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 1,1,1-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 1,1,1-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 1,1,1-trichloroethane was also conducted; the results of this review are presented in Appendix C.

Summaries of the human observational studies are presented in Table 2-1. Animal inhalation studies are presented in Table 2-2 and Figure 2-2, animal oral studies are presented in Table 2-3 and Figure 2-3, and animal dermal studies are presented in Table 2-4.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. Effects have been classified into “less serious LOAELs” or “serious LOAELs (SLOAELs).” "Serious" effects (SLOAELs) are those that evoke failure in a biological system and can lead to morbidity or

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

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

The health effects of 1,1,1-trichloroethane have been evaluated in epidemiological studies, human controlled trials, and experimental animal studies. As illustrated in Figure 2-1, most of the health effects data come from inhalation exposure studies in animals. Animal data are available for each health effect category and exposure duration category. Much of the data for 1,1,1-trichloroethane comes from toxicity studies that evaluated numerous endpoints. The most reported effects on systems from the literature include body weight, neurological, hepatic, and respiratory effects of 1,1,1-trichloroethane. A number of cohort studies mainly summarized the impact that 1,1,1-trichloroethane had on the nervous and reproductive systems and the potential association with various cancers.

As outlined in Chapter 1, the most sensitive effects from 1,1,1-trichloroethane exposure appear to be neurological and hepatic. A systematic review was conducted on these endpoints. The information in those human and animal studies indicates the following potential targets of 1,1,1-trichloroethane toxicity.

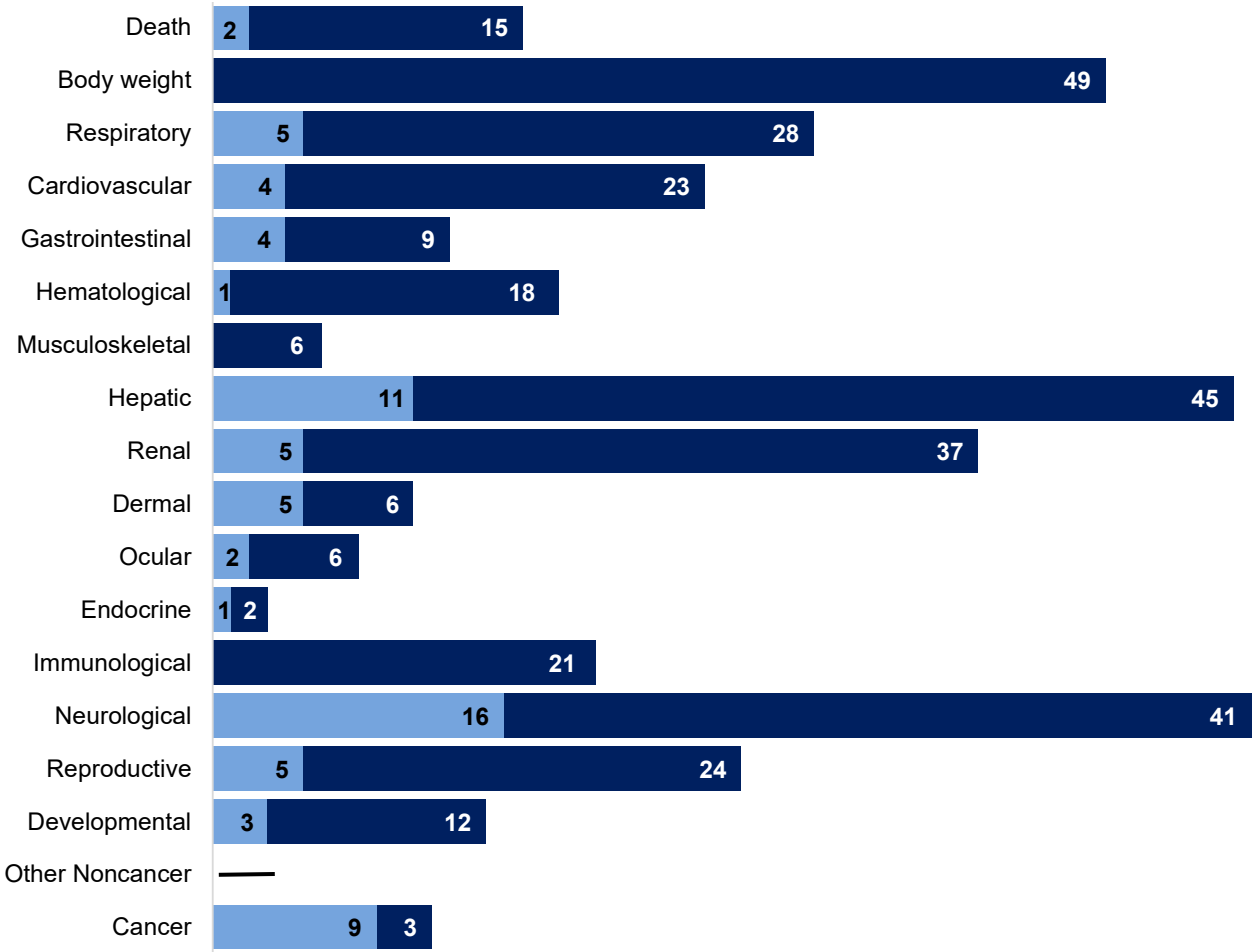
- **Neurological Endpoints.** Neurological effects are a known health effect associated with 1,1,1-trichloroethane exposure via inhalation based on the systematic review. Controlled human exposure studies clearly indicate neurological effects associated with 1,1,1-trichloroethane exposure (e.g., Gamberale and Hultengren 1973; Mackay et al. 1987; Muttray et al. 2000; Stewart et al. 1961; Torkelson et al. 1958). Animal studies provide strong supporting evidence from acute- and intermediate-duration assessments. The nervous system impacts ranging from observable changes in outcomes such as ataxia and behavior to neurophysiological changes such

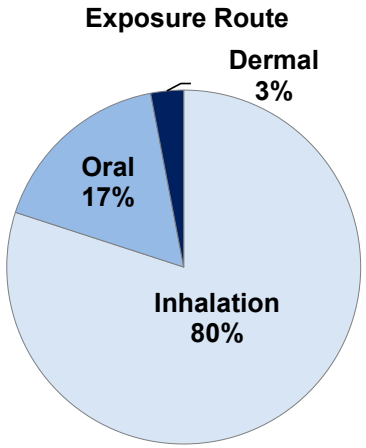
as changes in electroencephalogram or increased brain weight (Balster et al. 1982; Bowen and Balster 1996, 1998; Hougaard et al. 1984; Kjellstrand et al. 1985b; Mullin and Krivanek 1982; Torkelson et al. 1958).

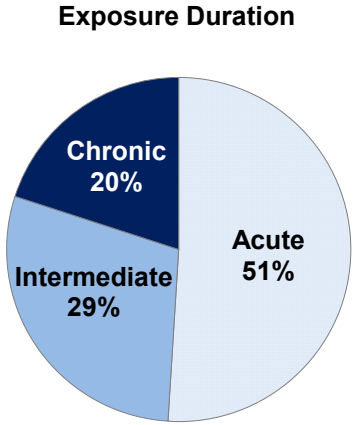
- **Hepatic Endpoints.** Hepatic effects are a presumed health effect for humans exposed to 1,1,1-trichloroethane via inhalation based on evidence in animals following acute-, intermediate-, and chronic-duration exposure. Although no evidence of liver effects was noted in controlled exposure studies in humans, data from case reports of overexposed humans suggest that the chemical may produce hepatic effects in humans exposed to high levels (Cohen and Frank 1994; Halevy et al. 1980; Hodgson et al. 1989). Consistent effects were observed in animal studies, which suggest that 1,1,1-trichloroethane produces hepatic effects after inhalation exposure. The liver effects include changes in relative liver weight, fatty changes in the liver, and swelling of hepatocytes (Adams et al. 1950; Koizumi et al. 1983; MacEwen and Vernot 1974; McNutt et al. 1975; Quast et al. 1988; Toftgard et al. 1981; Torkelson et al. 1958).

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

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







*Includes studies discussed in Chapter 2. A total of 163 studies (including those finding no effect) have examined toxicity. Studies may have examined more than one endpoint for health effects.

Table 2-1. Occupational Inhalation Exposures to 1,1,1-Trichloroethane and Health Outcome Associations

Reference, study type, and study population	Exposure	Outcomes
Cancer		
Rohr Indus Inc. 1986, 1987 Case-control study of esophageal and stomach cancer (22 cases and 88 controls) in Rohr factory workers, 1958–1982	Classified as ever versus never exposed.	Esophageal or stomach cancer: ↔
Spirtas et al. 1991 Retrospective cohort study of cancer mortality in aircraft maintenance facility workers (n=14,457), Hill Air Force Base, Utah,1952–1982	NR	All cancer mortality: ↓ NHL mortality: ↔ MM mortality: ↑ Leukemia: ↔
Heineman et al. 1994 Case-control study of astrocytic brain cancer (300 cases and 320 controls) in Louisiana, New Jersey, and Pennsylvania, 1978–1981	Qualitative exposure classified as no exposure, low, medium, and high	Astrocytic brain cancer: ↔
Anttila et al. 1995 Retrospective cohort study of cancer incidence in Finnish workers (n=4,004), 1967–2002	Urinary 1,1,1-trichloroethane Men: 6.4 mg/L Women: 8.4 mg/L	All cancer: ↑ Stomach cancer: ↑ nervous system cancer: ↑ cervical cancer: ↑ Prostate cancer: Leukemia: ↔ NHL: ↑ MM: ↔
Infante-Rivard et al. 2005 Case-control study of childhood leukemia following maternal exposure (790 cases and 790 controls) in Canada, 1980–2000	Maternal exposure classified as no exposure and any exposure	Acute lymphoblastic leukemia in children: ↔

Table 2-1. Occupational Inhalation Exposures to 1,1,1-Trichloroethane and Health Outcome Associations

Reference, study type, and study population	Exposure	Outcomes
Gold et al. 2011 Case-control study of multiple myeloma (180 cases and 481 controls) in Washington and Michigan, 2000–2002	Classified as ever exposed	MM: ↑
Neta et al. 2012 Case-control study of brain tumors (489 glioma cases, 197 meningioma cases, and 799 controls) in Boston, 1994–1998	Classified as unexposed, possible exposure, and probably exposure	Glioma: ↔ Meningioma: ↔
McLean et al. 2014 Case-control study of brain tumors (1,906 cases and 5,565 controls) in Australia, Canada, France, Germany, Israel, New Zealand, and the United Kingdom, 2000–2004	Mean cumulative exposure: Cases: 188 ppm Controls: 458 ppm	Meningioma: ↔
Purdue et al. 2017 Case-control study of kidney cancer (1,217 cases and 1,235 controls) in Michigan and Illinois, 2002–2007	Stratified by probability of exposure: 0, <10, 10–49, 50–89, and ≥90%	Kidney cancer: ↔ (≥90% probability of exposure)
Talibov et al. 2017 Case-control study of adult chronic lymphocytic leukemia (20,615 cases and 103,075 controls) in Finland, Iceland, Norway, and Sweden, 1961–2005	Cumulative exposure stratified in tertiles (T) T1: ≤5.6 ppm-years T2: 5.6–12.9 ppm-years T3: >12.9 ppm-years	Chronic lymphocytic leukemia: ↔
Cardiovascular		
Kramer et al. 1978 Cross-sectional matched-pair study of health effects in workers from two factories (151 matched pairs) in North Carolina, 1975	TWA exposure levels stratified by quintile: Q1: <15 ppm Q2: 15–49 ppm Q3: 50–99 ppm Q4: 100–149 ppm Q5: 150–249 ppm	Blood pressure: ↔ Heart rate: ↔ P-wave duration: ↑

