy in females
					Renal	1,000			
					Endocr	1,000			No histopathological lesions in adrenal glands
					Repro	1,000 M			No histopathological lesions in testes
Nitschke and Johnson 1983									
10	Rat (NS) 6 NS	8 hours (NS)	2,000	LE	Death			2,000	LC_{50}
Smyth et al. 1969									

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Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
11	Rat (Fischer-344) 3 NS	7 days 8 hours/day (WB)	0, 300, 1,000, 3,000	BI, LE, HP	Hepatic	1,000	3,000		Fat-droplets
Zhang et al. 2015									
12	Mouse	10 hours (NS)	300, 380, 390, 700, 715, 1,625	BC, CS	Death			480	LC_{50}
Dow Chemical Co. 1968									
13	Mouse (NS) 10–26 B	2–7 hours (WB)	1,000, 1,500, 2,200	CS, LE, HP	Death			1,000	100% mortality
					Hepatic		1,000		Fatty degeneration and centrilobular vacuolation and congestion at ≥1,000 ppm, necrosis at 2,200 ppm
					Renal		1,000		Fatty degeneration
					Neuro			2,200	Gross motor incoordination followed by prostration (effects at 1,000 ppm not reported)
Heppel et al. 1946a									
14	Mouse (C57BL/6N) 5–18 (NS)	1–12 days 7 hours/day (WB)	0, 400	LE, HP	Death			400	8/18 died after one exposure
					Hepatic		400		Slight fatty degeneration
Heppel et al. 1948									
15	Mouse (B6C3F1) 5 M	6 hours (WB)	0, 500, 1,500	CS, LE, HP	Death			500	2/5 died at 500 ppm; 5/5 died at 1,500 ppm
					Bd wt	500			
					Hepatic			500	Hemorrhagic necrosis
					Renal	1500			
					Neuro			500	Lethargy at 500 ppm, anesthesia at 1,500 ppm
Nitschke and Johnson 1983									

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Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
16	Mouse (B6C3F1) 5 M, 5 F	2 weeks 4–5 days/week 6 hours/day (WB)	0, 30, 100, 300	BC, BW, CS, GN, HE, HP, OW	Bd wt	300			
					Resp	100	300		Olfactory mucosal degeneration
					Hemato	300			
					Hepatic	100	300		Increased liver weight, hepatocellular hypertrophy, vacuolization
					Renal	300			
					Endocr	300			No histological changes in adrenal glands
					Immuno	100	300		Decreased thymus weight, decreased lymphoid cells
					Repro	300 M			No histological changes in testes
Nitschke and Johnson 1983									
17	Mouse (C57BL/6J) NS M	2 days 3–6 hours/day (WB)	0, 100, 200, 400	BC, OW	Hepatic	400			
Toyooka et al. 2017									
18	Mouse (B6C3F1) 5–6 M	1–4 hours (WB)	0, 300	BW, BC, OW, HP	Bd wt	300			
					Hepatic	300			
Wang et al. 2019									
19	Mouse (B6C3F1) 5–6 M	6 hours (WB)	0, 300	BW, BC, OW, HP	Bd wt	300			
					Hepatic		300		9–12% increase in liver weight; increased ALT and AST; hepatocellular hypertrophy, necrosis, and granular degeneration
Wang et al. 2019									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
20	Mouse (BALB/cA) 3 NS	7 days 8 hours/day (WB)	0, 300, 1,000, 3,000	BI, LE, HP	Death			1,000	100% mortality
					Hepatic		300		Vacuolization
Zhang et al. 2015									
21	Mouse (C57BL/6J) 3 NS	7 days 8 hours/day (WB)	0, 300, 1,000, 3,000	BI, LE, HP	Death			1,000	100% mortality
					Hepatic		300		Vacuolization
Zhang et al. 2015									
22	Mouse (BALB/cA) 8 NS	14 days 6 hours/day (WB)	0, 200, 400, 800	BI, BW, LE, OW, HP	Death			400	100% mortality
					Hepatic		200		Vacuolization
Zhang et al. 2015									
23	Guinea pig (NS) 10–16 B	5 days 7 hours/day (WB)	1,600, 2,200	CS, HP, LE	Death			2,200	11/16 died
					Bd wt		1,600		Body weight loss
					Resp		2,200		Lung congestion
					Cardio	2,200			
					Hepatic		2,200		Fatty degeneration, centrilobular congestion, necrosis
					Renal		2,200		Fatty degeneration
					Ocular	1,600	2,200		Conjunctivitis
					Endocr		2,200		Adrenal necrosis
					Neuro	1,600	2,200		Listlessness
Heppel et al. 1946a [Histology assessed at 2,200 ppm only]									
24	Guinea pig (NS) 4 NS	1–4 days 7 hours/day (WB)	0, 400	LE, HP	Cardio	400			
					Hepatic	400			
					Renal	400			
Heppel et al. 1948									

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Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
25	Guinea pig (NS) 33 NS; 3 controls	7 hours (WB)	0, 2,200	GN, HP, CS	Hepatic		2,200		Fatty degeneration, centrilobular swelling
					Renal		2,200		Fatty degeneration
					Endocr		2,200		Adrenal necrosis
Highman and Heppel 1946									
26	Guinea pig (NS) 30 NS; 6 controls	2–3 days 4 or 7 hours/day (WB)	0, 2,200	GN, HP, CS	Death			2,200	7/30 died
Highman and Heppel 1946									
27	Guinea pig (NS) 3 NS	7 days 8 hours/day (WB)	0, 300, 1,000, 3,000	BI, LE, HP	Death			3,000	100% mortality
					Hepatic	1,000			
Zhang et al. 2015									
28	Hamster (Golden Syrian) 3 NS	7 days 8 hours/day (WB)	0, 300, 1,000, 3,000	BI, LE, HP	Death			1,000	100% mortality
					Hepatic	300			
Zhang et al. 2015									
29	Hamster (Golden Syrian) 8 NS	14 days 6 hours/day (WB)	0, 200, 400, 800	BI, BW, LE, OW, HP	Death			800	100% mortality
					Hepatic	200	400		Slight dilatation of hepatic sinusoids
Zhang et al. 2015									
30	Rabbit (NS) 2–4 NS	2–8 days 7 hours/day (WB)	1,600, 2,200	CS, HP, LE	Death			1,600	1/2 died at 1,600 ppm; 2/4 died at 2,200 ppm
					Cardio	2,200			
					Hepatic		1,600		Fatty degeneration
					Renal		1,600		Fatty degeneration
Heppel et al. 1946a									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
31	Rabbit (New Zealand) 5 M	2 weeks 4–5 days/week 6 hours/day (WB)	0, 100, 300, 1,000	BC, BW, CS, GN, HP, OW	Bd wt	1,000			
					Resp	300	1,000		Olfactory mucosal degeneration
					Hepatic	1,000			
					Renal	1,000			
					Endocr	1,000			No histopathological changes in adrenal glands
					Immuno	1,000			No histopathological changes in thymus or bone marrow
					Repro	1,000			No histopathological changes in testes
Nitschke and Johnson 1983									
INTERMEDIATE EXPOSURE									
32	Rat (Wistar) 10–12 NS	15 days 7 hours/day; 1,000, 1,500 (WB)	1,500	LE	Death			1,500	3/12 died
Heppel et al. 1946b									
33	Rat (Wistar, Sprague-Dawley) 18–51 B	35–97 days 7 hours/day 5 days/week (WB)	0, 1,000, 1,500	CS, BW, HP, LE	Death			1,000	25/45 died at 1,000 ppm; 8/18 died at 1,500 ppm
					Bd wt		1,000		Decreased body weight gain
					Cardio	1,500			
					Hepatic	1,000	1,500		Slight centrilobular fatty degeneration
					Renal	1,500			
					Neuro		1,000		Mild incoordination and weakness
Heppel et al. 1946a									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
34	Rat (NS) 19–26 M, 10–23 F	Up to 28 weeks 5 days/week 7 hours/day (WB)	0, 400	BW, LE, HP	Bd wt	400			
					Cardio	400			
					Hepatic	400			
					Renal	400			
Heppel et al. 1948									
35	Rat (Fischer-344) 10 M, 10 F	13 weeks 5 days/week 6 hours/day (WB)	0, 15, 50, 150	BW, OW, GN, HP, BC, CS, UR, HE	Bd wt	50 M 150 F	150 M		10% decrease in body weight
					Resp		15[c]		Hyperplasia of the nasal respiratory epithelium at ≥15 ppm; degeneration of the olfactory mucosa at ≥50 ppm; submucosal inflammation in males at 150 ppm. $BMCL_{10}$=2.38 ppm.
					Cardio	150			
					Gastro	150			
					Hemato	150			
					Musc/skel	150			
					Hepatic	150			
					Renal	150			
					Dermal	150			
					Ocular	150			
					Endocr	150			
					Immuno	150			
					Neuro	150			
					Repro	150			
Nitschke et al. 1988									
36	Rat (Fischer-344) 6–9 F	21–24 days 8 hours/day (WB)	0, 50, 100, 200	BW, OW, RX	Bd wt	200			
					Repro	50	100		Lengthened estrous cycle at ≥100 ppm; decreased ovulation at 200 ppm
Sekiguchi et al. 2002									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
37	Rat (F344/DuCrj) 10 M, 10 F	13 weeks 5 days/week 6 hours/day (WB)	0, 125, 250, 500, 1,000, 2,000	BC, BW, CS, FI, GN, HE, HP, OW	Bd wt	500	1,000		>10% decrease in body weight
					Resp		125		Hyperplasia of respiratory epithelium, atrophy of olfactory epithelium at ≥125 ppm; inflammation of respiratory epithelium at ≥1,000 ppm
					Cardio	2,000			
					Gastro	2,000			
					Hemato	250	500		Hemolytic anemia, hemosiderosis in the spleen, increased hematopoiesis in the spleen and bone marrow
					Hepatic	1,000	2,000		Centrilobular hepatocyte swelling, increased liver weight in females
					Renal	2,000			
					Endocr	1,000 F 2,000 M	2,000 F		Fatty change in adrenal glands
					Neuro	2,000			
					Repro	2,000			
Umeda et al. 2010									
38	Mouse (C3H) 80 (NS)	37 days 4–7 hours/day (WB)	0, 400	LE, HP	Death			400	96% mortality
					Hepatic		400		Fatty degeneration, centrilobular congestion, necrosis
					Renal		400		Fatty degeneration
Heppel et al. 1948									
39	Mouse (B6D2F1/Crlj) 10 M, 10 F	13 weeks 5 days/week 6 hours/day (WB)	0, 50, 100, 200, 300, 400	BC, BW, CS, FI, GN, HE, HP, OW	Death			300 M	2/10 died at 300 ppm; 6/10 died at 400 ppm
					Bd wt	200 M 400 F	300 M		>10% decrease in body weight in males
					Resp	200	300		Respiratory metaplasia, atrophy, necrosis, and desquamation of nasal cavity
					Cardio	300	400		"Ground glass" appearance

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Gastro	300	400		Forestomach hyperplasia
					Hemato	200	300		Hemolytic anemia, increased extramedullary hematopoiesis and hemosiderin deposits in the spleen, and bone marrow congestion
					Hepatic	200	300		Increased liver weight and centrilobular hepatocyte swelling at ≥300 ppm; fatty and vacuolic changes and necrosis at 400 ppm
					Renal	400			
					Endocr	400			
					Neuro	400			
					Repro	400			
Matsumoto et al. 2013									
40	Mouse (B6C3F1) 10 M,10 F	13 weeks 5 days/week 6 hours/day (WB)	0, 15, 50, 150	BW, OW, GN, HP, CS, HE	Bd wt	150			
					Resp	150			
					Cardio	150			
					Gastro	150			
					Hemato	150			
					Musc/skel	150			
					Hepatic	150			
					Renal	150			
					Dermal	150			
					Ocular	150			
					Endocr	150			
					Immuno	150			
					Neuro	150			
					Repro	150			
Nitschke et al. 1988									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
41	Mouse (C57Bl/6JJcl) 6 M	4 weeks 8 hours/day 7 days/week (WB)	0, 50, 250	BW, BC, BI, LE, OW, HP	Bd wt	250			
					Hepatic	50	250		Increased ALT and bilirubin; increased liver weight; focal necrosis and bile duct hyperplasia
Zhang et al. 2018									
42	Guinea pig (NS) 12–39 B	39–126 days 7 hours/day 5 days/week (WB)	0, 1,000, 1,500	BW, CS, HP, LE	Death			1,000	3/12 died at 1,000 ppm, 5/18 died at 1,500 ppm
					Bd wt		1,000		Decreased body weight gain
					Cardio	1,500			
					Hepatic	1,000	1,500		Fatty degeneration, centrilobular congestion and necrosis
					Renal	1,000	1,500		Fatty degeneration
					Endocr		1,000		Subcortical fibrosis of the adrenal glands at ≥1,000 ppm, adrenal cortex necrosis at 1,500 ppm
					Neuro		1,000		Transient CNS depression
Heppel et al. 1946a									
43	Guinea pig (NS) 16–24 B	Up to 27 weeks 5 days/week 7 hours/day (WB)	0, 400	BW, LE, HP	Bd wt	400			
					Hepatic		400		Slight fatty degeneration
					Renal		400		Slight fatty degeneration
Heppel et al. 1948									
44	Dog (NS) 1–5 F	55–128 days 7 hours/day 5 days/week (WB)	0, 1,000	CS, LE, OF, HP	Death			1,000	5/9 died (severe anorexia noted)
					Cardio		1,000		Fatty degeneration
					Hemato	1,000			
					Hepatic		1,000		Fatty degeneration
					Renal		1,000		Fatty degeneration
					Endocr		1,000		Lipoid depletion of adrenal glands, atrophy and necrosis of adrenal cortex
Heppel et al. 1946a									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
45	Dog (NS) 5 NS	26 weeks 5 days/week 7 hours/day (WB)	0, 400	BW, LE, HP	Bd wt	400			
					Cardio	400			
					Hepatic	400			
					Renal	400			
Heppel et al. 1948									
46	Rabbit (NS) 4–8 B	39–126 days 7 hours/day 5 days/week (WB)	0, 1,000, 1,500	BW, CS, HE, HP, LE	Death			1,500	1/4 died
					Bd wt	1,500			
					Cardio	1,500			
					Hemato	1,500			
					Hepatic	1,500			
					Renal	1,500			
Heppel et al. 1946a									
47	Rabbit (New Zealand) 7 M, 7 F	13 weeks 5 days/week 6 hours/day (WB)	0, 150, 500, 1,000	BW, OW, GN HP, BC, HE,	Bd wt	1,000			
					Resp	500	1,000		Olfactory epithelium degeneration of nasal cavity
					Cardio	1,000			
					Gastro	1,000			
					Hemato		150		Anemia at ≥150 ppm; bone marrow hyperplasia at ≥500 ppm
					Musc/skel	1,000			
					Hepatic	1,000			
					Renal	1,000			
					Dermal	1,000			
					Ocular	1,000			
					Endocr	1,000			
					Immuno	1,000			
					Neuro	1,000			
					Repro	1,000			
Nitschke et al. 1988									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
CHRONIC EXPOSURE									
48	Rat (F344/DuCrj) 50 M, 50 F	104 weeks 5 days/week 6 hours/day (WB)	0, 80, 200, 500	BC, BW, CS, FI, GN, HE, HP, OW	Bd wt	200	500		8–11% decrease in body weight
					Resp		80		Atrophy of olfactory epithelium, inflammation and squamous cell metaplasia of respiratory epithelium, and hyperplasia of the transitional epithelium at ≥80 ppm; squamous cell hyperplasia and hyperplasia of the submucosal glands at ≥200 ppm
					Cardio	500			
					Gastro	500			
					Hemato	200 F 500 M	500 F		Mild anemia
					Hepatic	500			
					Renal	500			
					Endocr	500			
					Immuno	500			
					Neuro	500			
					Repro	500			
					Cancer			500	CEL: nasal papillomas
Umeda et al. 2010									
49	Mouse (B6D2F1/Crlj) 50 M, 50 F	104 weeks 5 days/week 6 hours/day (WB)	0, 32, 80, 200	BC, BW, CS, FI, GN, HE, HP, OW	Bd wt	200			
					Resp	32	80		Atrophy of olfactory epithelium at ≥80 ppm; metaplasia of the olfactory epithelium and submucosal glands at 200 ppm
					Cardio	200			
					Gastro	200			
					Hemato	200			
					Hepatic	200			

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Concentrations (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					Renal	200 F			
							32 M		Increased kidney weight, basophilic changes, and cortical mineralization
					Endocr	200			
					Immuno	200			
					Neuro	200			
					Cancer			200	CEL: bronchioloalveolar adenoma or carcinoma in males and females; Harderian gland adenomas and hemangioma/ hemangiosarcoma in spleen in males
Matsumoto et al. 2013									

[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 acute-duration inhalation minimal risk level (MRL). The LOAEL of 100 ppm was adjusted for continuous exposure and converted into a human equivalent concentration (HEC) of 1.8 ppm, and divided by and uncertainty factor of 90 (3 for use of a minimal LOAEL, 3 for animal to human with dosimetric adjustments, and 10 for human variability), resulting in an MRL of 0.02 ppm
[c]Use to derive an intermediate-duration inhalation MRL. Using benchmark dose modeling, BMC_{10} and $BMCL_{10}$ values of 6.76 and 2.38 ppm, respectively, were calculated for nasal respiratory epithelium hyperplasia in male and female rats. The $BMDL_{10}$ was adjusted for continuous exposure and converted into a HEC of 0.05 ppm divided by an uncertainty factor of 30 (3 for animal to human with dosimetric adjustments and 10 for human variability), resulting in an MRL of 0.002 ppm.

Principal studies for the MRLs

ALT = alanine aminotransferase; AST = aspartate aminotransferase; B = both sexes; BC = serum (blood) chemistry; Bd Wt or BW = body weight; BI = biochemical changes; BMC = benchmark concentration; BMCL= 95% lower confidence limit on the benchmark concentration (subscripts denote benchmark response: exposure level associated with 10% extra risk or 1 standard deviation change in endpoint); Cardio = cardiovascular; CEL = cancer effect level; CNS = central nervous system; CS = clinical signs; Endocr = endocrine; F = female(s); FI = food intake; Gastro = gastrointestinal; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LE = lethality; LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OW = organ weight; Repro = reproductive; Resp = respiratory; UR = urinalysis; WB = whole body

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

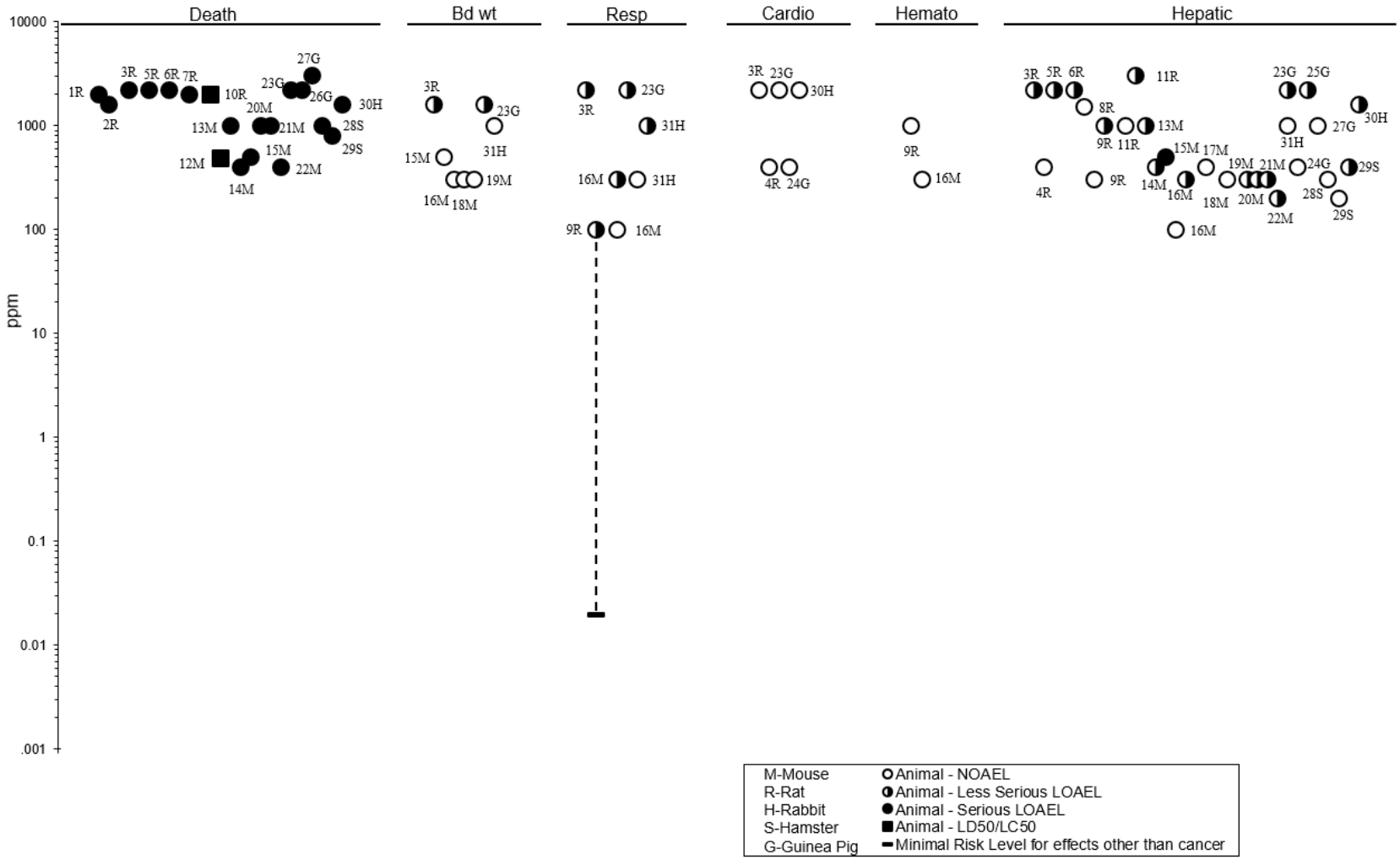

Figure 2-2. Levels of Significant Exposure to 1,2-Dichloropropane – Inhalation
Acute (≤ 14 days)

