CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of 1,1,2-trichloroethane. 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 1,1,2-trichloroethane, but may not be inclusive of the entire body of literature. A systematic review of the scientific evidence of the health effects associated with exposure to 1,1,2-trichloroethane was also conducted; the results of this review are presented in Appendix C.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. 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 human and animal dermal studies are presented in Table 2-3. 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 are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be classified as a

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

Most of the health effects data for 1,1,2-trichloroethane come from acute- and intermediate-duration oral studies and acute-duration inhalation studies in animals (Figure 2-1). In addition to the studies summarized in Figure 2-1, 16 studies examined lethality following inhalation, oral, or dermal exposure. One intermediate-duration inhalation toxicity study is available. Only four studies evaluated immunological endpoints; reproduction and development were evaluated in three to four oral studies of 1,1,2-trichloroethane exposure.

The available animal data suggest the following sensitive targets of toxicity:

- **Respiratory Endpoint:** Respiratory effects are a presumed health effect for humans based on the findings of histopathological changes to the olfactory epithelium following acute- and intermediate-duration inhalation exposure in animals.

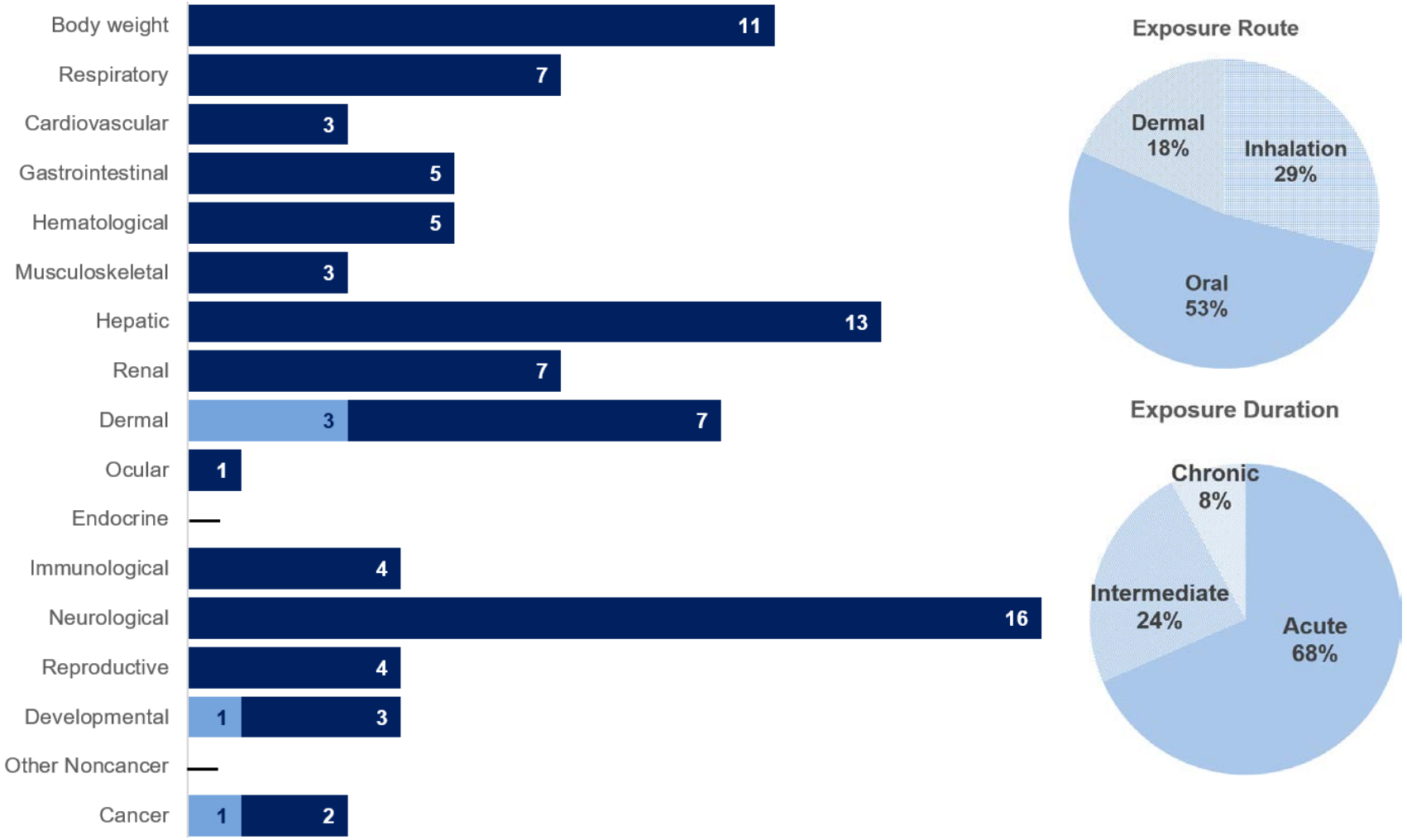
- **Hepatic Endpoint:** Hepatic effects are a presumed health effect for humans based on changes in the activities of liver enzymes (increased ALT and AST) and changes in liver pathology following oral and inhalation exposure in animals.

- **Neurological Endpoint:** Neurological effects following acute exposure are a presumed health effect in humans based on signs of central nervous system depression (sleepiness, loss of awareness, and sedation), taste aversion, and motor impairment following acute inhalation or oral exposure to 1,1,2-trichloroethane in animals.

- **Immunological Endpoint:** Immunological effects are a suspected health effect in humans based on the finding of decreased hemagglutination titers in an intermediate-duration oral exposure study in animals.

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

Most studies examined the potential body weight, hepatic, and neurological effects of 1,1,2-trichloroethane
Fewer studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 38 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
ACUTE EXPOSURE									
1	Rat (Sprague-Dawley) 12 M	6 hours	1,000–2,000	BW, GN, CS	Death			1,654	LC_{50}
					Neuro			1,654	Somnolent
Bonnet et al. 1980									
2	Rat (Albino) 5 M	2 hours	0, 890, 2,080	BW, OW, BC, BI	Death			2,080	3/5 died
					Hepatic	890	2,080		Increased ALT
Carlson 1973									
3	Rat (Sherman) 6 NS	4 hours	2,000	GN, HP, CS	Death			2,000	2–4/6 died
Carpenter et al. 1949									
4	Rat (Carworth Farms-Nelson) 6 F	8 hours	NR	CS	Death			999	LC_{50}
Pozzani et al. 1959									
5	Rat (Albino) 6 NS	8 hours	500	CS	Death			500	4/6 died
Smyth et al. 1969									
6	Rat (F344) 5 M, 5 F	4 hours	0, 58, 181, 1,527	BW, CS, GN, HP, LE, OW	Death			1,527 F	3/5 females died
					Resp		58[b]		Necrosis of the olfactory epithelium
					Hepatic	58		181	Hepatocellular necrosis
					Neuro			1,527	Sleepiness, decreased respiration
Kirkpatrick 2001									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
7	Rat (F344) 5 M, 5 F	4 hours	M: 0, 60, 205, 1,474 F: 0, 45, 170, 840	BI, BW, CS, LE	Death			840 F	3/5 females died
					Resp	205 M 170 F	1,474 M 840 F		Increased total protein content of BALF
					Neuro			1,474 M 840 F	Sleepiness, decreased respiration
Kirkpatrick 2001									
8	Mouse (Swiss OF_1) 10 M	4 hours	NR	CS	Neuro			418	CNS depression
de Ceaurriz et al. 1981									
9	Mouse (Swiss-Webster) 9–25 F	15 hours	0, 3,750	BC, CS	Death			3,750	Death
					Hepatic		3,750		Increased ALT
					Neuro			3,750	Anesthesia
Gehring 1968									
10	Mouse (OF_1 SPF) 20 F	6 hours	NR	CS	Death			416	LC_{50}
Gradiski et al. 1978									
11	Mouse (NS) NR	2 hours	NR	CS	Death			12,934	Death
					Neuro		1,833	2,749	Lie down on side (1,833 ppm); loss of reflex control (2,749 ppm)
Lazarew 1929									
12	Mouse (dd) 5 F	3 hours	800	BC, BI	Hepatic		800		Increased ALT and liver triglycerides; decreased plasma triglycerides and ATP
Takahara 1986a									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
INTERMEDIATE EXPOSURE									
13	Rat (F344 CDF Crl:BR) 10 M, 10 F	6 hours/ day 5 days/ week 13 weeks	0, 15, 40, 100	BC, BW, CS, FI, GN, HE, HP, LE, OP, OW	Bd wt	100			
					Resp	15[c]	40		Vacuolization/microcyst formation and atrophy of the olfactory epithelium; $BMCL_{10}$ of 3.15 ppm
					Cardio	100			
					Gastro	100			
					Hemato	100			
					Musc/skel	100			
					Hepatic	40	100		Hepatocellular vacuolization
					Renal	100			
					Dermal	100			
					Ocular	100			
Kirkpatrick 2002									

[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) of 0.03 ppm based on a rat LOAEL of 58 ppm, converted to a human equivalent concentration ($LOAEL_{HEC}$) of 7.5 ppm, and divided by an uncertainty factor of 90 (3 for the use of a minimal LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability) and a modifying factor of 3 for an incomplete database; see Appendix A for more detailed information regarding the MRL.
[c]Used to derive an intermediate-duration inhalation MRL of 0.002 ppm based on a rat $BMCL_{10}$ of 3.15 ppm, adjusted to continuous exposure and converted to a human equivalent concentration ($BMCL_{HEC}$) of 0.073 ppm, and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability); see Appendix A for more detailed information regarding the MRL.

ALT = alanine aminotransferase; ATP = adenosine triphosphate; BALF = bronchoalveolar lavage fluid; BC = serum (blood) chemistry; Bd wt or BW = body weight; BI = biochemical changes; Cardio = cardiovascular; CNS = central nervous system; CS = clinical signs; F = female(s); FI = food intake; Gastro = gastrointestinal; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; LC_{50} = lethal concentration, mortality 50%; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Neuro = neurological; NR = not reported; NS = not specified; OP = ophthalmology; OW = organ weight; Resp = respiratory