Table 2-1. Occupational Inhalation Exposures to 1,1,1-Trichloroethane and Health Outcome Associations

Reference, study type, and study population	Exposure	Outcomes
Hepatic		
Kramer et al. 1978 Cross-sectional matched-pair study of health effects in workers from two factories (151 matched pairs) in North Carolina, 1975	TWA exposure levels stratified by quintile: Q1: <15 ppm Q2: 15–49 ppm Q3: 50–99 ppm Q4: 100–149 ppm Q5: 150–249 ppm	Alkaline phosphatase: ↔ Bilirubin: ↔ gamma-Glutamyl transferase: ↑
Neurological		
Maroni et al. 1977 Cross-sectional study of neurological effects in female factory workers (n=29), circa 1977	Range of 1,1,1-trichloroethane concentrations in work areas: 200–990 ppm	Peripheral neuropathy: ↔ Superficial sensory response: ↔ Deep sensory response: ↔ Motor conduction (ulnar and peroneal nerves): ↔ Psychological test battery: ↔
Renal		
Radican et al. 2006 Retrospective cohort study of ESRD in U.S. aircraft workers (n=14,455), Hill Air Force Base, 1973–2002 (Utah)	Stratified in tertiles by years of exposure: T1: <2.5 years T2: 2.5–10 years T3: >10 years	ESRD: ↑ (T3)
Reproductive		
Taskinen et al. 1989 Case-control study of adverse pregnancy outcomes in partners of Finnish factory workers (103 cases, 182 controls), 1965–1983	Paternal exposure classified as unexposed, potentially exposed, and exposure likely	Spontaneous abortion: ↔
Lindbohm et al. 1990 Case-control study of spontaneous abortions (73 cases and 167 controls) in exposed female workers in Finland, 1973–1983	Classified as no, low, and high exposure	Spontaneous abortions: ↔

Table 2-1. Occupational Inhalation Exposures to 1,1,1-Trichloroethane and Health Outcome Associations

Reference, study type, and study population	Exposure	Outcomes
Sallmen et al. 1998 Cohort study of fertility in male Finnish factory workers (n=282), 1973–1983	Paternal exposure classified as none, low/intermediate, and high/frequent	Number of menstrual cycles to pregnancy: ↔

↑ = increase; ↓ = decrease; ↔ = no change; ESRD = end-stage renal disease; MM = multiple myeloma; NHL = Non-Hodgkin's lymphoma; NR = exposure not reported; Q = quintile; T = tertile; TWA = time-weighted average

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Gamberale and Hultengren 1973									
1	Human 12 M	1 day 4 times/day 30 minutes/ exposure	0, 239.2, 338.3, 451.2, 565.8	CS, NX	Cardio	565.8			
					Neuro	239.2	338.3		Impaired cognitive skills (reaction time, perceptual speed), impaired manual dexterity
Laine et al. 1996									
2	Human 9 M	5 hours	200 (TWA)	BI, CS	Neuro	200			
Mackay et al. 1987									
3	Human 12 M	3.5 hours	0, 175, 350	CS, NX	Neuro		175[b]		Impaired performance on measures of cognitive skills (simple reaction time, four choice reaction time, task tracking: target acquisition, root mean squared error, and time on target)
NIOSH 1975									
4	Human 10 M, 10 F	5 days 1–7.5 hours/day	0, 100 (M), 350 (M, F), 500 (M)	BC, CS, NX, UR	Resp	350 F 500 M			
					Hemato	350 F 500 M			
					Hepatic	350 F 500 M			
					Neuro	350	500 M		Altered EEG tracings: increased amplitude of alpha activity on the final day
					Renal	500			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Salvini et al. 1971									
5	Human 6 M	1 day 8 hours/day	0, 450	CS, NX	Neuro	450			
Savolainen et al. 1981									
6	Human 4–5 M	1 day 4 hours/day	0, 200, 400	CS, NX	Neuro	400			
Stewart et al. 1961									
7	Human 2–7 M	1 day 15–186 minutes/ day	0, 500, 900, 910, 955, 0–2,650[c]	BC, CS, UR	Resp		1,900		Throat irritation (subjective) in 6/7 subjects
					Hepatic	2,650			
					Neuro	496	900		Lightheadedness (subjective) in 2/6 subjects
					Renal	2,650			
Stewart et al. 1969									
8	Human 5 M	5 days 6.5–7 hours/day	500	CS	Neuro	500			
Geller et al. 1982									
9	Monkey (baboon) 4 M	4 hours	0, 700, 1,400, 1,800, 2,100	CS, NX	Neuro	1,400	1,800		Impaired performance in learning and memory in a match to sample test
Adams et al. 1950									
10	Rat (Wistar) 3–17 M	6–420 minutes	0, 5,000, 10,000, 12,000,	BW, CS, GN, HP, OW	Death				LC_{50} (3 hours): 18.000 ppm LC_{50} (7 hours): 14,250 ppm
					Bd wt	18,000			
					Cardio	18,000			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
			15,000, 18,000, 30,000		Hepatic		8,000		Increase in relative liver weight; slight fatty changes of the liver
					Renal	18,000			
					Neuro			5,000	Narcosis
BRRC 1987a									
11	Rat (CD) 30 F	GDs 6–15 4 hours/day	0, 1,000, 3,000, 6,000	CS, BW, OW, FI, WI, HP, DX	Develop	3,000	6,000		6% decrease in female fetal weight, delayed ossification was observed in 15 pups
Calhoun et al. 1981									
12	Rat (CDF) 5 M, 5 F	6 hours	0, 4,946	BC, BW, GN, OW	Bd wt	4,946			
					Ocular		4,946		Porphyrin like pigmentation around eyes
					Neuro		4,946		Motor incoordination
Carlson 1973									
13	Rat (Albino) 5 M	2 hours	0, 11,600	BI, BW, BC, OF	Hepatic	11,600			
Carlson 1973									
14	Rat (Albino) 5 M	2 hours	0, 13,070	BI, BW, BC, OF	Hepatic	13,070			
Cornish and Adefuin 1966									
15	Rat (Sprague-Dawley) 6 M	2 hours	0, 10,000, 15,000	HP, BC, CS	Bd wt	15,000			
					Resp	15,000			
					Hepatic	15,000			
					Renal	15,000			
					Immuno	15,000			
					Endocr	15,000			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Folbergrova et al. 1984									
16	Rat (Wistar) 6 M	5 or 60 minutes	0, 8,000	BI, CS, NX	Cardio		8,000		Decreased mean arterial blood pressure
					Neuro	8,000			
Fuller et al. 1970									
17	Rat (Sprague-Dawley) 10 M	24 hours	0, 2,500–3,000	BI, CS, OF	Hepatic		2,500		Increased absolute and relative liver weight
George et al. 1989									
18	Rat (Wistar) 30 NS	8 hours	0, 3000, 4800, 6400, 9600, 12000, 20000	CS	Neuro		3,000	4,800	LOAEL: Lethargy SLOAEL: Anesthesia
Hougaard et al. 1984									
19	Rat (Wistar) 6–11 M	0.5–2 hours	0, 3,500, 6,000, 7,800	NX	Neuro	3,500	6,000	7,800	LOAEL: 14–55% decrease in local cerebral glucose consumption, ”intoxication signs,” decreased motility and exploration SLOAEL: Ataxia
Koizumi et al. 1983									
20	Rat (Wistar) 6 M	10 days 24 hours/day	0, 200, 400, 800	BW, OW, BC, BI	Hepatic		200		Increase in relative liver weight

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Mullin and Krivanek 1982									
21	Rat (Charles River-CD) 6 M	0.5–4 hours	0, 1,750, 3,080, 6,100, 11,550	CS, NX	Death			11,550	2/6 died
					Resp			6,100	Respiratory distress
					Neuro	1,750		3,080	Ataxia and impaired placing, grasping, lift, and righting reflexes
Savolainen et al. 1977									
22	Rat (Sprague-Dawley) 10 M	4 days 6 hours/day 0, 2, 3, 4, or 6 hours of exposure on 5th day	0, 500	BI, CS, NX	Hepatic	500			
					Neuro	500			
Schwetz et al. 1975									
23	Rat (Sprague-Dawley) 23–30 F	10 days (GDs 6–15), 7 hours/day	0, 875	BW, CS, DX, OW, RX	Bd wt	875			
					Hemato	875			
					Hepatic	875			
					Repro	875			
					Develop	875			
Aranyi et al. 1986									
24	Mouse (CD-1) 140 F	3 hours	0, 350	CS, OF	Immuno	350			
Balster et al. 1982									
25	Mouse (CD-1) 8 M	20 minutes	0, 1,000, 2,000, 4,000, 8,000	CS, NX, OF	Neuro	1,000	2,000		Impaired operant learning

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Bowen and Balster 1996									
26	Mouse (CFW) 10 M	5 days 30 minutes/day	0, 500, 1,250, 2,500, 5,000, 7,500, 10,000	CS, NX	Neuro		1,250		Increase in locomotor activity
Bowen and Balster 1996									
27	Mouse (CFW) 10 M	5 days 30 minutes/day	0, 500, 1,250, 2,500, 5,000, 7,500, 10,000, 12,500	CS, NX	Neuro		2,500		Increase in motor activity
Bowen and Balster 1998									
28	Mouse (albino) 10 M	2 days 30 minutes/day	0, 500, 1,000, 2,000, 4,000, 6,000, 8,000, 10,000, 12,000, 14,000	CS, NX	Neuro	2,000	4,000		Increase in locomotor activity

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Bowen and Balster 1998									
29	Mouse (albino) 7 M	2 days 30 minutes/day	0 1,000, 2,000, 4,000, 8,000, 10,000, 12,000	BI, NX	Neuro	2,000	4,000		Impaired operant learning
Bowen and Balster 2006									
30	Mouse (Albino) 40 M	30 minutes	0, 2,000, 6,000, 10,000, 13,300	NX	Neuro	2,000	6,000		Increase in locomotor activity
Bowen et al. 1996a									
31	Mouse (albino) 10 M	30 minutes	0, 2,500, 5,000, 10,000	CS, NX	Neuro	5,000	10,000		Hyperactivity in elevated plus maze
Bowen et al. 1996b									
32	Mouse (albino) 8 M	20 minutes	0, 4,000, 8,000, 10,000, 13,300, 18,000	CS, NX	Neuro	8,000		10,000	Impaired motor coordination/ strength (inverted screen test), impaired gait and righting reflex
Calhoun et al. 1981									
33	Mouse (B6C3F1) 5 M, 5 F	6 hours	0, 4,946	BC, BI, BW, GN, OW, OF	Bd wt	4,946			
					Ocular	4,946			
					Neuro	4,946			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Evans and Balster 1993									
34	Mouse (CFW Swiss) 10 M	4 days 24 hours/day	0, 500, 1,000, 2,000, 4,000	CS, BW, NX, OP	Bd wt	2,000		4,000	25% decrease in body weight 96 hours after exposure
					Dermal	2,000	4,000		Dull fur coat
					Ocular	2,000	4,000		Eye irritation observed
					Neuro			500	5/10 experienced withdrawal convulsions upon handling after exposure
Jones et al. 1996									
35	Mouse (CD-1) 12	5 days (GDs 12–17), 3 exposures/day 60 minutes/ exposure	0, 8,000	BW, CS, DX, FI, NX, RX, WI	Bd wt	8,000			
					Neuro			8,000	Sedation, splayed hindlimb, clonic movements, severe sway, ataxia, and gait abnormalities in dams
					Repro	8,000			
					Develop			8,000	Decrease in litter weight on PNDs 2–19; delayed eye opening, Impaired righting reflex
Jones et al. 1996									
36	Mouse (CD-1) 10 F	6 days (GDs 12–17), 17 hours/day	0, 2,000	BW, CS, DX, FI, NX, RX, WI	Bd wt	2,000			
					Develop			2,000	Decreased litter weight; delayed eye opening in pups; impaired righting reflex; decrease in grip strength; delay in negative geotaxis
Kjellstrand et al. 1985a									
37	Mouse (NMRI) 14–54 M	1 hour	0,700, 900, 1,200, 2,300	CS	Neuro	900	1,200		Increase in motor activity