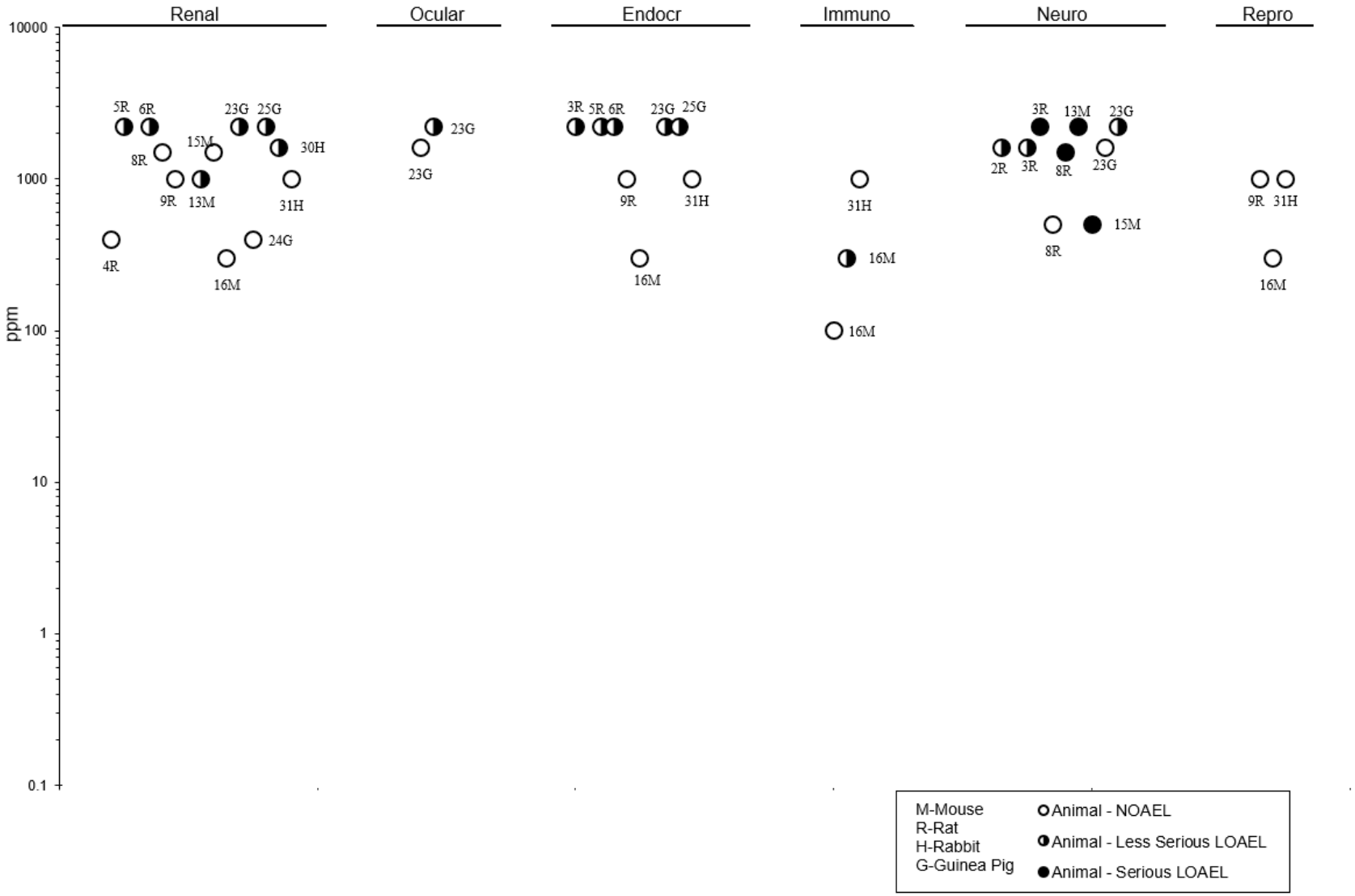

Figure 2-2. Levels of Significant Exposure to 1,2-Dichloropropane – Inhalation
Intermediate (15-364 days)

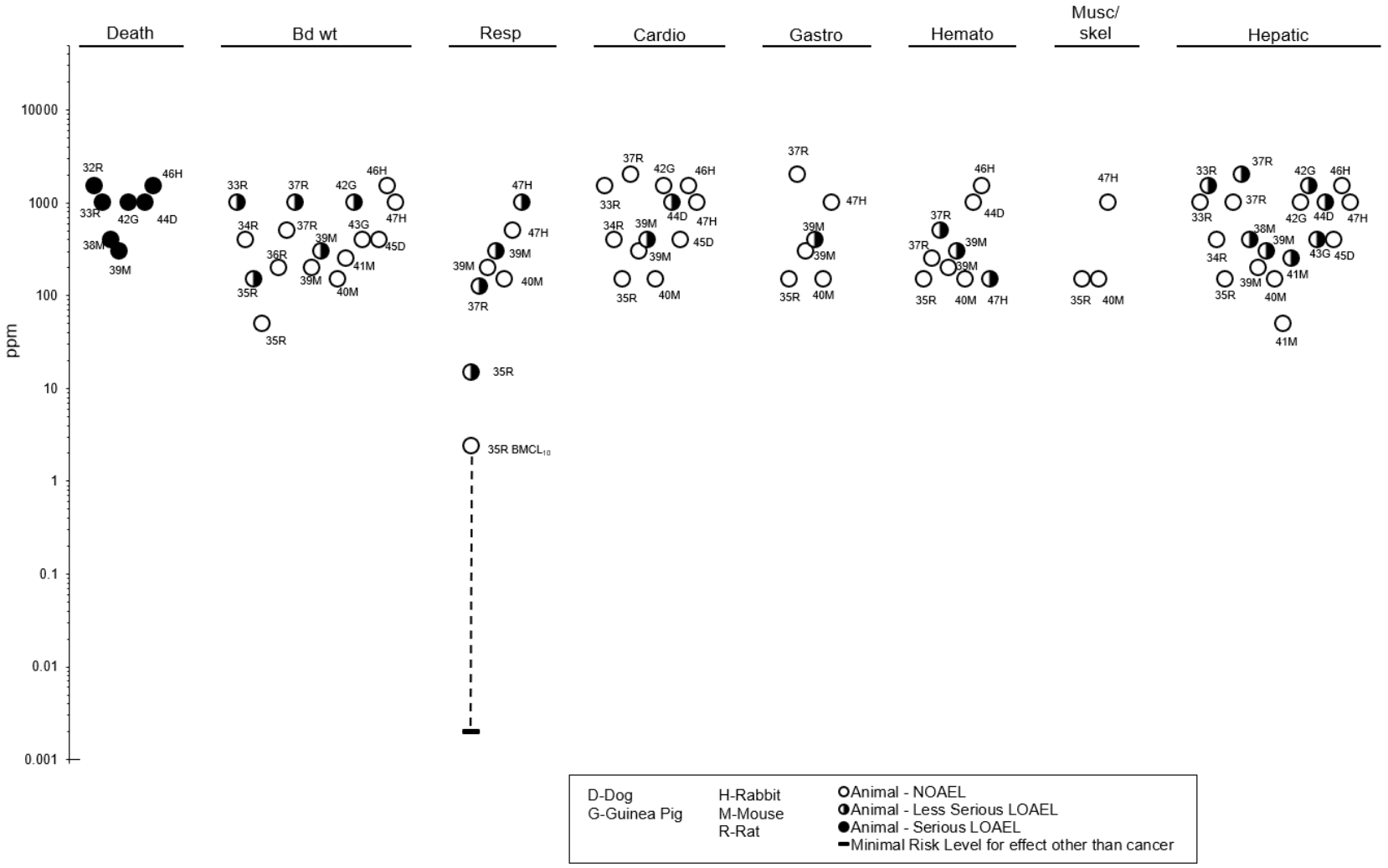

Figure 2-2. Levels of Significant Exposure to 1,2-Dichloropropane – Inhalation
Intermediate (15-364 days)

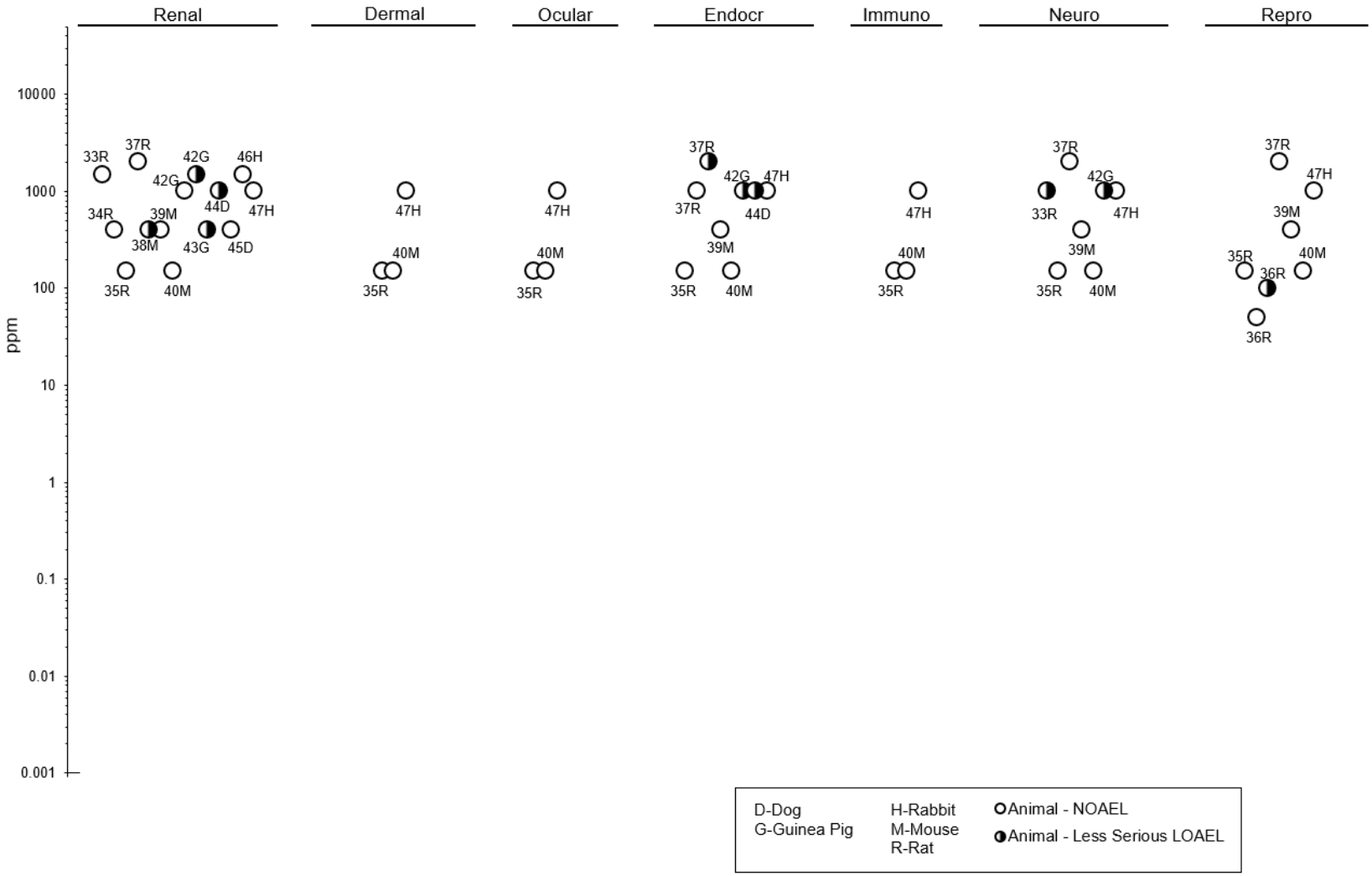

Figure 2-2. Levels of Significant Exposure to 1,2-Dichloropropane – Inhalation
Chronic (≥365 days)

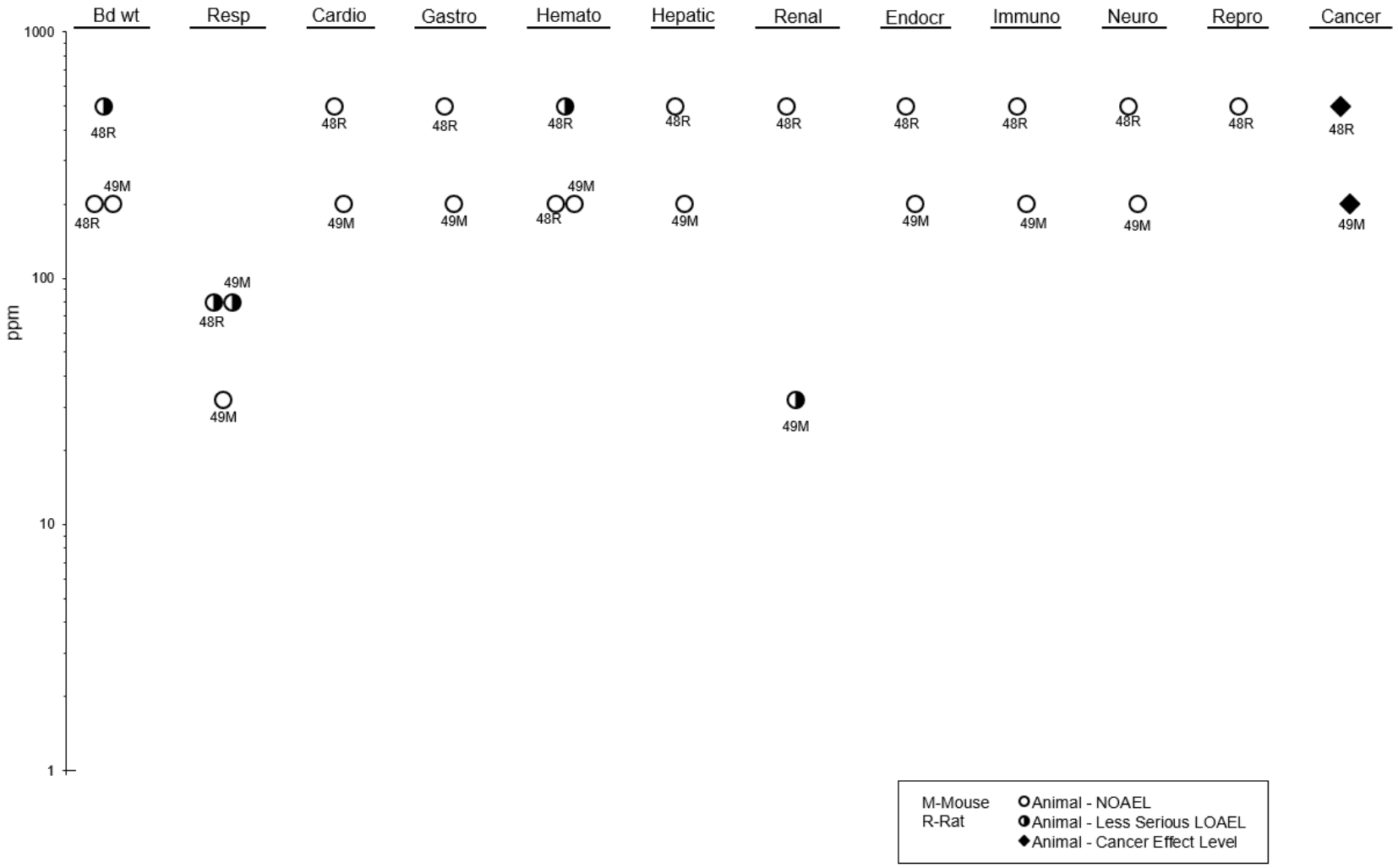

Table 2-2. Levels of Significant Exposure to 1,2-Dichloropropane – Oral

Figure key[a]	Species (strain) No./group	Exposure scenario	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) 6–8 M	1, 5, or 10 days (GO)	0, 100, 250, 500, 750, 1,000	BW, OW, HE, HP, BC, CS, UR	Bd wt	100	250		Decreased body weight gain
					Resp	1,000			
					Gastro	1,000			
					Hemato	100	250	500	Hemolytic anemia at ≥250 mg/kg/day; severe anemia at 500 mg/kg/day
					Hepatic	100	250		Centrilobular necrosis, inflammatory cell infiltration, early proliferation of fibroblasts
					Renal	500	1,000		Increased BUN
					Endocr	1,000			
					Neuro		100	250	Slight CNS depression at ≥100 mg/kg/day; pronounced CNS depression at ≥250 mg/kg/day
Bruckner et al. 1989									
2	Rat (NS) 5 M, 5 F	Once (G)	1,000, 1,470, 2,150, 3,160, 4,680, 6,810, 10,000	BW, CS, GN, LE	Death			1,600	LD_{50}
					Neuro		1,000		CNS depression
Exxon 1981a									
3	Rat (Fischer-344) 10 M, 10 F	14 days (GO)	0, 300, 500	BW, OW, GN, HP, CS, HE, NX	Bd wt	500 F	300 M		>10% decrease in body weight in males
					Hemato	500			
					Hepatic		300		Increased liver weight, degeneration and necrosis of individual hepatocytes, prominent nuclei in centrilobular hepatocytes
					Renal	500			

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Neuro		300		Transient clinical signs of CNS depression, decreased motor activity
Gorzinski and Johnson 1989									
4	Ray (Wistar) 5–12 M	Once (GO)	2,000	BC, BI, HE	Hemato		2,000		Transient hemolysis
Imberti et al. 1990									
5	Rat (NS) NS	Once (NS)	NS	LE	Death			1,900	LD_{50}
Kennedy and Graepel 1991									
6	Rat (Sprague-Dawley) 30 F	10 days GDs 6–15 (GO)	0, 10, 30, 125	BW, OW, WI, GN, CS, NX	Bd wt	30	125		>10% decrease in maternal body weight gain
					Neuro	30	125		Maternal CNS depression
					Repro	125			No change in the number of corpora lutea, implantations, resorptions, or fetuses
					Develop	30	125		Delayed skull ossification
Kirk et al. 1995									
7	Rat (Sprague-Dawley) 10 F	10 days (GO) GDs 6–15	0, 50, 125, 250, 500	BW, CS, GN, HE, LE, OW, RX	Bd wt	250	500		13% decrease in maternal body weight
					Hemato	500			
					Neuro	125	250	500	Transient CNS depression at ≥250 mg/kg/day; persistent CNS depression at 500 mg/kg/day
					Repro	500			No change in the number of corpora lutea, implantations, resorptions, or fetuses
Kirk et al. 1989									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
8	Rat (Fischer-344) 5 M, 5 F	14 days (GO)	0, 125, 250, 500, 1,000, 2,000	BW, GN, CS	Death			2,000	100% mortality
					Bd wt	250 M 500 F	500 M 1,000 F		>10% decrease in body weight
NTP 1986									
9	Rat (Wistar) 6 M, 6 F	Once (G)	145, 230, 366, 582, 926, 1,472	CS, BW, LE	Death			582	6/6 males died at ≥582 mg/kg/day; 2/6, 5/6, and 6/6 females died at 582, 9,266, and 1,472 mg/kg/day, respectively (LD_{50}=487 mg/kg/day)
					Neuro		145	582	Slight CNS depression at all doses; severe CNS depression at ≥582 mg/kg/day
Shell Oil Co. 1982									
10	Rat (NS) 5 M	Once (G)	1,965–2,428	LE	Death			2,000	LD_{50}
Smyth et al. 1969									
11	Mouse (B6C3F1) 5 M	Once (GO)	0, 500	BI, BW, CS, FI, HP, LE, OW, WI	Hepatic		500		Diffuse fatty change
Gi et al. 2015a									
12	Mouse (B6C3F1) 5 M	3 days (GO)	0, 500	BI, BW, CS, FI, HP, LE, OW, WI	Bd wt	500			
					Resp	500			
					Hepatic			500	Extensive centrilobular necrosis and mild fatty change
					Renal	500			
Gi et al. 2015a									
13	Mouse (ddY) NS M	Once (GO)	NS	LE	Death			960	LD_{50}
Matsumoto et al. 1982 [abstract only]									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
14	Mouse (B6C3F1) 5 M, 5 F	2 weeks (GO)	0, 125, 250, 500, 1,000, 2,000	BW, GN, CS	Death			500 M 1,000 F	3/5 males died at 500 mg/kg/day, 5/5 males and 4/5 females died at 1,000 mg/kg/day, 100% mortality at 2,000 mg/kg/day
					Bd wt	500			
NTP 1986									
15	Hamster (Golden Syrian) 5 M	Once (GO)	0, 500	BI, BW, CS, FI, HP, LE, OW, WI	Hepatic		500		Mild fatty change
Gi et al. 2015a									
16	Hamster (Golden Syrian) 5 M	3 days (GO)	0, 500→250	BI, BW, CS, FI, HP, LE, OW, WI	Death			500	1/5 dead on day 1 (dose lowered on day 2)
					Bd wt		333		11% decrease in body weight
					Resp	333			
					Hepatic			333	Severe fatty change and extensive centrilobular necrosis
					Renal	333			
Gi et al. 2015a (Dose was decreased from 500 to 250 mg/kg/day on day 2 due to one mortality and toxicity (listlessness) in remaining animals.)									
17	Rabbit (New Zealand) 7 F	13 days (GO) GDs 7–19	0, 25, 100, 250	BW, CS, GN, HE, LE, OW, RX	Death			250	2/7 died
					Hemato	25[b]	100		Maternal anemia. $BMDL_{1SD}$=30 mg/kg/day.
					Repro	100		250	Complete litter resorption (2/5)
Berdasco et al. 1988									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
18	Rabbit (New Zealand) 18 F	13 days (GO) GDs 7–19	0, 15, 50, 150	BW, OW, FI, WI, GN, CS, HE	Bd wt	50	150		Decreased body weight gain associated with anorexia
					Hemato	50[b]	150		Maternal anemia. $BMDL_{1SD}$=30 mg/kg/day.
					Repro	150			No change in the number of corpora lutea, implantations, resorptions, or fetuses
					Develop	50	150		Delayed skull ossification
Kirk et al. 1995									
INTERMEDIATE EXPOSURE									
19	Rat (Sprague-Dawley) 15 M	13 weeks 5 days/week (GO)	0, 100, 250, 500, 750	BW, HE, HP, BC, BI, UR	Death			500	>50% mortality
					Bd wt	100	250		~10% decrease in body weight
					Resp	500			
					Gastro	500			
					Hemato		100[c]	250	Hemolytic anemia, including increased serum bilirubin levels and hemosiderosis and hyperplasia of erythropoietic elements of the spleen at ≥100 mg/kg/day; pronounced anemia at ≥250 mg/kg/day. $LOAEL_{ADJ}$= 71 mg/kg/day.
					Hepatic	100	250		Increased relative liver weight at ≥250 mg/kg/day; periportal vacuolization and active fibroplasia at 500 mg/kg/day
					Renal	250	500		Increased relative kidney weight
					Endocr	250 M 500 F	500 M		Fatty adrenal cortex at ≥500 mg/kg/day; vacuolization of the adrenal medulla, lipidosis of the adrenal cortex at 750 mg/kg/day

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Neuro			500	Pronounced CNS depression (CNS effects not reported at lower doses)
					Repro	250	500		Testicular degeneration, altered sperm production
Bruckner et al. 1989									
20	Rat (Fischer-344) 15 M, 15 F	13 weeks (GO) 5 days/week	0, 20, 65, 200	BW, CS, HP, GN, LE, OW, RX	Bd wt	65 M 200 F	200 M		10% decrease in body weight in males
					Neuro	200			No changes in FOB, strength, motor activity, brain size, or nervous tissue histology
Johnson and Gorzinski 1988									
21	Rat (Sprague-Dawley) 30 M, 30 F	13–21 weeks 2 generations (W)	M: 0, 27, 96, 182 F: 0, 41, 137, 274	BW, CS, DX, FI, GN, HE, HP, OP, OW, RX	Bd wt	96	182		Decreased body weight in F0 and F1 adults
					Hemato	137 F 182 M	274 F		Anemia in F0 dams
					Hepatic	96	182		Granularity of the hepatocellular cytoplasm in high-dose male and female F0 and F1 adults
					Renal	274			
					Ocular	274			
					Repro	274			
					Develop	137		274	Decreased F1 neonatal survival, decreased F1 pup weight during lactation
Kirk et al. 1990 [Doses averaged across both generations]									

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

Figure key[a]	Species (strain) No./group	Exposure scenario	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 (Fischer-344) 10 M, 10 F	13 weeks 5 days/week (GO)	0, 60, 125, 250, 500, 1,000	GN, HP, CS, BW	Death			500 M 1,000 F	50% mortality in males at 500 mg/kg/day; 100% mortality in males and females at 1,000 mg/kg/day
					Bd wt	250 M 500 F	500 M 1,000 F		>10% decrease in body weight
					Resp	1,000			
					Cardio	1,000			
					Gastro	1,000			
					Musc/skel	1,000			
					Hepatic	500	1,000		Centrilobular congestion and necrosis, hepatic fatty changes
					Renal	1,000			
					Dermal	1,000			
					Endocr	1,000			
					Immuno	1,000			
					Neuro	1,000			
					Repro	1,000			
NTP 1986									
23	Mouse (B6C3F1) 5 M	4 weeks 5 days/week (GO)	0, 125, 250	BI, BW, CS, FI, HP, LE, OW, WI	Bd wt	250			
					Resp	250			
					Hepatic		125		Increased liver weight and mild fatty change at ≥125 mg/kg/day; increased serum total cholesterol and triglycerides at 250 mg/kg/day
					Renal	250			
Gi et al. 2015a									
24	Mouse (B6C3F1) 10 M,10 F	13 weeks 5 days/week (GO)	0, 30, 60, 125, 250, 500	BW, GN, HP, CS	Bd wt	500			
					Resp	500			
					Cardio	500			
					Gastro	500			

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Musc/skel	500			
					Hepatic	500			
					Renal	500			
					Dermal	500			
					Endocr	500			
					Immuno	500			
					Neuro	500			
					Repro	500			
NTP 1986									
25	Hamster (Golden Syrian) 5 M	4 weeks 5 days/week (GO)	0, 125, 250	BI, BW, CS, FI, HE, HP, LE, OW, WI	Death			250	3/5 died
					Bd wt	250			
					Resp	250			
					Hemato	250			
					Hepatic		125		Moderate fatty change
					Renal	250			
Gi et al. 2015a									
26	Hamster (Golden Syrian) 24 M	15–17 weeks 5 days/week (GO)	0, 65, 125	BW, FI, HP, OW, WI	Bd wt	125			
					Hepatic	125			
					Cancer				No tumor promotion activity in liver, pancreas, kidney, or lung following initiation with BOP
Gi et al. 2015b									
CHRONIC EXPOSURE									
27	Rat (Fischer-344) 50 M, 50 F	103 weeks 5 days/week (GO)	M: 0, 62, 125 F: 0, 125, 250	BW, GN, CS, HP	Death			250 F	42% decrease in survival rate
					Bd wt	62 M 125 F	125 M 250 F		>10% decrease in body weight
					Resp	250 F			
					Cardio	250 F			
					Gastro	250 F			

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Hemato	125 B	250 F		Hemosiderosis of the spleen; blood hematological parameters not evaluated
					Musc/skel	250 F			
					Hepatic	125 B	250 F		Clear cell foci, necrosis
					Renal	250 F			
					Dermal	250 F			
					Immuno	250 F			
					Neuro	250 F			
					Repro	125 M 250 F			
					Cancer			250 F	CEL: mammary tumors (mammary gland hyperplasia at 125 mg/kg/day); no exposure-related neoplasms in males
NTP 1986									
28	Mouse (B6C3F1) 50 M, 50 F	103 weeks 5 days/week (GO)	0, 125, 250	BW, GN, CS, HP	Bd wt	250			
					Resp	250			
					Cardio	250			
					Musc/skel	250			
					Hepatic	125 M 250 F	250 M		Hepatocytomegaly and necrosis
					Renal	250			
					Dermal	250			
					Endocr	250			
					Immuno	250			

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

Figure key[a]	Species (strain) No./group	Exposure scenario	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
					Neuro	250			
					Repro	250			
					Cancer			125	CEL: hepatic tumors at ≥125 and 250 mg/kg/day in females and males, respectively; thyroid follicular cell tumors in females at 250 mg/kg/day

NTP 1986

[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 an acute-duration oral minimal risk level (MRL). Using benchmark dose modeling, a $BMDL_{1SD}$ value of 30 mg/kg/day was calculated for increased reticulocyte counts in maternal rabbits. The MRL is based on the $BMDL_{1SD}$ of 30 divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability), resulting in an MRL of 0.3 mg/kg/day.
[c]Used to derive an intermediate-duration oral MRL. The LOAEL of 100 mg/kg/day was adjusted for continuous exposure and divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability), resulting in an MRL of 0.07 mg/kg/day.