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

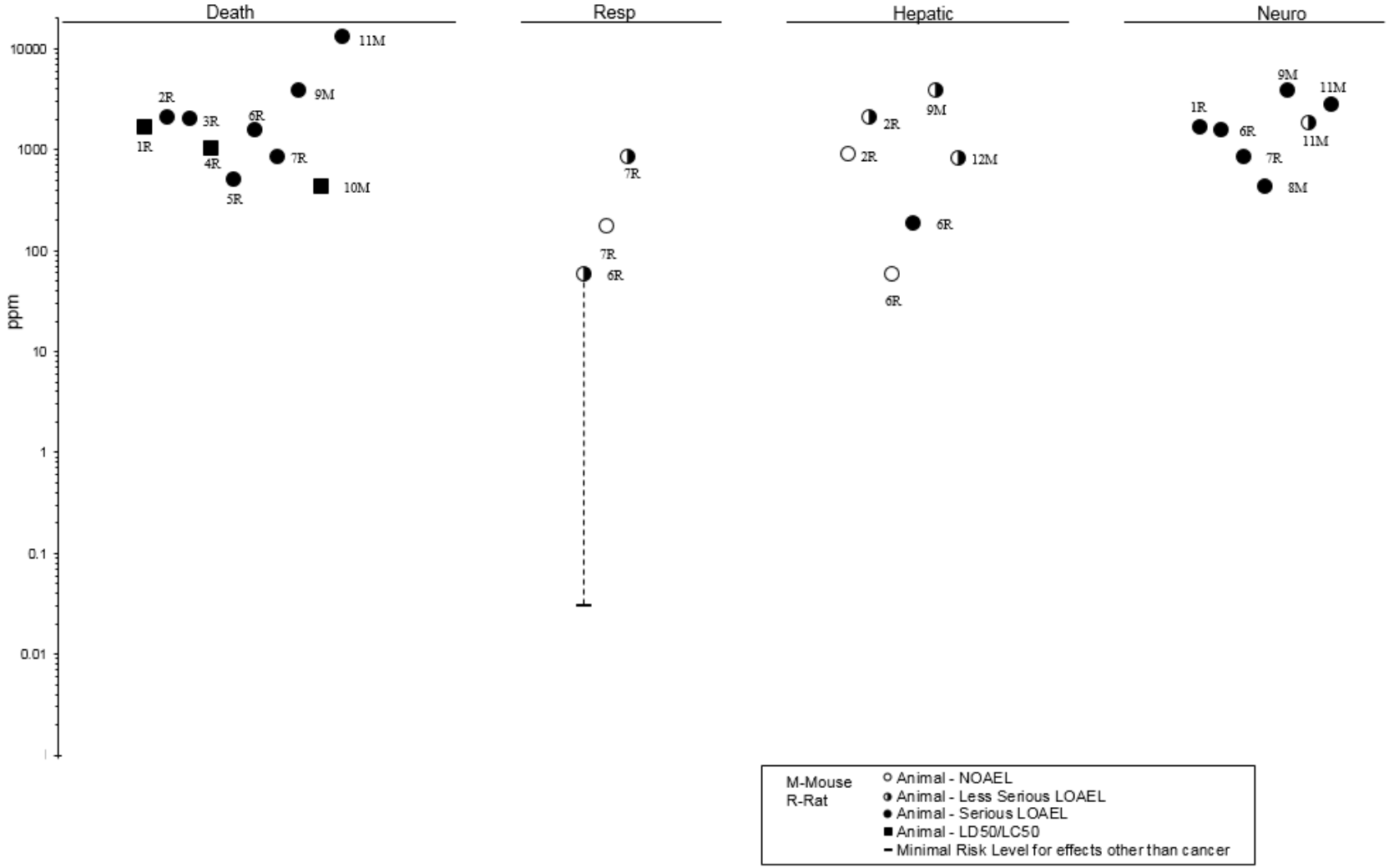


Figure 2-2. Levels of Significant Exposure to 1,1,2-Trichloroethane – Inhalation
Intermediate (15-364 days)

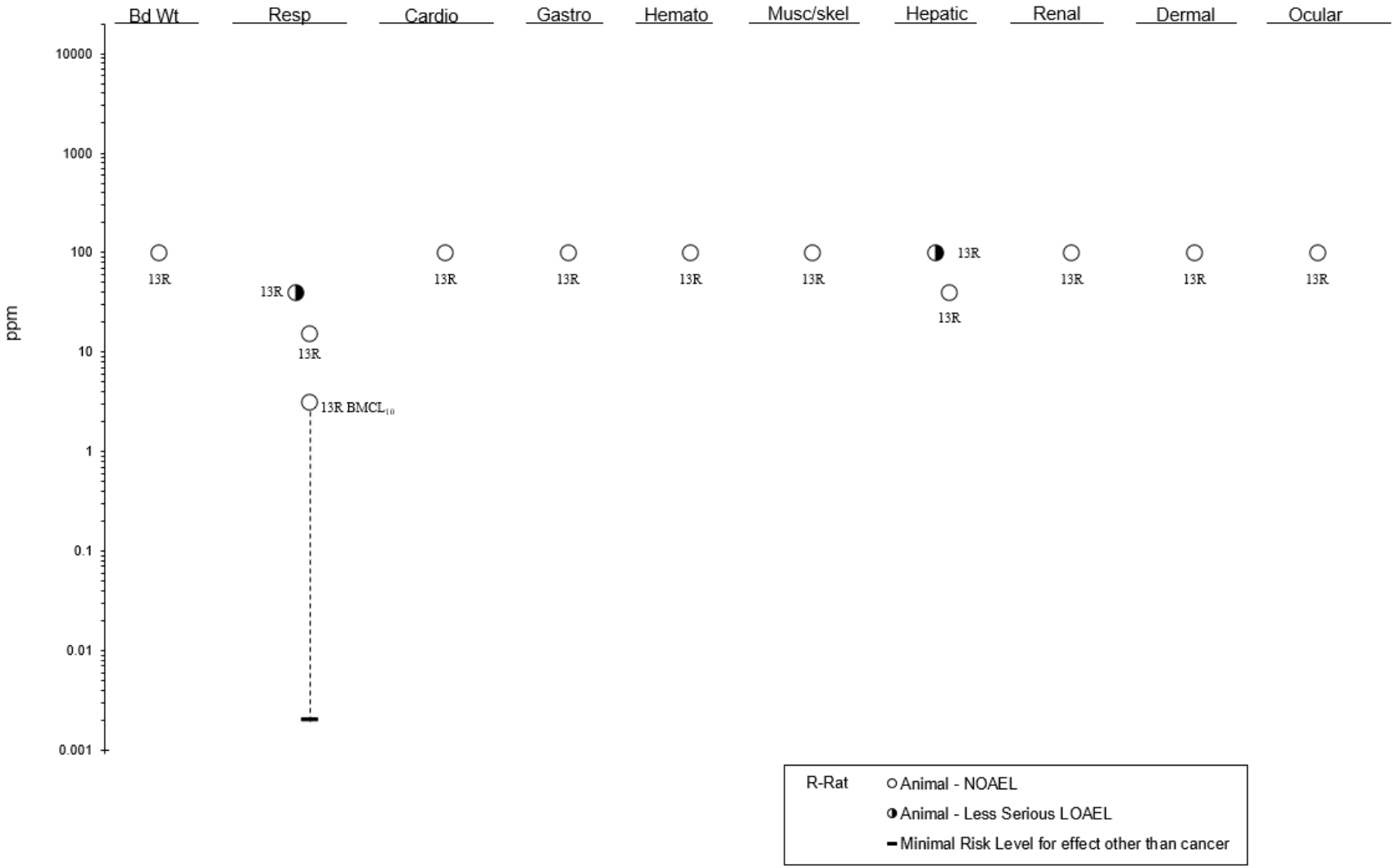


Table 2-2. Levels of Significant Exposure to 1,1,2-Trichloroethane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
ACUTE EXPOSURE									
1	Rat (Wistar-derived Alderley Park) 5 M	7 days (G)	0, 180	BW, OW, BI	Bd wt		180		Decreased body weight gain (19%)
					Hepatic	180			
Platt and Cockrill 1969									
2	Rat (Carworth-Wistar) 5 M	once (G)	NR	CS	Death			837	LD_{50}
Smyth et al. 1969									
3	Rat (Sprague-Dawley) 3–5 M	once (G)	0, 46, 92, 228[b]	BC	Hepatic	46[c]	92		Increased AST and ALT
Tyson et al. 1983									
4	Rat (Crl:CD (SD) IGS) 12 M, 12 F	once (GO)	0, 55, 95, 200	BH, BW, CS, HP, LE, OF, OW	Bd wt	95 M 200 F		200 M	Decreased body weight gain on days 0–7 (27%)
					Neuro	95	200		Gait impairment on study day 0 (4/12 males; 5/12 females; 0/12 controls)
Beck 2004									
5	Rat (Wistar) F NS	once (G)	667	BC	Hepatic		667		Increased ALT, SDH, glutamate dehydrogenase
Xia and Yu 1992									
6	Mouse (CD-1) NR	once (G)	NR	CS	Neuro		128		Motor impairment
Borzelleca 1983									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
7	Mouse (CD-1) 7 M	7 days (G)	3, 10, 30, 100, 300	WI, CS	Death			300	7/7 dead
					Neuro	30	100		Taste aversion to saccharin
Kallman et al. 1983									
8	Mouse (CD-1) 4 M	4 days (W)	0, 46	WI	Neuro	46			No taste aversion
Kallman and Kaempf 1984									
9	Mouse (CD-1) 11–12 M	14 days (G)	0, 3.8, 38	BW, OW, OF	Immuno	38			
Sanders et al. 1985									
10	Mouse (ICR/SIM) 30 F	5 days GDs 8–12 (G)	0, 350	BW, CS	Repro Develop	350 350			
Seidenberg et al. 1986									
11	Mouse (CD-1) 8 M	once (G)	200–600	GN, CS	Death			378 M 491 F	LD_{50}
					Gastro			200	Gastric irritation (animals that died)
					Neuro			450	Sedation
White et al. 1985									
12	Mouse (CD-1) 12 M	14 days (G)	0, 3.8, 38	BW, OW, BC, CS, Bl	Bd wt	38			
					Resp	38			No changes in lung weight
					Hemato	38			
					Hepatic	38			
					Renal	38			
White et al. 1985									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
13	Dog (NS) 1–2 NS	Once	144, 289, 433, 722	GN, HP, CS	Death			722	1/1 died
					Gastro		144	433	Mild inflammation and congestion (144 mg/kg); hemorrhage (433 mg/kg)
					Hepatic		144	433	Mild congestion, fatty acid degeneration and edema (144 mg/kg); necrosis (433 mg/kg)
					Renal		144		Mild congestion and cloudy swelling
					Neuro	144		289	Drowsiness
Wright and Schaffer 1932									
INTERMEDIATE EXPOSURE									
14	Rat (F344/ DUCRL) 10 M, 10 F	13 weeks (W)	M: 0, 12.1, 37.7, 86.0 F: 0, 17.1, 55.9, 98.2	BH, BW, CS, FI, HP, OF, WI	Bd wt	98.2			
					Neuro	98.2			
Maurissen et al. 2005									
15	Rat Crl:CD(SD) IGS 30 M, 30 F	2-generation (W)	Parental P1 and F1 (range): 0, 12.1–24.7, 40.6–82.5, 82.2–173	BW, CS, DX, FI, FX, GN, HP, OF	Bd wt	40.6 F	82.2 F		Decreased body weight gain during gestation in P1 and F1 females (12–17%)
					Repro	173			Decreased F1 and F2 pup weights on PNDs 4–21
					Develop	40.6	82.2		
Mylchreest 2006									
16	Rat (Crl:CD(SD)IGS BR) 25 F	GDs 6–20 (W)	0, 17, 48, 111	BW, CS, DX, FI, FX, LE, MX, OW, TG, WI	Bd wt	48	111		Decreased body weight gain (13%)
					Develop	111			
Wilson 2005									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
17	Rat (Osborne-Mendel) 10 M	7 weeks 5 days/week (G)	0, 69	BW, OW, HP	Bd wt		69		Decreased body weight gain (60%)
Story et al. 1986									
18	Mouse (CD-1) 8–25 M, 8–25 F	90 days (W)	M: 0, 4.4, 46, 305 F: 0, 3.9, 44, 384	BC, OF	Immuno	4.4 M 3.9 F[d]	46 M 44 F		Decreased hemagglutination titers
Sanders et al. 1985									
19	Mouse (CD-1) 32–48 M, 32–48 F	90 days (W)	M: 0, 4.4, 46, 305 F: 0, 3.9, 44, 384	BW, OW, WI, BC, HE, BI	Bd wt	46 M 384 F	305 M		Decreased body weight gain (10%)
					Resp	305 M 384 F			No changes in lung weight
					Hemato	305 M 384 F			
					Hepatic	305 M 44 F	384 F		Increased absolute (32%) and relative (26%) liver weight (females)
					Renal	305 M 384 F			
White et al. 1985									

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
CHRONIC EXPOSURE									
20	Rat (Osborne-Mendel) 20–50 M, 20–50 F	78 weeks 5 days/week (G)	0, 46, 92	BW, GN, HP, CS	Bd wt	92			
					Resp	92			
					Cardio	92			
					Gastro	92			
					Hemato	92			No histological alterations
					Musc/skel	92			
					Hepatic	92			
					Renal	92			
					Dermal	92			
					Ocular	92			
					Immuno	92			No histological alterations
					Neuro	92			No histological alterations
					Repro	92			No histological alterations
					Cancer				No increase in neoplasms
NCI 1978									
21	Mouse (B6C3F1) 20–50 M, 20–50 F	78 weeks 5 days/week (G)	0, 195, 390	BW, GN, HP, CS	Death			195	Increased mortality
					Bd wt	390			
					Resp	390			
					Cardio	390			
					Gastro	390			
					Hemato	390			No histological alterations
					Musc/skel	390			
					Hepatic	390			
					Renal	390			
					Dermal	390			
					Ocular	390			
					Immuno	390			No histological alterations
					Neuro	390			No histological alterations