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Moser and Balster 1986									
38	Mouse (CD-1) 15 M	30 minutes	0, 1,800, 3,600, 7,200, 10,800	CS, NX	Neuro	3,600	7,200		Impaired operant learning
Ohnishi et al. 2013									
39	Mouse (C57Bl/ 6J) 6 M	5 days 6 hours/day	0, 5, 50, 500	BI, HP	Repro	500			
Páez-Martínez et al. 2003									
40	Mouse (Swiss-Webster) 12	30 minutes	0, 2,000, 4,000, 8,000, 10,000	CS, NX	Neuro	4,000	8,000		Decreased anxiety in conditioned defensive burying
Schwetz et al. 1975									
41	Mouse (Swiss Webster) 13–30 F	10 days (GDs 6–15), 7 hours/day	0, 875	BW, CS, DX, OW, RX	Bd wt	875			
					Hemato	875			
					Hepatic	875			
					Repro	875			
					Develop	875			
Woolverton and Balster 1981									
42	Mouse (CD-1) 12 M	30 minutes	0, 3,600–23,000	CS, LE, NX, OF	Death			22,241	6/12 mice died
					Neuro		7,000		Impaired motor coordination/strength (inverted screen test)

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Egle et al. 1976									
43	Dog (Beagle) 6 M, 6 F	15 minutes	0, 5,000, 10,000	CS	Cardio	10,000			
					Neuro	10,000			
Herd et al. 1974									
44	Dog (NS) 9 NS	5 minutes	0, 8,000, 15,000, 20,000, 25,000	CS, GN, HP, NX, OF	Cardio			8,000	50 mm Hg reduction in mean arterial blood pressure
					Hepatic	25,000			
					Neuro	25,000			
BRRC 1987b									
45	Rabbit (New Zealand) 24 F	12 days (GDs 618) 6 hours/day	0, 1,000, 3,000, 6,000	BW, DX, OW, RX	Bd wt	6,000			
					Hepatic	6,000			
					Repro	1,000			
					Develop	3,000	6,000		42/72 fetuses (18/20 litters) showed bilateral 13th rib
INTERMEDIATE EXPOSURE									
MacEwen and Vernot 1974									
46	Monkey (NS) 4 NS	14 weeks 7 days/week 24 hours/day	0, 250, 1,000	GN, HP, BC	Bd wt	1,000			
					Resp	1,000			
					Hemato	1,000			
					Hepatic	1,000			
					Renal	1,000			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Prendergast et al. 1967									
47	Monkey (Squirrel) 3 NS	6 weeks 5 days/week 8 hours/day	0, 2,210	BW, GN, HP, CS	Bd wt	2,210			
					Resp	2,210			
					Cardio	2,210			
					Hepatic	2,210			
					Renal	2,210			
					Immuno	2,210			
					Neuro	2,210			
Prendergast et al. 1967									
48	Monkey (Squirrel) 3 NS	90 days 24 hours/day	0, 140, 380	BW, GN, HP	Bd wt	380			
					Resp	380			
					Cardio	380			
					Hepatic	380			
					Renal	380			
					Immuno	380			
Torkelson et al. 1958									
49	Monkey (NS) 2 F	6 months 5 days/week 7 hours/day	0, 500		Resp	500			
					Cardio	500			
					Hemato	500			
					Hepatic	500			
					Renal	500			
					Immuno	500			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Adams et al. 1950									
50	Rat (Wistar) 6 M, 7 F	67 days 5 days/week 7 hours/day	0, 3,000	BW, CS, GN, HP, OW	Bd wt	3,000			
					Cardio	3,000			
					Hepatic	3,000			
					Renal	3,000			
					Repro	3,000			
Adams et al. 1950									
51	Rat (Wistar) 5 M, 5 F	44 days 5 days/week 7 hours/day	0, 5,000	BW, CS, GN, HP, OW	Bd wt	5,000			
					Resp	5,000			
					Cardio	5,000			
					Hepatic	5,000			
					Renal	5,000			
					Repro	5,000			
Calhoun et al. 1981									
52	Rat (CDF) 28 M, 28 F	13 weeks 5 days/week 6 hours/day	0, 150, 508, 1,008, 1,976	BC, BI, BW, GN, HP, OW, UR	Bd wt	1,976			
					Resp	1,008	1,976		Degenerative changes in the olfactory epithelium of the nasal turbinates; 10/10 males 10/10 females
					Cardio	1,976			
					Gastro	1,976			
					Hemato	1,976			
					Musc/skel	1,976			
					Hepatic	1,008			
					Renal	1,976			
					Dermal	1,976			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Ocular	1,976			
					Immuno	1,976			
					Neuro	1,976			
					Repro	1,976			
MacEwen and Vernot 1974									
53	Rat (NS) 40 NS	14 weeks 24 hours/day	0, 250, 1,000	BW, OW, GN, HP	Bd wt	1,000			
					Resp	1,000			
					Hepatic	1,000			
					Renal	1,000			
Mattsson et al. 1993									
54	Rat (Fischer 344) 14 M, 14 F	13 weeks 5 days/week 6 hours/day	0, 209, 620, 2,016	BW, CS, GN, HP, OF	Bd wt	2,016			
					Neuro	620	2,016		Impaired forelimb grip strength
Prendergast et al. 1967									
55	Rat (Sprague-Dawley) 15 NS	6 weeks 5 days/week 8 hours/day	0, 2,210	BW, GN, HP, BC	Bd wt	2,210			
					Resp	2,210			
					Cardio	2,210			
					Hemato	2,210			
					Hepatic	2,210			
					Renal	2,210			
					Immuno	2,210			
					Neuro	2,210			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Prendergast et al. 1967									
56	Rat (Sprague-Dawley) 1–5 NS	90 days 24 hours/day	0, 140, 380	BW, GN, HP, BC, CS	Bd wt	380			
					Resp	380			
					Cardio	380			
					Hemato	380			
					Hepatic	380			
					Renal	380			
					Immuno	380			
Toftgard et al. 1981									
57	Rat (Sprague-Dawley) 4 M	4 weeks 5 days/week 6 hours/day	0, 820	BW, OW, BI	Bd wt	820			
					Hepatic		820		Increased absolute and relative liver weights
Torkelson et al. 1958									
58	Rat (NS) 5 M, 5 F	6 months 5 days/week 7 hours/day	0, 500	BW, OW, GN, HP, BC	Bd wt	500			
					Resp	500			
					Cardio	500			
					Hemato	500			
					Hepatic	500			
					Renal	500			
					Immuno	500			
					Repro	500 M			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Torkelson et al. 1958									
59	Rat (NS) 5 M	3 months 5 days/week 3–60 minutes/day	0, 10,000	BW, OW, GN, HP, CS	Bd wt	10,000			
					Hepatic	10,000			
					Renal	10,000			
					Neuro			10,000	Ataxia, narcosis
Truffert et al. 1977									
60	Rat (Sprague-Dawley) 55 F	15 weeks 5 days/week 5–6 hours/day	0, 1,100	CS, BW, BC, GN, OW, HP	Bd wt	1,100			
					Resp	1,100			
					Hemato	1,100			
					Hepatic	1,100			
					Renal	1,100			
					Repro	1,100			
York et al. 1982									
61	Rat Long-Evans 11–20 F	Premating: 2 weeks 5 days/week 6 hours/day Pregnancy: 20 days (GDs 1–20), 7 days/week 6 hours/day	0, 2,100	CS, BW, FI, WI, HE, BC, OW, NX, RX, DX	Bd wt	2,100			
					Hepatic	2,100			
					Repro	2,100			
					Develop		2,100		Increased total skeletal anomalies 19/78 fetuses; reduced clavicle size in 5/78 fetuses; Increased soft tissue anomalies in 6/71 fetuses
Bowen and Balster 2006									
62	Mouse (Albino) 8 M	15 days 30 minutes/day	0, 2,000, 6,000, 10,000, 13,300	NX	Neuro	2,000	6,000		Increase in locomotor activity

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Calhoun et al. 1981									
63	Mouse (B6C3F1) 20 M, 20 F	13 weeks 5 days/week 6 hours/day	0, 150, 508, 1,008, 1,976	BC, BI, BW, GN, HP, OW, UR	Bd wt	1,976			
					Resp	1,008	1,976		Olfactory epithelial changes in the nasal turbinates in 5/10 M and 6/10 F
					Cardio	1,976			
					Gastro	1,976			
					Hemato	1,976			
					Musc/skel	1,976			
					Hepatic	1,976			
					Renal	1,976			
					Dermal	1,976			
					Ocular	1,976			
					Immuno	1,976			
					Neuro	1,976			
					Repro	1,976			
MacEwen and Vernot 1974									
64	Mouse (NS) 3 NS	14 weeks 24 hours/day (NS)	0, 250, 1,000	BI, HP	Bd wt	1,000			
					Hepatic	250	1,000		Increased centrilobular fat accumulation; increase in liver triglycerides
McNutt et al. 1975									
65	Mouse (CF1) 10 M	14 weeks 24 hours/day	0, 250, 1,000	BW, OW, FI, WI, GN, HP, CS, BI	Hepatic	250	1,000		Increase in relative liver weight; increase in liver triglycerides; hepatocyte vacuolation, degeneration, and necrosis

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
MacEwen and Vernot 1974									
66	Dog (NS) 8 NS	14 weeks 24 hours/day	0, 250, 1,000	GN, HP, BC	Gastro	1,000			
					Hemato	1,000			
					Hepatic	1,000			
					Renal	1,000			
Adams et al. 1950									
67	Guinea pig (NS) 5 M, 4 F	29 days 5 days/week 7 hours/day	0, 3,000	BW, CS, GN, HP, OW	Bd wt			3,000	13% decreased final body weight and 49% decrease in body weight gain in females; 12% decreased final body weight and 53% decrease in body weight gain in males
					Resp	3,000			
					Cardio	3,000			
					Hepatic	3,000			
					Renal	3,000			
					Immuno	3,000			
					Repro	3,000			
Adams et al. 1950									
68	Guinea pig (NS) 5 M, 5 F	45 days 5 days/week 7 hours/day	0, 5,000	BW, CS, GN, HP, OW	Bd wt			5,000	11% decrease final body weight and 33% decrease in body weight gain in females; 10% decrease in final body weight and 19% decrease in body weight gain in males
					Resp	5,000			
					Hepatic		5,000		8/8 had slight to moderate central fatty degeneration the liver