Principal studies for the MRLs.

ADJ = adjusted for continuous exposure; B = both sexes; BC = serum (blood) chemistry; Bd Wt or BW = body weight; BI = biochemical changes; BMDL= 95% lower confidence limit on the benchmark dose (subscripts denote benchmark response: exposure level associated with 10% extra risk or 1 SD change in endpoint); BOP = N-nitrosobis(2-oxopropyl)amine; BUN = blood urea nitrogen; Cardio = cardiovascular; CEL = cancer effect level; CNS = central nervous system; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; F = female(s); F0 = parental generation; F1 = first generation; FI = food intake; FOB = functional observation battery; (G) = gavage; Gastro = gastrointestinal; GD = gestational day; GN = gross necropsy; (GO) = gavage in oil; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LE = lethality; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OF = organ function; OP = ophthalmology; OW = organ weight; Repro = reproductive; Resp = respiratory; RX = reproductive function; SD = standard deviation; UR = urinalysis; (W) = drinking water; WI = water intake

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

Acute (≤ 14 days)

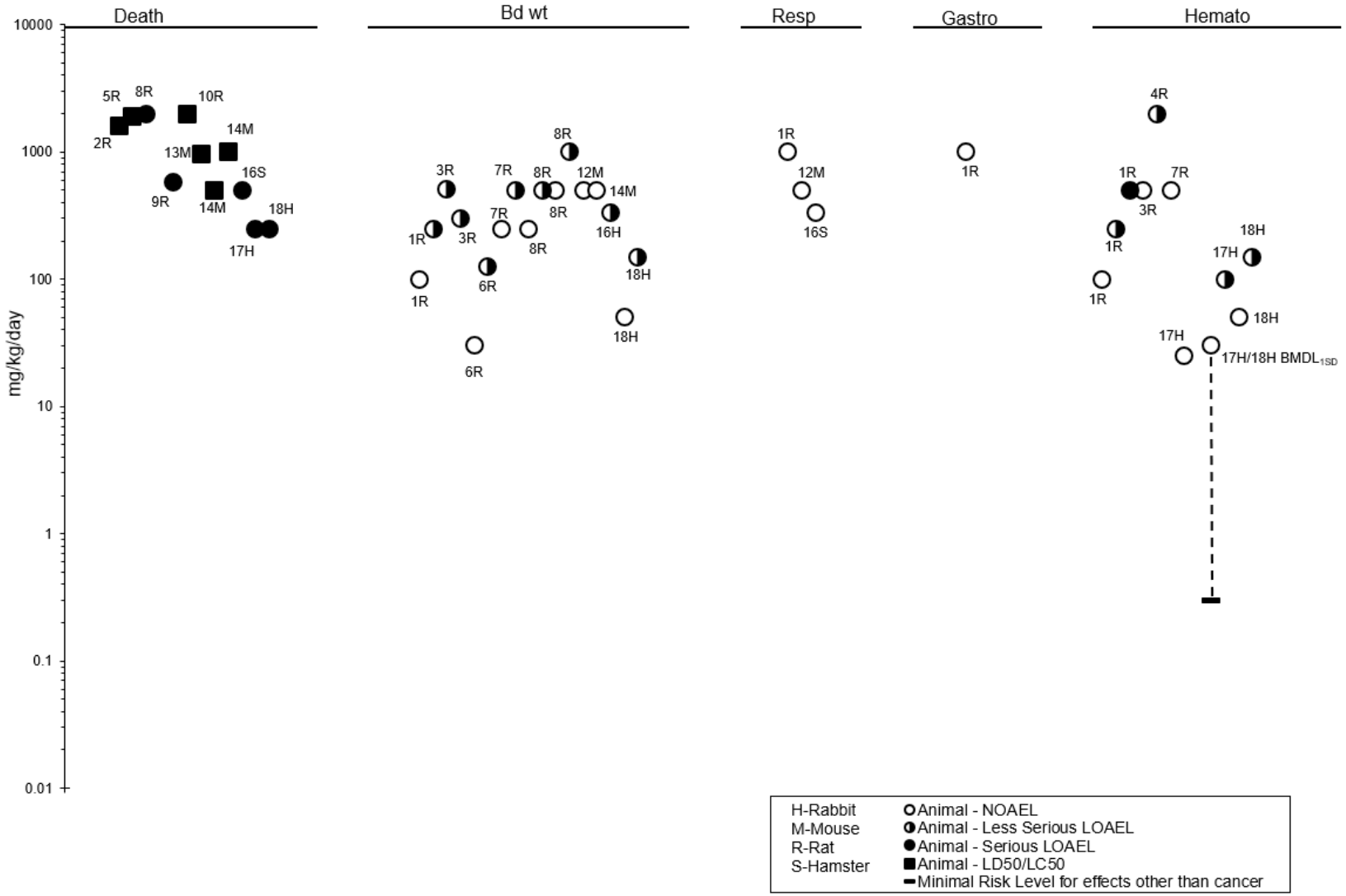

Figure 2-3. Levels of Significant Exposure to 1,2-Dichloropropane – Oral
Acute (≤ 14 days)

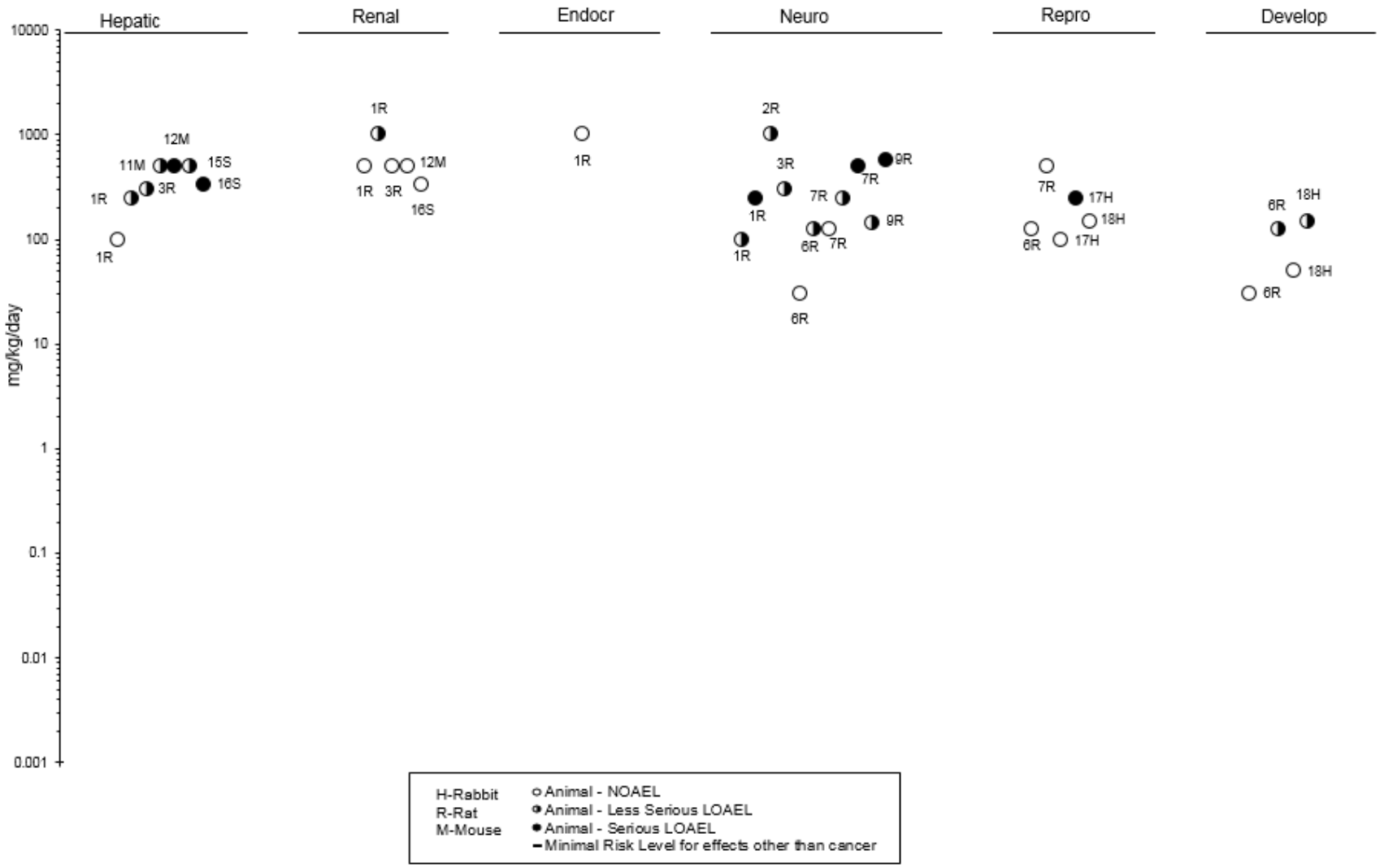

Figure 2-3. Levels of Significant Exposure to 1,2-Dichloropropane – Oral
Intermediate (15-364 days)

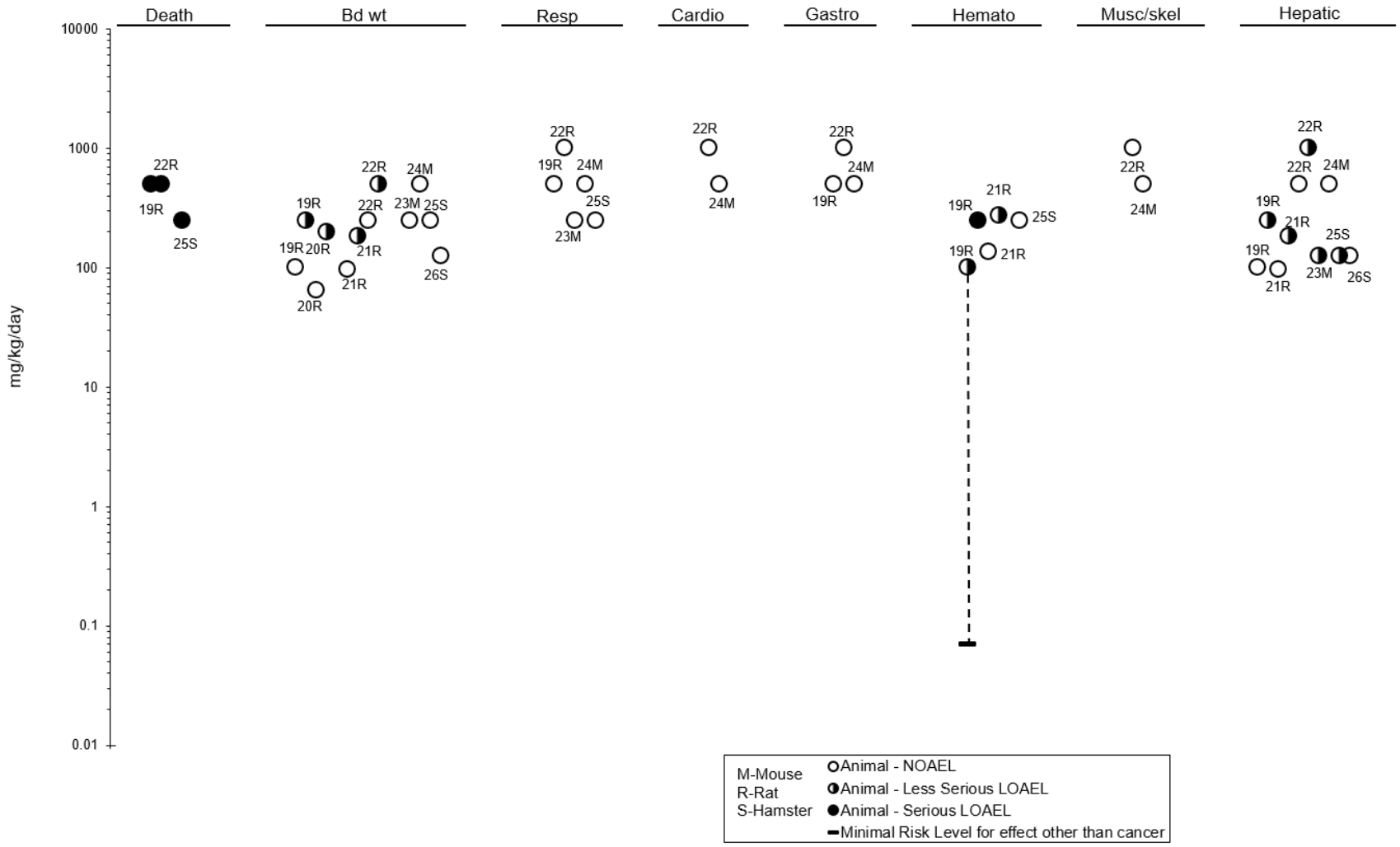

Figure 2-3. Levels of Significant Exposure to 1,2-Dichloropropane – Oral
Intermediate (15-364 days)

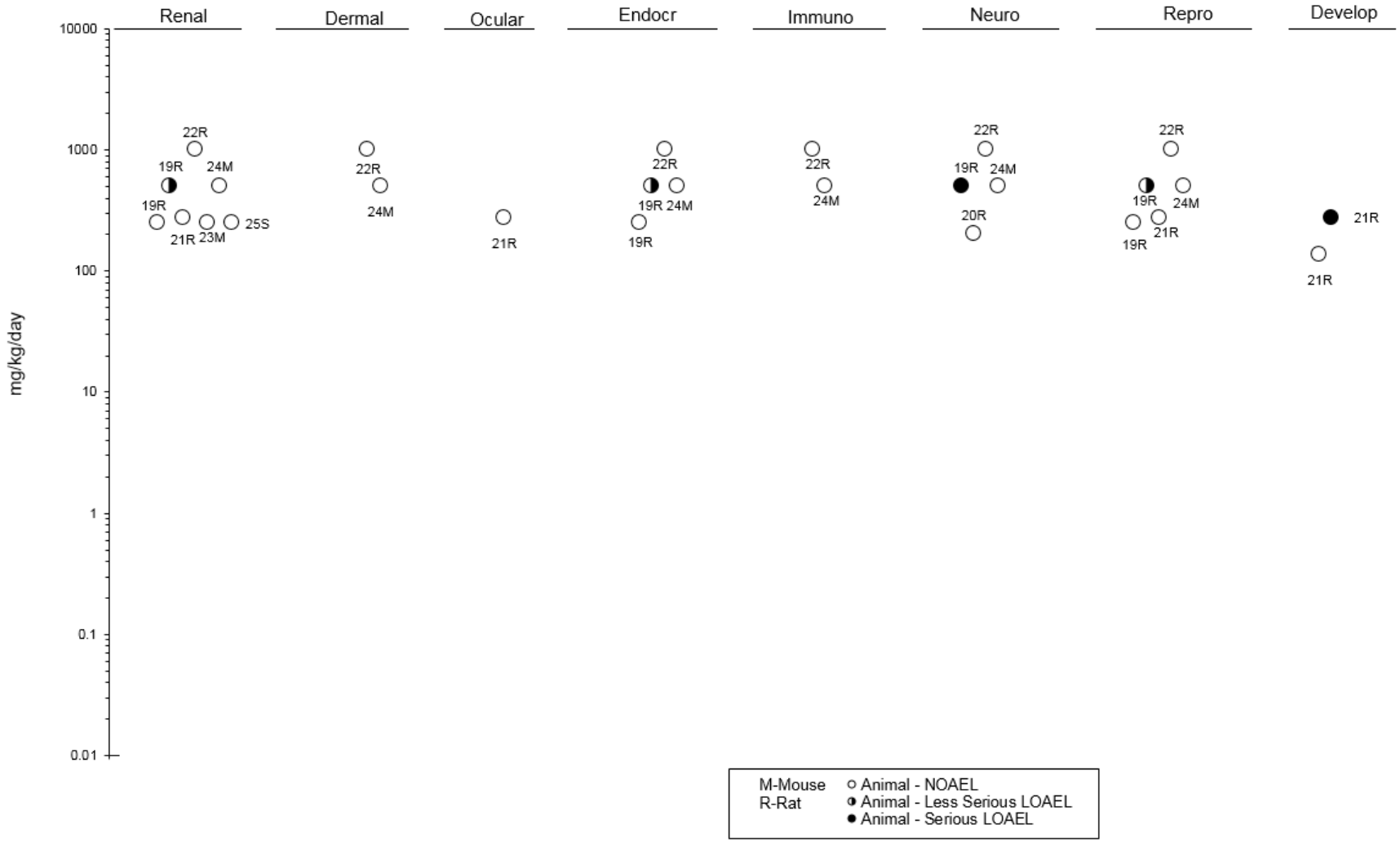

Figure 2-3. Levels of Significant Exposure to 1,2-Dichloropropane – Oral
Chronic (≥365 days)

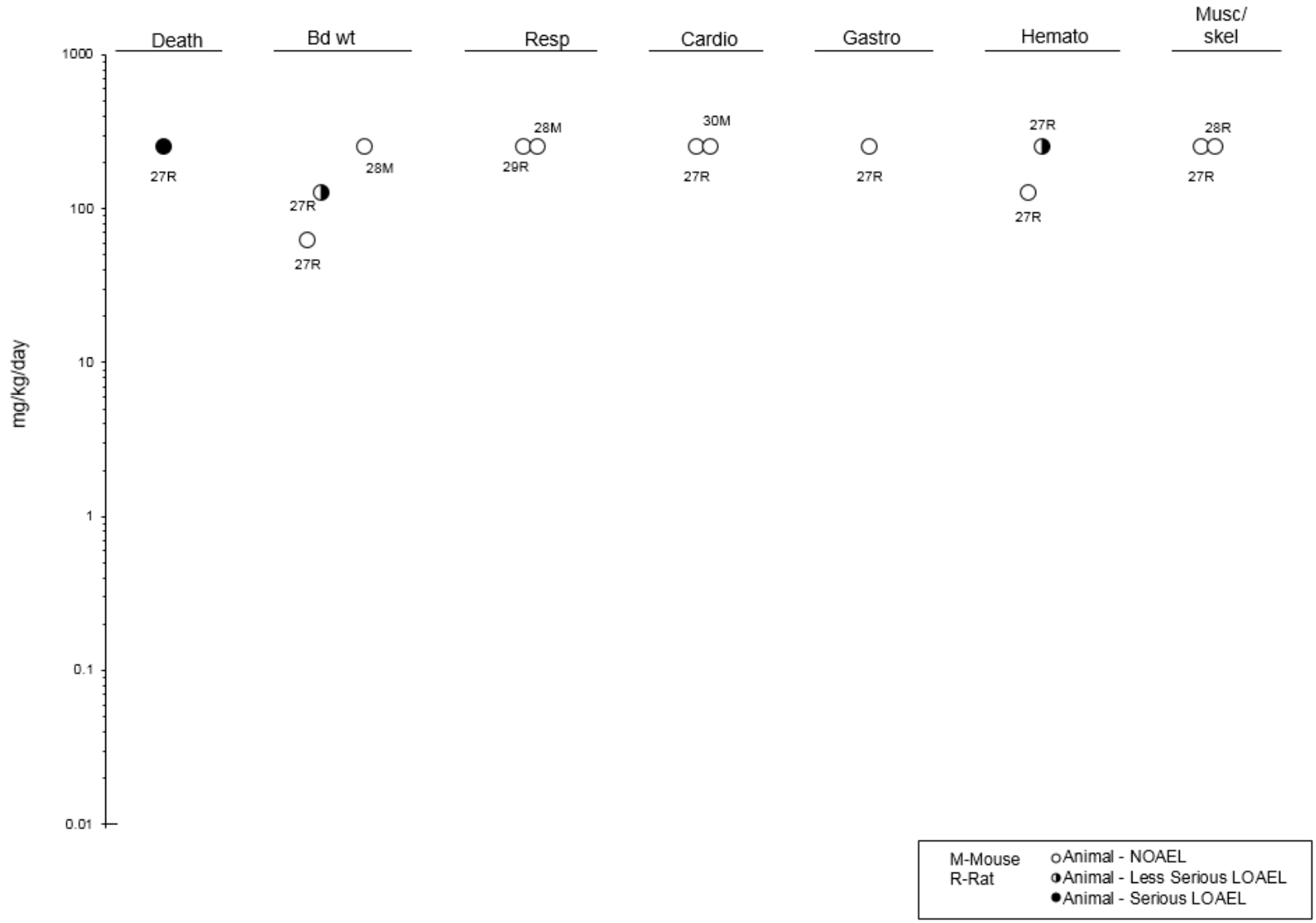

Figure 2-3. Levels of Significant Exposure to 1,2-Dichloropropane – Oral
Chronic (≥365 days)