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
					Repro	390			No histological alterations
					Cancer			195	CEL: hepatocellular carcinomas at ≥195 mg/kg and adrenal pheochromocytomas (not specified as benign or malignant) at 390 mg/kg
NCI 1978									

[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]Doses were estimated from data presented graphically in the study report (Tyson et al. 1983) using GrabIt! Software.
[c]Used to derive an acute-duration oral MRL of 0.5 mg/kg/day; based on a NOAEL of 46 mg/kg divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans, and 10 for human variability).
[d]Used to derive an intermediate-duration oral MRL of 0.04 mg/kg/day; based on a NOAEL of 3.9 mg/kg/day divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BC = serum (blood) chemistry; Bd wt or BW = body weight; BH = behavioral; BI = biochemical changes; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; F = female(s); FI = food intake; FX = fetal toxicity; (G) = gavage; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; (GO) = gavage in oil; Hemato = hematological; HP = histopathology; Immuno = immunological; LD_{50} = lethal dose; 50% kill; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; MX = maternal toxicity; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NR = not reported; OF = organ function; OW = organ weight; PND = postnatal day; Repro = reproductive; Resp = respiratory; SDH = sorbitol dehydrogenase; TG = teratogenicity; (W) = drinking water; WI = water intake

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

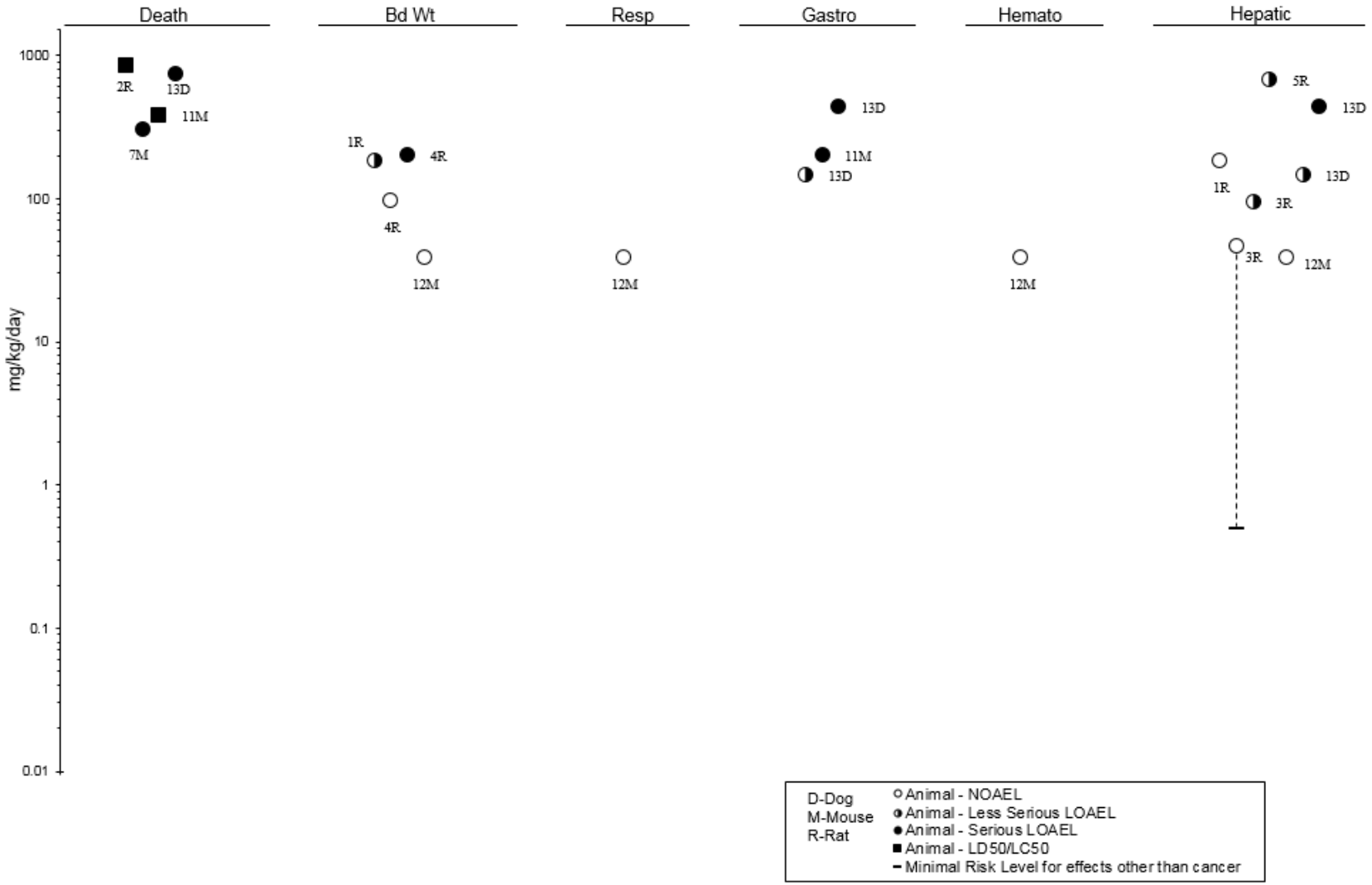


Figure 2-3. Levels of Significant Exposure to 1,1,2-Trichloroethane – Oral
Acute (≤14 days)

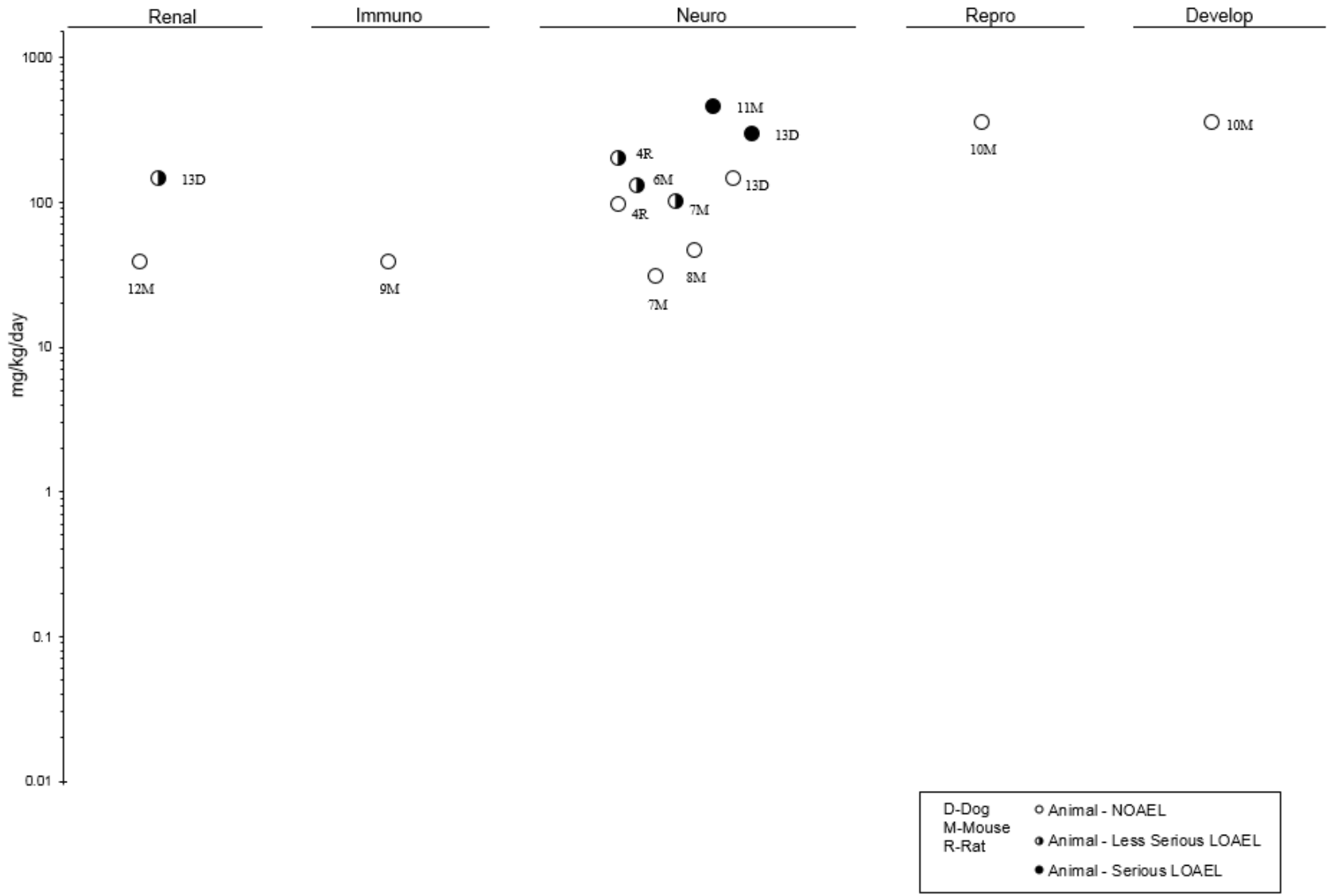


Figure 2-3. Levels of Significant Exposure to 1,1,2-Trichloroethane – Oral
Intermediate (15-364)

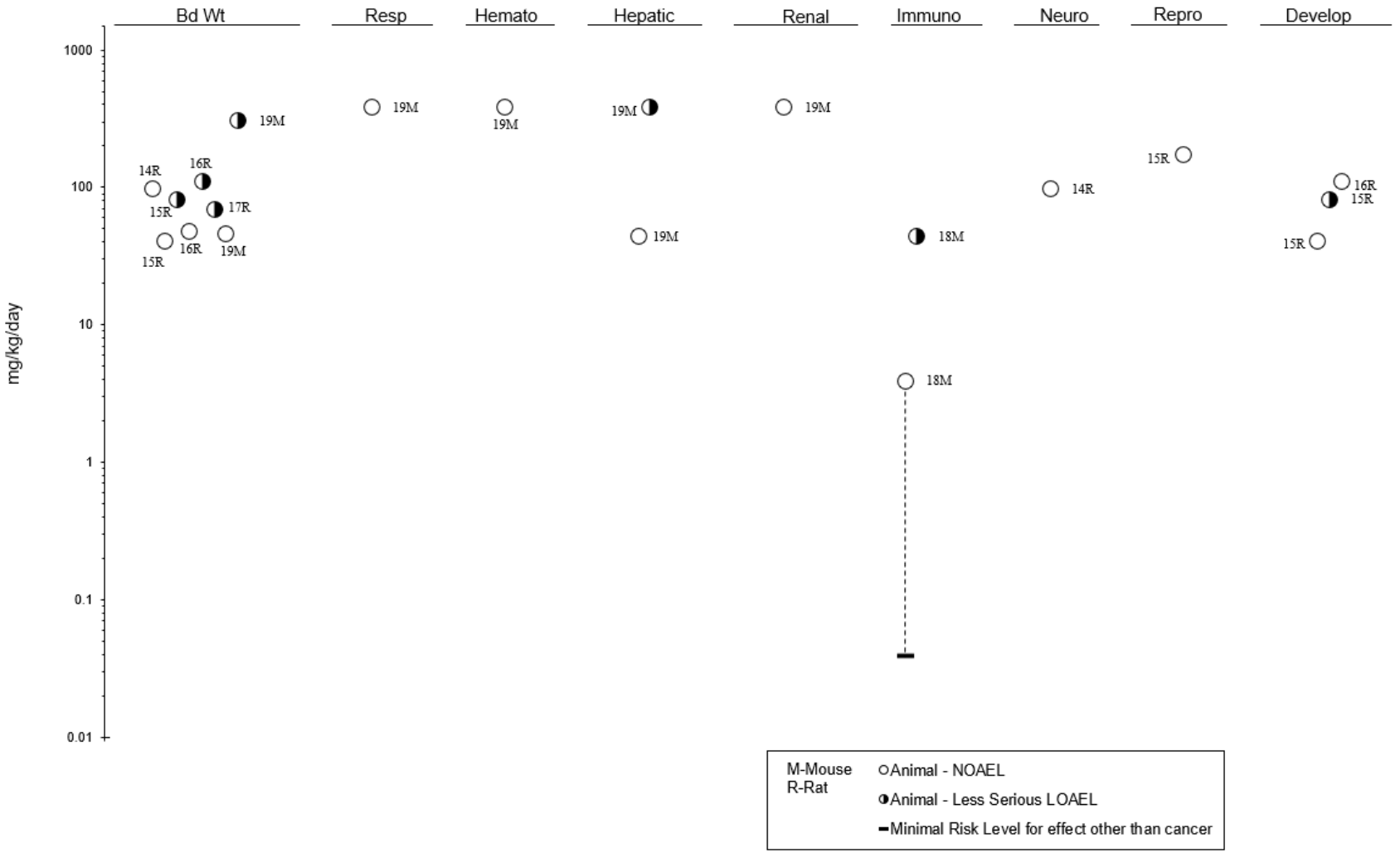


Figure 2-3. Levels of Significant Exposure to 1,1,2-Trichloroethane – Oral
Chronic (≥365 days)