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Renal	5,000			
					Immuno	5,000			
Adams et al. 1950									
69	Guinea pig 9 M, 10 F	93 days 5 days/week 7 hours/day	0, 650	BW, CS, GN, HP, OW	Bd wt	650 F		650 M	10% decrease in final body weight; 37% decrease in body weight gain
					Resp	650			
					Cardio	650			
					Hepatic	650			
					Renal	650			
					Immuno	650			
					Repro	650			
Adams et al. 1950									
70	Guinea pig 8 M, 6 F	58 days 5 days/week 7 hours/day	0, 650	BW, CS, GN, HP, OW	Bd wt	650 M		650 F	11% decrease in final body weight; 35% decrease in final body weight gain
					Resp	650			
					Cardio	650			
					Hepatic	650			
					Renal	650			
					Immuno	650			
					Repro	650			
Adams et al. 1950									
71	Guinea pig 12 M, 7–8 F	60 days 5 days/week 7 hours/day	0, 1,500	BW, CS, GN, HP, OW	Bd wt	1,500			
					Resp	1,500			
					Cardio	1,500			
					Hepatic	1,500			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Renal	1,500			
					Immuno	1,500			
					Repro	1,500			
Prendergast et al. 1967									
72	Guinea pig (Hartley) 15 NS	90 days 24 hours/day	0, 140, 380	BW, GN, HP, BC, CS	Bd wt	380			
					Resp	380			
					Cardio	380			
					Hemato	380			
					Hepatic	380			
					Renal	380			
					Immuno	380			
Prendergast et al. 1967									
73	Guinea pig (Hartley) 15 NS	6 weeks 5 days/week 8 hours/day	0, 2,210	BW, GN, HP, BC, CS	Bd wt	2,210			
					Resp	2,210			
					Cardio	2,210			
					Hemato	2,210			
					Hepatic	2,210			
					Renal	2,210			
					Immuno	2,210			
					Neuro	2,210			
Rosengren et al. 1985									
74	Gerbil (Mongolian) 4 M, 4 F	3 months 24 hours/day	0, 70, 210, 1,000	BI, BW, CS, NX, OF	Bd wt	1,000			
					Neuro	70[d]		210	Reactive gliosis (increase in GFAP)

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Torkelson et al. 1958									
75	Guinea pig (NS) 8 M, 8 F	6 months 5 days/week 7 hours/day	0, 500	BW, OW, GN, HP, BC, CS	Bd wt	500			
					Resp	500			
					Gastro	500			
					Hepatic	500			
					Renal	500			
					Immuno	500			
					Repro	500			
Torkelson et al. 1958									
76	Guinea pig (NS) 5 F	3 months 5 days/week 18–180 minutes/day	0, 1,000, 2,000	OW, GN, HP, BW	Bd wt	2,000			
					Resp		1,000		Lung irritation and inflammation
					Hepatic		1,000		Increased relative liver weight; centrilobular fatty change
					Renal	2,000			
CHRONIC EXPOSURE									
Kramer et al. 1978									
77	Human 19–53	Up to 6 years (occupational)	0, <15, 15–49, 50–99, 100–149, 150–249 (TWA)	BC, CS	Cardio	150			
					Hemato	150			
					Hepatic	150			
					Renal	150			
Maroni et al. 1977									
78	Human 7–8 F	6.7 years average (occupational)	0, 110, 140–160, 200–990	CS	Neuro	200			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Ohnishi et al. 2013									
79	Rat (Fischer-344) 50 M, 50 F	104 weeks 5 days/week 6 hours/day	0, 200, 797, 3,181	LE, CS, BW, FI, BC, UR, GN, HP, OW	Bd wt	3,181			
					Resp	3,181			
					Hemato	3,181			
					Renal	3,181			
					Neuro	3,181			
					Other noncancer	3,181			
					Cancer			3,181 M	CEL: mesothelioma in the peritoneum in 16/50
Quast et al. 1988									
80	Rat (Fischer 344) 80 M, 80 F	2 years 5 days/week 6 hours/day	0, 150, 500, 1,500	BW, OW, GN, HP, BC, UR, CS	Bd wt	1,500			
					Resp	1,500			
					Cardio	1,500			
					Gastro	1,500			
					Hemato	1,500			
					Musc/skel	1,500			
					Hepatic	500	1,500		Mild liver histopathology-accentuation of the normal hepatic lobular pattern, alteration in the size of the hepatocytes
					Renal	1,500			
					Immuno	1,500			
					Neuro	1,500			
					Repro	1,500			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Ohnishi et al. 2013									
81	Mouse (BDF1) 50 M, 50 F	104 weeks 5 days/week 6 hours/day	0, 201, 801, 3,204	BC, BW, CS, FI, GN, HP, LE, OW, UR	Death			3,204 M	18% decrease in survival
					Bd wt	3,204			
					Hemato	3,204			
					Hepatic	3,204			
					Renal	3,204			
					Ocular	3,204			
					Neuro	3,204			
					Other noncancer	3,204			
					Cancer	801 M		201 F	CEL: hepatocellular adenoma in 9/50 female mice
								3,204 M	CEL: malignant lymphoma of spleen observed in 9/50 mice; hepatocellular adenoma increased trend, harderian gland adenoma in 8/50
Quast et al. 1988									
82	Mouse (B6C3F1) 80 M, 80 F	2 years 5 days/week 6 hours/day	0, 150, 500, 1,500	BW, OW, GN, HP, BC, CS	Bd wt	1,500			
					Resp	1,500			
					Cardio	1,500			
					Gastro	1,500			
					Hemato	1,500			
					Musc/skel	1,500			
					Hepatic	1,500			
					Renal	1,500			
					Dermal	1,500			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Immuno	1,500			
					Neuro	1,500			
					Repro	1,500			

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2 Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive an acute-duration inhalation MRL of 1 ppm based on decreased performance in psychomotor tests. See Appendix A for more detailed information regarding the MRL.
[c]Anesthetic dose, 0 progressively to 2,650 ppm.
[d]Used to derive an intermediate-duration inhalation MRL of 0.7 ppm based on reactive gliosis measured by glial fibrillary acid protein. See Appendix A for more detailed information regarding the MRL.

BI = biochemical changes; BC = blood chemistry; Bd wt or BW = body weight; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; EEG = electroencephalograph; Endocr = endocrine; F = female(s); FI = food intake; Gastro = gastrointestinal; GD = gestation day; GFAP = glial fibrillary acid protein; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathological; Immuno = immunological; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OF = organ function; OW = organ weight; PND = postnatal day; Repro = reproductive; Resp = respiratory; RX = reproductive toxicity; SLOAEL = serious LOAEL; TWA = time-weighted average; UR = urinalysis; WI = water intake

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

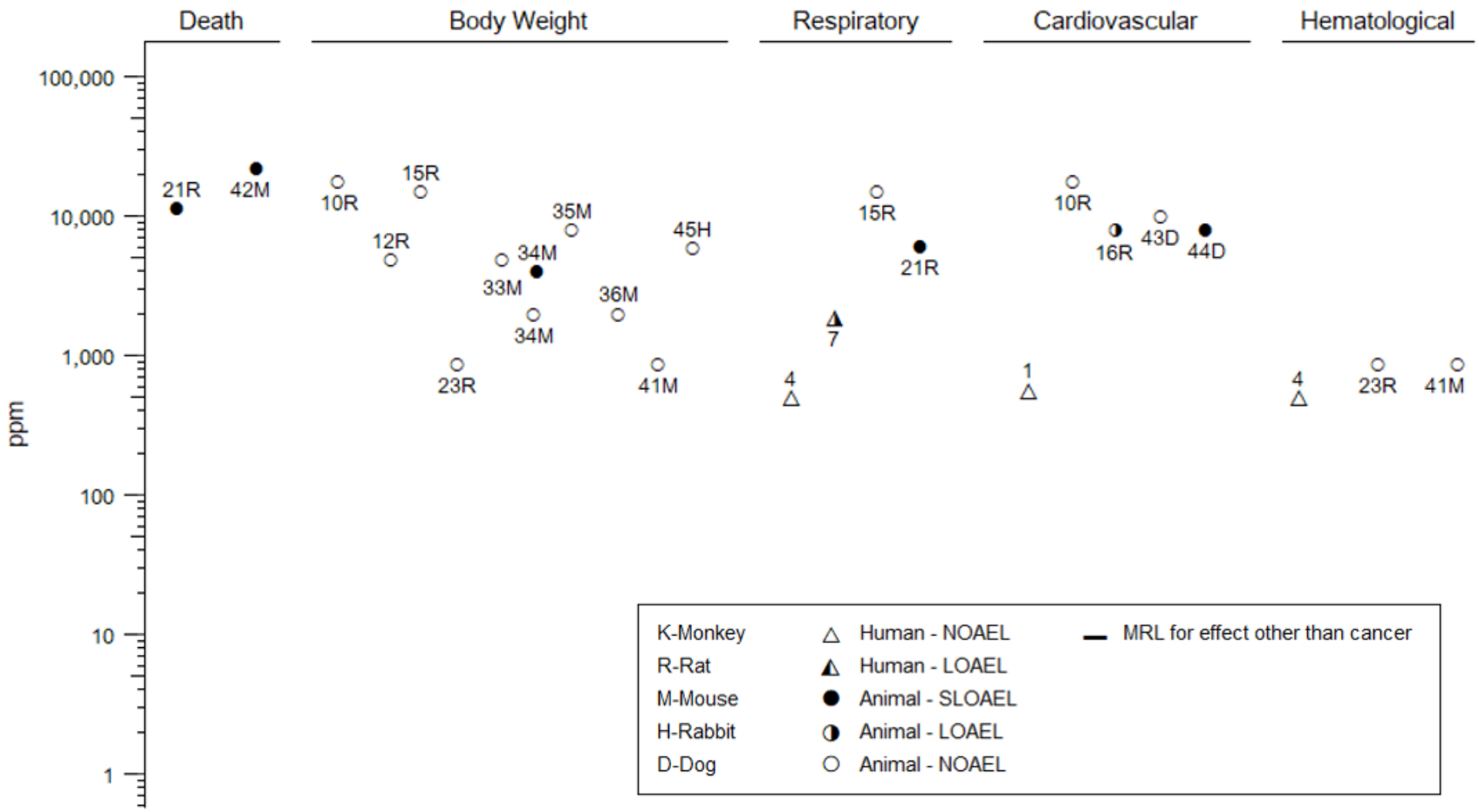


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Acute (≤14 days)