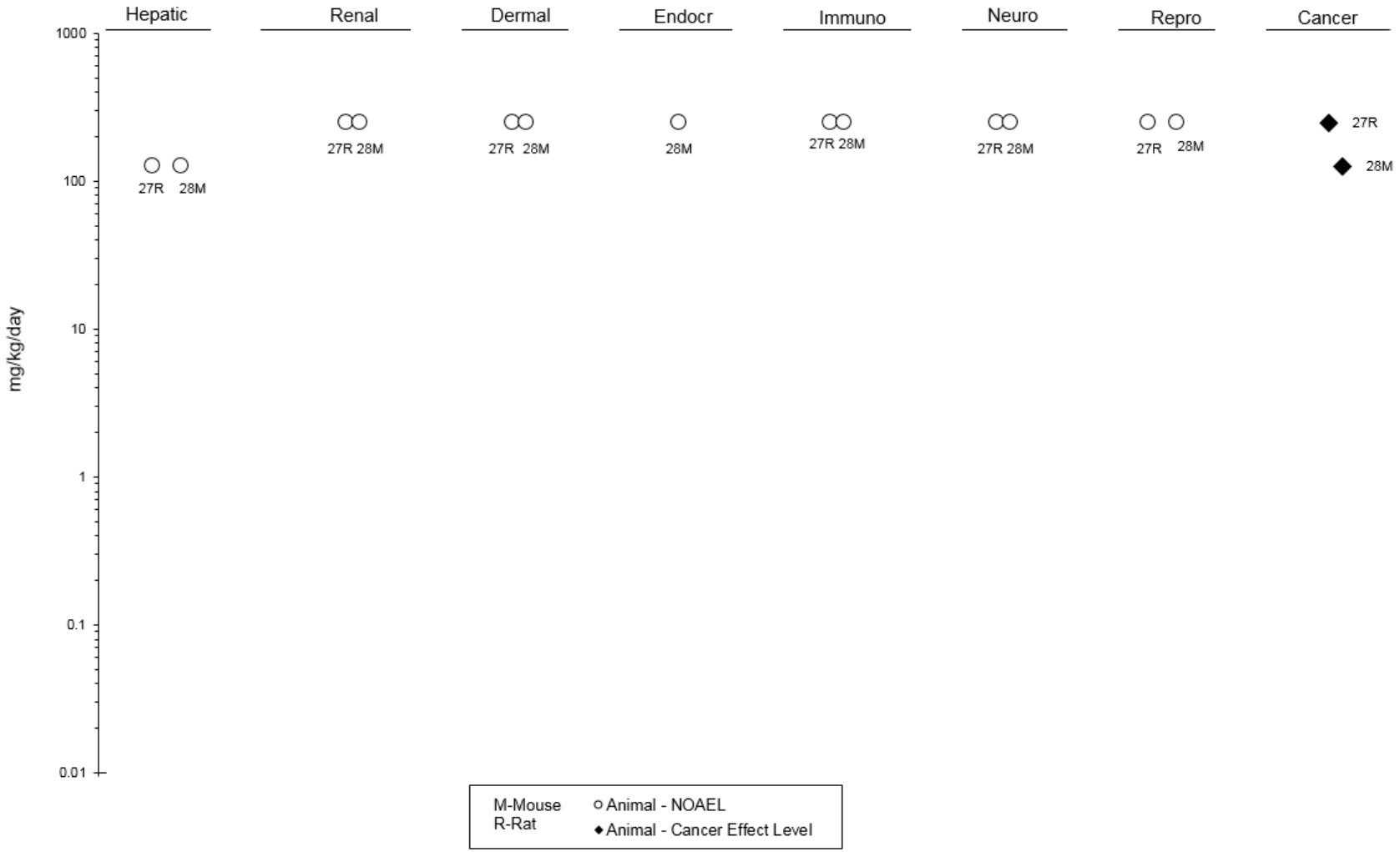

Table 2-3. Levels of Significant Exposure to 1,2-Dichloropropane – Dermal

Species (strain) No./group	Exposure scenario	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE								
Rat (Wistar) 6 M, 6 F	24 hours	2.34 g/kg	BW, CS, LE	Bd wt	2.34 g/kg			
				Dermal		2.34 g/kg		Erythema
Shell Oil Co. 1982								
Mouse (C57Bl/6J) 5 NS	7 days 1 time/day	0, 2.73, 5.75, 8.75 mL/kg	BC, CS, HP	Dermal		2.73 mL/kg		Dermatitis and angiogenesis of the skin
Jin et al. 2019								
Guinea pig (NS) 5–10 M, 5–10 F	NS	0.58 g/mL (induction), 0.29 g/mL (challenge)	CS	Immuno		0.58 g/mL		Skin sensitizer
Shell Oil Co. 1982								
Rabbit (NS) 2 M, 2 F	NS	0, 3.16 g/kg	BW, CS, GN, LE	Bd wt	3.16 g/kg			
				Dermal		3.16 g/kg		Erythema and edema
Exxon 1981b								
Rabbit (New Zealand) 3 M, 3 F	24 hours	1.16 g/mL	CS	Dermal		1.16 g/mL		Skin irritation; chemical burns in females
Shell Oil Co. 1982								
Rabbit (NS) 4 M	24 hours	8.3–9.2 mL/kg	LE	Death			8.75 mL/kg	LD_{50}
Smyth et al. 1969								

Bd Wt or BW = body weight; CS = clinical signs; F = female(s); GN = gross necropsy; Immuno = immunological; LD_{50} = lethal dose, 50% kill; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; NS = not specified

2.2 DEATH

Worker fatalities have been reported following accidental inhalation overexposure to commercial mixtures containing 1,2-dichloropropane (e.g., from chemical spills) (reviewed by ACGIH 2014; IARC 1986). Fatalities have also been reported in cases of accidental or intentional ingestion or intentional inhalation abuse ("sniffing" or "huffing") of large amounts of mixtures containing 1,2-dichloropropane, such as household stain removers (Di Nucci et al. 1988; Larcan et al. 1977; Pozzi et al. 1985). Following these exposures, death was primarily attributed to cardiac arrest, shock, or liver failure, but cases of renal failure, pulmonary edema, disseminated intravascular coagulation, and severe hemolytic anemia have also been reported. The exposure levels in these case studies cannot be determined accurately; therefore, they are not included in the LSE tables or figures.

Exposure-related deaths have been reported in laboratory animals following acute or intermediate inhalation exposures; acute, intermediate, and chronic oral exposures; and acute dermal exposures.

Inhalation Exposure. Smyth et al. (1969) reported an 8-hour inhalation LC_{50} value of 2,000 ppm in rats. Following a single 4-hour inhalation exposure, the concentration at which the first death was observed in rats (approximate lethal concentration [ALC]) was 2,000 ppm; the study authors assumed that the ALC was half of the 4-hour LC_{50} (Kennedy and Graepel 1991). 1,2-Dichloropropane was reported in a group of chemicals causing death in two, three, or four out of six rats following exposure to 2,000 ppm for 4 hours, but the exact number of deaths was not reported for 1,2-dichloropropane alone (Carpenter et al. 1949). No mortality was observed in rats exposed to concentrations up to 1,060 ppm for 4–6 hours (Di Nucci et al. 1990; Drew et al. 1978; Nitschke and Johnson 1983), but 3/12 rats died following a 7-hour exposure to 1,600 ppm (Heppel et al. 1946a). In acute-duration, repeat-exposure studies (6–8 hours/day, up to 14 exposures), mortality in rats was observed at concentrations as low as 1,600 ppm, but not at concentrations ≤1,000 ppm (Heppel et al. 1946a; Highman and Heppel 1946; Nitschke and Johnson 1983; Zhang et al. 2015).

In an intermediate-duration study, exposure-related mortality was observed in rats exposed to 1,500 ppm for 15 days (7 hours/day), but not 1,000 ppm, when a standard diet was used (Heppel et al. 1946b, 1946b). However, 100% mortality was observed after 3–4 exposures to 1,000 or 1,500 ppm when rats were fed a low-casein, high-fat diet; the study authors suggested that this may be due to decreased detoxification due to deficiency of sulfur-containing amino acids associated with this diet (Heppel et al. 1946b). In another series of intermediate-duration studies in Wistar and Sprague-Dawley rats,

8/18 Wistar rats died following exposure to 1,500 ppm (7 hours/day, up to 35 exposures) and 9/27 Wistar rats and 16/18 Sprague-Dawley rats died following exposure to 1,000 ppm (7 hours/day, up to 97 exposures) (Heppel et al. 1946a). However, in other studies, no exposure-related deaths were observed in rats following intermittent exposure to concentrations up to 2,000 ppm for up to 13 weeks (Nitschke et al. 1988; Sekiguchi et al. 2002; Umeda et al. 2010), or 80–500 ppm for 2 years (Umeda et al. 2010).

In mice, a 10-hour inhalation LC_{50} value of 480 ppm was reported; all mice (22–26 animals) died after a single exposure of 4 hours to 1,000 or 1,500 ppm, while 3/10 mice died after a single 2-hour exposure to 1,500 ppm (Dow Chemical Co. 1968). Heppel et al. (1946b) reported 100% mortality in mice following a single 7-hour exposure to ≥1,000 ppm. Similarly, 100% mortality was observed in mice within 24 hours of a 6-hour exposure to 1,500 ppm; at 500 ppm mice became lethargic and 2/5 mice died within 3 days of exposure (Nitschke and Johnson 1983). Zhang et al. (2015) also reported 100% mortality in mice exposed to ≥1,000 ppm for 8 hours/day for up to 7 days or ≥400 ppm for 6 hours/day for up to 14 days. Heppel et al. (1948) reported 44% mortality after a single 7-hour exposure to 400 ppm, with 96% mortality following 37 exposures to 400 ppm (4–7 hours/exposure). No compound-related mortality was observed in mice exposed to concentrations up to 300 ppm for 6 hours/day, 4–5 days/week (Nitschke and Johnson 1983), or up to 250 ppm for 4 weeks (8 hours/day) (Zhang et al. 2018). In longer-duration studies, exposure-related deaths were observed at ≥300 ppm following intermittent exposure for 13 weeks (6 hours/day, 5 days/week), but not at concentrations ≤200 ppm for up to 2 years (Matsumoto et al. 2013; Nitschke et al. 1988).

In guinea pigs, 7/20 animals died after two or three 7-hour exposures to 2,200 ppm (Highman and Heppel 1946). Heppel et al. (1946b) also reported deaths in 11/16 guinea pigs exposed to 2,200 ppm for 7 hours/day for up to 5 days; no deaths occurred with exposure to 1,600 ppm. In another study, 100% mortality was observed in guinea pigs exposed to ≥3,000 ppm for 8 hours/day for up to 7 days; no mortality was observed at concentrations ≤1,000 ppm (Zhang et al. 2015). Intermediate-duration exposure resulted in 3/12 deaths after exposure to 1,000 ppm (7 hours/day) for up to 39 exposures and 5/18 deaths after exposure to 1,500 ppm (7 hours/day) for up to 126 exposures (Heppel et al. 1946a).

In hamsters, 100% mortality was observed following exposure to concentrations ≥1,000 ppm for 8 hours/day for up to 7 days or ≥800 ppm for 6 hours/day for up to 14 days (Zhang et al. 2015).

In rabbits, no compound-related mortality was observed following intermittent exposure to concentrations up to 1,000 ppm for up to 18 weeks (6–7 hours/day, 5 days/week) (Heppel et al. 1946a; Nitschke and Johnson 1983; Nitschke et al. 1988). Exposure to 2,200 ppm for 7 hours/day for up to 8 days resulted in 2/4 deaths in exposed rabbits, and exposure to 1,500 ppm for 7 hours/day for up to 39 days resulted in 1/4 deaths (Heppel et al. 1946a).

One study reported death in 4/5 dogs and 1/4 puppies exposed to 1,2-dichloropropane for up to 128 days (7 hours/day) at 1,000 ppm; however, severe anorexia was also observed and starvation was the likely cause of death (Heppel et al. 1946a).

Oral Exposure. An acute study in Wistar rats statistically determined an oral LD_{50} value of 487 mg/kg (Shell Oil Co. 1982). However, other reported oral LD_{50} values in rats of unspecified strain(s) are much higher, ranging from 1,600 to 2,000 mg/kg (Exxon 1981a; Kennedy and Graepel 1991; Smyth et al. 1969). Since the strain was not reported in the studies with the higher LD_{50} values, it is unclear if the discrepancy is due to strain susceptibility. However, Imberti et al. (1990) did not report any deaths in Wistar rats following a single exposure to 2,000 mg/kg. In acute-duration, repeat-exposure studies up to 14 days, 100% mortality was observed at 2,000 mg/kg/day in F344 rats (NTP 1986), with no exposure-related deaths in F344 or Sprague-Dawley rats at doses up to 1,000 mg/kg/day (Bruckner et al. 1989; Gorzinski and Johnson 1989; Kirk et al. 1989, 1995). In intermediate-duration studies, exposure-related mortalities were reported in both F344 and Sprague-Dawley rats following exposure to ≥500 mg/kg/day for 13 weeks, but not ≤250 mg/kg/day for 13–21 weeks (Bruckner et al. 1989; Johnson and Gorzinski 1988; Kirk et al. 1990; NTP 1986). In chronic studies, increased mortality was observed in F344 female rats following exposure to 250 mg/kg/day for up to 103 weeks (NTP 1986).

An oral LD_{50} value of 960 mg/kg was reported in ddY mice in an abstract by Matsumoto et al. (1982). No deaths were reported in B6C3F1 mice exposed once to 500 mg/kg (Gi et al. 2015a). In acute-duration, repeat-exposure studies up to 14 days, mortality occurred in B6C3F1 mice at ≥500 mg/kg/day (Gi et al. 2015a; NTP 1986). No mortalities clearly related to exposure were observed following intermediate-duration exposure to doses up to 500 mg/kg/day (Gi et al. 2015a; NTP 1986) or chronic-duration exposure to doses up to 250 mg/kg/day for 103 weeks (NTP 1986).

In rabbits, death occurred in 1/2, 2/2, and 2/2 animals exposed to 250, 500, and 1,000 mg/kg/day for 13 days (Kirk et al. 1988); however, this study was not included in the LSE table due to inadequate animal number. In pregnant rabbits, 2/7 does died following exposure to 250 mg/kg/day on gestation

days (GDs) 6–15; however, it is unclear if the deaths were exposure-related because the cause of death was undetermined (Berdasco et al. 1988). No exposure-related mortalities were observed in pregnant rabbits exposed to doses up to 150 mg/kg/day (Berdasco et al. 1988; Kirk et al. 1995).

In hamsters, no deaths occurred after a single exposure to 500 mg/kg; however, 3-day exposure at that dose caused death in 1/5 animals (Gi et al. 2015a). In a 4-week study, 1/5 and 3/5 animals died at 125 and 250 mg/kg/day, respectively (Gi et al. 2015a). No exposure-related deaths were observed in hamsters exposed to doses up to 125 mg/kg/day for 15–17 weeks (Gi et al. 2015b).

Dermal Exposure. A dermal LD_{50} of 8.75 mL/kg (10.2 g/kg) was calculated for rabbits (Smyth et al. 1969). The treatment site was covered with an impervious plastic film for 24 hours following application and the animals were observed for 14 days. No rats or rabbits died following a single dermal application of 2.34–3.16 g/kg (Exxon 1981b; Shell Oil Co. 1982).

2.3 BODY WEIGHT

No studies were located regarding body weight effects in humans following exposure to 1,2-dichloropropane.

Decreased body weight following exposure to 1,2-dichloropropane has been reported in laboratory animals following acute-, intermediate-, and chronic-duration inhalation exposures and acute, intermediate, and chronic oral exposures.

Inhalation Exposure. Body weight loss was reported in rats and guinea pigs following acute exposure to ≥1,600 ppm (7 hours/day) for 5–8 days (Heppel et al. 1946a). Nitschke and Johnson (1983) also reported decreased body weight gain in rats at ≥100 ppm during a 2-week exposure (6 hours/day, 4–5 days/week), but this finding was attributed to decreased food intake. No body weight effects were reported in mice or rabbits following acute exposure to concentrations up to 300 and 1,000 ppm, respectively (Nitschke and Johnson 1983; Wang et al. 2019).

In intermediate-duration studies, the lowest LOAEL for decreases in body weight >10% was in F344 male rats exposed to 150 ppm for 13 weeks (6 hours/day, 5 days/week); the associated NOAEL was 50 ppm (Nitschke et al. 1988). No body weight effects were observed in similarly exposed female F344 rats exposed at concentrations up to 150 ppm (Nitschke et al. 1988). However, another study using the

same exposure protocol in F344/DuCrj rats reported a NOAEL and LOAEL of 500 and 1,000 ppm, respectively, for both male and female rats (Umeda et al. 2010). Body weights were also unaffected in female rats exposed to concentrations up to 200 ppm for 8 hours/day for 21–24 days (Sekiguchi et al. 2002). Decreased body weight gains were observed in rats and guinea pigs exposed to ≥1,000 ppm for >30 days (7 hours/day; lowest concentration evaluated), but not similarly exposed rabbits at concentrations up to 1,500 ppm (Heppel et al. 1946a). In mice, terminal body weights were decreased by >10% in males exposed at ≥300 ppm for 13 weeks (6 hours/day, 5 days/week), but not at lower concentrations; body weights were comparable to controls in females up to 400 ppm (Matsumoto et al. 2013; Nitschke et al. 1988). Body weight in male mice was not affected at concentrations up to 250 ppm for 4 weeks (8 hours/day, 7 days/week) (Zhang et al. 2018). No body weight effects were observed in rabbits similarly exposed to concentrations up to 1,000 ppm (Nitschke et al. 1988).

In chronic-duration studies, terminal body weights in rats were significantly decreased by 11% in males and 8% in females exposed to 500 ppm for up to 104 weeks (6 hours/day, 5 days/week); body weights were comparable to controls in rats and mice at concentrations up to 200 ppm (Matsumoto et al. 2013; Umeda et al. 2010).

Oral Exposure. Body weight decreases >10% were observed in F344 male rats at ≥500 mg/kg/day and female rats at ≥1,000 mg/kg/day following gavage exposure for 2 weeks (5 days/week) (NTP 1986). In F344 rats exposed via gavage 7 days/week for 2 weeks, male rats showed body weight decreases >10% at ≥300 mg/kg/day; no body weight effects were noted in female rats at doses up to 500 mg/kg/day (Gorzinski and Johnson 1989). In Sprague-Dawley rats, a significant dose-related decrease in body weight gain was observed in males, following exposure to doses ≥250 mg/kg/day via gavage for 10 days (Bruckner et al. 1989). No body weight effects were observed in mice exposed to 500 mg/kg/day for 3 days or at doses up to 2,000 mg/kg/day for 2 weeks (5 days/week) (Gi et al. 2015a; NTP 1986). In hamsters, an 11% decrease in body weight was observed in animals exposed to 500 mg/kg/day for 1 day followed by 250 mg/kg/day for 2 days (time-weighted average [TWA] of 333 mg/kg/day); the initial dose was decreased after one animal died and the surviving animals showed listlessness (Gi et al. 2015a).

In intermediate- and chronic-duration studies, decreased body weight was observed in Sprague-Dawley rats at ≥250 mg/kg/day for 13 weeks (Bruckner et al. 1989); in F344 male and female rats at doses as low as 200 and 1,000 mg/kg/day, respectively, for 13 weeks (Johnson and Gorzinski 1988; NTP 1986); and in F344 male and female rats at 125 and 250 mg/kg/day, respectively, for up to 103 weeks (NTP 1986). No body weight effects were observed in B6C3F1 mice exposed to doses up 250 mg/kg/day for 4 weeks,

500 mg/kg/day for 13 weeks, or 250 mg/kg/day for up to 103 weeks (Gi et al. 2015a; NTP 1986). No body weight effects were observed in hamsters exposed to doses up 250 mg/kg/day for 4 weeks (Gi et al. 2015a)

In a 2-generation study in rats, both F0 and F1 parental animals showed decreased body weight following exposure to drinking water concentrations up to 0.24% (estimated doses of 152–293 mg/kg/day per sex per generation), but not concentrations ≤0.10% (estimated doses of 83–148 mg/kg/day per sex per generation) (Kirk et al. 1990). Similarly, maternal body weight gain was significantly decreased in rat dams and rabbit does exposed to 125 mg/kg/day on GDs 6–15 or 7–19, respectively, but not ≤30 mg/kg/day (Kirk et al. 1995). In dose-range finding studies with fewer animals, significant maternal body weight effects were not observed in rats or rabbits at doses up to 250 mg/kg/day, but rat dams showed significant weight loss at 500 mg/kg/day (Berdasco et al. 1988; Kirk et al. 1989).

Dermal Exposure. No changes in body weight were observed in rats or rabbits following a 24-hour dermal exposure to 2.34 or 3.16 g/kg, respectively, of undiluted 1,2-dichloropropane (Shell Oil Co. 1982).

2.4 RESPIRATORY

Rubin (1988) described respiratory effects in humans resulting from exposure to an accidental spill of 2,000 gallons of 1,2-dichloropropane. The exposure resulted in chest discomfort, dyspnea, and cough in some of the patients, indicating that 1,2-dichloropropane is a respiratory tract irritant. Following a railway accident in which 3,000 gallons of a mixture containing 4 parts *o*-dichlorobenzene, 2 parts 1,2-dichloropropane, and 1 part ethylene dichloride spilled, 10 workers died and 3 additional men were hospitalized with pulmonary edema, emphysema, bronchopneumonia, tachycardia, and destruction of the airways (see ACGIH 2014). Air concentrations of 1,2-dichloropropane were not measured or estimated in either spill.

Nasal lesions have been observed in rats, mice, and rabbits following acute-, intermediate-, and chronic-duration inhalation exposure to 1,2-dichloropropane; the rat appears to be the most sensitive species. Evidence of nasal tumors in rats and lung tumors in mice following chronic inhalation exposure to 1,2-dichloropropane is discussed in Section 2.19 (Cancer). No respiratory lesions have been observed in rats, mice, or hamsters orally exposed to 1,2-dichloropropane; however, the nasal cavity has not been evaluated in any available oral exposure studies.

Inhalation Exposure. Nasal cavity lesions were observed in rats, mice, and rabbits following acute exposure to 1,2-dichloropropane for 2 weeks (6 hours/day, 4–5 days/week) (Nitschke and Johnson 1983). Degeneration of the nasal mucosa was found in all rats exposed to concentrations ≥100 ppm (lowest concentration tested); the severity of the lesions increased in a concentration-related manner. Additional effects observed in rats at ≥300 ppm included inflammatory and exudative changes in the nasal tissue. Degeneration of the nasal mucosa was also found in all mice exposed to 300 ppm, although lesions were less severe than those observed in rats. At 100 ppm, nasal lesions were only observed in 2/5 female mice and 0/5 male mice; no lesions were observed at 30 ppm. In the rabbits, some animals showed slight nasal mucosa degeneration at 1,000 ppm, with no exposure-related nasal lesions at ≤300 ppm. Therefore, rats appear to be the most sensitive species to the respiratory effects of 1,2-dichloropropane exposure.

Nasal cavity lesions were also reported in rats, mice, and rabbits following intermittent exposure for 13 weeks (6 hours/day, 5 days/week). Nasal cavity lesions were observed in rats exposed to ≥15 ppm, including hyperplasia of the respiratory epithelium at ≥15 ppm, degeneration of the olfactory epithelium at ≥50 ppm, atrophy of the olfactory epithelium at ≥125 ppm, submucosal inflammation at ≥150 ppm, and inflammation of the respiratory epithelium at ≥1,000 ppm (Nitschke et al. 1988; Umeda et al. 2010). No NOAEL was established for nasal lesions in rats. In mice, nasal lesions, including respiratory metaplasia, atrophy, necrosis, and desquamation, were observed following exposure to ≥300 ppm, but not at concentrations up to 200 ppm (Matsumoto et al. 2013; Nitschke et al. 1988). Rabbits exposed to 1,000 ppm also had slight degeneration of the olfactory epithelium; no adverse effects on the respiratory system were found in rabbits exposed to concentrations up to 500 ppm (Nitschke et al. 1988).

Nasal lesions were reported in rodents following chronic-duration exposure to 1,2-dichloropropane for up to 104 weeks (6 hours/day, 5 days/week). In rats, nasal cavity lesions were observed at ≥80 ppm (lowest concentration tested), including atrophy of olfactory epithelium, inflammation of the respiratory epithelium, squamous cell metaplasia of respiratory epithelium, and hyperplasia of the transitional epithelium at ≥80 ppm and squamous cell hyperplasia and hyperplasia of the submucosal glands at ≥200 ppm (Umeda et al. 2010). In mice, nasal lesions were also observed at ≥80 ppm, but not at 32 ppm (Matsumoto et al. 2013). Observed lesions in mice included atrophy of olfactory epithelium at ≥80 ppm and metaplasia of the olfactory epithelium and submucosal glands at 200 ppm.