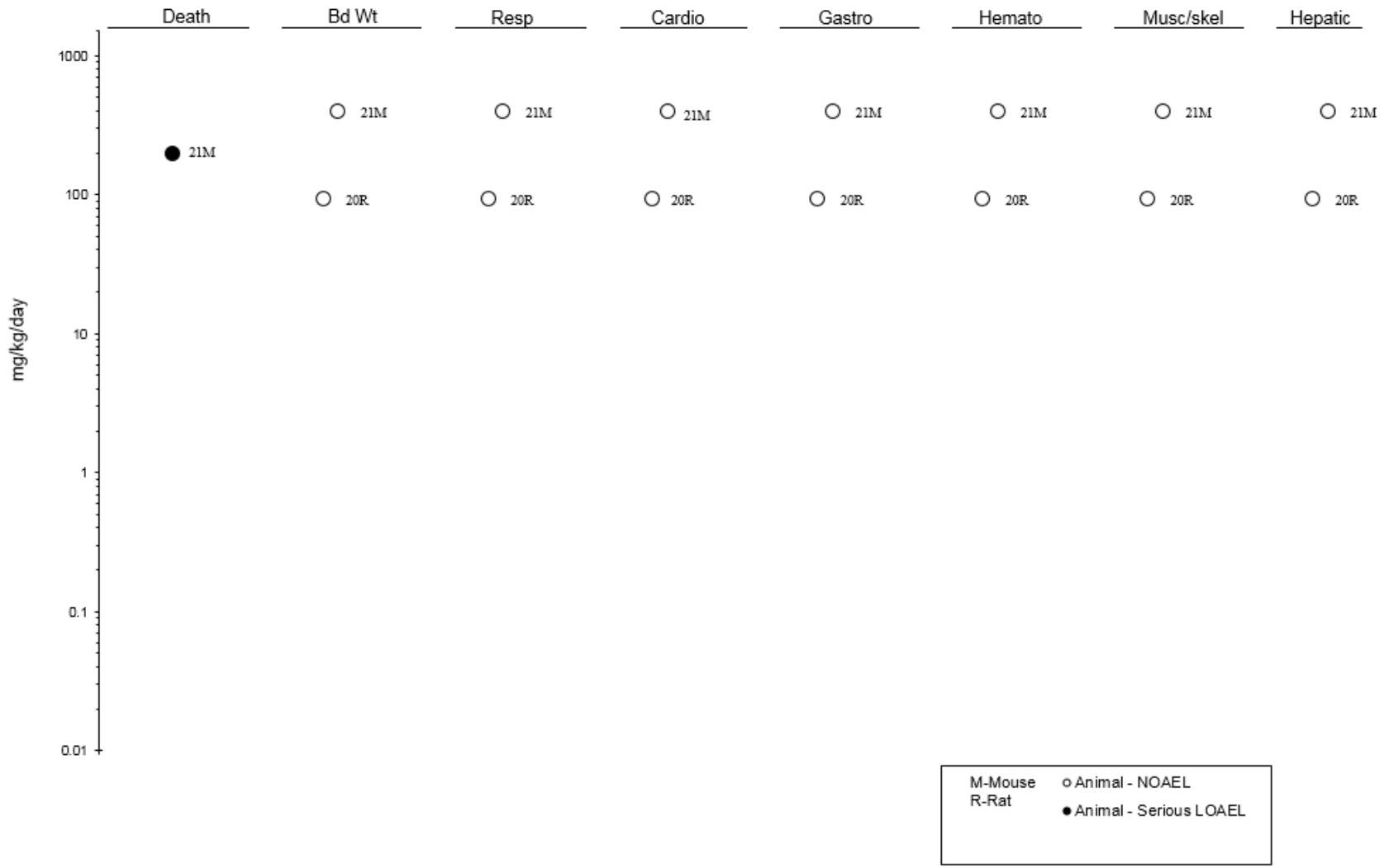


Figure 2-3. Levels of Significant Exposure to 1,1,2-Trichloroethane – Oral
Chronic (≥365 days)

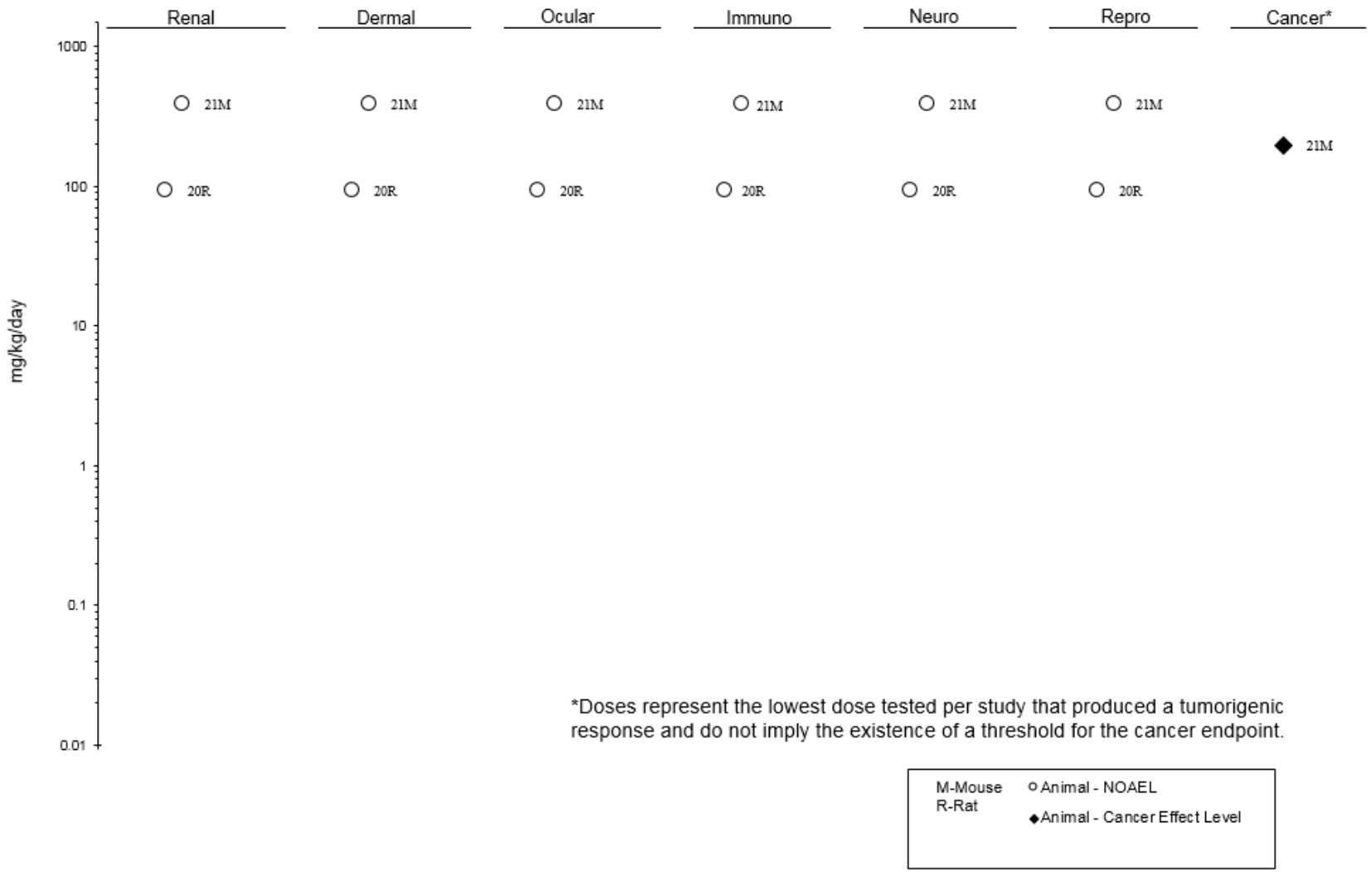


Table 2-3. Levels of Significant Exposure to 1,1,2-Trichloroethane – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effect
ACUTE EXPOSURE								
Human 1 M	5 minutes	698 mg/m^2	CS	Dermal		698		Stinging pain
Wahlberg 1984a								
Human 1 M	5 minutes	0.1 mL	CS	Dermal	0.1			
Wahlberg 1984a								
Rabbit (NS) 4 M	1 time	NR (mL/kg)	CS	Death			3.73	LD_{50}
Smyth et al. 1969								
Rabbit (NS) 5 NS	24 hours	0.01 mL	CS	Dermal	0.01			
Smyth et al. 1969								
Rabbit (NS) 4 NS	10 days 1 time/day	0.1 mL	CS	Dermal		0.1		Irritation
Wahlberg 1984b								
Guinea pig (NS) 6 NS	10 days 1 time/day	0.1 mL	CS	Dermal		0.1		Irritation
Wahlberg 1984b								
Guinea pig (NS) 11 M, F	12 hours	465 mg/cm^2	HP	Renal Dermal Neuro	465 465	 465 	 	 Skin damage No histological alterations
Kronevi et al. 1977								
Guinea pig (NS) 20 M, F	5–7 days	0, 116, 233, 931 mg/m^2	BW, CS	Death			116	5/20 dead
Wahlberg 1976								

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

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effect
INTERMEDIATE EXPOSURE								
Human 1 M **Wahlberg 1984a**	15 days 1 time/day	0.1 mL		Dermal	0.1			

BW = body weight; CS = clinical signs; d = day(s) F = female(s); HP = histopathology; LD_{50} = mortality; 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; NR = not reported; NS = not specified

2.2 DEATH

No studies were located regarding death in humans following exposure to 1,1,2-trichloroethane.