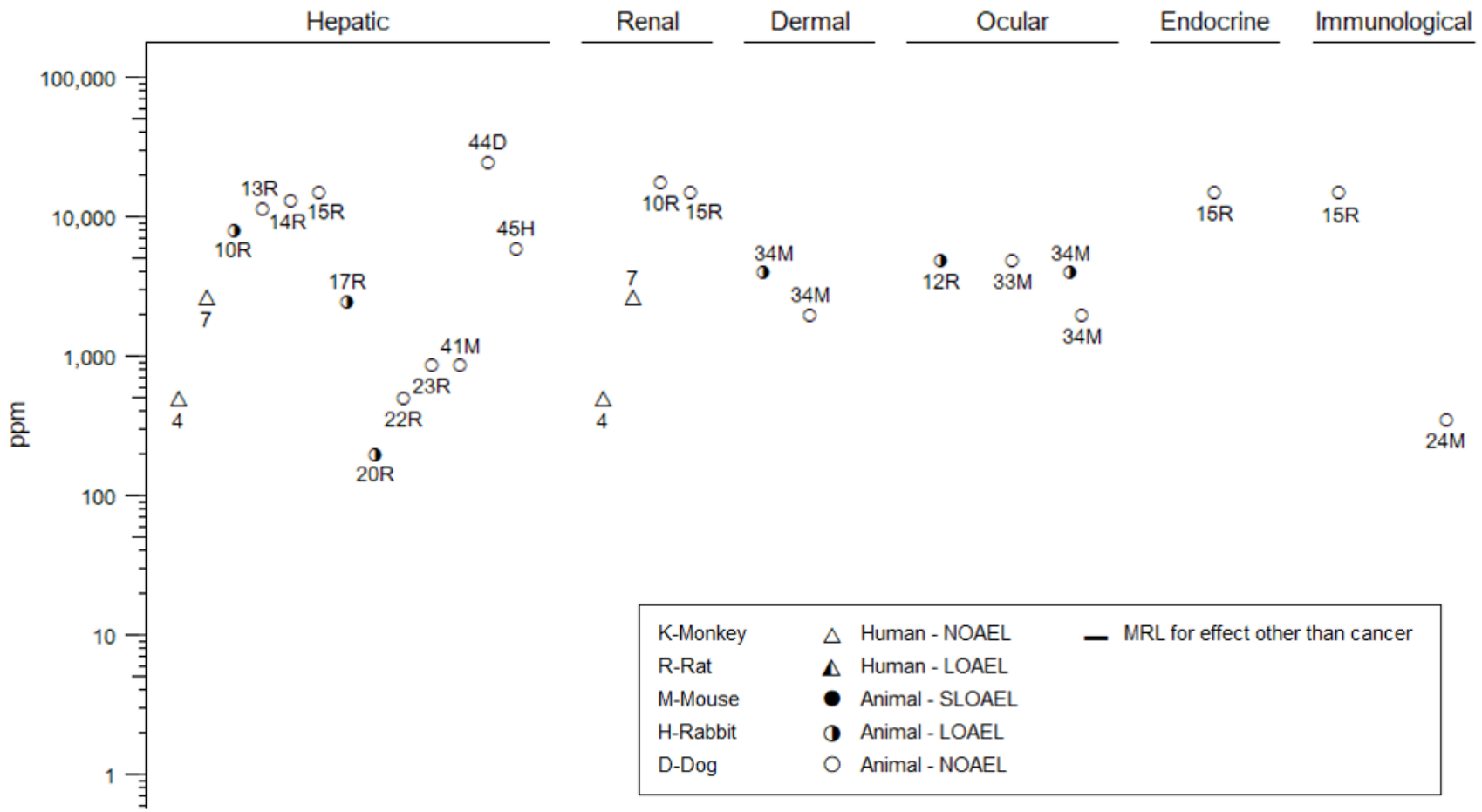


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Acute (≤14 days)

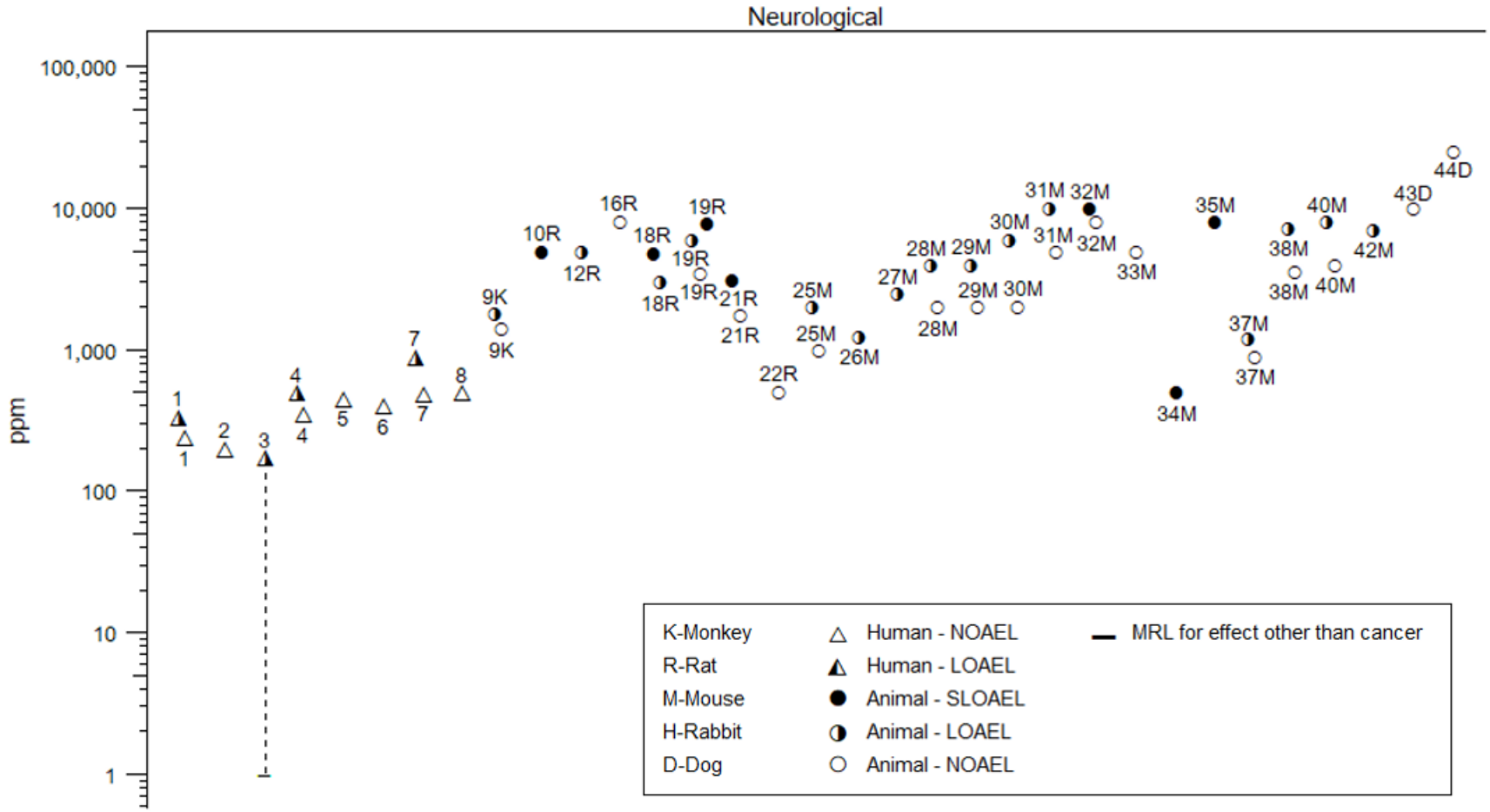


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Acute (≤14 days)

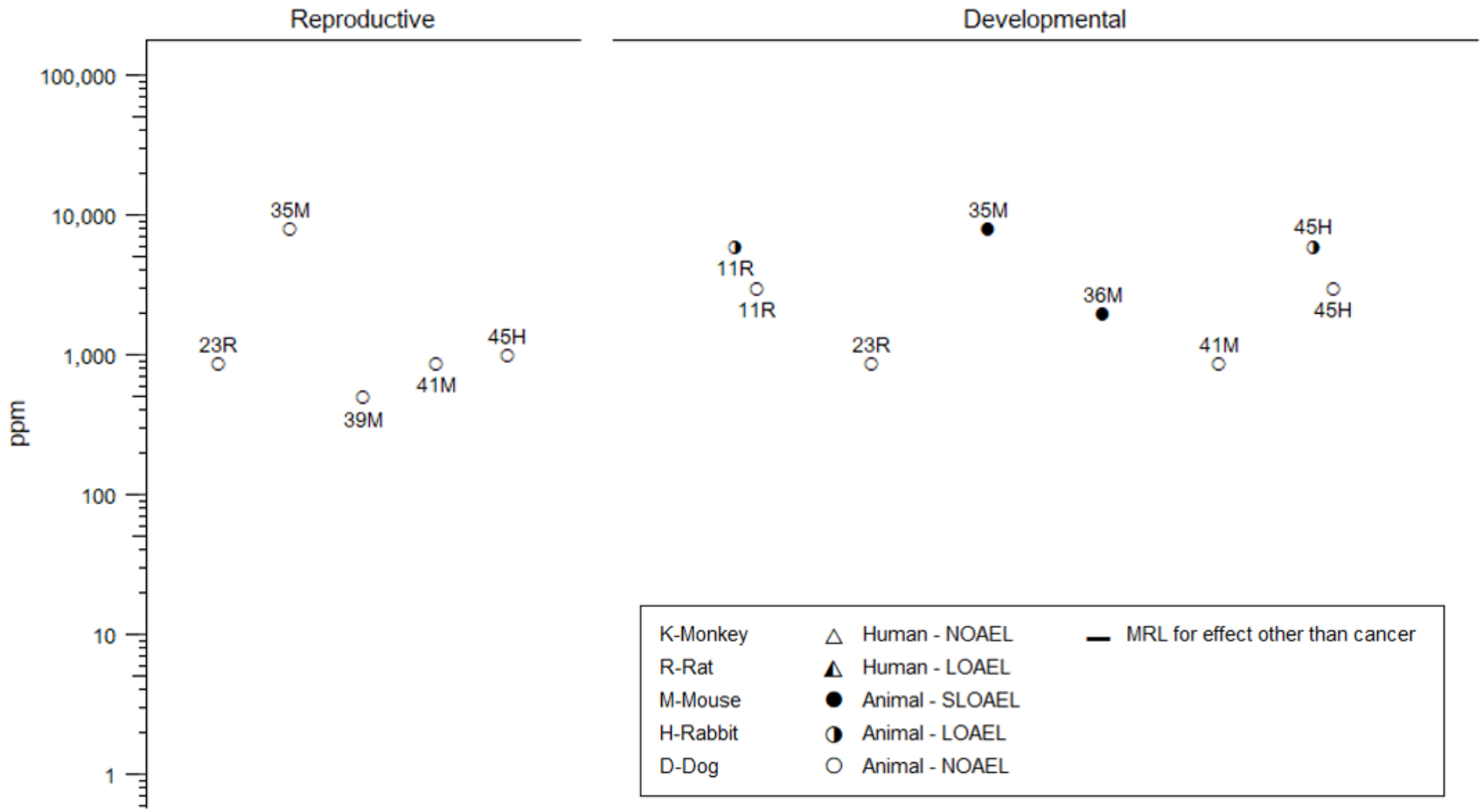


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Intermediate (15–364 days)