Lung congestion was observed in rats and guinea pigs following acute exposure to 1,2-dichloropropane at 2,200 ppm (1–8 days, 7 hours/day; only concentration evaluated) (Heppel et al. 1946a). However, increased incidences of nonneoplastic histopathological lung lesions were not observed following

1,2-dichloropropane exposure in rats, mice, or rabbits following exposure to concentrations up to 2,000 ppm for 13 weeks (Matsumoto et al. 2013; Nitschke et al. 1988; Umeda et al. 2010) or rats or mice following exposure to concentrations up to 500 ppm for 104 weeks (Matsumoto et al. 2013; Umeda et al. 2010)

Oral Exposure. No histopathologic changes in the lungs were observed following acute (Bruckner et al. 1989; Gi et al. 2015a), intermediate (Bruckner et al. 1989; Gi et al. 2015a; NTP 1986), or chronic (NTP 1986) oral exposure in rats, mice, or hamsters. The highest NOAEL values for each duration category are 1,000, 1,000, and 250 mg/kg/day, respectively. The nasal cavity has not been assessed in any available oral exposure study.

Mechanisms of Respiratory Tract Toxicity. There are no specific mechanisms of toxicity proposed for respiratory tract toxicity. However, available data indicate that glutathione depletion may underlie toxicity in the liver and kidney as well as hemolytic anemia (Di Nucci et al. 1988; Imberti et al. 1990). This mechanism may be applicable to respiratory tract toxicity as well, as it has been proposed for other chemicals known to lead to glutathione depletion (e.g., naphthalene; ATSDR 2005). However, this mechanism has not been specifically evaluated for respiratory tract toxicity associated with 1,2-dichloropropane exposure. The only available data are from an *in vitro* study that showed that 1,2-dichloropropane caused decreased cell viability in cultured human embryonic lung fibroblasts (Kawasaki et al. 2015).

2.5 CARDIOVASCULAR

Cardiovascular collapse and cardiac arrest have been reported in fatal cases of 1,2-dichloropropane poisoning (Di Nucci et al. 1988; Larcan et al. 1977; see also ACGIH 2014). These effects are likely secondary to CNS depression and widespread systemic toxicity, as opposed to direct effects on the cardiovascular system. Tachycardia was reported in a 43-year-old man following prolonged dermal exposure (~5 hours) to a commercial fixative (30–40% 1,2-dichloropropane, 33–38% toluene); the increased heart rate was attributed to hyperkalemia secondary to acute renal failure (Fiaccadori et al. 2003). No additional information regarding the potential for cardiovascular effects in humans following exposure to 1,2-dichloropropane was available.

No histopathological changes were observed in the heart or aorta following acute- or intermediate-duration exposure to concentrations up to 2,200 ppm (6–7 hours/day, 5 days/week) in rats, guinea pigs,

rabbits, or dogs (Heppel et al. 1946a, 1948; Nitschke et al. 1988; Umeda et al. 2010) or chronic-duration exposure in rats to concentrations up to 500 ppm for up to 104 weeks (Umeda et al. 2010). A "ground glass" appearance was noted in mice exposed to 400 ppm for 6 hours/day, 5 days/week, for 13 weeks, which was an exposure level associated with significant mortality (Matsumoto et al. 2013). No exposure-related changes in the heart or aorta of mice were observed at concentrations ≤300 ppm for 13 weeks (Matsumoto et al. 2013; Nitschke et al. 1988), or ≤200 ppm for up to 104 weeks (Matsumoto et al. 2013).

No adverse effects of 1,2-dichloropropane on the cardiovascular system were found following histological examination of the heart in rats following gavage doses up to 1,000 mg/kg/day for 13 weeks, or 125 mg/kg/day in males and 250 mg/kg/day in females for 103 weeks (5 days/week) (NTP 1986). Similarly, no histopathological changes were observed in mice following gavage doses up to 500 mg/kg/day for 13 weeks, or 250 mg/kg/day for 103 weeks (5 days/week) (NTP 1986).

2.6 GASTROINTESTINAL

Pozzi et al. (1985) reported vomiting and abdominal pain in a young woman who admitted to intentional inhalation abuse of a stain remover ("sniffing" or "huffing") to alleviate nervousness the previous night. The stain remover consisted of primarily (98%) of 1,2-dichloropropane, but an exposure estimate was not reported. In another case report, abdominal pain and vomiting upon hospitalization were observed in a 73-year-old woman who fell asleep in close proximity to an open bottle of stain remover containing 1,2-dichloropropane (Lucantoni et al. 1992). The woman was admitted to the hospital 3 days after exposure. Nausea was reported in a 43-year-old man following prolonged dermal exposure (~5 hours) to a commercial fixative (30–40% 1,2-dichloropropane, 33–38% toluene); he was admitted to the hospital for renal failure 4 days after exposure (Fiaccadori et al. 2003). Vomiting was also reported in a case of accidental ingestion of a commercial preparation of 1,2-dichloropropane (trilene) (Chiappino and Secchi 1968). All cases showed complete recovery.

No histopathological changes in the gastrointestinal system were observed in rats intermittently exposed (6 hours/day, 5 days/week) to air concentrations of 1,2-dichloropropane up to 2,000 ppm for 13 weeks (Nitschke et al. 1988; Umeda et al. 2010), or up to 500 ppm for up to 104 weeks (Umeda et al. 2010). Forestomach hyperplasia was noted in mice exposed to 400 ppm for 6 hours/day, 5 days/week, for 13 weeks, which was an exposure level associated with significant mortality (Matsumoto et al. 2013). No histopathological changes in the gastrointestinal system were observed in mice at concentrations up to 300 ppm for 13 weeks (Matsumoto et al. 2013; Nitschke et al. 1988), or up to 200 ppm for up to

104 weeks (Matsumoto et al. 2013). In rabbits, no histopathological changes in the gastrointestinal system were observed at concentrations up to 1,000 ppm, 6 hours/day, 5 days/week for 13 weeks (Nitschke et al. 1988).

No histopathological changes in the gastrointestinal system were observed in rats exposed to gavage doses up to 1,000 mg/kg/day for 1–10 days (Bruckner et al. 1989) or 13 weeks (5 days/week) (Bruckner et al. 1989; NTP 1986). Similarly, gastrointestinal lesions were not observed in mice exposed to gavage doses up to 500 mg/kg/day for 13 weeks (5 days/week) (NTP 1986). However, erosion of the mucosal lining of the stomach was observed in 2/2 rabbits exposed to gavage doses of 500 or 1,000 mg/kg/day for 13 days; no erosion was observed at 250 mg/kg/day (Kirk et al. 1988). The rabbit study was not included in the LSE tables or figures due to inadequate animal number.

Rats that were treated with 1,2-dichloropropane doses as high as 250 mg/kg/day (5 days/week) for 103 weeks did not have histological alterations in the gastrointestinal tract (NTP 1986). In female mice that were treated by gavage with 1,2-dichloropropane doses of 125 or 250 mg/kg/day (5 days/week) for 103 weeks, acanthosis of the forestomach was observed in 5/50 and 4/50 of animals, respectively. In male mice similarly treated, this effect was only observed in 2/50 animals from the high-dose group. Because it is uncertain whether the acanthosis is compound-related due to low incidences and lack of increase in incidence with increasing dose, a LOAEL or NOAEL for gastrointestinal effects following chronic oral exposure to 1,2-dichloropropane cannot be determined for mice.

2.7 HEMATOLOGICAL

Hemolytic anemia, disseminated intravascular coagulation, and/or severe blood coagulation disorders have been reported in several accidental or intentional cases of 1,2-dichloropropane poisoning via ingestion (Di Nucci et al. 1988; Perbellini et al. 1985) or inhalation exposure (Lucantoni et al. 1991, 1992; Pozzi et al. 1985). Some of these cases were fatal. Disseminated intravascular coagulation was also reported in a 43-year-old man 4 days after a prolonged dermal exposure (~5 hours) to a commercial fixative containing 30–40% 1,2-dichloropropane and 33–38% toluene; the patient made a full recovery (Fiaccadori et al. 2003). Exposure levels could not be accurately determined in these cases, so a LOAEL could not be determined. No hematological changes were observed in 11 Japanese print shop workers diagnosed with CCA following exposure to 1,2-dichloropropane and/or dichloromethane (see Table 2-4 in Section 2.19 Cancer for more details); air levels were not measured, but estimated exposure levels

based on reported quantities were 190–310 ppm 1,2-dichloropropane and 140–360 ppm dichloromethane (Kumagai et al. 2013, 2014).

As observed in human case reports, hemolytic anemia has been observed in rats, mice, and rabbits following exposure to high levels of 1,2-dichloropropane.

Inhalation Exposure. No exposure-related changes were observed in the hematological parameters in rats or mice exposed to concentration up to 1,000 ppm and 300 ppm, respectively, for 2 weeks (6 hours/day, 4–5 days/week) (Nitschke and Johnson 1983).

Hemolytic anemia, characterized by increased serum bilirubin levels, bone marrow congestion, hemosiderosis in the spleen, and increased hematopoiesis in the spleen and bone marrow, was observed following exposure for 13 weeks (6 hours/day, 5 days/week) in rats at ≥500 ppm, mice at ≥300 ppm, and rabbits at ≥150 ppm; no hematological effects were observed in rats or mice similarly exposed to concentrations up to 250 ppm for up to 104 weeks (Matsumoto et al. 2013; Nitschke et al. 1988; Umeda et al. 2010). However, exposure to 500 ppm for 6 hours/day, 5 days/week for 104 weeks only caused mild anemia in female, but not male, rats, with no exposure-related changes in hematopoietic tissues in either sex (Umeda et al. 2010). The discrepancies in findings between the intermediate- and chronic-duration studies in rats at 500 ppm were not discussed or explained by the study authors.

In older studies, splenic hemosiderosis was observed in acute studies in rats, guinea pigs, and rabbits exposed to ≥1,600 ppm and in intermediate-duration studies in rats exposed to ≥1,000 ppm and dogs exposed to 400 ppm, but hematological parameters were not assessed in these studies (Heppel et al. 1946a, 1948). In rabbits and dogs, no clear evidence of hematological changes was observed following intermediate-duration exposure to concentrations up to 1,500 ppm (Heppel et al. 1946a). These studies are considered inadequate due to poor study design (e.g., low animal number), lack of comprehensive endpoint evaluation, and/or poor data reporting, and are not included in the LSE tables or figures.

Oral Exposure. Transient hemolysis was reported in Wistar rats exposed once to a gavage dose of 2,000 mg/kg/day (Imberti et al. 1990); however, no exposure-related changes in hematological parameters were observed in Sprague-Dawley rats exposed once to a gavage dose up to 2,000 mg/kg/day (Bruckner et al. 1989). In repeated-dose, acute-duration rat studies, a dose-related increase in the severity of hemolytic anemia was found in male Sprague-Dawley rats treated with gavage doses ≥250 mg/kg/day for 5 or 10 consecutive days, or ≥100 mg/kg/day for 13 weeks (5 days/week) (Bruckner et al. 1989). As

observed in inhalation studies, findings were characterized by increased serum bilirubin levels, hemosiderosis, and hyperplasia of erythropoietic elements of the hematopoietic tissues. Evidence of anemia was also observed in F0 rat dams exposed to gavage doses of 254 mg/kg/day for up to 21 weeks in a 2-generation study (Kirk et al. 1990), and rabbit does exposed to gavage doses ≥100 mg/kg/day on GDs 7–19 (Berdasco et al. 1988; Kirk et al. 1995). However, no exposure-related hematological changes were observed in male or female F344 rats exposed to gavage doses up to 500 mg/kg/day for 14 days (Gorzinski and Johnson 1989), or Sprague-Dawley rat dams exposed to gavage doses up 500 mg/kg/day on GDs 6–15 (Kirk et al. 1989).

No exposure-related hematological changes or lesions in hematopoietic tissues were observed in hamsters exposed to gavage doses up to 250 mg/kg/day for 4 weeks (Gi et al. 2015a). Gi et al. (2015a) also reported a lack of compound-related histopathological lesions in the hematopoietic tissues of B6C3F1 mice or Golden Syrian hamsters exposed to gavage doses of 500 mg/kg/day for 3 days or to doses of 250 mg/kg/day for 4 weeks (5 days/week); however, blood hematology was not evaluated in these studies. Similarly, no compound-related histopathological lesions in hematopoietic tissues were observed in F344/N rats and B6C3F1 mice treated 5 days/week with 1,2-dichloropropane at doses of 30–1,000 mg/kg/day for 13 weeks, or 62–125 mg/kg/day for 103 weeks (NTP 1986). However, female rats exposed to 250 mg/kg/day for 103 weeks showed evidence of slight hemosiderosis of the spleen in 20/47 animals, compared with 0/50 controls (NTP 1986). NOAELs from these studies are not included in the LSE or Figure 2-3 due to lack of clinical hematological parameter evaluation.

Mechanisms of Hemolytic Anemia. Imberti et al. (1990) proposed that glutathione depletion may contribute to hematological toxicity because a statistically significant association between GSH depletion in the blood and hemolysis was observed following acute oral exposure to 1,2-dichloropropane. When the glutathione precursor, N-acetylcysteine, was administered prior to 1,2-dichloropropane, hemolysis did not occur. Glutathione depletion is a well-established mechanism of hemolytic anemia following exposure to naphthalene (ATSDR 2005). Based on intraperitoneal injection experiments, Trevisan et al. (1989) proposed that with repeated exposure, adaptive mechanisms in the liver may compensate for glutathione depletion. This may explain the apparent decrease in susceptibility to hemolytic anemia in laboratory animals with increasing duration of exposure to 1,2-dichloropropane (see Inhalation Exposure section above).

2.8 MUSCULOSKELETAL

Rhabdomyolysis was reported in a 43-year-old man 4 days after a prolonged dermal exposure (~5 hours) to a commercial fixative containing 30–40% 1,2-dichloropropane and 33–38% toluene; the patient made a full recovery (Fiaccadori et al. 2003). No additional studies were located regarding musculoskeletal effects in humans following exposure to 1,2-dichloropropane.

No adverse effects of 1,2-dichloropropane on the musculoskeletal system were found following histological examination of the bone of rats and mice exposed to air concentrations of 1,2-dichloropropane up to 150 ppm, or rabbits exposed to concentrations up to 1,000 ppm, 6 hours/day, 5 days/week for 13 weeks (Nitschke et al. 1988). Similarly, no adverse effects of 1,2-dichloropropane on the musculoskeletal system were found following histological examination of the sternum or costochondral joints of rats and mice exposed 5 days/week via gavage to 1,2-dichlropropane doses as high as 1,000 mg/kg/day for 13 weeks, or 250 mg/kg/day for 103 weeks (NTP 1986).

2.9 HEPATIC

Based on several case reports of occupational exposure, accidental or intentional ingestion, or intentional inhalation abuse (“sniffing” or “huffing”) of large amounts of mixtures containing 1,2-dichloropropane, the liver is one of the main target organs for the toxic effects of 1,2-dichloropropane (Chiappino and Secchi 1968; Di Nucci et al. 1988; Larcan et al. 1977; Lucantoni et al. 1991, 1992; Kubo et al. 2015; Perbellini et al. 1985; Pozzi et al. 1985; Secchi and Alessio 1968; Thorel et al. 1986). Effects associated with exposure include altered serum liver enzymes, impaired liver function, toxic hepatitis, centrilobular and midlobular hepatic necrosis, and liver failure. Recovery was complete in nonfatal cases. Impaired liver function, jaundice, and acute hepatocellular necrosis were also reported in a 43-year-old man 4 days after a prolonged dermal exposure (~5 hours) to a commercial fixative containing 30–40% 1,2-dichloropropane and 33–38% toluene; the patient made a full recovery within 2 weeks (Fiaccadori et al. 2003). Exact exposure levels cannot be determined in these case studies, so a LOAEL cannot be determined.

Several case-series reports and retrospective cohort studies of Japanese print shop workers suggest a potential association between 1,2-dichloropropane (and other chlorinated solvents) and CCA, a rare form of bile duct cancer (Kubo et al. 2014a, 2014b; Kumagai et al. 2013, 2014, 2016; Sobue et al. 2015; Yamada et al. 2014, 2015a, 2015b); see Table 2-4 in Section 2.19 (Cancer) for more details. Elevated serum γ-glutamyl transferase (GGT), alanine aminotransferase (ALT), and aspartate aminotransferase

(AST) levels and jaundice were reported in exposed individuals with CCA (Kubo et al. 2014b; Kumagai et al. 2014).

Hepatic damage has been consistently observed following inhalation and oral exposure to 1,2-dichloropropane in multiple species. Evidence of hepatic tumors following chronic exposure to 1,2-dichloropropane is discussed in Section 2.19 (Cancer).

Inhalation Exposure. In rats, fat-like droplets were observed following intermittent exposure to 3,000 ppm for 7 days (8 hours/day); no exposure-related lesions were observed at ≤1,000 ppm (Zhang et al. 2015). Consistent with these findings, Nitschke and Johnson (1983) found no exposure-related histopathological lesions in the liver of rats exposed to concentrations up to 1,500 ppm for 6 hours. However, exposure to 1,000 ppm for 2 weeks (6 hours/day, 4–5 days/week) resulted in mild liver hepatocellular hypertrophy and elevated liver weights in rats (Nitschke and Johnson 1983). In other acute rat studies, no alterations in serum levels of liver enzymes, which would indicate liver damage, were observed in rats exposed to concentrations up to 1,060 ppm for 4 hours (Di Nucci et al. 1990; Drew et al. 1978); however, highest concentrations were not identified as NOAELs due to lack of liver weight and histology evaluations. Hepatic lesions were observed at lower concentrations in mice and hamsters. In mice, observations included extensive hemorrhagic necrosis after exposure to 500 ppm for 6 hours, vacuolization after exposure to ≥300 ppm for 7 days (8 hours/day) or ≥200 ppm for 14 days (6 hours/day), and increased liver weight and hepatocellular hypertrophy after exposure to 300 ppm for 2 weeks (6 hours/day, 4–5 days/week) (Nitschke and Johnson 1983; Zhang et al. 2015). Increased relative liver weights, altered clinical chemistry (increased AST and ALT), and hepatocellular hypertrophy, necrosis, and granular degeneration were also observed in mice exposed to 300 ppm for 6 hours; these changes were not observed in mice exposed for up to 4 hours (Wang et al. 2019). However, no changes in liver weight or clinical chemistry were observed in mice exposed to concentrations up to 400 ppm for 2 days (6 hours on day 1, 3 hours on day 2) (Toyooka et al. 2017). In hamsters, a slight dilation of hepatic sinusoids was observed following exposure to 400 ppm for 14 days (6 hours/day), but not at concentrations up to 300 ppm for 7–14 days (6–8 hours/day) (Zhang et al. 2015). No exposure-related hepatic lesions were observed at concentrations up to 1,000 ppm in guinea pigs (7 days, 8 hours/day) (Zhang et al. 2015), or rabbits (2 weeks, 6 hours/day, 4–5 days/week) (Nitschke and Johnson 1983).

Increased absolute and relative liver weights were observed in female rats exposed to concentrations ≥500 ppm for 13 weeks (6 hours/day, 5 days/week); however, histopathological changes were only observed at 2,000 ppm (in both sexes) (Umeda et al. 2010). No exposure-related hepatic changes were

observed in male or female rats similarly exposed to concentrations up 250 ppm for 13 weeks (Nitschke et al. 1988), or to 500 ppm for 104 weeks (Umeda et al. 2010). In mice, increased absolute liver weight, changes in clinical chemistry (increased ALT and bilirubin), focal necrosis, and bile duct hyperplasia were seen in males exposed to 250 ppm for 4 weeks (8 hours/day, 7 days/week) (Zhang et al. 2018). Following exposure for 13 weeks (6 hours/day, 5 days/week), increased absolute and relative liver weights accompanied by swelling of centrilobular hepatocytes was observed after exposure to concentrations ≥300 ppm; clinical chemistry alterations (increased AST, ALT, and alkaline phosphatase [ALP] in males), fatty and vacuolic changes, mineralization, and necrosis were also observed at 400 ppm (Matsumoto et al. 2013). No exposure-related hepatic changes were observed in male or female mice similarly exposed to concentrations up to 200 ppm for 13 or 104 weeks (Matsumoto et al. 2013; Nitschke et al. 1988).

Evidence from older studies support that hepatic damage (fatty degeneration, centrilobular congestion, necrosis) can occur following acute exposure to 2,200 ppm in rats and guinea pigs, ≥1,600 ppm in rabbits, and ≥400 ppm in mice (Heppel et al. 1946a, 1948; Highman and Heppel 1946). Similar effects were noted in intermediate-duration studies in rats at ≥1,500 ppm, guinea pigs and mice at ≥400 ppm, and dogs at 1,000 ppm; no adverse effects were observed in the livers of rabbits at concentrations up to 1,500 ppm (Heppel et al. 1946a, 1948; Highman and Heppel 1946).

Oral Exposure. Hepatic effects were consistently observed in laboratory animals acutely exposed to 1,2-dichloropropane at doses as low as 250 mg/kg/day. Liver necrosis, characterized by degenerative effects on the centrilobular hepatocytes and mild to moderate hepatitis, was observed in Sprague-Dawley rats exposed to gavage doses ≥250 mg/kg/day for 1, 5, or 10 consecutive days (Bruckner et al. 1989). No adverse hepatic effects were observed at 100 mg/kg/day. Consistent with these findings, increased liver weight, hepatocyte degeneration and necrosis, and prominent nuclei in centrilobular hepatocytes were observed in F344 rats exposed to gavage doses ≥300 mg/kg/day for 14 days (Gorzinski and Johnson 1989), and hepatic necrosis was observed in rabbits exposed to ≥500 mg/kg/day for 13 days (Kirk et al. 1988). However, the rabbit study (Kirk et al. 1988) was considered inadequate due to low animal numbers per group (n=2). In mice and hamsters, mild and diffuse fatty changes were observed following single gavage administration of 500 mg/kg (only dose tested) (Gi et al. 2015a). The severity of fatty changes increased and extensive centrilobular necrosis was observed when mice received the same dose for 3 days, and when hamsters received 500 mg/kg for 1 day followed by 250 mg/kg/day for 2 days (TWA: 333 mg/kg/day) (Gi et al. 2015a). The dose in hamsters was decreased on day 2 due to one death and toxicity (listlessness) in remaining animals.

Other acute studies evaluated limited hepatic endpoints, but they were not included in the LSE tables or figures due to lack of histological examinations. Increased serum ALT and AST were reported in rats exposed once to 2,000 mg mg/kg/day via gavage (only dose level) (Imberti et al. 1990); liver weights and histology were not assessed in these studies. No changes were observed in rat liver weight following a single exposure to 55 mg/kg (Di Nucci et al. 1988). No changes in maternal liver weight were observed in pregnant rats exposed to gavage doses up to 500 mg/kg/day on GDs 6–15, or pregnant rabbits exposed to gavage doses up to 250 mg/kg/day on GDs 7–19 (Berdasco et al. 1988; Kirk et al. 1989, 1995); serum chemistry and histology were not assessed.

Hepatic lesions were observed at doses as low as 125 mg/kg/day following intermediate exposure to 1,2-dichloropropane; however, observed lesions and NOAEL and LOAEL values were not consistent between all studies. Periportal vacuolization and fibroplasia were found in Sprague-Dawley rats treated with ≥500 mg/kg/day for 13 weeks (5 days/week), with increased liver weights at ≥250 mg/kg/day (Bruckner et al. 1989). No adverse hepatic effects were observed at 100 mg/kg/day. In a 2-generation study with Sprague-Dawley rats, granularity of the hepatocellular cytoplasm was observed in F0 and F1 adults following exposure to estimated doses of 152–293 mg/kg/day in drinking water doses for 13–21 weeks; however, the adversity of this effect, accompanied by increased liver weight in females only, is uncertain (Kirk et al. 1990). In B6C3F1 mice and hamsters, gavage doses of ≥125 mg/kg/day for 4 weeks (5 days/week) resulted in mild to moderate fatty changes in both species and increased liver weight in mice; mice also showed increased serum total cholesterol and triglycerides at 250 mg/kg/day (Gi et al. 2015a). In contrast, NTP (1986) did not report any exposure-related hepatic lesions in B6C3F1 mice exposed to gavage doses up to 500 mg/kg/day for 13 weeks (5 days/week) (NTP 1986).