Mortality produced by inhalation of 1,1,2-trichloroethane has been studied in animals. Three of five rats exposed to 2,080 ppm of 1,1,2-trichloroethane for 2 hours died within about 24 hours, but five rats exposed to 890 ppm for 2 hours survived (Carlson 1973). Carpenter et al. (1949) reported that 2–4/6 rats died within 14 days following exposure to 2,000 ppm and 0–1/6 rats died following exposure to 1,000 ppm. The exact number of rats that died in each treatment group was not reported. In two experiments, 3/5 females exposed to 1,1,2-trichloroethane at 840 ppm and 3/5 females exposed to 1,527 ppm for 4 hours died; males treated at 1,474 and 1,527 ppm survived until study termination (Kirkpatrick 2001). The LC_{50} of 1,1,2-trichloroethane in rats exposed for 6 hours was 1,654 ppm (Bonnet et al. 1980). During exposure, animals were first excited and then somnolent. Most mortality occurred within 24 hours of exposure, but some deaths were reported up to 8 days later. No macroscopic lesions in the lungs, liver, or kidneys were found at autopsy. In rats exposed to 1,1,2-trichloroethane for 8 hours, the LC_{50} was 999 ppm (Pozzani et al. 1959). These authors reported, in a later study, that exposure to 500 ppm for 8 hours produced death in four out of six rats within 14 days (Smyth et al. 1969).

In mice, 12,934 ppm of 1,1,2-trichloroethane was found to be the minimum lethal concentration in a 2-hour exposure test (Lazarew 1929). The animals laid down on their sides and lost control of their reflexes prior to death. An LC_{50} value of 416 ppm was calculated in mice exposed for 6 hours and observed for 14 days (Gradiski et al. 1978). In mice exposed to 3,750 ppm of 1,1,2-trichloroethane, the LT_{50}, or exposure duration that produced mortality in one-half of the mice tested, was calculated to be 600 minutes (Gehring 1968).

No exposure-related effects on mortality were observed in Fischer 344 CDF Crl:BR rats exposed whole-body to 1,1,2-trichloroethane at up to 100 ppm 6 hours/day, 5 days/week for 13 weeks (Kirkpatrick 2002).

Several reports indicate that 1,1,2-trichloroethane may be lethal to animals following oral exposure. An LD_{50} of 837 mg/kg was calculated for gavage-administered, undiluted 1,1,2-trichloroethane in female rats (Smyth et al. 1956, 1969). Moody et al. (1981) reported no mortality among fasted rats given single oral doses of 1,1,2-trichloroethane in mineral oil at 1,080 mg/kg; however, only deaths during the first 18 hours after administration were recorded, and only three rats were tested. In mice, the oral LD_{50} of

1,1,2-trichloroethane administered by gavage in water was reported to be 378 mg/kg for males and 491 mg/kg for females (White et al. 1985). Necropsy of mice that died in this study revealed hemorrhagic areas in the lungs and pale coloration of the liver, which may also have been caused by hemorrhage. These effects may have contributed to the death of these animals. The only dog given 1,1,2-trichloroethane (vehicle not specified) at 722 mg/kg died, but all five that received doses ranging from 144 to 433 mg/kg survived (Wright and Schaffer 1932).

Lethality was also investigated in two short-term, repeated-dose studies. Oral doses of 1,1,2-trichloroethane given by gavage in water at 300 mg/kg for 7 days resulted in the death of all seven mice tested (Kallman et al. 1983). Doses up to 100 mg/kg/day did not produce death in this study. Oral administration by gavage of 38 mg/kg/day in 10% Emulphor for 14 days did not produce mortality in mice (White et al. 1985).

One long-term study investigated the effect of 1,1,2-trichloroethane on animal survival. A large number of the deaths occurred in female mice administered 195 mg/kg 5 days/week for 78 weeks; the deaths occurred early in the experiment, were not tumor-related, and did not appear to have a common cause (NCI 1978). No deaths were observed in male mice. In rats, survival was not affected by oral administration of doses of 1,1,2-trichloroethane as high as 92 mg/kg for 78 weeks (NCI 1978). However, rat vehicle controls had unusually high mortality in this study.

Dermally applied 1,1,2-trichloroethane has been reported to cause death in animals. A single dermal application of 116 mg/cm^2 (0.25 mL applied to a 3.1-cm^2 area of the back) was allowed to remain on the skin of guinea pigs until it disappeared (5–7 days). This treatment resulted in the death of 25% of the guinea pigs tested within 28 days (Wahlberg 1976). Doses of 233 and 931 mg/cm^2 killed all tested animals within 3 days in this study.

2.3 BODY WEIGHT

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

No alterations in body weight gain were observed in rats exposed to up to 100 ppm 1,1,2-trichlorothane by inhalation for 13 weeks (Kirkpatrick 2002).

Alterations in body weight gain were observed in several oral exposure studies. Male rats administered a single gavage dose of 1,1,2-trichloroethane (in 10 mL/kg corn oil) at 200 mg/kg showed decreased body weight gain (27% lower than controls on days 0–7), whereas body weights were unaffected in females (Beck 2004). Rats given 180 mg/kg/day in liquid paraffin for 7 days grew only 8% over the course of the experiment, whereas control rats grew 34% (Platt and Cockrill 1969). In mice, body weight gain was not significantly affected by gavage administration of 1,1,2-trichloroethane in 10% Emulphor at 38 mg/kg/day for 14 days (White et al. 1985).

In intermediate-duration studies, body weight gain was decreased approximately 60% in rats given 69 mg/kg/day by gavage in corn oil for 7 weeks (Story et al. 1986). In rats administered 1,1,2-trichloroethane at up to 98 mg/kg/day in drinking water for 13 weeks, the body weights of treated males were 3–7% higher than controls, and females treated at the highest dose showed only a nonsignificant reduction in body weights (4% lower than controls) at study termination; these effects were not considered treatment-related (Maurissen et al. 2005). However, decreased body weight gain was reported in P1 and F1 female rats exposed to 1,1,2-trichloroethane in drinking water at 82 mg/kg/day for two generations (Mylchreest 2006) and rats exposed to 1,1,2-trichloroethane in drinking water at 111 mg/kg/day on gestation days (GDs) 6–20 (Wilson 2005). Kallman and Kaempf (1984) reported that body growth in male mice was unchanged by 90-day exposure to 46 mg/kg/day in the drinking water. In a second study, exposure to 1,1,2-trichloroethane in the drinking water for 90 days produced a dose-related inverse response in male mice that was significant at 305 mg/kg/day (White et al. 1985). Weight gain in female mice was not affected in this study.

When administered by gavage in corn oil, doses of 92 mg/kg/day in rats and 390 mg/kg/day in mice for 78 weeks (NCI 1978) did not inhibit body growth.

2.4 RESPIRATORY

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

Several studies investigated the respiratory effects of acute 1,1,2-trichloroethane inhalation in animals. In two studies conducted by Kirkpatrick (2001), rats were exposed to 1,1,2-trichloroethane for 4 hours. Increased protein content of bronchoalveolar lavage fluid was observed in male rats exposed to 1,473 ppm and in female rats exposed to 840 ppm. Rats exposed to ≥58 ppm showed necrosis of the

olfactory epithelium (at nasal levels III, IV, and V); the incidence and severity of these lesions increased in an exposure-related manner. No gross alterations of respiratory organs and tissues were observed in rats that survived a 6-hour exposure test from which an LC_{50} of 1,654 ppm was calculated (Bonnet et al. (1980).

In an intermediate-duration study, no significant changes in absolute or relative lung weights were observed in Fischer 344 CDF Crl:BR rats exposed whole-body to 1,1,2-trichloroethane at up to 100 ppm 6 hours/day, 5 days/week for 13 weeks. However, nasal lesions of the olfactory epithelium of the nasal turbinates (including vacuolization and microcyst formation, respiratory epithelial metaplasia, and/or atrophy) were observed at 40 and 100 ppm (Kirkpatrick 2002). The mechanisms involved in 1,1,2-trichloroethane-mediated respiratory toxicity are not known.

No studies were located regarding respiratory effects in humans following oral exposure to 1,1,2-trichloroethane.

Respiratory effects have been studied in orally exposed animals. No alterations in absolute or relative lung weights were observed in mice administered 38 mg/kg/day 1,1,2-trichloroethane by gavage for 14 days (White et al. 1985) or 305 mg/kg/day (males) or 384 mg/kg/day (females) in the drinking water for 90 days (White et al. 1985). These dose levels were considered NOAEL values (in the absence of evaluations of respiratory function) based on biomedical judgement. Histopathological examination of respiratory organs and tissues (lungs, bronchi, and trachea) found no increase in the occurrence of non-neoplastic lesions following 78 weeks of oral 1,1,2-trichloroethane administration in corn oil at doses of 46 or 92 mg/kg/day in rats and 195 or 390 mg/kg/day in mice (NCI 1978).

2.5 CARDIOVASCULAR

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

There are limited data in animals on the potential cardiotoxicity of 1,1,2-trichloroethane. No histological alterations were observed in rats exposed to 100 ppm 6 hours/day, 5 days/week for 13 weeks (Kirkpatrick 2002), in rats administered via gavage 92 mg/kg 5 days/week for 78 weeks (NCI 1978), or in mice receiving gavage doses of 390 mg/kg 5 days/week for 78 weeks (NCI 1978).

2.6 GASTROINTESTINAL

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

No histopathological alterations were observed in gastrointestinal organs and tissues from rats following 13 weeks of inhalation exposure to 1,1,2-trichloroethane at up to 100 ppm (Kirkpatrick 2002). In contrast, there is some evidence for adverse gastrointestinal effects in animals following oral exposure. Mice that died following administration by gavage of single oral doses of 1,1,2-trichloroethane >200 mg/kg displayed a dose-related increase in the incidence of gastric irritation (White et al. 1985). Mild inflammation and congestion of the gastrointestinal tract, as well as nausea, were noted in a dog given oral administration of 144 mg/kg (Wright and Schaffer 1932). Severe irritation and hemorrhage were found in two of the three dogs given doses of 433 or 722 mg/kg. In chronic exposure studies, histopathological examination of gastrointestinal organs and tissues revealed no increase in the occurrence of non-neoplastic lesions following 78 weeks of oral 1,1,2-trichloroethane administration by gavage (5 days/week) at doses of 92 mg/kg in rats and 390 mg/kg in mice (NCI 1978).

2.7 HEMATOLOGICAL

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

In the one study identified that examined hematological effects in animals following inhalation exposure to 1,1,2-trichloroethane, no significant effects on a comprehensive set of hematological parameters were observed in rats exposed to up to 100 ppm 6 hours/day, 5 days/week for 13 weeks (Kirkpatrick 2002).

Hematological effects (total and differential blood cell counts and coagulation parameters) were the subject of several oral studies in animals. No hematological effects were found after daily administration to mice of 1,1,2-trichloroethane by gavage at 38 mg/kg for 14 days (White et al. 1985). No hematological effects were found in male mice exposed to ≤305 mg/kg/day in drinking water for 90 days, but changes in hematological parameters were recorded in females that received doses as low as 3.9 mg/kg/day (White et al. 1985). These included mild decreases in hematocrit and hemoglobin at 384 mg/kg/day; increases in platelets and fibrinogen were found in all groups (≥3.9 mg/kg/day), but were not dose-related. In the 384 mg/kg/day group, leukocytes were elevated, compared to controls, and only slightly higher than the historical control value in this laboratory. There was also a decrease in prothrombin time that appeared to

be dose-related and became statistically significant at 44 mg/kg/day in female mice. The biological significance of the small magnitude of changes is unclear, particularly for humans because test results vary widely between species. Additionally, hepatic effects, which occurred in test subjects at low concentrations, may influence prothrombin time; therefore, the highest dose of 384 mg/kg/day was considered a NOAEL.

Histopathological examination of spleen and bone marrow found no increase in the occurrence of non-neoplastic lesions following 78 weeks of oral 1,1,2-trichloroethane administration of 92 mg/kg/day in rats and 390 mg/kg/day in mice (NCI 1978).

2.8 MUSCULOSKELETAL

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

Studies in animals have not found histological alterations in bone or skeletal muscle in rats exposed up to 100 ppm 6 hours/day, 5 days/week for 13 weeks (Kirkpatrick 2002) or in rats and mice administered via gavage up to 92 or 390 mg/kg, respectively, for 78 weeks (NCI 1978).