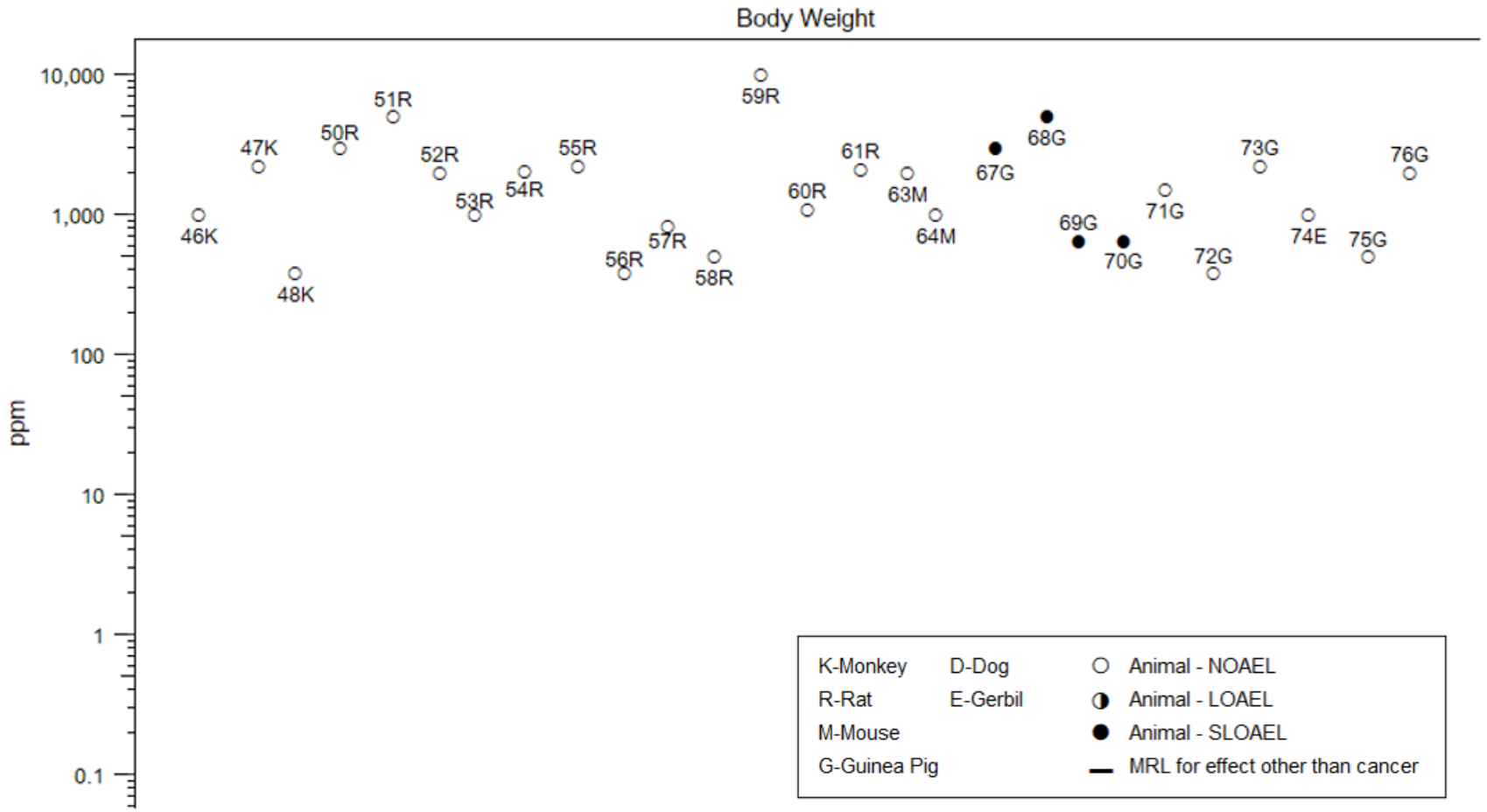


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Intermediate (15–364 days)

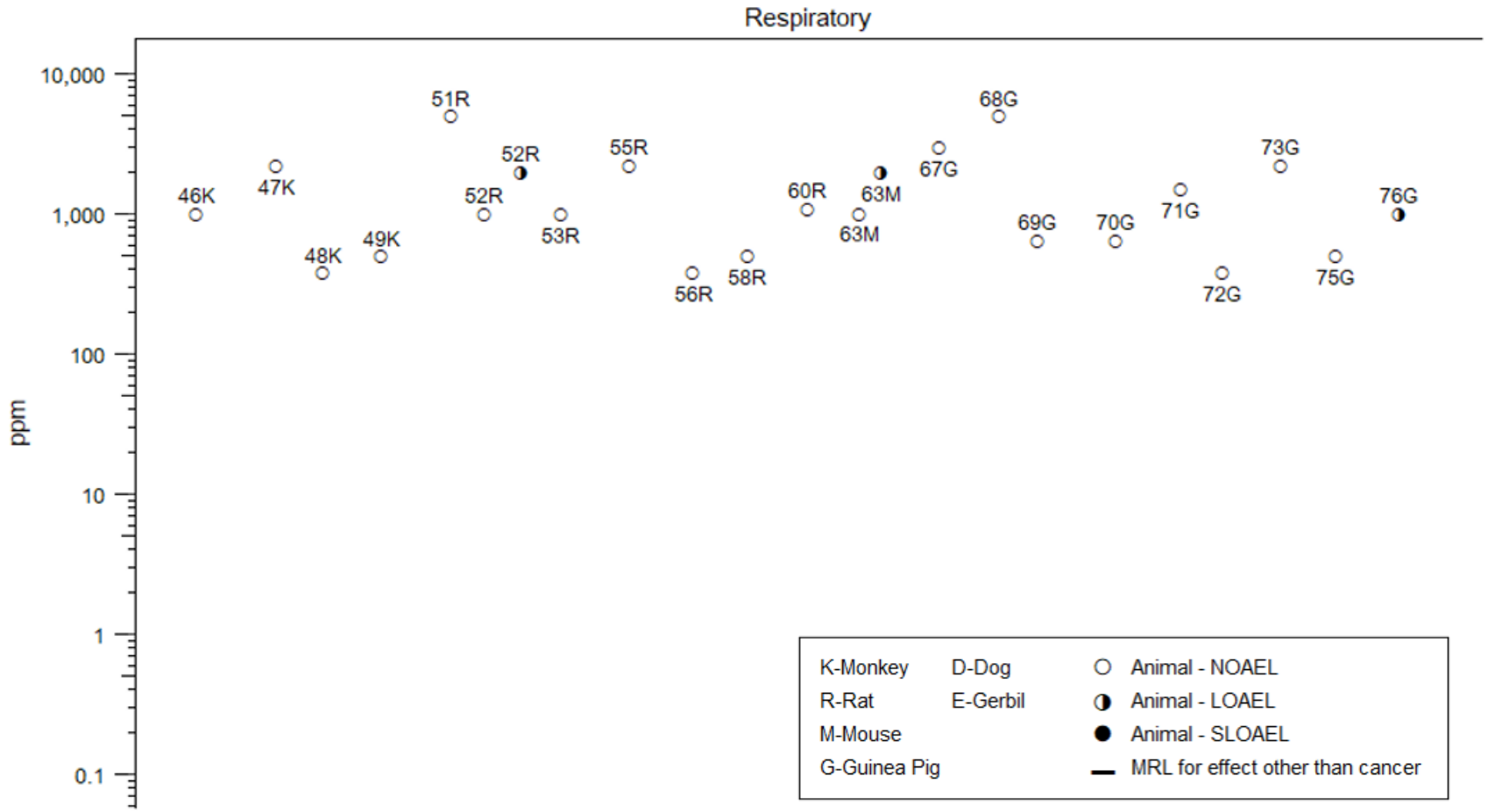


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Intermediate (15–364 days)

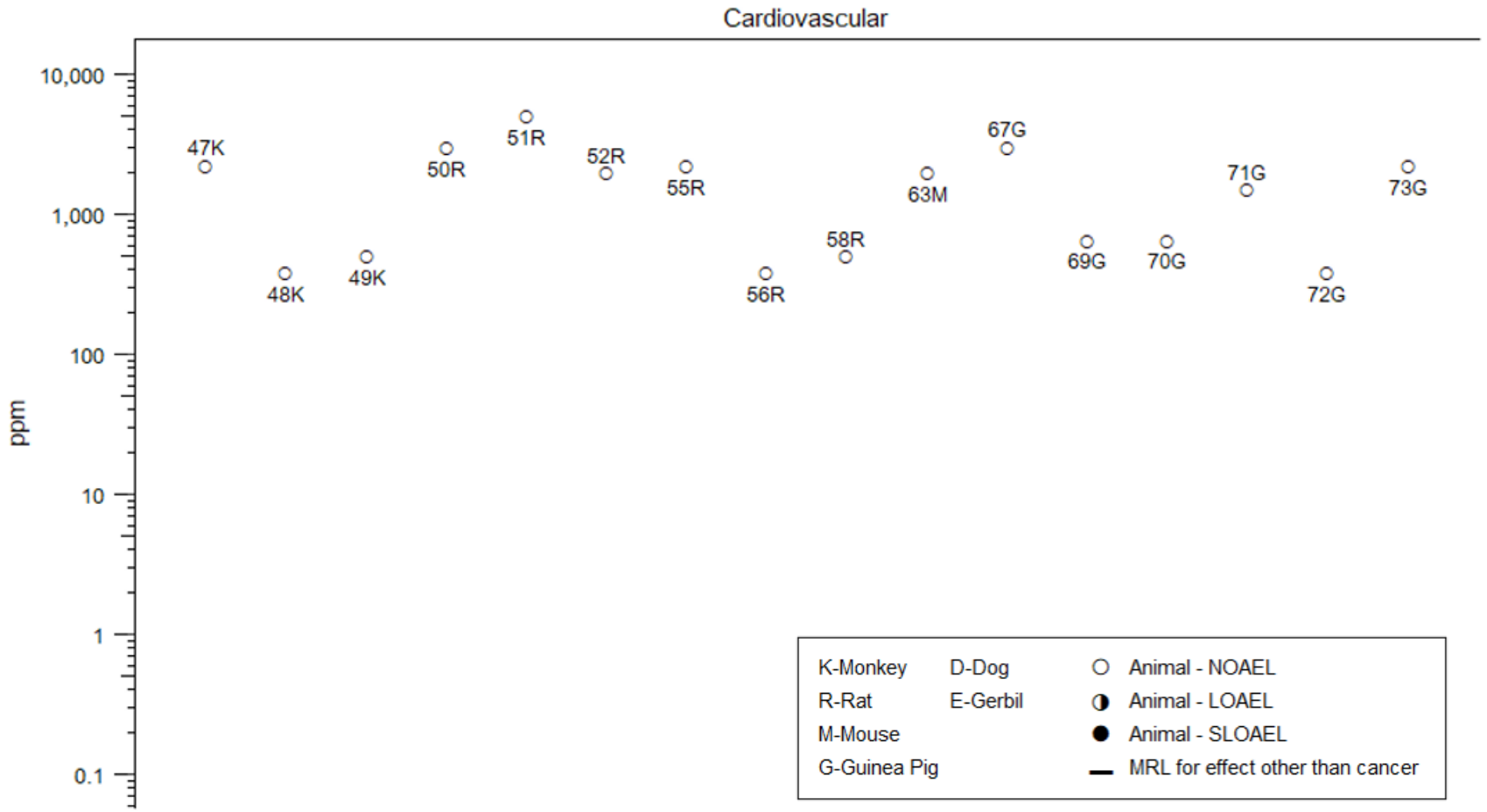


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Intermediate (15–364 days)