In the chronic study by NTP (1986), liver necrosis was observed in female rats exposed to gavage doses of 250 mg/kg/day for 103 weeks (5 days/week), but not in females or males exposed to 125 mg/kg/day. The chronic NTP study (1986) also reported necrosis of the liver in male mice similarly exposed to 250 mg/kg/day, but not in males at 125 mg/kg/day, or in females at either dose.

Mechanisms of Hepatotoxicity. Data regarding mechanisms of hepatotoxicity following exposure to 1,2-dichloropropane are limited. A proposed mechanism of general toxicity is glutathione depletion due to glutathione-conjugation of reactive metabolites (Di Nucci et al. 1988; Imberti et al. 1990). Glutathione depletion has been observed in the liver following acute oral or intraperitoneal exposure (Di Nucci et al. 1988, 1990; Imberti et al. 1990; Trevisan et al. 1989, 1991), and Imberti et al. (1990) have shown a

statistically significant association between glutathione depletion in the liver and altered clinical chemistry parameters. If a glutathione precursor (N-acetylcysteine) is administered prior to 1,2-dichloropropane, the extent of liver injury is decreased. Oxidation of 1,2-dichloropropane by CYP2E1 prior to glutathione-conjugation appears to be an important step in hepatotoxicity (Gi et al. 2015a; Yanagiba et al. 2016). In CYP2E1-null mice, intraperitoneal injections of 1,2-dichloropropane did not cause hepatotoxic effects in similarly exposed wild-type mice (Yanagiba et al. 2016). Additionally, treating mice with a CYP450 inhibitor during intermediate-duration inhalation exposure to 1,2-dichloropropane attenuated the compound-induced proliferation of cholangiocytes and hepatocytes, apoptosis of cholangiocytes, and induction of proteins associated with catalytic and carboxylic ester hydrolase activities (Zhang et al. 2018, 2020). Based on intraperitoneal injection experiments, Trevisan et al. (1989) proposed that with repeated exposure, adaptive mechanisms in the liver may compensate for glutathione depletion, resulting in decreased liver toxicity. This is consistent with findings in oral and inhalation studies, which generally observed hepatic effects at lower exposure levels following acute- or intermediate-duration exposures than observed with chronic exposures.

Wang et al (2019) proposed mitochondrial dysfunction in hepatocytes following exposure to 1,2-dichloropropane as a possible mechanism of hepatotoxicity. In mice, inhalation of 1,2-dichloropropane at 300 ppm for 6 hours resulted in inhibition of the mitochondrial electron transport chain complex activities, resulting in mitochondrial dysfunction and increased ATP consumption. The study authors proposed that this decrease in ATP consumption leads to hepatic necrosis. ATP depletion inhibits mitochondrial cytochrome c release. Since release of mitochondrial cytochrome c triggers apoptosis, decreased mitochondrial cytochrome c release inhibits cell apoptosis. Therefore, excessive ATP depletion can result in inhibition of the apoptotic death pathway, leading to cell death via necrosis. Exposure also reduced the activity of microsomal glutathione S-transferase, a key enzyme in the mitochondria that protects against oxidative stress.

2.10 RENAL

Based on several case reports of occupational exposure, accidental or intentional ingestion, or intentional inhalation abuse (“sniffing” or “huffing”) of large amounts of mixtures containing 1,2-dichloropropane, the kidney is a target for the toxic effects of 1,2-dichloropropane (Di Nucci et al. 1988; Perbellini et al. 1985; Pozzi et al. 1985; see also ACGIH 2014; EPA 2016a; IARC 1986, 2017). Effects associated with exposure included impaired kidney function, tubular necrosis, and acute kidney failure. Recovery was complete in nonfatal cases. Acute renal failure, characterized by increased serum creatinine and blood

urea nitrogen (BUN), hyperkalemia, and oliguria, was reported in a 43-year-old man 4 days after a prolonged dermal exposure (~5 hours) to a commercial fixative containing 30–40% 1,2-dichloropropane and 33–38% toluene; the patient made a full recovery within 2 weeks (Fiaccadori et al. 2003). Exact exposure levels cannot be determined in these case studies, so a LOAEL cannot be determined.

Inconsistent findings of kidney damage were observed following inhalation exposure to 1,2-dichloropropane in laboratory animals, and no histopathological lesions of the kidney were associated with oral exposure to 1,2-dichloropropane in any of the species evaluated.

Inhalation Exposure. No exposure-related changes in kidney histology were observed in rats or mice exposed to 1,2-dichloropropane at concentrations up to 1,500 ppm for 6 hours, rats or rabbits exposed to concentrations up to 1,000 ppm for up to 2 weeks (6–7 hours/day, 4–5 days/week), or mice exposed to concentrations up to 300 ppm for 2 weeks (6 hours/day, 4–5 days/week) (Nitschke and Johnson 1983). Similarly, no exposure-related histopathologic effects on the kidneys were observed in 13-week studies (6 hours/day, 5 days/week) in rats exposed to concentrations up to 2,000 ppm, mice exposed to concentrations up to 400 ppm, or rabbits exposed to concentrations up to 1,000 ppm (Matsumoto et al. 2013; Nitschke et al. 1988; Umeda et al. 2010). However, older studies reported fatty degeneration in the kidney in acute-duration studies at concentrations of 2,200 ppm in rats and guinea pigs, ≥1,600 ppm in rabbits, and ≥1,000 ppm in mice (Heppel et al. 1946a, 1948; Highman and Heppel 1946). Similar effects were noted in older intermediate-duration studies in rats and guinea pigs at 1,500 ppm, mice at 400 ppm, and dogs at 1,000 ppm; no changes in kidney histology were observed in rabbits at acute- or intermediate-duration concentrations up to 1,500 ppm (Heppel et al. 1946a, 1948; Highman and Heppel 1946).

In chronic studies, no exposure-related histopathologic effects on the kidneys were observed in rats exposed to concentrations up to 500 ppm (Matsumoto et al. 2013; Umeda et al. 2010) or female mice exposed to concentrations up to 200 ppm for 104 weeks (5 days/week, 6 hours/day). However, increased kidney weight and basophilic changes and cortical mineralization were observed in male mice at all tested concentrations (≥32 ppm) (Matsumoto et al. 2013).

Oral Exposure. No histopathologic changes in the kidneys were observed following acute gavage exposure to 1,2-dichloropropane in rats at doses up to 1,000 mg/kg/day (Bruckner et al. 1989; Gorzinski and Johnson 1989), mice at doses up to 500 mg/kg/day (Gi et al. 2015a), rabbits at doses up to 500 mg/kg/day (Kirk et al. 1988), or hamsters at TWA doses up to 333 mg/kg/day (500 mg/kg/day for 1 day followed by 250 mg/kg/day for 2 days) (Gi et al. 2015a). However, the rabbit study (Kirk et al.

1988) was considered inadequate due to low animal numbers per group (n=2). While no histopathological effects were observed, serum BUN levels were elevated by 1.5–2-fold in rats treated with 1,000 mg/kg/day for 5 or 10 days (Bruckner et al. 1989). Imberti et al. (1990) also reported a significant 2–3-fold increase in serum urea levels in rats 24 and 98 hours after a single administration of 2,000 mg/kg/day (only dose tested); however, increases in serum urea levels at 48 hours were not significant. Due to limited endpoint evaluation (no assessment of kidney weight or histology) and lack of consistency across time points, renal endpoints from the study by Imberti et al. (1990) were not included in the LSE tables or figures.

Other acute studies evaluated limited renal endpoints, but they were not included in the LSE tables or figures due to lack of histological examinations. In a 2-week NTP study (1986), gross pathologic examinations showed reddened renal medullae in almost all rats that were treated with 2,000 mg/kg/day by gavage for 2 weeks. This effect was also observed in mice that were similarly treated at doses ≥125 mg/kg/day. Histological examinations were not performed. NTP (1986) considered the reddened medullae to be a compound-related, but not an adverse effect. No changes in maternal kidney weight were observed in pregnant rats exposed to gavage doses up to 500 mg/kg/day on GDs 6–15, or pregnant rabbits exposed to gavage doses up to 250 mg/kg/day on GDs 7–19 (Berdasco et al. 1988; Kirk et al. 1989, 1995); serum chemistry and histology were not assessed.

In longer-duration studies, no exposure-related histopathological kidney lesions were observed following intermittent gavage exposure (5 days/week) in mice or hamsters at doses up to 250 mg/kg/day for 4 weeks (Gi et al. 2015a), in rats at doses up to 1,000 mg/kg/day for 13 weeks (Bruckner et al. 1989; NTP 1986), in mice at doses up to 500 mg/kg/day for 13 weeks (NTP 1986), or in rats or mice treated with gavage doses up to 250 mg/kg/day for 103 weeks (NTP 1986). Exposure-related kidney lesions were not observed in a 2-generation study in F0 or F1 adult rats exposed to drinking water concentrations up to 0.24% (estimated doses of 152–293 mg/kg/day per sex per generation) for 13–21 weeks (Kirk et al. 1990).

Mechanisms of Renal Toxicity. Data regarding mechanisms of toxicity following exposure to 1,2-dichloropropane are limited. Imberti et al. (1990) proposed that glutathione depletion may contribute to toxicity because a statistically significant association between glutathione depletion in the kidney (and liver) and altered clinical chemistry parameters were observed following acute oral exposure to 1,2-dichloropropane. If a glutathione precursor (N-acetylcysteine) is administered prior to 1,2-dichloro-propane, the extent of kidney injury is decreased.

Odinecs et al. (1995) suggested that males may be more susceptible to renal toxicity following exposure to 1,2-dichloropropane due to sex-specific differences in CYP2E1 expression in the kidney. Differential expression appears to be mediated by testosterone levels. As discussed in Section 2.9 (Hepatic), oxidation of 1,2-dichloropropane by CYP2E1 prior to glutathione conjugation appears to be an important step in hepatotoxicity (Gi et al. 2015a; Yanagiba et al. 2016). Data from Odinecs et al. (1995) suggested that this is also an important step for renal toxicity. In support, glutathione depletion and cytotoxicity following *in vitro* exposure to 1,2-dichloropropane were significantly higher in renal slices from male rats compared with female rats (Trevisan et al. 1992).

2.11 DERMAL

Allergic contact dermatitis has been reported in case studies of humans following chronic occupational exposure to mixtures containing 1,2-dichloropropane; skin symptoms generally resolved following cessation of exposure (Baruffini et al. 1989; Grzywa and Rudzki 1981). Patch testing for reactions to 1,2-dichloropropane was positive in all 12 cases evaluated (Baruffini et al. 1989; Grzywa and Rudzki 1981). In the general population without occupational exposure to 1,2-dichloropropane, only 2/12 subjects showed slight skin erythema in patch testing (Baruffini et al. 1989). Transient skin reddening was reported in a 43-year-old man after a prolonged dermal exposure (~5 hours) to a commercial fixative containing 30–40% 1,2-dichloropropane and 33–38% toluene (Fiaccadori et al. 2003).

Reddened and inflamed skin were observed in rats following exposure to 2.34 g/kg for 24 hours in occluded conditions (Shell Oil Co. 1982). In a 24-hour Draize occlusive patch test, mild skin irritation was observed in male rabbits, and extreme skin irritation (chemical burns, superficial necrosis) was observed in female rabbits following exposure to 1.16 g/mL; skin effects were still evident in both sexes 21 days later, including hardening and lifting of skin in female rabbits (Shell Oil Co. 1982). The cause for the differential effects in males and females is unknown. Following repeated application of 1,2-dichloropropane to the dorsal skin of the ear for 7 days, dermatitis and angiogenesis were observed in mice at doses≥2.73 mL/kg (Jin et al. 2019). Inflammatory markers (IL-6 and TNF-alpha) and an angiogenesis marker (VEGF) were elevated in the skin in a dose-related manner. Shell Oil Co. (1982) also determined that 1,2-dichloropropane is a strong skin sensitizer in guinea pigs at 0.56 g/mL.

No treatment-related skin lesions were observed histologically in rats and mice exposed to air concentrations of 1,2-dichloropropane up to 150 ppm, or rabbits exposed to concentrations up to 1,000 ppm, 6 hours/day, 5 days/week for 13 weeks (Nitschke et al. 1988). No treatment-related skin lesions were observed histologically in rats or mice treated with 1,2-dichloropropane by gavage 5 days/week at doses up to 1,000 mg/kg/day for 13 weeks (NTP 1986), or 250 mg/kg/day for 103 weeks (NTP 1986).

2.12 OCULAR

Periorbital and conjunctival hemorrhages were seen in a patient who was admitted to a hospital after exposure to vapors of 1,2-dichloropropane (Pozzi et al. 1985). It was not clear if the hemorrhages resulted from inhalation of 1,2-dichloropropane or from direct exposure of the eye to the 1,2-dichloropropane vapor. No concentration information was provided.

1,2-Dichloropropane is an eye irritant in rabbits. Initial pain, redness, iridial irritation, and corneal ulceration were observed following direct ocular instillation of undiluted 1,2-dichloropropane (Exxon 1981c; Shell Oil Co. 1982). All animals recovered within 7–14 days. Conjunctivitis was observed in guinea pigs following acute inhalation exposure to 2,200 ppm (7 hours) (Heppel et al. 1946a).

No adverse effects on the eye were found following gross and histopathologic examination of rats and mice exposed to air concentrations of 1,2-dichloropropane up to 150 ppm, or rabbits exposed to concentrations up to 1,000 ppm for 13 weeks (6 hours/day, 5 days/week) (Nitschke et al. 1988). No exposure-related effects were observed in ophthalmological examinations conducted before and after drinking water exposure in F0 rats in a 2-generation study by Kirk et al. (1990). F0 males were exposed to doses up to 152 mg/kg/day for 10–12 weeks prior to mating through mating, and F0 females were exposed to doses up to 254 mg/kg/day for 10–12 weeks prior to mating through lactation.

2.13 ENDOCRINE

No studies were located regarding endocrine effects in humans following exposure to 1,2-dichloropropane.

Inhalation and oral exposure studies in laboratory animals show inconsistent evidence of histopathological effects in the adrenal glands following exposure to very high levels of 1,2-dichloropropane associated with mortality. No histopathological changes were observed in other endocrine organs

(thyroid, parathyroids, pancreas, pituitary gland) in exposed laboratory animals. Although some reproductive organs have endocrine functions, all reproductive organ effects are discussed in Section 2.16 (Reproductive).

Inhalation Exposure. Histopathological changes in the adrenal glands were observed following 1–8 exposures to 2,200 ppm (7 hours/exposure), including depletion of the lipoid material of the adrenal cortex in rats and adrenal necrosis in guinea pigs (Heppel et al. 1946a; Highman and Heppel 1946). Similar effects were noted in a limited number of dogs exposed to 1,000 ppm (7 hours/day, 5 days/week) for up to 96 exposures (Heppel et al. 1946a). Fatty changes were observed in the adrenal glands of female rats, but not male rats, following exposure to 2,000 ppm for 13 weeks (6 hours/day, 5 days/week) (Umeda et al. 2010). No adrenal gland changes were observed in rats following exposure to concentrations up to 1,000 ppm for 2 or 13 weeks (Nitschke and Johnson 1983; Nitschke et al. 1988; Umeda et al. 2010), or up to 500 ppm for 104 weeks (Umeda et al. 2010). In mice, no histopathological changes in the adrenal glands were observed following intermittent exposure (6 hours/day, 4–5 days/week) to concentrations up to 300 ppm for 2 weeks (Nitschke and Johnson 1983), 400 ppm for 13 weeks (Matsumoto et al. 2013; Nitschke et al. 1988), or 200 ppm for 104 weeks (Matsumoto et al. 2013). Additionally, no histopathological changes in the adrenal glands were observed in rabbits following intermittent exposure (6 hours/day, 5 days/week) to concentrations up to 1,000 ppm for 2 weeks (Nitschke and Johnson 1983), or 150 ppm for 13 weeks (Nitschke et al. 1988).

No histopathological changes were reported in the thyroid, parathyroids, pancreas, or pituitary gland in rats, mice, or rabbits following exposure to concentrations as high as 2,000 ppm for 13 weeks, or 500 ppm for 104 weeks (6 hours/day, 5 days/week) (Matsumoto et al. 2013; Nitschke et al. 1988; Umeda et al. 2010).

Oral Exposure. Increased fat deposition in the adrenal glands was observed in male rats exposed to gavage doses of ≥500 mg/kg/day for 13 weeks (5 days/week); vacuolization of the adrenal medulla and lipidosis of the adrenal cortex were also observed in Sprague-Dawley male rats exposed to 750 mg/kg/day and sacrificed moribund on day 10 (Bruckner et al. 1989). No fatty changes were observed in the adrenal glands of similarly exposed females or male or female rats exposed to gavage doses up to 1,000 mg/kg/day for 1–10 days (Bruckner et al. 1989). In F344 rats, no histopathological alterations were observed in the adrenal glands of males or females exposed to gavage doses up to 1,000 mg/kg/day for 13 weeks, or 250 mg/kg/day for 103 weeks (5 days/week) (NTP 1986). No histopathological changes

were observed in male or female mice following gavage doses up to 500 mg/kg/day for 13 weeks or 250 mg/kg/day for 103 weeks (5 days/week) (NTP 1986).

No histopathological changes were observed in the thyroid, parathyroids, pancreas, or pituitary gland in rats or mice following gavage doses up to 1,000 mg/kg/day for 13 weeks, or 250 mg/kg/day for 103 weeks (5 days/week) (NTP 1986).

2.14 IMMUNOLOGICAL

As reported in the Section 2.11 (dermal), allergic contact dermatitis with positive patch testing has been reported in case-studies of humans following chronic occupational exposure to mixtures containing 1,2-dichloropropane; skin symptoms generally resolved following cessation of exposure (Baruffini et al. 1989; Grzywa and Rudzki 1981). Mild reactions were only observed in patch testing of 2/120 subjects who did not have prior occupational exposure to 1,2-dichloropropane (Baruffini et al. 1989). In a case-control study in South Korea, Choi et al. (2009) did not find a significant difference in indoor and outdoor residential air levels of 1,2-dichloropropane between individuals with dermatitis (n=50) or asthma (n=36) and control subjects (n=28); 34 VOCs were measured in this study. No additional information regarding the potential for immunological effects in humans following exposure to 1,2-dichloropropane were available.

As reported in Section 2.11 (dermal), 1,2-dichloropropane is a strong skin sensitizer in guinea pigs (Shell Oil Co. 1982). No additional parameters of immunological function have been directly assessed following exposure to 1,2-dichloropropane in any available laboratory animal study. Immune system evaluation in additional studies is limited to organ weight and/or histology, without evaluation of potential effects on immunological function.

Most inhalation studies did not observe exposure-related weight or histopathological changes in the thymus following intermediate exposure in rats, mice, and rabbits at concentrations up to 2,000 ppm (Matsumoto et al. 2013; Nitschke et al. 1988; Umeda et al. 2010), or chronic exposure in rats or mice at concentrations up to 500 ppm (Matsumoto et al. 2013; Umeda et al. 2010). However, a decrease in the absolute and relative thymus weight and a decrease in cortical lymphoid cells were observed in mice exposed to 300 ppm 6 hours/day, 4–5 days/week, for 2 weeks (Nitschke and Johnson 1983).

No treatment-related histopathological lesions were observed in the thymus of rats or mice exposed 5 days/week via gavage doses up to 1,000 mg/kg/day for 13 weeks or up to 250 mg/kg/day for 103 weeks (NTP 1986). Reduced survival of the high-dose female mice in the 103-week study may have been partly due to infections of the reproductive system, as inflammation of the reproductive system was observed in many of the animals that died during the study (5/11 controls, 9/14 at 125 mg/kg/day, and 14/22 at 250 mg/kg/day). However, available data is inadequate to determine if 1,2-dichloropropane caused an increased susceptibility to the infection observed in this study.

Histopathological lesions observed in the spleen and bone marrow following inhalation and oral exposure to 1,2-dichloropropane are secondary to hemolytic anemia (e.g., elevated spleen weight, hemosiderin deposits, increased hematopoiesis) rather than immunotoxicity; see Section 2.7 (Hematological) for more information. Evidence of splenic tumors following chronic exposure to 1,2-dichloropropane is discussed in Section 2.19 (Cancer).

2.15 NEUROLOGICAL

As expected with high-level solvent exposure, severe CNS depression and coma have been reported in cases of accidental or intentional ingestion or intentional inhalation abuse (“sniffing” or “huffing”) of large amounts of mixtures containing 1,2-dichloropropane (Larcan et al. 1977; Perbellini et al. 1985; see also reviews by ACGIH 2014; EPA 2016a; IARC 2017). Rubin (1988) also reported fatigue, possibly attributable to CNS depression, in people who were exposed to unknown concentrations of 1,2-dichloropropane from a tank truck that leaked 2,000 gallons of the chemical. Exact exposure levels cannot be determined in these case studies, so a LOAEL cannot be determined.

An occupational case study reported dizziness, headache, double vision, nausea and vomiting, and ataxia in a Korean worker exposed to 1,2-dichloropropane over the course of 7 work days in June 2017 while removing rust from inside cleaning trays of an ultrasonicator that used 1,2-dichloropropane as a detergent to clean automotive parts; the worker did not wear provided personal protective equipment (Kwak et al. 2018). Symptoms improved over the weekend but worsened during the workday, and CNS effects did not reoccur once the worker was reassigned to a job without exposure to detergents or organic solvents. Time-weighted air levels in the automotive accessory manufacturing plant ranged from 8.4 ppm in June 2017 to 26.9–41.5 ppm in September 2017; peak measurements taken during rust removal ranged from 49.8 to 76.6 ppm in September 2017. The time spent engaged in rust removal over the course of a workday was not reported.

1,2-Dichloropropane is a CNS depressant in animals at high exposure levels via inhalation and oral routes. There is no evidence that exposure leads to damage of CNS tissues.

Inhalation Exposure. Mild CNS depression (drowsiness, listlessness, incoordination) was observed in rats, mice, and guinea pigs during 7-hour exposures to concentrations ≥1,000 ppm, with gross motor incoordination and prostration at 2,200 ppm (Heppel et al. 1946a). Animals became less susceptible to CNS depression with repeated exposures. CNS depression has been observed following 6-hour inhalation exposure to 1,2-dichloropropane in both mice and rats (Nitschke and Johnson 1983). Anesthesia was observed in rats at 1,500 ppm. In mice, lethargy was observed at ≥500 ppm, with lethal CNS depression at 1,500 ppm.

Sidorenko et al. (1976) described the sequence of signs of intoxication in mice that were acutely exposed by inhalation to 1,2-dichloropropane. General agitation and decreased coordination of movements occurred initially, followed by sluggishness, amyotonia, and sporadic clonic spasms, and subsequently by loss of righting reflex. The loss of the righting reflex occurred at the lowest concentration given (1,000 ppm). Sidorenko et al. (1979) evaluated the neurological effects in rats resulting from acute and intermediate duration exposure to 1,2-dichloropropane. A total threshold indicator (TTI) was used to assess the effects on the CNS, but the details of the TTI were not explained in the study. In addition, control data and numbers of treated rats and mice were not reported. Due to these inadequacies, these studies were not included in the LSE tables or figures.

No overt signs of neurotoxicity, changes in brain weight, or exposure-related lesions in nervous system tissue were reported in rats or mice intermittently exposed (6 hours/day, 5 days/week) to concentrations up to 2,000 or 400 ppm, respectively, for 13 weeks, or 500 or 200 ppm, respectively, for up to 103 weeks (Masumoto et al. 2013; Nitschke et al. 1988; Umeda et al. 2010). No overt signs of neurotoxicity or exposure-related lesions in nervous system tissue were reported in rabbits similarly exposed to concentrations up to 1,000 ppm for 13 weeks (Nitschke et al. 1988). No tests of neurological function or behavioral assays were conducted in these studies.