2.9 HEPATIC

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

Several studies examined the hepatotoxicity of inhaled 1,1,2-trichloroethane vapor in animals. In rats, inhalation of 2,080 ppm of 1,1,2-trichloroethane for 2 hours resulted in a small, but significant, increase in ALT levels measured 22 hours after exposure ended (Carlson 1973). This treatment did not affect AST, glucose-6-phosphatase, or liver weight. Macroscopic examination of rats that survived (number not specified) exposure to 250 ppm of 1,1,2-trichloroethane for 4 hours and 250–500 ppm for 7 hours revealed necrosis and tissue damage in the liver (Unpublished data, Dow Chemical Co., cited in Torkelson and Rowe 1981). Hepatocellular necrosis was also noted in rats exposed to 1,1,2-trichloroethane at ≥181 ppm for 4 hours; clinical chemistry parameters of liver function were not evaluated and liver weights were not affected (Kirkpatrick 2001). Mice exposed to 800 ppm of 1,1,2-trichloroethane for 3 hours had decreased adenosine triphosphate (ATP), increased liver triglycerides, decreased plasma triglycerides, and increased ALT (Takahara 1986b). Recovery occurred within 20 hours for all parameters except ALT, which remained elevated. The ET_{50} (duration of exposure that produced

increased ALT levels in one-half of the exposed mice) for increased ALT levels in mice exposed to 3,750 ppm of 1,1,2-trichloroethane was 17.5 minutes (Gehring 1968).

Minor fatty changes and cloudy swelling were found in the livers of female rats exposed to 30 ppm of 1,1,2-trichloroethane for 16 days (Unpublished data, Dow Chemical Co., cited in Torkelson and Rowe 1981). Rats exposed to 1,1,2-trichloroethane 6 hours/day, 5 days/week for 13 weeks showed increased cholesterol at 100 ppm (males) or 40 ppm and 100 ppm (females); this effect was not strictly dose-related. Rats of both sexes exposed to 100 ppm showed increased incidences of hepatocellular vacuolization (minimal in severity). The study authors suggested that while this effect was probably degenerative, the lesions did not progress to centrilobular hepatocellular necrosis (Kirkpatrick 2002). The toxicological significance of increased cholesterol is unclear in the absence of effects on ALT or AST or liver weights. Six months of exposure up to 15 ppm 1,1,2-trichloroethane did not have histopathological effects on the liver in rats, guinea pigs, or rabbits (Unpublished data, Dow Chemical Co., cited in Torkelson and Rowe 1981).

Numerous studies examined hepatic effects in animals following oral exposure to 1,1,2-trichloroethane. Rats administered a single gavage dose of 1,1,2-trichloroethane at 667 mg/kg/day and sacrificed 6–72 hours after treatment showed significantly increased levels of ALT, sorbitol dehydrogenase, and glutamate dehydrogenase in the serum (Xia and Yu 1992). Tyson et al. (1983) found significant increases in AST and ALT following one-time gavage administration of 1,1,2-trichloroethane at about 92 mg/kg/day to rats (based on data obtained using GrabIt! Software). The NOAEL for this effect was about 46 mg/kg/day; the ED_{50} (the dose that produced an elevation in enzyme levels above the normal range in 50% of the test animals) was 60 mg/kg. Biochemical changes, characterized by decreased cytochrome P-450 and ALA-dehydratase, and changes in microsomal fatty acid content occurred after administration of 1,080 mg/kg by gavage in rats (Moody and Smuckler 1986; Moody et al. 1981); the toxicological significance of these effects is unclear. Increased relative liver weight was also seen in this study, which was limited by small sample size (Moody et al. 1981). Glucose-6-phosphate dehydrogenase levels increased 195% and NADH2-cytochrome c reductase levels decreased 33%, in rats administered 1,1,2-trichloroethane orally in liquid paraffin at 180 mg/kg/day for 7 days (Platt and Cockrill 1969). Liver weight (relative) and other liver biochemical endpoints were not significantly changed in this study. The toxicological significance of these biochemical changes (in the absence of effects on other liver endpoints) is unclear. Necropsy of mice that died following single oral doses of 1,1,2-trichloroethane by gavage in water at 200–600 mg/kg revealed pale coloration of the liver (White et al. 1985). Dogs given a single dose of ≥144 mg/kg 1,1,2-trichloroethane had congestion, fatty degeneration, edema, and the onset

of necrosis in the liver (Wright and Schaffer 1932). Extensive liver necrosis occurred in one of the three dogs given ≥433 mg/kg. ALT levels were not affected by 14-day administration of 1,1,2-trichloroethane by gavage at 38 mg/kg/day in mice (White et al. 1985).

No adverse liver effects were observed in male mice exposed to 1,1,2-trichloroethane for 90 days in the drinking water at doses up to 305 mg/kg/day (White et al. 1985). In the same study, absolute and relative liver weights were increased by 32 and 26%, respectively, in female mice that received 384 mg/kg/day. No increase in the occurrence of non-neoplastic lesions in the liver was found in histopathological examinations following 78 weeks of oral 1,1,2-trichloroethane administration by gavage in corn oil at doses of 92 mg/kg/day in rats and 390 mg/kg/day in mice (NCI 1978).

One study investigated the hepatotoxicity of dermally applied 1,1,2-trichloroethane in animals. Guinea pig liver glycogen content was reduced within 2 hours following dermal application of 1 mL of 1,1,2-trichloroethane to a 3.1 cm^2 area of the back (465 mg/cm^2) (Kronevi et al. 1977). Hydropic changes in the liver were also found. These effects may not have been compound-related, however, since they were found in animals killed under anesthesia produced by pentobarbital, but not unanesthetized animals. Untreated controls were not used in this study. The authors suggested that these liver effects may have been due to an interaction between 1,1,2-trichloroethane and pentobarbital. This possibility is discussed further in Section 3.4.

In male mice administered 1,1,2-trichloroethane via a single intraperitoneal injection, the reported ED_{50} values for increased serum ALT were approximately 144 mg/kg (based on the ED_{50} reported in mL/kg) and 240 mg/kg (based on the ED_{50} reported in mmol/kg) (Klaassen and Plaa 1966).

Although the mechanisms of action associated with 1,1,2-trichloroethane-mediated hepatotoxicity are largely unknown, limited data suggest that free radicals and aryl chlorides (including chloroacetic acid) generated from the metabolism of 1,1,2-trichloroethane and DNA adduct formation may play a role (Mazzullo et al. 1986; Tyson et al. 1983). One study showed that 1,1,2-trichloroethane tested positive for DNA adduct formation in rat and mouse liver (Mazzullo et al. 1986).

2.10 RENAL

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

The renal effects of 1,1,2-trichloroethane have been studied in animals following inhalation exposure. In the rat, inhalation of 250 ppm of 1,1,2-trichloroethane for 4 hours produced kidney necrosis. Exposure to 250 or 500 ppm for 7 hours produced marked kidney damage (Unpublished data, Dow Chemical Co., cited in Torkelson and Rowe 1981). No macroscopic lesions were found in the kidneys of rats that survived a 6-hour exposure test from which an LC_{50} of 1,654 ppm was calculated (Bonnet et al. 1980). No alterations in kidney weight (absolute or relative) or histopathology were observed in rats exposed to up to 100 ppm 1,1,2-trichloroethane 6 hours/day, 5 days/week for 13 weeks; additionally, there were no significant effects on serum chemistry parameters indicative of kidney function (Kirkpatrick 2002). Similarly, no renal histopathological effects were observed in rats, guinea pigs, or rabbits exposed to 15 ppm of 1,1,2-trichloroethane for 6 months (Unpublished data, Dow Chemical Co., cited in Torkelson and Rowe 1981).

There are some reports of renal toxicity in animals after oral exposure to 1,1,2-trichloroethane, although most studies did not report significant findings. Cloudy swelling and congestion of the kidney were found by histopathological examination in dogs given 1,1,2-trichloroethane orally at ≥144 mg/kg (Wright and Schaffer 1932). There was a significant, low-level depression of *in vitro* organic ion uptake in renal cortical slices taken from rats given single gavage doses of 1,1,2-trichloroethane at 72–505 mg/kg (Watrous and Plaa 1972), although there was no clear dose response. In mice administered 1,1,2-trichloroethane at up to 2,886 mg/kg, the renal toxicity results were inconsistent, with varying positive and inverse dose-response relationships in different trials (Watrous and Plaa 1972). There were no significant changes in absolute or relative kidney weight or blood urea nitrogen in mice given 1,1,2-trichloroethane by gavage for 14 days at a dose of 38 mg/kg/day or in the drinking water for 90 days at a dose of 305 mg/kg/day in males and 384 mg/kg/day in females (White et al. 1985). No increase in the occurrence of non-neoplastic lesions was found in the kidney histopathological examination following 78 weeks of oral 1,1,2-trichloroethane administration in corn oil at doses of 92 mg/kg/day in rats and 390 mg/kg/day in mice (NCI 1978).

The renal effects of dermally applied 1,1,2-trichloroethane in animals were examined in one study. No histopathological changes were found in the kidneys of guinea pigs 2, 6, or 12 hours after dermal application of 1,1,2-trichloroethane at 465 mg/cm^2 (Kronevi et al. 1977).

2.11 DERMAL

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

No histological skin alterations were observed in animals following inhalation exposure of rats to up to 100 ppm 6 hours/day, 5 days/week for 13 weeks (Kirkpatrick 2002) or in rats or mice administered via gavage 92 or 390 mg/kg, respectively, 5 days/week for 78 weeks (NCI 1978).

Several studies have evaluated the dermal toxicity of 1,1,2-trichloroethane in humans. A subject dermally exposed to 698 mg/cm^2 (1.5 mL on 3.1 cm^2 of the forearm) 1,1,2-trichloroethane under occlusion for 5 minutes reported stinging and burning sensations and displayed transient whitening of the skin (Wahlberg 1984a). A small, immediate increase in blood flow was measured by laser Doppler flowmetry, but no visible erythema was present. In an open test on the same subject, in which 0.1 mL of 1,1,2-trichloroethane was applied to the skin without a cover disc, there was no effect on blood flow and no visible erythema was found (Wahlberg 1984a). A volunteer given daily open application of 0.1 mL of 1,1,2-trichloroethane for 15 days did not have any visible skin reactions, nor was there any increase in skin-fold thickness, which was measured using calipers (Wahlberg 1984b).

The dermal effects of 1,1,2-trichloroethane have also been studied in animals. Dermal application of 1,1,2-trichloroethane at 465 mg/cm^2 produced pyknotic nuclei in epidermal cells within 15 minutes in guinea pigs (Kronevi et al. 1977). As the duration of exposure increased, damage progressed to vesicle formation and separation of skin layers (Kronevi et al. 1977). Rabbits given a single application of 0.01 mL of 1,1,2-trichloroethane had no effects other than slight capillary congestion (Smyth et al. 1969). Duprat et al. (1976) compared the dermal irritancy of chlorinated aliphatic solvents in rabbits and determined that 1,1,2-trichloroethane (concentration not reported) was a severe skin irritant compared to other compounds in this group, producing serious erythema, serious edema, and necrosis. In a repeated-dose study, daily open application of 0.1 mL for 10 days increased skin-fold thickness 170% in guinea pigs and 218% in rabbits (Wahlberg 1984b). All animals in this study displayed marked erythema and edema, and fissuring and scaling were also seen.

2.12 OCULAR

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

No exposure-related ocular effects, as evaluated by an ophthalmologic examination, were observed in rats after inhalation exposure to 1,1,2-trichloroethane up to 100 ppm 6 hours/day, 5 days/week for 13 weeks (Kirkpatrick 2002). Similarly, histopathological examination of the eye found no increase in the occurrence of non-neoplastic lesions following 78 weeks of oral 1,1,2-trichloroethane administration at doses of 92 mg/kg in rats and 390 mg/kg in mice (NCI 1978). 1,1,2-Trichloroethane (presumably neat, but not explicitly specified in the study report) applied directly to the eye did not produce significant cornea1 necrosis in rabbits (Smyth et al. 1969). It was classified as a slight eye irritant by Duprat et al. (1976), who found moderate catarrhal conjunctivitis and epithelial abrasion following application in rabbits. Neither study reported the dose of 1,1,2-trichloroethane applied.