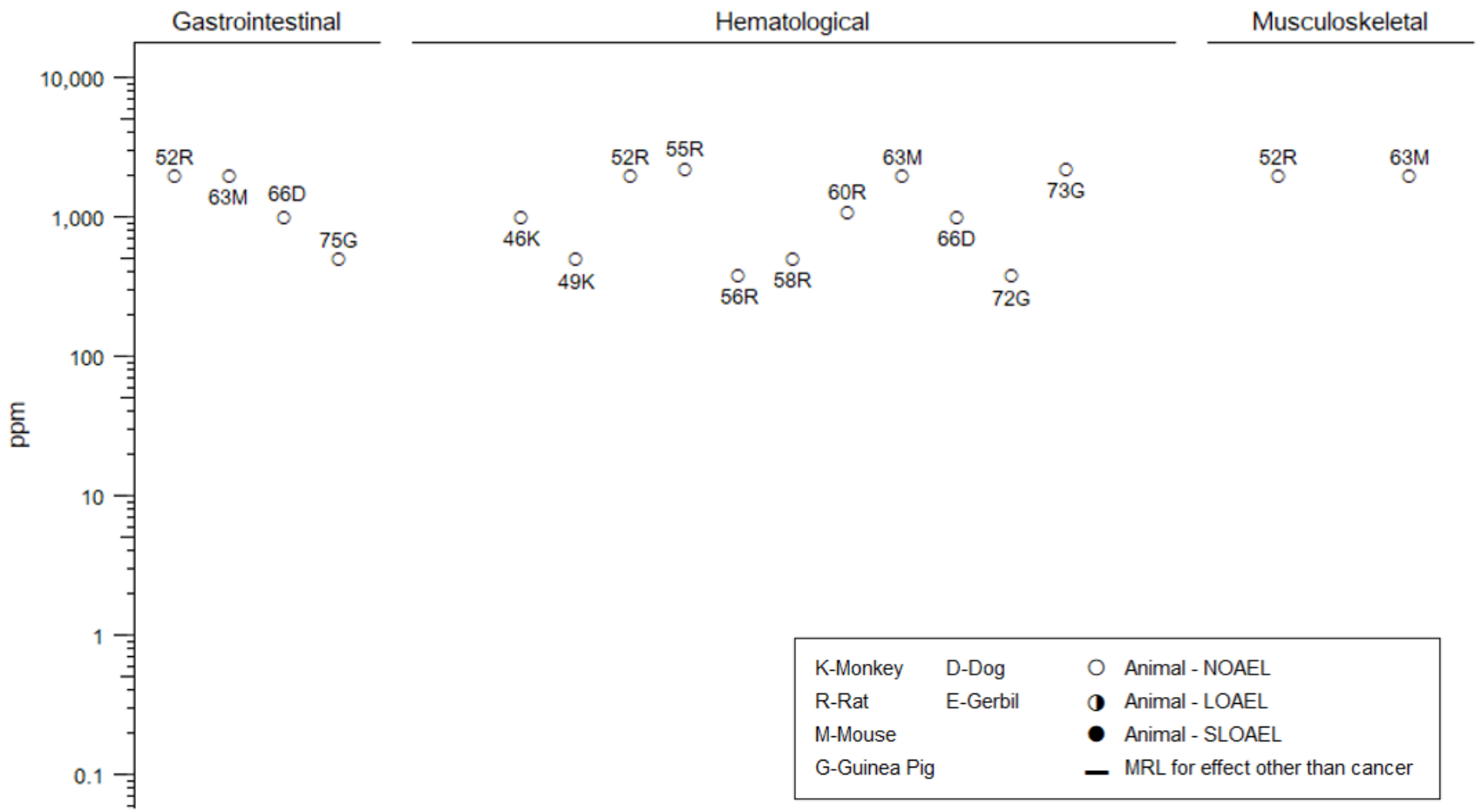


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Intermediate (15–364 days)

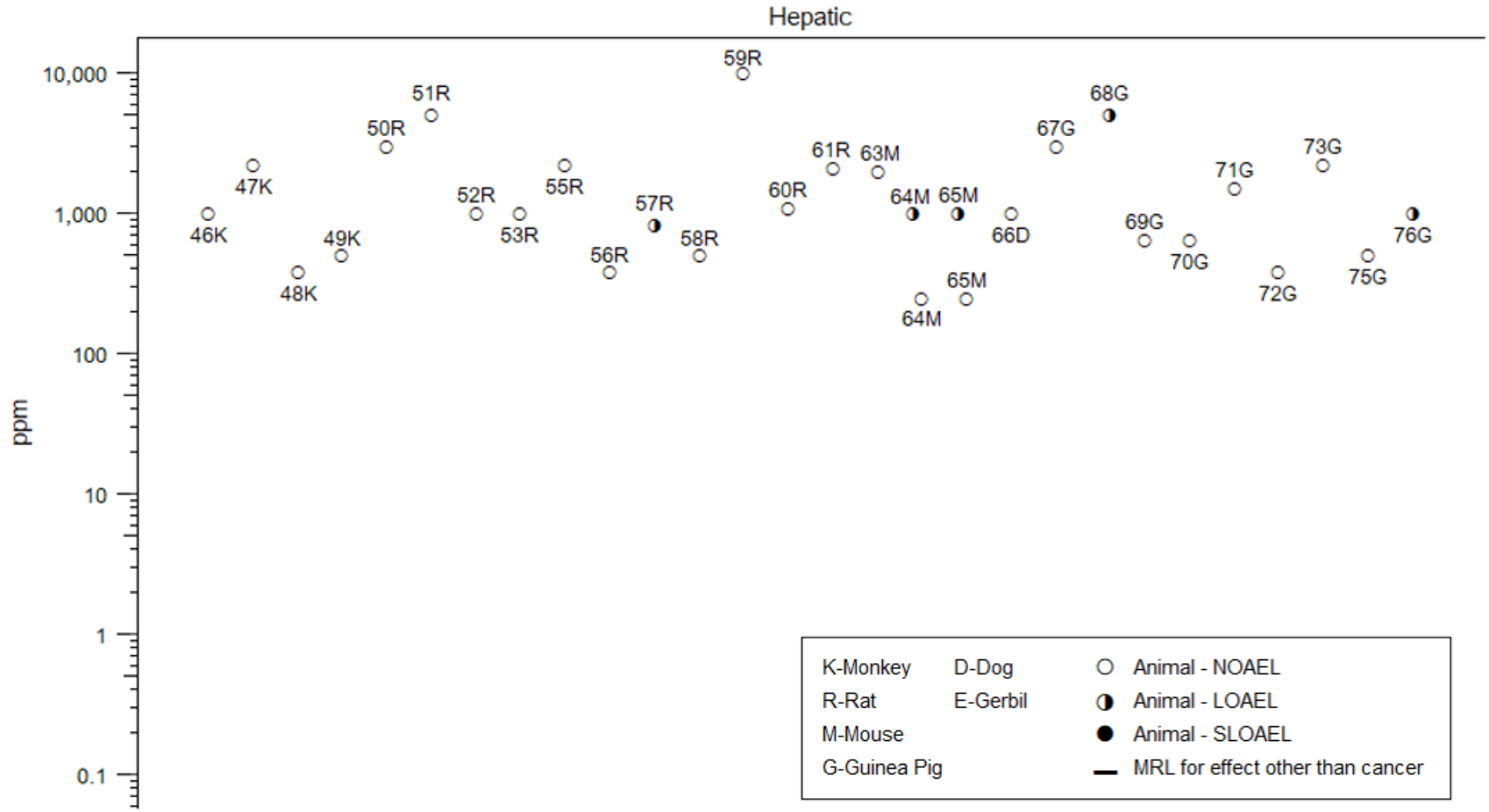


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Intermediate (15–364 days)

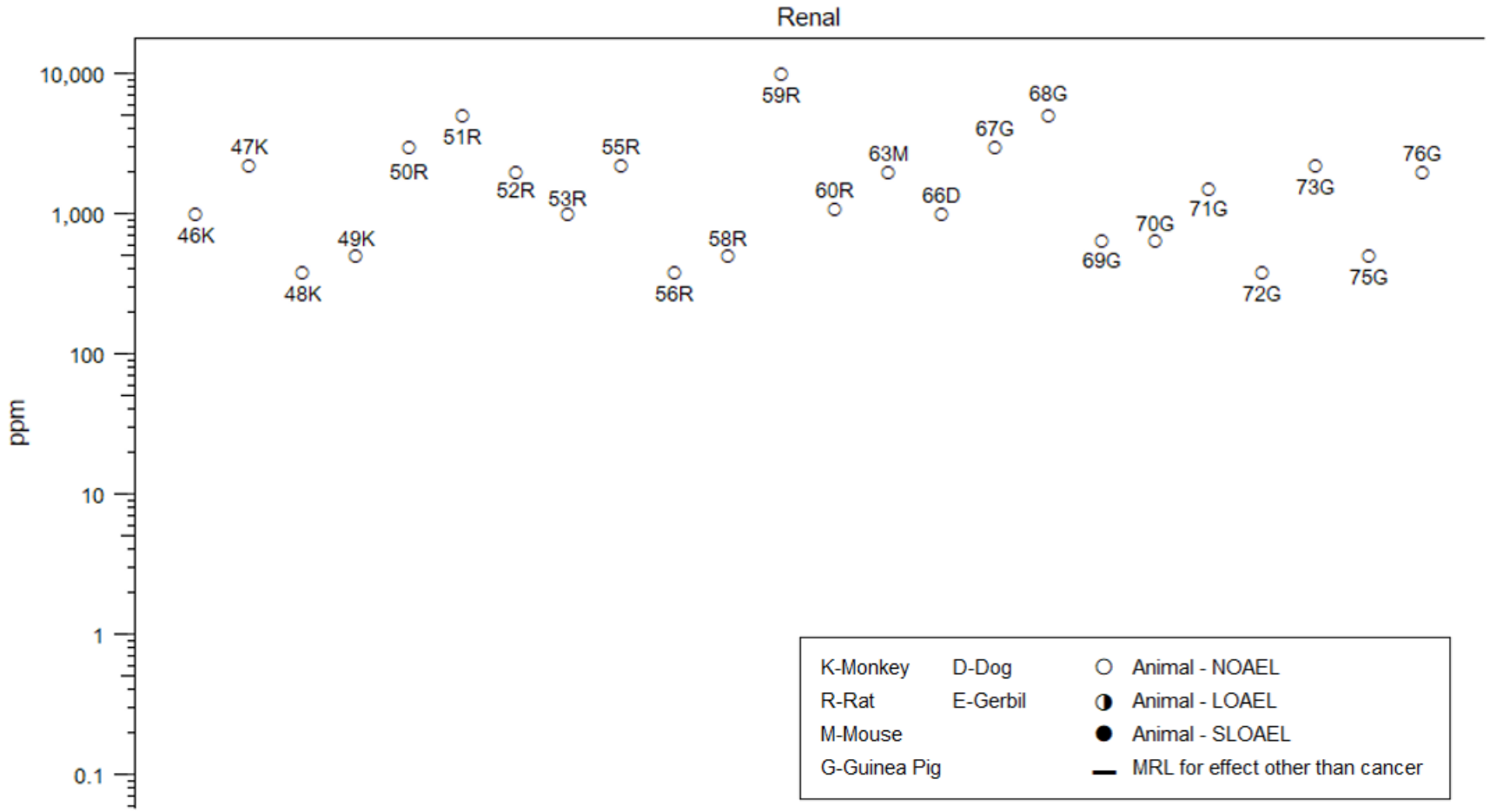


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Intermediate (15–364 days)