Oral Exposure. Three studies were specifically designed to assess neurobehavior following acute oral exposure to 1,2-dichloropropane. In both 2- and 13-week neurotoxicity studies, transient mild clinical signs (blinking, lacrimation, salivation) were observed in rats following gavage administration for 3–4 days, but not during the remainder of the study duration (Gorzinski and Johnson 1989; Johnson and

Gorzinski 1988). A trend toward reduced locomotion was reported at ≥300 mg/kg/day in the 2-week study (Gorzinski and Johnson 1989). The 13-week study reported no exposure-related changes in monthly assessments of neurological function (functional observation battery, hindlimb grip strength, motor activity) at doses up to 200 mg/kg/day; based on the lack of effects in behavioral testing, a NOAEL of 200 mg/kg/day was established for neurological effects following repeated exposure (Johnson and Gorzinski 1988). In a gestational exposure study, adverse effects observed during an observational battery in pregnant rats exposed via gavage on GDs 6–21 included decreased movement, muscle tone, and extensor thrust reflex, and increased salivation and lacrimation at 125 mg/kg/day, but not ≤30 mg/kg/day (Kirk et al. 1995).

Clinical signs of neurotoxicity were observed in other oral studies that were not specifically designed to evaluate neurological function or behavior. Dose-related increases were noted in CNS depression in rats following gavage doses ≥100 mg/kg/day for 1–10 consecutive days, with transient effects at lower doses and prolonged and/or severe depression at ≥500 mg/kg/day (Bruckner et al. 1989; Exxon 1981a; Kirk et al. 1989; Shell Oil Co. 1982). CNS depression was also reported in rabbits following gavage doses ≥500 mg/kg/day for 13 consecutive days (Kirk et al. 1988); however, this study is considered inadequate due to low animal numbers per group (n=2). In an intermediate-duration study, Bruckner et al. (1989) also observed pronounced CNS depression in rats treated with 500 mg/kg/day by gavage for 13 weeks (5 days/week). No CNS depression was reported at doses up to 250 mg/kg/day; it is unclear if no effects were observed, or if effects were not reported due to the expected transient nature of effects at doses <500 mg/kg/day (based on observations in acute studies).

No histopathologic lesions were found in the brain of rats at doses up to 1,000 mg/kg/day for up to 13 weeks (Bruckner et al. 1989; Johnson and Gorzinski 1988; NTP 1986); mice at doses up to 500 mg/kg/day for 13 weeks (NTP 1986); or rats and mice at doses up to 250 mg/kg/day for 103 weeks (NTP 1986).

2.16 REPRODUCTIVE

Pozzi et al. (1985) reported the case of a woman who was hospitalized with metrorrhagia (bleeding from the uterus between menstrual periods) after acute inhalation of 1,2-dichloropropane. The metrorrhagia was a transient effect. No information regarding concentration was given. No additional information regarding the potential for reproductive system effects in humans following exposure to 1,2-dichloropropane were available.

The reproductive system does not appear to be a sensitive target of 1,2-dichloropropane toxicity in laboratory animals.

Inhalation Exposure. No inhalation studies evaluating the potential for 1,2-dichloropropane to alter reproductive capability in laboratory animals were available. However, Sekiguchi et al. (2002) observed that exposure to 1,2-dichloropropane for approximately 3 weeks (8 hours/day) significantly increased the incidence of lengthened estrous cycles (≥6 days) in nulliparous female rats at ≥100 ppm and decreased ovulation at 200 ppm; no changes in the estrous cycle or ovulation were observed at 50 ppm. No exposure-related changes in the weight of the ovaries or uterus were observed; organs were not examined for histopathological lesions, and fertility was not assessed (Sekiguchi et al. 2002).

Several inhalation studies reported a lack of exposure-related histopathological changes in reproductive organs following exposure to 1,2-dichloropropane; however, they did not assess reproductive function. In 2-week studies (6 hours/day, 4–5 days/week), no histopathological changes were observed in the testes of rats, mice, or rabbits exposed to concentrations up to 1,000, 300, or 1,000 ppm, respectively (Nitschke and Johnson 1983). In intermediate- and chronic-duration studies (6 hours/day, 5 days/week), no histological changes were observed in reproductive organs in rats at ≤2,000 ppm for 13 weeks or ≤500 ppm for up to 104 weeks (Nitschke et al. 1988; Umeda et al. 2010), mice at ≤400 ppm for 13 weeks or ≤200 ppm for up to 104 weeks (Matsumoto et al. 2013; Nitschke et al. 1988), or rabbits at ≤1,000 ppm for 13 weeks (Nitschke et al. 1988).

Oral Exposure. Reproductive endpoints have been assessed following oral exposure to 1,2-dichloropropane in a 2-generation drinking water study in rats and gestational gavage studies in rats and rabbits. In the 2-generation study, there were no exposure-related changes in mating, fertility, or litter indices in either generation at drinking water concentrations up to 0.24% (estimated doses ranged from 152 to 293 mg/kg/day per sex per generation); additionally, no exposure-related changes in reproductive organ histology were observed in parental animals (Kirk et al. 1990). Similarly, in gestational studies, no dose-related effects on the number of corpora lutea, number of implantation sites, number of resorptions, gravid uterine weight, or number of live and dead fetuses were found at doses up to 500 mg/kg/day in rats exposed on GDs 6–21, or 150 mg/kg/day in rabbits exposed on GDs 7–19 (Kirk et al. 1989; 1995). In a dose-range finding study, complete litter resorption was observed in 2/5 surviving rabbit does at 250 mg/kg/day; however, this dose was associated with maternal toxicity (2/7 maternal deaths) (Berdasco et al. 1988).

In a series of studies in Sprague-Dawley male rats, Bruckner et al. (1989) reported testicular degeneration in males treated with gavage doses ≥500 mg/kg/day for 10 consecutive days or for 13 weeks (5 days/week). The degeneration included reduced sperm production, increased numbers of degenerate sperm, and reduced numbers of sperm in the epididymis. However, no exposure-related changes were observed in the testes of F344 rats similarly exposed to doses up to 1,000 mg/kg/day for 13 weeks (NTP 1986). No testicular effects were observed in rats of either strain exposed to doses up to 1,000 mg/kg/day for 1–5 days, or up to 250 mg/kg/day for 10 days, 13 weeks, or 103 weeks (Bruckner et al. 1989, NTP 1986). In male mice, no exposure-related histopathological lesions were observed in male reproductive organs following exposure to doses up to 500 mg/kg/day for 13 weeks, or 250 mg/kg/day for 103 weeks (NTP 1986). Reproductive function was not assessed in these studies.

No exposure-related histopathological changes were observed in female reproductive organs in rats exposed to gavage doses up to 1,000 mg/kg/day for 13 weeks (5 days/week); however, rats exposed to ≥250 mg/kg/day for up to 103 weeks had significantly increased incidences of mammary gland hyperplasia and mammary tumors (NTP 1986); see more details in Section 2.19 (Cancer). In female mice, increased incidences of suppurative infection of the ovary, uterus, or other organs were observed following exposure to gavage doses of 125 and 250 mg/kg/day for 103 weeks (5 days/week); however, it is not known if these infections were related to 1,2-dichloropropane treatment since controls were also infected (NTP 1986). Reproductive function was not assessed in these studies.

2.17 DEVELOPMENTAL

No studies were located regarding developmental effects in humans following exposure to 1,2-dichloropropane.

The potential for developmental effects in laboratory animals has been assessed via the oral route only. In gestational studies, an increased incidence of delayed ossification of the bones of the skull was observed in the fetuses of rat dams exposed to 125 mg/kg/day via gavage on GDs 6–21, and rabbit does exposed to 150 mg/kg/day via gavage on GDs 7–19 (Kirk et al. 1995). In both species, maternal toxicity occurred at the fetotoxic dose, including clinical signs (CNS depression, salivation, and lacrimation) and decreased body weight in rat dams, and anorexia and anemia in rabbit does (Kirk et al. 1995). No maternal toxicity or fetal effects were observed at doses up to 30 mg/kg/day in rats, or 50 mg/kg/day in rabbits, and no

evidence of embryotoxic effects or increased incidences of malformations were observed at any dose. Observed fetotoxicity may be secondary to maternal toxicity in both species.

In a 2-generation study, decreased neonatal survival and reduced neonatal body weights were observed in the F1 offspring following parental exposure to a drinking water concentration of 0.24% (estimated doses of 152–254 mg/kg/day) prior to mating through lactation (Kirk et al. 1990). Parental toxicity was also observed at this dose (decreased body weight, maternal anemia, hepatic toxicity); therefore, observed neonatal effects may be secondary to parental toxicity. No parental or offspring toxicity was observed at lower concentration levels ≤0.10% (estimated doses 83–127 mg/kg/day), and no external malformations were observed at any dose (offspring were not assessed for skeletal or visceral malformations or variations).

2.18 OTHER NONCANCER

Studies evaluating potential other noncancer effects following exposure to 1,2-dichloropropane in humans or animals were not located.

2.19 CANCER

A series of case reports and retrospective cohort studies from Japanese printing companies indicate that exposure to 1,2-dichloropropane (and/or other chlorinated solvents) may increase the risk of developing cholangiocarcinoma (CCA), a rare form of bile duct cancer (Kinoshita et al. 2019; Kubo et al. 2013, 2014a, 2014b; Kumagai 2014; Kumagai et al. 2013, 2014, 2016; Nakagawa et al. 2015; Ogawa et al. 2020; Sobue et al. 2015; Tomimaru et al. 2015; Yamada et al. 2014, 2015a, 2015b). The case-series reports and cohort studies are discussed below; additional details can be found in Table 2-4.

Initial studies focused on a cluster of CCA cases in male print shop workers from Osaka, Japan (Kubo et al. 2014a; Kumagai et al. 2013, 2014, 2016; Sobue et al. 2015). In all, 17 cases were diagnosed between 1996 and 2012, 9 of which were fatal. None of the workers had known risk factors for developing CCA (e.g., primary sclerosing cholangitis, hepatolithiasis, pancreaticobiliary maljunction, or infection with liver flukes), and all were below the average age of diagnosis in Japan (65.5 years of age) (Kubo et al. 2014a). Based on work history, all 17 cases were exposed to 1,2-dichloropropane, 11/17 cases were exposed to dichloromethane, and 8/17 cases were exposed to 1,1,1-trichloroethane (Kubo et al. 2014a; Kumagai et al. 2016; Sobue et al. 2015). No air monitoring data were available; however, using exposure estimates based on reported chemical quantities used per year, estimated 1,2-dichloropropane air levels

Table 2-4. Cholangiocarcinoma (CCA) in Humans Exposed to 1,2-Dichloropropane

Reference and study population	Exposure	Outcomes
Occupational studies from a printing company based in Osaka, Japan		
Kumagai et al. 2013, 2014 Retrospective cohort study of print shops in Osaka, Japan; 51 male printers and 11 male workers from adjacent front room employed between 1991 and 2006 Employment duration: 1–17 years (mean 10 years)	**Exposure:** Exposure estimates were generated based on amounts of the chemicals reportedly used between 1991 and 2006 using experimental data generated by JNIOSH 1,2-DCP (used from 1991–2006): Print-shop: 190–310 ppm Front-room: 70–110 ppm DCM (used from 1991 to 1997/1998): Print-shop: 140–360 ppm Front-room: 50–130 ppm	**Cancer effect:** CCA observed in 11/51 printers (22%) and 0/11 front-room workers 11/11 cases were exposed to 1,2-DCP 10/11 cases were exposed to DCM SMR (95% CI) for CCA among 1,2-DCP-exposed workers (using national incidence): 2,900 (1,100–6,400)
Kubo et al. 2014a Case-series report of 17 male print shop workers diagnosed with CCA between 1996 and 2012 in Osaka, Japan; all printers were employed at the printing company described by Kumagai et al. (2013, 2014) Employment duration: 6–19 years (mean 11 years)	**Exposure:** Exposure to 1,2-DCP, DCM, and TCE was determined based on job history; no exposure estimates were calculated 1,2-DCP (used from 1991 to 2006) DCM (used from 1991 to 1996) TCE (used from 1991 to 1992)	**Cancer effect:** Based on employment records, estimated CCA incidence from 1981 to 2012 was 17/111 (15%) Based on job history: 17/17 cases exposed to 1,2-DCP 11/17 cases exposed to DCM 8/17 cases exposed to TCE
Sobue et al. 2015 Retrospective cohort study of print shop in Osaka, Japan; 86 male and 20 female workers employed between 1985 and 2012; all printers were employed at the printing company described by Kumagai et al. (2013, 2014, 2016) and Kubo et al. (2014a)	**Exposure:** Exposure to 1,2-DCP and DCM was determined based on job history; no exposure estimates were calculated 1,2-DCP (used from 1991 to 2006) DCM (used from 1991 to 1996) Note: Exposure to TCE expected from 1985-1992 based on report by Kubo et al. (2014a) and Kumagai et al. (2016)	**Cancer effect:** CCA incidence was 17/106 (16%); same cases initially described by Kubo et al. (2014a) SIR (95% CI) for CCA among 1,2-DCP-exposed workers All workers: 1,319.9 (658.9–2,361.7) Male workers 1,163.2 (677.6–1,862.4)

Table 2-4. Cholangiocarcinoma (CCA) in Humans Exposed to 1,2-Dichloropropane

Reference and study population	Exposure	Outcomes
Employment duration: 1–16 years (1,452.4 total person-years of exposure)		Workers exposed to 1,2-DCP only: 1,002.8 (368.0–2182.8) Workers exposed to 1,2-DCP + DCM: 1,319.9 (658.9–2361.7)
Kumagai et al. 2016 Retrospective cohort study of three print shops in Osaka, Japan and one print shop in Tokyo, Japan (all run by the same company; only Osaka Plant 2 currently operational); 78 male workers and 17 female workers employed between 1985 and 2006 (71 printers, 20 front room workers, 4 delivery workers); some workers were employed in multiple plants during working history Employment duration: Employment duration not reported; median (range) exposure to 1,2-DCP was reported as 3.3 years (0.3–15.1 years)	**Exposure:** Exposure estimates were generated based on amounts of the chemicals reportedly used between 1985 and 2006 using experimental data generated by JNIOSH Printers: November 1987–February 1996 (Osaka Plants 1 and 2) 1,2-DCP: 130–210 ppm DCM: 65–170 ppm March 1996–October 2006 (Osaka Plants 2 and 3; Tokyo Plant) 1,2-DCP: 84–346 ppm Front room workers: April 1991–February 1996 (Osaka Plant 2) 1,2-DCP: 51–76 ppm DCM: 45–100 ppm March 1996–October 2006 (Osaka Plant 2; Tokyo Plant) 1,2-DCP: 55–130 ppm Workers were also exposed to TCE in Osaka Plants 1 and 2 until 1992 (exposure estimates not reported).	**Cancer effect:** CCA incidence was 17/95 (18%); same cases initially described by Kubo et al. (2014a); all cases were men SIR (95% CI) for CCA among 1,2-DCP-exposed workers All workers (n=95): 1,171 (682–1,875) Male workers (n=78): 1,203 (701–1,927) Workers exposed to 1,2-DCP only (n=62): 1,019 (374–2,218) Workers exposed to 1,2-DCP + DCM (n=33): 1,275 (636–2,280) RR (95% CI) of CCA per tertile increase in cumulative exposure to 1,2-DCP (ppm-years; lag=0) Tertile 1 (1–1,599) 1 (Referent) Tertile 2 (1,600–2,399) 14.9 (4.1–54.3) Tertile 3 (2,400–3,499) 17.1 (3.8–76.2) RR (95% CI) of CCA per inter-tertile increase in cumulative exposure to 1,2-DCP (ppm-years; lag=5 years) Tertile 1 (1–1,199) 1 (Referent) Tertile 2 (1,200–2,049) 11.4 (3.3–39.6) Tertile 3 (2,050–3,499) 32.4 (6.4–163.9) For both models, a trend test in RR values across cumulative exposure levels (adjusted

Table 2-4. Cholangiocarcinoma (CCA) in Humans Exposed to 1,2-Dichloropropane

Reference and study population	Exposure	Outcomes
		for sex, age, calendar year, and exposure to DCM) was statistically significant (p<0.001)
Occupational reports from print shops in multiple Japanese cities[a]		
Okamoto et al. (2013) Retrospective cohort study (using Japan Health Insurance Association database); 201,937 workers employed in printing and related industries Employment duration: not reported	**Exposure:** No exposure estimates were made; chemicals used in "printing and related industries" not reported	**Cancer effect:** CCA incidence (based on health insurance claims) was 76/201,937 (0.04%) of workers in printing and related industries SPRR (95% CI) for CCA among workers in printing and related industries All: 1.28 (0.91–1.79) Males: 1.31 (0.91–1.89) Males ages 30–49: 1.78 (0.63–5.00)
Kubo et al. 2014b Case-series report of nine male printers diagnosed with CCA between 1988 and 2011 from 11 print shops in Japan (Osaka, Miyagi, Fukuoka, Hokkaido, Aomori, Saitama, Aichi) Employment duration: 3–19 years (mean 13 years)	**Exposure:** Exposure to 1,2-DCP, DCM, and TCE was determined based on job history; reported "high" levels of all three chemicals, but no quantitative exposure estimates were calculated 1,2-DCP (3–16 years exposure) DCM (3–19 years exposure) TCE (duration of exposure not reported) Note: not all cases exposed to all three solvents	**Cancer effect:** Case reports of nine CCA cases in seven print shops (cancer incidence not estimated) Based on job history: 7/9 cases exposed to 1,2-DCP 9/9 cases exposed to DCM 4/9 cases exposed to TCE Note: The two cases without 1,2-DCP exposure were exposed to both DCM and TCE

Table 2-4. Cholangiocarcinoma (CCA) in Humans Exposed to 1,2-Dichloropropane

Reference and study population	Exposure	Outcomes
Yamada et al. 2014 Case-series report of six male printers diagnosed with CCA between 1998 and 2013 from three print shops in Japan (Miyagi, Fukuoka, Hokkaido) Employment duration: 10–16 years	**Exposure:** Exposure levels were not measured; estimates were based on amounts of the chemicals reportedly used 1,2-DCP (ppm): Shop 1: 80–170; Shop 2: 62–200; Shop 3: 110–240 DCM (ppm): Shop 1: <1; Shop 2: 0–180; Shop 3: 0–180 TCE Shops 1 and 3: used (no exposure estimates) DCFE: Shop 2: used (no exposure estimates)	**Cancer effect:** Case reports of six CCA cases in three print shops (cancer incidence not estimated) Based on job history: 6/6 cases exposed to 1,2-DCP 4/6 cases exposed to DCM 4/6 cases exposed to TCE 2/6 cases exposed to DCFE
Yamada et al. 2015a Case-series report of seven male printers diagnosed with CCA between 2002 and 2011 from eight print shops in Japan from five cities (Osaka, Aichi, Shizuoka, Saitama, Aomori); one printer worked in both Shop 2 and 3 Employment duration: 4–19 years	**Exposure:** Exposure levels were not measured; estimates were based on amounts of the chemicals reportedly used 1,2-DCP (shift TWAs in ppm) Shop 1: 92–100; Shop 2: 16–29; Shop 4: 7–17; Shop 5: 58–210; no exposure in Shops 3, 6, 7, 8 DCM (shift TWAs in ppm) Shop 1: 15–18; Shop 2: 25–55; Shop 3: 68–94; Shop 4: 20; Shop 5: 31–270; Shop 6: 84–90; Shop 7: 440; Shop 8: 77–110 TCE Shops 5, 6, and 7: used (no exposure estimates) DCFE: Shop 5: used (no exposure estimates)	**Cancer effect:** Case reports of seven CCA cases in eight print shops (cancer incidence not estimated) Based on job history: 4/7 cases exposed to 1,2-DCP 7/7 cases exposed to DCM 3/7 cases exposed to TCE 1/7 cases exposed to DCFE

Table 2-4. Cholangiocarcinoma (CCA) in Humans Exposed to 1,2-Dichloropropane

Reference and study population	Exposure	Outcomes
Yamada et al. 2015b Case-series report of five male printers and one male coater diagnosed with CCA between 1993 and 2013 from seven print shops and two coating shops in Japan from four cities (Fukuoka, Aichi, Tokyo, Kyoto); one printer worked in Shops 2–4, and the one coater worked in Shops 8+9; there is no case overlap with Yamada et al. (2014) or (2015a) Employment duration: 9–30 years	**Exposure:** Exposure levels were not measured; estimates were based on amounts of the chemicals reportedly used Print shops: 1,2-DCP (shift TWAs in ppm) Shop 1: 74–170; Shop 3: 200; Shop 4: 230; Shop 5: 130–160; Shop 6: 13–65; Shop 7: 59; no exposure in Shop 2 DCM (shift TWAs in ppm) Shop 1: 35–140; Shop 3: 300; Shop 4: 350; Shop 5: 240–470; Shop 6: 20–98; Shop 7: 170–370; no exposure in Shops 2, 8, 9 TCE Shops 6 and 7: used (no exposure estimates) DCFE: Shops 1 and 6: used (no exposure estimates) Coating shops: 1,2-DCP (shift TWAs in ppm): Shop 8: 19; Shop 9: 5 DCFE: Shops 8 and 9: used (no exposure estimates)	**Cancer effect:** Case reports of six CCA cases in seven print shops and two coating shops (cancer incidence not estimated) Based on job history: 6/6 cases exposed to 1,2-DCP 5/6 cases exposed to DCM 2/6 cases exposed to TCE 3/6 cases exposed to DCFE

[a]The cases reported by Okamoto et al. (2013), Kubo et al. (2014a), and Yamada et al. (2014, 2015a, 2015b) are distinct from the 17 cases reported by Kumagai et al. (2013, 2014, 2016), Kubo et al. (2014a), or Sobue et al. (2015). However, it is unclear if there is overlap between the cases reported by Okamoto et al. (2013), Kubo et al. (2014b), or Yamada et al. (2014, 2015a, 2015b).

1,2-DCP = 1,2-dichloropropane; CI = confidence interval; DCFE = 1,1-dichloro-1-fluoroethane; DCM = dichloromethane; JNIOSH = Japanese National Institute of Occupational Safety and Health; RR = relative risk; SIR = standardized incidence ratio; SMR = standardized mortality ratio; SPRR = standardized prevalence rate ratio; TCE = 1,1,1-trichloroethane; TWA = time-weighted average

from 1991 to 2006 in the currently operational shop ranged from 190 to 310 ppm in the printing area and from 70 to 110 ppm in the front room (Kumagai et al. 2013). Between 1991 and 1997/1998, dichloromethane estimated exposure levels ranged from 140 to 360 ppm in the print shop and from 50 to 130 ppm in the front room; 1,1,1-trichloroethane exposure levels from 1991 to 1992 were not estimated (Kumagai et al. 2013). Of the 17 cases, 16 were male printers and 1 was a male front-room worker (Kumagai et al. 2016). The lack of female cases cannot be interpreted due to the low number of female subjects.

Several analyses have been conducted to estimate the potential risk of developing CCA following exposure to chlorinated solvents using employment records from the Japanese printing company described above (Kumagai et al. 2013, 2014; Sobue et al. 2015; see Table 2-4). The most complete analysis combined workers from the four plants that were open continuously including 71 printers (65 males, 6 females) and 24 front room/delivery workers (13 males, 11 females). When considering these four plants together, the CCA incidence was 17/95 (18%), which was significantly elevated compared with the incidence expected based on the rates in the general Japanese population (0.02%), both in workers exposed to 1,2-dichloropropane only or both 1,2-dichloropropane and dichloromethane (Kumagai et al. 2016). Further analysis reported a statistically significant increase in relative risk across cumulative exposure to 1,2-dichloropropane (see Table 2-4). The relative risk of CCA in workers exposed to dichloromethane, compared to those not exposed, was not significantly elevated (Kumagai et al. 2016). Based on this analysis, the study authors concluded that there was a dose-related increased risk of CCA in printers exposed to 1,2-dichloropropane (Kumagai et al. 2016).