2.13 ENDOCRINE

No studies were located regarding non-neoplastic endocrine effects in humans or animals following exposure to 1,1,2-trichloroethane. 1,1,2-Trichloroethane induced increased incidences of adrenal pheochromocytomas (not specified as benign or malignant) in mice after exposure for 78 weeks (NCI 1978).

2.14 IMMUNOLOGICAL

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

Immunological effects in mice orally exposed to 1,1,2-trichloroethane were studied by Sanders and co-workers (Sanders et al. 1985; White et al. 1985). Gavage administration of up to 38 mg/kg/day for 14 days had no effect on humoral or cell-mediated immune response to sRBCs in male mice (Sanders et al. 1985). Humoral immune response was measured by the number of IgM antibody forming cells (AFCs) produced against sRBCs in the spleen. Spleen and thymus weight (absolute or relative) were not affected by treatment (White et al. 1985). In a longer-term study, mice were exposed to 1,1,2-trichloroethane in the drinking water for 90 days (Sanders et al. 1985, White et al. 1985). Humoral immune response was measured by the number of spleen AFCs produced in response to sRBCs, hemagglutination titers, and spleen lymphocyte response to B-cell and T-cell mitogens (Sanders et al. 1985). The number of spleen AFCs to sRBC (reported as ratio of AFC/spleen weight and AFC/per 10^6 spleen cells) was not consistently affected by treatment. A significant increase was obtained in females that received 384 mg/kg/day, on day 4 following immunization and no effect was observed on an AFC/spleen basis. Significant increases for the AFC/10^6 cell ratio were detected in males treated at 4.4 and 46 mg/kg/day,

while the AFC/total spleen ratio was significantly increased at 46 mg/kg/day; neither outcome was affected in males treated at 305 mg/kg/day. The response of splenic lymphocytes to mitogens was unaffected by treatment. Hemagglutination titers (expressed as $\log_2$ titers) exhibited an inverse dose-related depression that was significant starting at 44 mg/kg/day in females and 46 mg/kg/day in males. Based on the transformation of $\log_2$ titers to antibody dilutions, hemagglutination levels were decreased 47 and 59% in males treated at 46 and 305 mg/kg/day, respectively, and 40 and 45% in females treated at 3.9 and 384 mg/kg/day, respectively. Both delayed-type hypersensitivity and popliteal lymph node proliferation responses were examined in the 90-day study. Peritoneal macrophages from males exposed to 305 mg/kg/day had a significantly depressed ability to phagocytize sRBCs; this effect was not found in females. Changes in the activity of fixed macrophages of the reticuloendothelial system to clear and distribute sRBCs (observed in females only) were not considered treatment-related owing to variations in the direction and magnitude of effects. Relative spleen weight was increased by 18% in females exposed to 384 mg/kg/day, but no increases were observed in males at doses up to 305 mg/kg/day (White et al. 1985). No changes in absolute or relative thymus weight were observed in males or females at doses up to 305 and 384 mg/kg/day, respectively (White et al. 1985). On the basis of the Sanders et al. (1985) study, 44 mg/kg/day was chosen as the LOAEL based on decreased hemagglutination titers; 3.9 mg/kg/day was identified as the NOAEL. The mechanisms involved in 1,1,2- trichloroethane-mediated immunotoxicity are not known.

No increase in the occurrence of non-neoplastic lesions was found in the spleen, thymus, bone marrow, or lymph nodes following 78 weeks (5 days/week) of gavage 1,1,2-trichloroethane administration at doses of 92 mg/kg/day in rats and 390 mg/kg/day in mice (NCI 1978).

2.15 NEUROLOGICAL

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

Studies in animals indicate that inhalation of 1,1,2-trichloroethane may produce neurological effects. Rats exposed to 1,1,2-trichloroethane at about 350–1,720 ppm for up to 1 hour showed significant effects on the central vestibular system (namely slow-phase eye velocity [SPV] and the duration of nystagmus) following optokinetic, vestibular, and combined optokinetic and vestibular stimulation. The duration of nystagmus and the generation of saccades (quick reposition of the eyes) were unaffected by 1,1,2-trichloroethane exposure (Niklasson et al. 1993).This study was not used as the basis of a LOAEL because

all data in the report were presented graphically (statistical significance based on simple regression analysis were provided in the text; pairwise-tests were not performed). Two studies by Kirkpatrick (2001) showed that exposure to 1,1,2-trichloroethane for 4 hours resulted in sleepiness and decreased respiration in male rats at ≥1,474 ppm and in female rats at ≥840 ppm. Exposure to 1,654 ppm of 1,1,2-trichloroethane for 6 hours produced excitation, followed by sleepiness, in rats (Bonnet et al. 1980). Mice exposed to 1,1,2-trichloroethane vapor for 2 hours laid down on their sides at 1,833 ppm and lost control of their reflexes at 2,749 ppm. These concentrations are substantially lower than the minimum lethal concentration of 12,934 ppm that was reported in this study, which suggests that 1,1,2-trichloroethane exhibits increased central nervous system depression (Lazarew 1929). The ET_{50} for anesthesia (duration of exposure that produced anesthesia in one-half of the exposed mice) in mice exposed to 3,750 ppm was 18 minutes (Gehring 1968). This was substantially shorter than the LT_{50} of 600 minutes for lethality, indicating increasing central nervous system depressant potency. A 50% elevation in the threshold for pentylenetetrazol-induced seizures of central nervous system function occurred in mice after exposure to 418 ppm of 1,1,2-trichloroethane for 4 hours (de Ceaurriz et al. 1981). This effect may indicate depression of central nervous system function. The mechanisms involved in 1,1,2-trichloroethane-mediated neurotoxicity are not known.

Neurological effects have also been reported in oral exposure studies, particularly via gavage administration of 1,1,2-trichloroethane. Rats administered a single gavage dose of 1,1,2-trichloroethane (in 10 mL/kg corn oil) at 200 mg/kg showed an increased incidence of slight (but definite) gait impairment on study day 0 (4/12 males and 5/12 females; 0/12 controls). Motor activity counts were significantly altered at ≥55 mg/kg for some testing intervals; however, these changes were not consistently dose- or duration-related. There were no statistically significant effects on mean total or ambulatory motor activity counts on study days 0, 7, or 14. Brain weight (absolute) and microscopic examinations of the nervous tissues did not show treatment-related effects (Beck 2004). All mice given single gavage doses of 1,1,2-trichloroethane at ≥450 mg/kg were sedated within 1 hour of administration (White et al. 1985). The ED_{50} for motor impairment (the dose that produced motor impairment in one-half of the test animals) in mice was 128 mg/kg, with the peak effect occurring within 5 minutes of exposure to a single dose (Borzelleca 1983). In dogs, single doses of 1,1,2-trichloroethane at 289–722 mg/kg produced drowsiness, incoordination, and partial narcosis after 12–50 minutes (Wright and Schaffer 1932).

Kallman et al. (1983) reported that 1,1,2-trichloroethane administered by gavage for 7 days produced a significant dose-related taste aversion to saccharin in the drinking water at 100 mg/kg, but not at

≤30 mg/kg. An ED_{50} of 32 mg/kg was calculated. Mice did not display a taste aversion to 1,1,2-trichloroethane itself when 46 mg/kg/day was added to the drinking water for 4 days (Kallman and Kaempf 1984). The mechanisms involved in 1,1,2-trichloroethane-mediated neurotoxicity are not known.

Longer-term studies did not report neurological effects following oral administration of 1,1,2-trichloroethane. Gavage administration of 38 mg/kg/day for 14 days did not affect absolute or relative (to body weight) brain weight in mice (White et al. 1985). Mouse brain weight (absolute or relative to body weight) was also unaffected by exposure to 305 mg/kg/day (males) and 384 mg/kg/day (females) in the drinking water for 90 days (White et al. 1985). NOAEL values were not derived from these studies because brain weight alone is not an adequate endpoint to assess neurotoxicity. Rats administered 1,1,2-trichloroethane at up to 98 mg/kg/day in drinking water for 13 weeks showed no evidence of neurological effects, based on functional observational battery tests and light microscopic examinations of nervous system tissues (Maurissen et al. 2005). No effect on the occurrence of non-neoplastic lesions in nervous system organs and tissues was found by histopathological examination following 78 weeks of oral 1,1,2-trichloroethane administration at doses of 92 mg/kg/day in rats and 390 mg/kg/day in mice (NCI 1978).

One study of neurological effects in animals following dermal exposure was located. No histopathological changes were found in the brains of guinea pigs 2, 6, or 12 hours after dermal application of 1,1,2-trichloroethane at 465 mg/cm^2 (Kronevi et al. 1977).

2.16 REPRODUCTIVE

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

Studies of orally administered 1,1,2-trichloroethane did not report significant reproductive effects in animals. In a two-generation study (Mylchreest 2006), rats showed no significant effects on reproduction, based on evaluations of mating, fertility, implantations, sperm and estrous parameters, and light microscopic examinations of the reproductive tissues. Seidenberg et al. (1986) found no effect on number of litters resorbed or average number of neonates per litter in mice following 5 days of oral administration of 350 mg/kg/day in corn oil on days 8–12 of gestation.

Testes weight (absolute or relative) in mice was not affected when 1,1,2-trichloroethane was administered by gavage for 14 days at a dose of 38 mg/kg/day (White et al. 1985). Exposure to ≥46 mg/kg/day in the drinking water for 90 days produced a significant increase in relative, but not absolute, testes weight in mice (White et al. 1985). NOAEL and LOAEL values were not derived from these studies, however, because testes weight alone may not be an adequate endpoint to assess reproductive toxicity. Also, changes in testes weight are not necessarily associated with reproductive dysfunction. No effect on the occurrence of non-neoplastic lesions in structures of the reproductive system was found following administration of 92 mg/kg in rats and 390 mg/kg in mice for 78 weeks (5 days/week) (NCI 1978).

2.17 DEVELOPMENTAL

One study was located regarding developmental effects in humans due to exposure to 1,1,2-trichloroethane. A case-control study examined the association between the proximity to industrial air releases of 14 chlorinated solvents (including 1,1,2-tricholoroethane) and birth defects (including neural tube, oral cleft, limb deficiency, and congenital heart defects). Exposure was estimated with metrics that accounted for the proximity of residences to industrial release sites and the amount of chemicals released annually. All risk estimates were adjusted for year of delivery and maternal age, education, race/ethnicity, and region of residence. Most associations were not significant. However, proximity of emissions to several chlorinated solvents (including 1,1,2-trichloroethane, carbon tetrachloride, chloroform, ethyl chloride, and 1,2,3-trichloropropane) were positively associated with neural tube defects; associations were also observed for a few solvents and other types of defects. With respect to 1,1,2-trichloroethane, positive associations were found between maternal residential proximity to 1,1,2-trichloroethane emissions and neural tube defects (odds ratio [OR] 1.56; 95% confidence interval [CI] 1.11–1.28), spina bifida (OR 1.94; 95% CI 1.32–2.84), and septal heart defects (albeit weak; OR 1.12; 95% CI 1.01–1.24), but not limb deficiencies (OR 0.91; 95% CI 0.56–1.46) (Brender et al. 2014). When exposure risk values were examined as quartiles, there was a significant inverse linear trend for spina bifida (p=0.026), significant positive linear trend for septal defects (p=0.031), and a marginally significant (p=0.059) non-monotonic trend for isolated cleft palate. Strengths of the study included the large size (allowing for stratification by age) and the ability to account for the recurrence of birth defects (a known risk factor). No additive or multiplicative interactions between exposure and birth defects by maternal age were detected. Weaknesses of the study include: (1) no direct air measurements of chlorinated solvents; and (2) residential histories of mothers throughout pregnancy were not available. Since mothers were exposed to multiple chemicals, the observed effects cannot be attributed to 1,1,2-trichloroethane alone. In addition, Wikoff et al. (2018) suggest that proximity to exposure sources (as a proxy of exposure) is likely

to introduce bias; the use of a continuous variable to quantify exposure rather than an undefined threshold distance would eliminate some of the bias. Despite the use of proximity to emissions as an exposure metric, Brender et al. (2014) showed a correlation between estimated exposures and air measurements from the Texas Commission of Environmental Quality.

Several studies of the developmental effects of 1,1,2-trichloroethane in animals were found. Female rats administered 1,1,2-trichloroethane at up to 111 mg/kg/day in drinking water on days 6–20 of gestation showed no effects on fetal weight, fetal sex distribution, or incidences of external, visceral, or skeletal abnormalities on GD 20 (Wilson 2005). In a 2-generation study in rats (Mylchreest 2006), F1 and F2 pups exposed to 1,1,2-trichloroethane at 82.2 mg/kg/day showed decreased body weights on postnatal days 4 to 21 (13–18% lower than controls). There were no significant effects on pup body weights at birth or on the timing of developmental milestones (vaginal opening or preputial separation). In pregnant female mice administered 350 mg/kg/day 1,1,2-trichloroethane via gavage on days 8–12 of gestation, the percent survival of neonates from day 1 through day 3 was not affected by treatment, and neither was average neonatal weight measured on days 1 and 3 postpartum (Seidenberg et al. 1986).

2.18 OTHER NONCANCER

No studies were located regarding other noncancer effects in humans or animals following exposure to 1,1,2-trichloroethane.

2.19 CANCER

One study was located regarding cancer in humans following inhalation exposure to 1,1,2-trichloroethane. A case-control study by Dosemeci et al. (1999) that investigated the risks of RCC caused by occupational exposures to solvents, chlorinated aliphatic hydrocarbons (CAHCs), and nine individual CAHCs (including 1,1,2-trichloroethane) failed to show an association between exposure to 1,1,2-trichloroethane and RCC, with ORs and 95% CIs for males and females of 0.90 (0.5–1.6) and 0.95 (0.2–4.4), respectively.

One study of cancer in animals orally exposed to 1,1,2-trichloroethane was located. There was no significant increase in the occurrence of neoplasms in male or female rats following 78 weeks (5 days/week) of gavage administration of 92 mg/kg (NCI 1978). In mice, there was a significant dose-related increase in the incidence of hepatocellular carcinomas in both males and females following 78 weeks of gavage administration at doses of 195 or 390 mg/kg/day (NCI 1978). These carcinomas

were found in 10% of untreated control males, 12% of vehicle control males, 37% of low-dose males, and 76% of high-dose males. In female mice, they were found in 10% of untreated controls, 0% of vehicle controls, 33% of low-dose animals, and 89% of high-dose animals. In addition, there was a significant increase in the occurrence of adrenal pheochromocytomas (not specified as benign or malignant) in mice of both sexes at 390 mg/kg/day. These lesions, not found in the control or 195 mg/kg/day groups, had incidences of 17% in 390 mg/kg/day males and 28% in 390 mg/kg/day females. 1,1,2-Trichloroethane was classified as a possible human carcinogen in the Integrated Risk Information System (IRIS) (EPA 1987) and as Group 3 (not classifiable as to its carcinogenicity in humans) by IARC (1999).

Data from a subcutaneous carcinogenicity study in Sprague-Dawley rats conducted by Norpoth et al. (1988) found that treatment with 1,1,2-trichloroethane for 2 years had no significant effect on the incidence of benign mesenchymal and epithelial tumors. Although there was a dose-related increased incidence of sarcomas in treated rats of both sexes compared to untreated controls, untreated controls showed an unusually low number of sarcomas, and this effect was not significant based on comparison to vehicle controls. A cancer initiation and promotion study in rats was also negative (Story et al. 1986).

2.20 GENOTOXICITY

1,1,2-Trichloroethane has been tested for genotoxicity in a variety of *in vivo* and *in vitro* test systems (see Tables 2-4 and 2-5). Mixed results have been obtained in *in vivo* tests. As shown in Table 2-4, 1,1,2-trichloroethane tested negative for sex-linked recessive lethal mutations in *Drosophila melanogaster* (Foureman et al. 1994). Although a weakly positive response was elicited in a mitotic recombination (eye mosaic) assay in *Drosophila*, this response was seen only at a cytotoxic concentration (Vogel and Nivard 1993). The frequency of micronucleated polychromatic erythrocytes in the bone marrow of male and female mice was not significantly affected by treatment with 1,1,2-trichloroethane (Crebelli et al. 1999). In a study that evaluated DNA damage (as measured by unwinding), 1,1,2-trichloroethane did not induce damage in mouse hepatocytes (Taningher et al. 1991). However, 1,1,2-trichloroethane tested positive for DNA adduct formation in rat and mouse liver, with adducts occurring to a greater extent in mice relative to rats (Mazzullo et al. 1986). The authors pointed out that there is a correlation between these adduct formation results and species susceptibility to cancer, as the incidence of hepatocellular carcinomas was increased in mice, but not rats, given 1,1,2-trichloroethane for 78 weeks. Positive results were also seen in several assays that evaluated DNA synthesis in the hepatocytes of mice (Mirsalis et al. 1989; Miyagawa et al. 1995). The authors of these studies suggested that the induction of DNA synthesis may be an important mechanism of hepatocarcinogenicity (Mirsalis et al. 1989). Finally, 1,1,2-trichloroethane

was positive for the inhibition of DNA synthesis in mice administered 1,1,2-triochloroethane via intratesticular injection (Borzelleca 1983).

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

Species (exposure route)	Endpoint	Results	Reference
Drosophila melanogaster (feed)	Sex-linked recessive lethal	–	Foureman et al. 1994
D. melanogaster (inhalation)	Mitotic recombination	+	Vogel and Nivard 1993
Mouse (intraperitoneal)	Micronuclei in bone marrow cells	–	Crebelli et al. 1999
Mouse (intraperitoneal)	DNA damage (unwinding) in hepatocytes	–	Taningher et al. 1991
Rat (intraperitoneal)	DNA adduct formation with liver DNA	+	Mazzullo et al. 1986
Mouse (intraperitoneal)	DNA adduct formation with liver DNA	+	Mazzullo et al. 1986
Mouse (gavage)	Unscheduled DNA synthesis in hepatocytes	–	Mirsalis et al. 1989
Mouse (gavage)	S-phase DNA synthesis in hepatocytes	+	Mirsalis et al. 1989
Mouse (gavage)	Replicative DNA synthesis in hepatocytes	+	Miyagawa et al. 1995
Mouse (intratesticular)	Inhibition of DNA synthesis in the testis	+	Borzelleca 1983

+ = positive results; – = negative results; DNA = deoxyribonucleic acid

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

		Results		
		Activation		
Species (test system)	Endpoint	With	Without	Reference
Salmonella typhimurium (TA1535, TA98, TA100)	Gene mutation	–	–	Barber and Donish 1982
S. typhimurium (TA100, TA1535)	Gene mutation	–	–	Milman et al. 1988
S. typhimurium (TA1535, TA1537, TA98, TA100)	Gene mutation	–	–	Mitoma et al. 1985
S. typhimurium (TA1535)	Gene mutation	–	–	Rannug et al. 1978
S. typhimurium (BA13)	Gene mutation (Ara test)	–	–	Roldan-Arjona et al. 1991
S. typhimurium (TA100)	Gene mutation	–	–	Simmon et al. 1977
S. typhimurium (TA97, TA98, TA100, TA1535, TA1537)	Gene mutation	–	–	Zeiger et al. 1988
Escherichia coli PQ37	Gene mutation	–	–	Mersch-Sundermann et al. 1989
E. coli WP2$_S$ (λ)	λ Prophage induction	+	+	DeMarini and Brooks 1992

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

Species (test system)	Endpoint	Results: Activation With	Results: Activation Without	Reference
Saccharomyces cerevisiae	Mitotic gene conversion	+	+	Bronzetti et al. 1987
Aspergillus nidulans P1	Chromosome malsegregation	NA	+	Crebelli et al. 1988
Human lymphocytes	Micronuclei	–	+	Tafazoli and Kirch-Volders 1996
Human AHH-1 cells	Micronuclei	NA	–	Doherty et al. 1996
Human MCL-5 cells	Micronuclei	NA	+	Doherty et al. 1996
Human lymphoblastoid cells	Micronuclei	NA	+	Doherty et al. 1996
Human lymphocytes	DNA damage	+	+	Tafazoli and Kirch-Volders 1996
Rat hepatocytes	DNA synthesis	NA	+	Reddy 1993
Rat hepatocytes	DNA repair	NA	+	Milman et al. 1988
Rat hepatocytes	DNA repair	NA	+	Williams 1983
Mouse hepatocytes	DNA repair	NA	–	Milman et al. 1988
Mouse hepatocytes	DNA repair	NA	–	Williams 1983
Calf thymus cells	DNA adduct formation	NA	+	DiRenzo et al. 1982
Mouse BALB/c-3T3 cells	Cellular transformation	NA	+	Milman et al. 1988
Mouse BALB/c-3T3 cells	Cellular transformation	NA	–	Tu et al. 1985

– = negative result; + = positive result; DNA = deoxyribonucleic acid; NA = not applicable

Mixed results have also been obtained in *in vitro* assays of 1,1,2-trichloroethane (Table 2-5). In tests for reverse mutations in *Salmonella typhimurium*, results were consistently negative with and/or without metabolic activation in several strains (Barber and Donish 1982; Milman et al. 1988; Mitoma et al. 1985; Rannug et al. 1978; Roldan-Arjona et al. 1991; Simmon et al. 1977; Zeiger et al. 1988). 1,1,2-Trichloroethane tested weakly positive for prophage induction in *Escherichia coli* WP2 (DeMarini and Brooks 1992), but was not mutagenic to *E. coli* PQ37 strain in the SOS-chromotest (Mersch-Sundermann et al. 1989). Positive results were seen for mutagenicity and chromosome malsegregation in fungi (Bronzetti et al. 1987; Crebelli et al. 1988). Human lymphocytes exposed to 1,1,2-trichloroethane showed an approximately 2-fold increase in micronuclei in the absence, but not the presence, of exogenous metabolic activation. It was noted that this response did not exhibit dose-dependent characteristics (Tafazoli and Kirsch-Volders 1996). In another study, increases in micronucleated cells observed in human lymphoblastoid and MCL-5 cell lines (approximately 3.5- and 4-fold, respectively, compared to controls)

were statistically significant and dose-related. Kinetochore staining revealed dose-related increases in kinetochore-positive signals in both cell lines (Doherty et al. 1996). However, similar exposure of the AHH-1 cell line failed to induce micronuclei (Doherty et al. 1996). In the comet assay conducted by Tafazoli and Kirsch-Volders (1996), there was a 1,1,2-trichloroethane-induced DNA breakage in the presence and absence of exogenous metabolic activation. Tests of DNA repair were positive in rat hepatocytes, but negative in mouse hepatocytes (Milman et al. 1988; Williams 1983). Significant adduct formation of 1,1,2-trichloroethane with calf thymus DNA also occurred *in vitro* (DiRenzo et al. 1982). In two cell transformation assays performed in the absence of activation on mouse BALB/c-3T3 cells, one result was negative and the other was positive (Milman et al. 1988; Tu et al. 1985). Although there are negative as well as positive results (reported in the absence of cytotoxicity), it is evident that this compound does have some genetic effects both *in vitro* and *in vivo*. The significance of these effects for humans is not clear, especially since results of *in vivo* mammalian assays showed species variability.