Additional case-series reports from Japan have demonstrated that CCA cases in printers are not limited to a single company (see Table 2-4). In a series of papers, Yamada et al. (2014, 2015a, 2015b) identified 19 male printers diagnosed with CCA between 1993 and 2013 from 19 print shops across several Japanese cities. Most printers diagnosed with CCA were exposed to both 1,2-dichloropropane and dichloromethane (13/19) at estimated levels of 5–240 and 15–470 ppm, respectively. Of the remaining six cases, three were exposed to1,2-dichloropropane and three were exposed to dichloromethane. Additional exposures in some cases included unreported levels of 1,1,1-trichloroethane and/or 1,1-dichloro-1-fluorethane. Kubo et al. (2014b) also reported a series of nine cases of CCA diagnosed between 1988 and 2011 in male printers from 11 print shops in seven different Japanese cites; it is not clear if there is any overlap between these cases and the ones reported by Yamada et al. (2014, 2015a, 2015b). Based on work history, these men were exposed to 1,2-dichloropropane (7/9), dichloromethane (9/9), and/or 1,1,1-trichloroethane (4/9); no exposure estimates were calculated. Both cases without 1,2-dichloropropane exposure were exposed to both dichloromethane and 1,1,1-trichloroethane (Kubo et

al. 2014b). Collectively, these case-series reports concluded that occupational exposure to high levels of chlorinated solvents, including 1,2-dichloropropane, may increase the risk of CCA. However, using health insurance claims to the Japan Health Insurance Association, Okamoto et al. (2013) did not find a nationwide excess prevalence of CCA in workers from printing and related industries (n=201, 937), compared with other industries. Chemical exposures were not discussed or estimated in this report, so it is unclear if all workers from printing and related industries were occupationally exposed to chlorinated solvents (Okamoto et al. 2013).

Only two reports evaluated the potential association between CCA and working in printing occupations outside of Japan, neither of which specifically indicated exposure to 1,2-dichloropropane. In Finland, Iceland, Norway, and Sweden, the incidence for intrahepatic CCA was significantly elevated in men employed as "printers or related workers", compared to the general population (standardized incidence ratio [SIR] 2.34, 95% confidence interval [CI] 1.45–3.57), but not female printers or related workers (SIR 1.95, 95% CI 0.84–3.85) (Vlaanderen et al. 2013). The incidence of extrahepatic CCA was not significantly elevated in either male or female printers or related workers (SIRs 1.13 and 0.84, 95% CIs 0.85–1.48 and 0.59–1.19, respectively) (Vlaanderen et al. 2013). In a similar population-based, case-control study conducted in nine unidentified European countries, the risk of extrahepatic CCA was significantly elevated among typesetters, compared with other occupations (odds ratio [OR] 5.78, 95% CI 1.43–23.29), but not printing workers (OR 2.42, 95% CI 0.81–7.24) (Ahrens et al. 2014). While these two reports do not inform regarding the potential association between 1,2-dichloropropane and CCA, they establish that CCA in printers is not exclusive to print shops in Japan or to individuals of Japanese descent.

One study reported a potential association between 1,2-dichloropropane exposure and breast cancer in the general population. In the prospective Sister Study cohort of 49,718 women in the United States, the potential association between air pollutants and breast cancer was examined using census tract air toxic concentration estimates of residential addresses based on the 2005 National Air Toxics Assessment (Niehoff et al. 2019). Mean 1,2-dichloroprane exposure levels were $1.59x10^{-3}$ $\mu g/m^3$ (Quintile 1: $<5.15x10^{-4}$ $\mu g/m^3$; Quintile 5: $>1.93x10^{-3}$ $\mu g/m^3$). No significant increase in risk was found between quintiles of estimated 1,2-dichloropropane exposure and overall rates of breast cancer. However, there was a significant trend toward increased risk of estrogen receptor positive (ER+) invasive breast cancer with increased 1,2-dichloropropane exposure, and the hazard ratio (HR) for ER+ breast cancer in the highest quintile of 1,2-dichloropropane exposure was significantly increased (HR_{Q5} 1.19, 95% CI 01.02–1.38) after adjustment for age, race, education, cigarette smoking, and residence type.

1,2-Dichloropropane is carcinogenic in laboratory animals following both inhalation and oral exposure. There is evidence for respiratory tract cancer following inhalation exposure (nasal tumors in rats, lung tumors in mice) and some evidence for neoplastic lesions in the Harderian gland and spleen in male mice. Following oral exposure, there is equivocal evidence of mammary tumors in female rats and some evidence of liver tumors in male and female mice.

Inhalation Exposure. In rats exposed to 500 ppm 1,2-dichloropropane for 104 weeks (5 days/week, 6 hours/day), a statistically significant increase in the number of nasal papillomas was observed in the nasal cavity of male and female rats (15/50 and 9/50, respectively), compared with zero incidence in controls (Umeda et al. 2010). Incidences at 80 or 200 ppm in males were 2/50 and 4/50, respectively; no papillomas were observed in females at these concentrations. These tumors were observed in the anterior nasal region (levels 1 and 2). Additionally, a rare nasal tumor (esthesioneuroepithelioma) was observed in two male rats at 80 ppm and one male rat at 200 ppm. Due to rarity of this tumor (zero incidence in concurrent and historical controls), these tumors may be attributable to 1,2-dichloropropane exposure. However, due to the nonsignificant association with exposure, the CEL for this study was based on nasal papilloma incidence. 1,2-Dichloropropane was not found to be carcinogenic in other tissues in male or female rats.

In mice exposed to 1,2-dichloropropane for 104 weeks (5 days/week, 6 hours/day), exposure-related neoplastic lesions were observed in the lungs of males and females, and the spleen and Harderian gland of males (Matsumoto et al. 2013). The incidence of bronchioloalveolar adenoma and/or carcinoma was significantly increased in male mice at 32 (18/50) and 200 ppm (18/50), but not 80 ppm (14/50), compared with control (9/50). In female mice, a significant concentration-related trend was observed in the incidence of bronchioloalveolar adenoma and/or carcinoma, with a significant increase at 200 ppm (8/50), compared with control (2/50). A significant increase in the incidence of hemangioma and/or hemangiosarcoma in the spleen was also observed in males at 200 ppm (6/50), compared with control (0/50). The incidence of Harderian gland adenomas was significantly concentration-related in male mice (1/50, 2/50, 3/50, and 6/50 at 0, 32, 80, and 200 ppm, respectively). 1,2-Dichloropropane was not found to be carcinogenic in other tissues in male or female mice.

Heppel et al. (1948) examined the hepatocarcinogenic effects of 1,2-dichloropropane resulting from intermediate-duration exposure (37 exposures to 400 ppm for 4–7 hours/exposure). High mortality occurred throughout the study; only three mice survived all exposures plus a 7-month observation period.

Hepatomas were observed in all three mice that survived. The morphology of the hepatomas was inadequately characterized and the incidence in controls was not reported. Due to high mortality and inadequate reporting, this study was not used as a basis for a CEL in mice after intermediate inhalation exposure.

Oral Exposure. In rats exposed to 1,2-dichloropropane via gavage for 103 weeks (5 days/week), the only exposure-related neoplastic finding was a marginal, but statistically significant, increased incidence of adenocarcinomas of the mammary gland in females at 250 mg/kg/day (NTP 1986). Incidences in control, 125, and 250 mg/kg/day females were 1/50, 2/50, and 5/50, respectively. NTP (1986) considered this to be equivocal evidence for carcinogenicity. In support, mammary gland hyperplasia was also significantly elevated in female rats at 125 mg/kg/day. 1,2-Dichloropropane was not found to be carcinogenic in other tissues in the females or in any tissues in male rats (the highest dose tested was 125 mg/kg/day).

In mice exposed via gavage for 103 weeks (5 days/week), exposure-related neoplastic lesions were observed in the liver in males and females, and the thyroid in females (NTP 1986). A significant dose-related increase in liver adenomas was observed in both male and female mice. After adjustment for intercurrent mortality, the incidences in males and females administered 250 mg/kg/day (45.5 and 19.25%, respectively) were significantly increased compared with male and female controls (20 and 2.9%, respectively). Similarly, the incidences of hepatocellular adenoma or carcinoma (combined) were significantly increased in a dose-related manner, with significantly increased incidence at 250 mg/kg/day in males (74.7%), and at 125 and 250 mg/kg/day in females (26.4 and 30.8%, respectively) compared with male and female controls (46.7 and 5.7%, respectively). The incidences of hepatocellular carcinoma alone were not significantly increased in a dose-related manner. A significant increase in thyroid follicular cell adenoma or carcinoma (combined) was also observed in females at 250 mg/kg/day (20.8%), compared with controls (2%), after adjustment for intercurrent mortality. NTP (1986) concluded that there was some evidence for carcinogenicity in male and female mice based on the increased incidences of hepatocellular neoplasms, primarily adenomas.

Gi et al. (2015b) evaluated the potential for 1,2-dichloropropane to promote N-nitrosobis-(2-oxopropyl)amine (BOP)-induced preneoplastic and neoplastic lesions in the liver (including cholangioma), pancreas, lungs, or kidneys in hamsters. Exposure to 1,2-dichloropropane at gavage doses of 62.5 or 125 mg/kg/day for 15–17 weeks (5 days/week) after BOP-initiation (four injections over 7 days) did not promote BOP-induced pre-neoplastic or neoplastic lesions in any tissue examined.

1,2-Dichloropropane also did not increase the incidence of pre-neoplastic or neoplastic lesions in saline-initiated controls.

IARC (2017) concluded that 1,2-dichloropropane is carcinogenic to humans (Group 1) based on evidence that 1,2-dichloropropane exposure causes cancer of the biliary tract (CCA) in occupationally exposed workers and supporting mechanistic data. The EPA PPRTV program determined that 1,2-dichloro-propane is likely to be carcinogenic to humans based on evidence of a potential correlation between occupational exposure to 1,2-dichloropropane and CCA cancer and adequate evidence in laboratory animals (EPA 2016a). The NTP Report on Carcinogens (NTP 2016) has not classified the potential for 1,2-dichloropropane to cause cancer in humans.

Mechanisms of Cancer. The carcinogenic mode of action for 1,2-dichloroprone is not yet fully elucidated (reviewed by Kubo et al. 2018). The available evidence suggests that 1,2-dichloropropane is not a potent mutagen, but it can cause deoxyribonucleic acid (DNA) and chromosomal damage under certain conditions (see Section 2.20, Genotoxicity). Examination of pathological characteristics in 16 printers with CCA associated with 1,2-dichloropropane and/or dichloromethane exposure showed a progression from chronic bile duct injury with DNA damage in large bile ducts, to precursor lesions (biliary intraepithelial neoplasia [BiIIN] and/or intraductal papillary neoplasm of the bile duct [IPNB]), followed by invasive carcinoma (Kinoshita et al. 2016). Specifically, immunohistochemical analysis of surgically resected specimens of CCA cases associated with 1,2-dichloropropane and/or dichloromethane exposure showed increased DNA double-strand breaks in precursor lesions (BiIIN and/or IPNB) compared with CCA cases associated with other causes (e.g., hepatolithiasis) (Sato et al. 2014). Sato et al. (2014) proposed that direct DNA damage caused by glutathione-conjugated reactive metabolites as a contributing factor to the pathogenesis of CCA in humans occupationally exposed to 1,2-dichloropropane (and/or dichloromethane), as studies of bile duct, peribiliary gland, and gallbladder tissue from humans indicates expression of GST T1-1 but low or no expression of CYP2E1. Similar expression patterns were also observed in rats and mice (Sato et al. 2014), and biliary excretion of glutathione conjugated metabolites of 1,2-dichloropropane was observed in rodent species following oral administration (Toyoda et al. 2016). Additional studies in transgenic mouse strains indicate that metabolites are excreted into the bile via the bile canalicular membrane transporter ABCC2 (Toyoda et al. 2016).

An *in vitro* study was conducted to evaluate potential differences in GSH conjugation of 1,2-dichloro propane and dichloromethane, which have both been implicated in the development of occupational CCA (Toyoda et al. 2017). This study showed that 1,2-dichloropropane spontaneously conjugates with GSH

under physiological conditions, while dichloromethane shows very little spontaneous activity. However, GST T1-1 greatly enhanced GSH conjugation with dichloromethane, and only had a mild effect on GSH conjugation with 1,2-dichloropropane. Therefore, while both 1,2-dichloropropane and dichloromethane produce glutathione-conjugated reactive metabolites, there are differences in the metabolic activation processes.

In four cases of occupational CCA, Mimaki et al. (2016) identified a characteristic trinucleotide mutational signature using whole genome analysis, showing strand bias in C:G to T:A mutations. Mimaki et al. (2016) suggested that 1,2-dichloropropane exposure results in DNA adducts on G residues, with mutations occurring during repair processes. Mimaki et al. (2016) further suggested that there may be a distinct mutational signature associated with occupational CCA, which was partially reproduced in *Salmonella typhimurium* bacteria; however, it was not reproduced in human epithelial cells. The potential roles of the DNA editing enzyme activation-induced cytidine deaminase (AID), one of the induced proteins in the transformed epithelial cells in occupational cases of CCA identified by Mimaki et al. (2016), was evaluated in an *in vitro* study in human cholangiocytes (Zong et al. 2019). No changes in AID levels in human cholangiocytes were observed following exposure to 1,2-dichloropropane at concentrations associated with DNA damage; however, when human cholangiocytes were co-incubated with human macrophages, AID protein levels were increased in exposed cholangiocytes and DNA damage was enhanced. The study authors proposed that inflammatory responses in the macrophages mediated via the NF-κB pathway contributed to increased AID induction and DNA damage in cholangiocytes. Support for this mechanism included induction of TNF-α in exposed macrophages; induction of AID, NF-κB, and IκB in cholangiocytes exposed to TNF-α; and decreased induction of TNF-α and AID when cells were co-cultured with SN50, a NF-κB inhibitor.

2.20 GENOTOXICITY

Available evidence indicates that 1,2-dichloropropane is not a potent mutagen. However, there is evidence that it directly interacts with DNA, and is capable of causing DNA damage and chromosomal alterations under certain conditions. Results of *in vitro* and *in vivo* genetic testing of 1,2-dichloropropane are presented in Tables 2-5 and 2-6, respectively, and are summarized below.

Table 2-5. Genotoxicity of 1,2-Dichloropropane *In Vitro*

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
Genotoxicity studies in prokaryotic organisms				
Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, TA1538	Gene mutation	+ (TA100, TA1535) – (TA98, TA1537, TA1538)	+ (TA100, TA1535) – (TA98, TA1537, TA1538)	Principe et al. 1981
S. typhimurium strains TA100, TA1535, TA1978	Gene mutation	+	+	De Lorenzo et al. 1977
S. typhimurium strain TA100	Gene mutation	NT	+	Akiba et al. 2017; Mimaki et al. 2016
S. typhimurium strain TA100	Gene mutation	–	–	Stolzenberg and Hine 1980
S. typhimurium strains TA98, TA100, TA1535, TA1537	Gene mutation	–[a]	–[a]	Haworth et al. 1983; Prival and Dunkel 1989
S. typhimurium strains TA98, TA100, TA1535, TA1537	Gene mutation	–	–	NTP 1986; Tennant et al. 1987; Zeiger 1987
S. typhimurium strains TA98, TA100, TA1535, TA1537, TA1538	Gene mutation	–	–	SRI 1975
S. typhimurium strain TA100-GSTT1[b]	Gene mutation	NT	+	Akiba et al. 2017
Streptomyces coelicolor A3	Gene mutation	NT	–	Principe et al. 1981
S. typhimurium TA1535/pSK1002	DNA repair	–	–	Yasunaga et al. 2004
Escherichia coli PQ37	DNA repair	–	–	von der Hude et al. 1988
Genotoxicity studies in nonmammalian eukaryotic organisms				
Aspergillus nidulans	Gene mutation	NT	+	Principe et al. 1981
A. nidulans	Mitotic recombination	NT	–	Crebelli et al. 1984
Saccharomyces cerevisiae D3	Mitotic recombination	–	–	SRI 1975
Genotoxicity studies in mammalian cells				
Human lymphocytes	Unscheduled DNA synthesis	–	–	Perocco et al. 1983
Human hepatocytes	DNA damage	–	+	Toyooka et al. 2017
Human cholangiocytes	DNA damage	–	+	Toyooka et al. 2017
Human cholangiocytes	DNA damage	NT	+	Zong et al. 2019
Mouse lymphoma cells	Gene mutation	+	+	Tennant et al. 1987

Table 2-5. Genotoxicity of 1,2-Dichloropropane *In Vitro*

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
Mouse lymphoma cells	Gene mutation	–	+	Myhr and Caspary 1991
Chinese hamster ovary cells	Gene mutation	–	–	Myhr et al. 1988
Chinese hamster ovary cells	Chromosomal aberrations	+	+	Galloway et al. 1987; NTP 1986; Tennant et al. 1987
Chinese hamster ovary cells	Sister chromatid exchanges	+	+	Galloway et al. 1987; NTP 1986; Tennant et al. 1987
Chinese hamster ovary cells	Sister chromatid exchanges	–	+	von der Hude et al. 1987

[a]Marginal (<2-fold increase) results were reported positive by Haworth et al. (1983); however, upon re-evaluation using more stringent criteria (>2-fold induction at concentrations ≤500 µg/plate), Prival and Dunkel (1989) reclassified results as negative
[b]*S. typhimurium* strain expressing human GSTT1.

+ = positive results; – = negative results; DNA = deoxyribonucleic acid; NT = not tested

Table 2-6. Genotoxicity of 1,2-Dichloropropane *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Human (occupational)	DNA damage (S100P- and γH2AX-postive cells) in invasive carcinoma and precursor lesions (BiIIN and IPNB) from human CCA cases in print shop workers (n=3)	+	Kinoshita et al. 2016
Human (occupational)	DNA damage in cells from precursor lesions (BiIIN and IPNB) from human CCA cases in print shop workers (n=8) or associated with hepatolithiasis (n=16)	+ (7/8 print shop workers; 6/19 hepato-lithiasis cases)	Sato et al. 2014
Rat (oral)	Dominant lethal mutations	–	Hanley et al. 1989
Mouse (inhalation)	*Pig*-a-gene mutations in RBCs	–	Suzuki et al. 2014
Mouse (inhalation)	*gpt* mutations in liver	–	Suzuki et al. 2014
Mouse (inhalation)	Micronuclei in reticulocytes and RBCs	–	Suzuki et al. 2014
Mouse (inhalation)	DNA damage in liver	+	Suzuki et al. 2014
Mouse (inhalation)	DNA damage in liver	+	Toyooka et al. 2017
Mouse (oral)	Oxidative DNA damage in liver	–	Gi et al. 2015a
Hamster (oral)	Oxidative DNA damage in liver	–	Gi et al. 2015a
Drosophila melanogaster (inhalation)	Mitotic recombination (wing spot assay)	+	Chroust et al. 2007

Table 2-6. Genotoxicity of 1,2-Dichloropropane *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
D. melanogaster (inhalation)	Sex-linked recessive lethal mutations	–	Kramers et al. 1991
D. melanogaster (inhalation)	Sex-linked recessive lethal mutations	–	Woodruff et al. 1985
D. melanogaster (injection)	Sex-linked recessive lethal mutations	–	Woodruff et al. 1985

– = negative result; + = positive result; BiIIN = biliary intraepithelial neoplasia; DNA = deoxyribonucleic acid; IPNB = intraductal papillary neoplasm of the bile duct; RBC = red blood cell

Mutagenicity. High concentrations of 1,2-dichloropropane (≥750 µg/plate) were reported as mutagenic in various strains of *S. typhimurium* with or without metabolic activation in some early assays (De Lorenzo et al. 1977; Haworth et al. 1983; Principe et al. 1981). More stringent criteria established in the mid-1980s, requiring >2-fold induction at concentrations of <500 µg/plate, resulted in a lack of significant mutagenicity in the Haworth et al. (1983) study (Prival and Dunkel 1989). Other evaluations determined that 1,2-dichloropropane was not mutagenic to *S. typhimurium* or *Streptomyces coelicolor* with or without metabolic activation. (NTP 1986; Principe et al. 1981; SRI 1975; Stolzenberg and Hine 1980; Tennant et al. 1987; Zeiger 1987). However, dose-dependent mutagenicity was reported in *S. typhimurium* strain TA100 at vapor concentrations ranging from 600 to 4,000 ppm without metabolic activation using a closed plate system (Akiba et al. 2017; Mimaki et al. 2016); Mimaki et al. (2016) did not report cell survival, but Akiba et al. (2017) reported no cytotoxicity at concentrations up to 3,000 ppm. Akiba et al. (2017) also reported dose-dependent mutagenicity in an *S. typhimurium* strain TA100 that expressed human GSTT1 at vapor concentrations ranging from 600 to 3,000 ppm without metabolic activation using a closed system; no cytotoxicity was observed, and mutagenic potential was similar to the standard TA100 strain. In one study, 1,2-dichloropropane induced gene mutations in *Aspergillus nidulans* (Principe et al. 1981). In mammalian cells, Tennant et al. (1987) reported gene mutation in mouse lymphoma cells with or without metabolic activation, while Myhr and Caspary (1991) only observed mutations in mouse lymphoma cells without activation. In *in vivo* studies, 1,2-dichloro-propane did not induce sex-linked recessive lethal mutations in *Drosophila melanogaster* exposed via injection or inhalation for up to 2 weeks (Kramers et al. 1991; Woodruff et al. 1985), dominant lethal mutations in rats exposed to doses up to 162 mg/kg/day via drinking water for 14 weeks (Hanley et al. 1989), *gpt* mutations in mouse liver following exposure to 300 ppm via inhalation for 4 weeks (Suzuki et al. 2014), or *Pig*-a-gene mutations in mouse erythrocytes following exposure to concentrations up to 600 ppm via inhalation for 6 weeks (Suzuki et al. 2014).

Clastogenicity. Chromosomal aberrations and sister chromatid exchanges were induced in Chinese hamster ovary cells with and without metabolic activation (Galloway et al. 1987; NTP 1986; Tennant et al. 1987; von der Hude et al. 1987). Mitotic recombination was not observed in *A. nidulans* or *Saccharomyces cerevisiae* (Crebelli et al. 1984; SRI 1975). Data from *in vivo* studies show that 1,2-dichloropropane does not induce micronuclei in mouse reticulocytes or erythrocytes following inhalation exposure (Suzuki et al. 2014). Additionally, 1,2-dichloropropane induced mitotic recombination in *D. melanogaster* (Chroust et al. 2007).

DNA Damage. Sato et al. (2014) reported that double-stranded DNA breaks were observed in precursor lesions associated with CCA (BiIIN and IPNB) more than twice as often in cases attributed to 1,2-dichloropropane and/or dichloromethane exposure in Japanese print shops compared with cases associated with hepatolithiasis or conventional IPNB. Double-stranded DNA breaks in IPNB lesions were observed in 7/8 cases associated with occupational exposure to 1,2-dichloropropane and/or dichloromethane (88%), 7/16 cases associated with hepatolithiasis (44%), and 6/19 cases of conventional IPNB (32%). Similarly, double-stranded DNA breaks in BiIIN lesions were observed in 6/8 cases associated with occupational exposure to 1,2-dichloropropane and/or dichloromethane (75%) and 3/16 cases associated with hepatolithiasis (19%). Using immunohistochemical markers of DNA damage (S100P and γH2AX), Kinoshita et al. (2016) reported DNA damage localized to invasive carcinoma and precursor lesions (BiIIN and IPNB) in the bile ducts of Japanese printers with CCA attributed to 1,2-dichloropropane and/or dichloromethane exposure; γH2AX-positive cells were also observed in non-neoplastic biliary epithelium (no S100-P positive cells). In laboratory animals, DNA damage was also observed in the livers of mice following acute- or intermediate-duration inhalation exposure to concentrations ≥100 ppm (Suzuki et al. 2014; Toyooka et al. 2017). Observed damage is likely due to direct interaction with DNA, as levels of 8-OHdG (a marker of oxidative DNA damage) were not elevated in the livers of mice or hamsters following exposure to gavage doses up to 250 mg/kg/day for 4 weeks (Gi et al. 2015a).

1,2-Dichloropropane did not induce DNA repair in bacterial systems (von der Hude et al. 1988; Yasunaga et al. 2004) or unscheduled DNA synthesis in cultured human lymphocytes (Perocco et al. 1983). However, DNA damage was observed in cultured human hepatocytes and cholangiocytes exposed to 1,2-dichloropropane (Toyooka et al. 2017; Zong et al. 2019). Observed DNA damage was enhanced in cholangiocytes when they were cocultured with human macrophages; the study authors attributed this to proinflammatory signaling from the exposed macrophages (Zong et al. 2019).