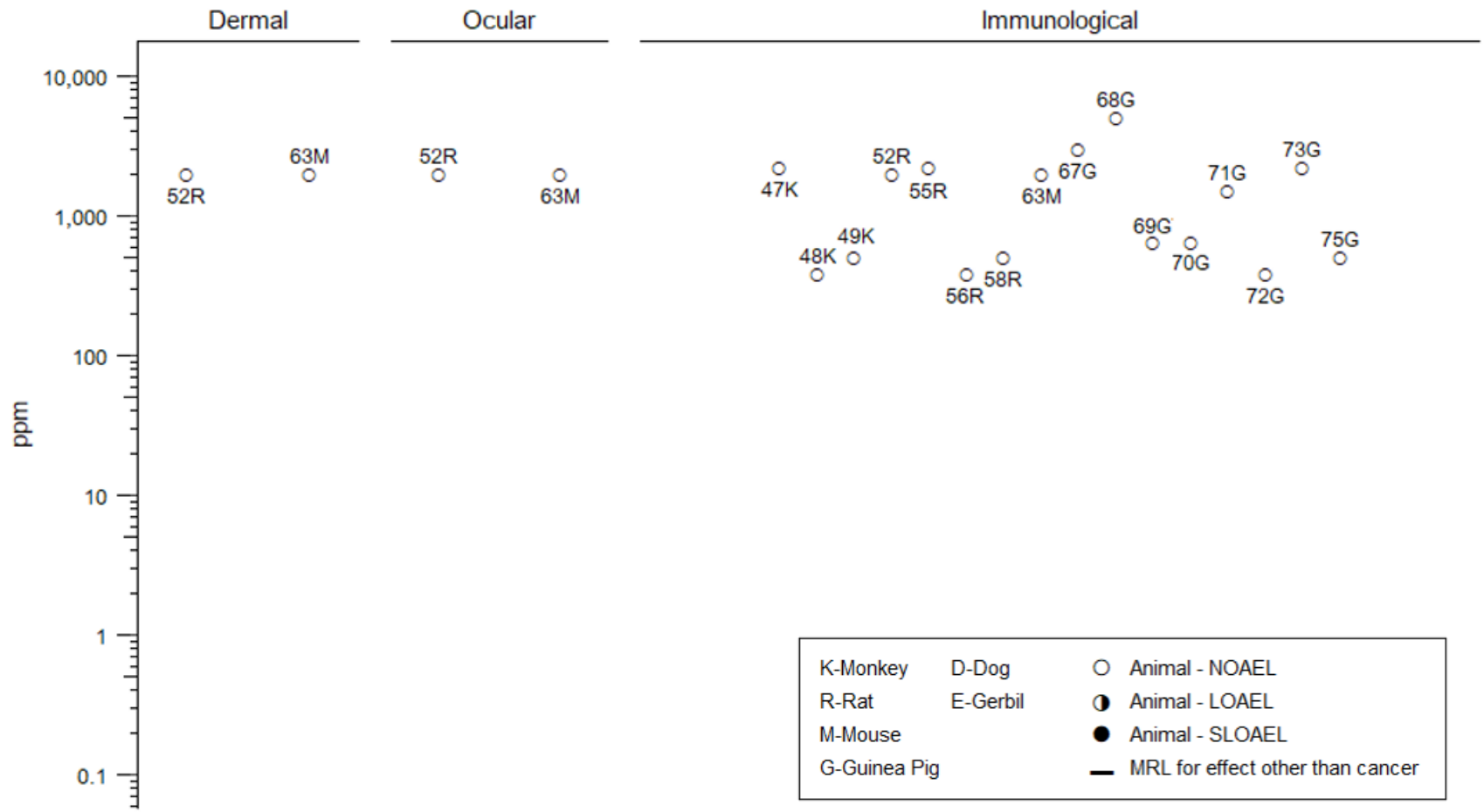


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Intermediate (15–364 days)

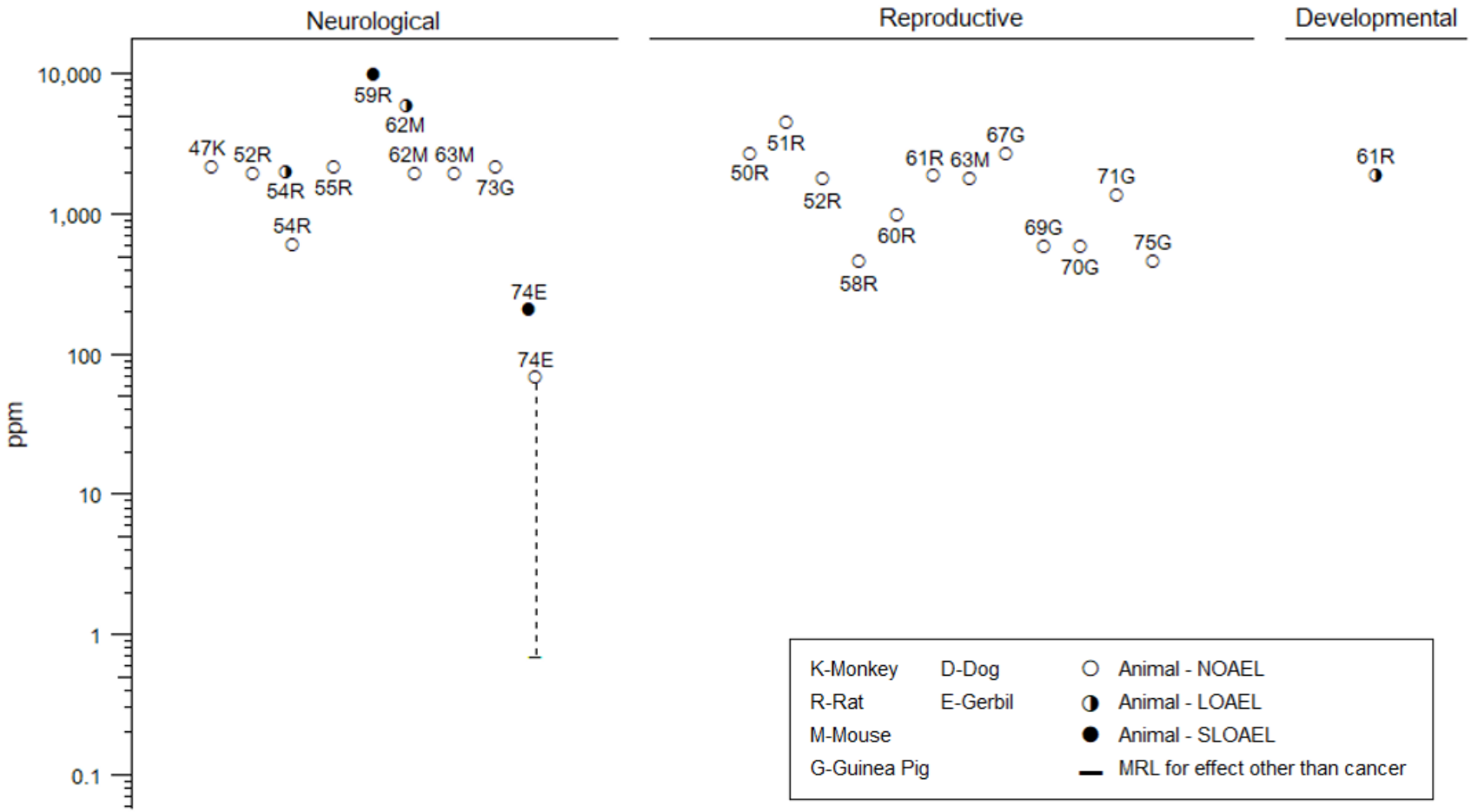


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Chronic (≥365 days)

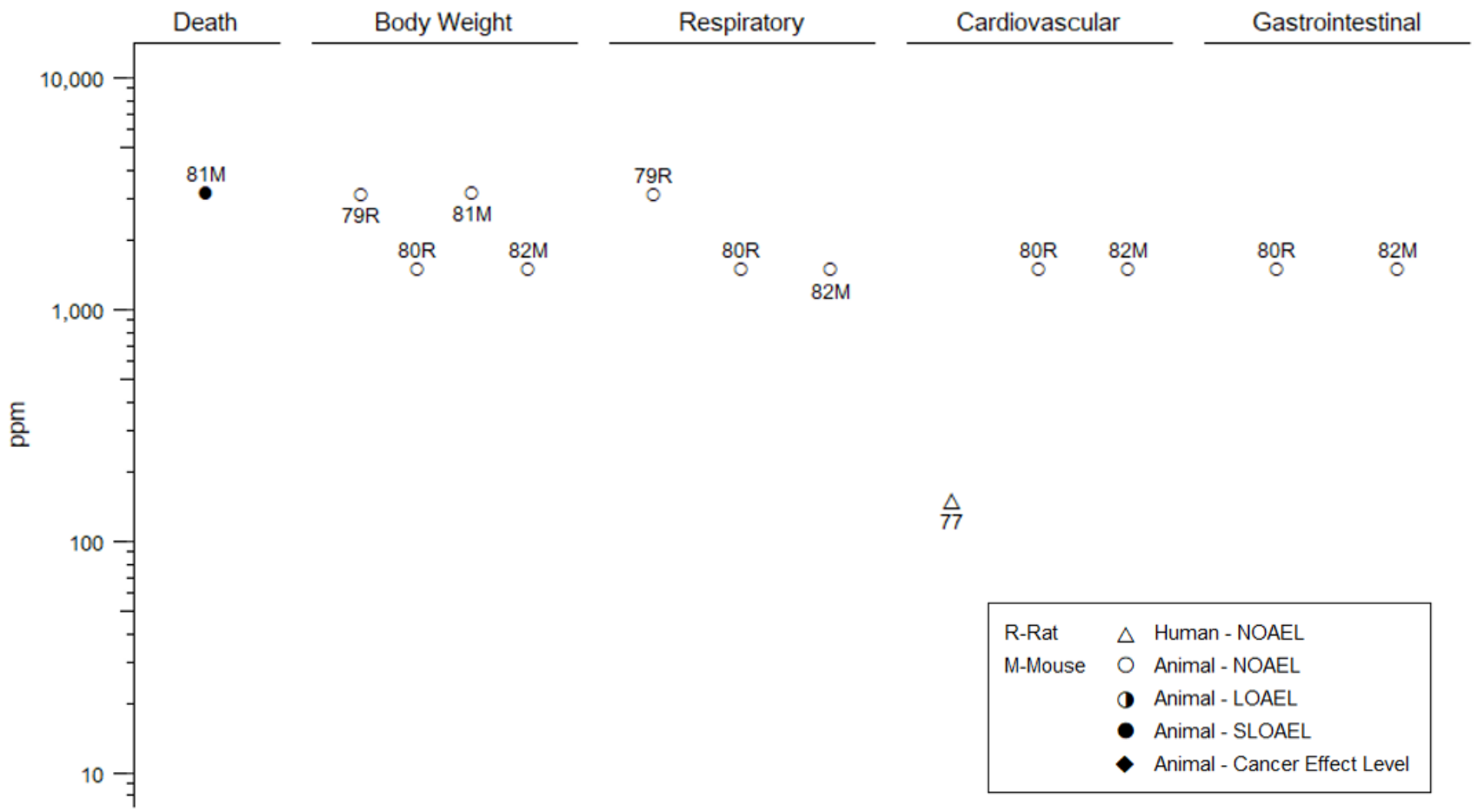


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Chronic (≥365 days)

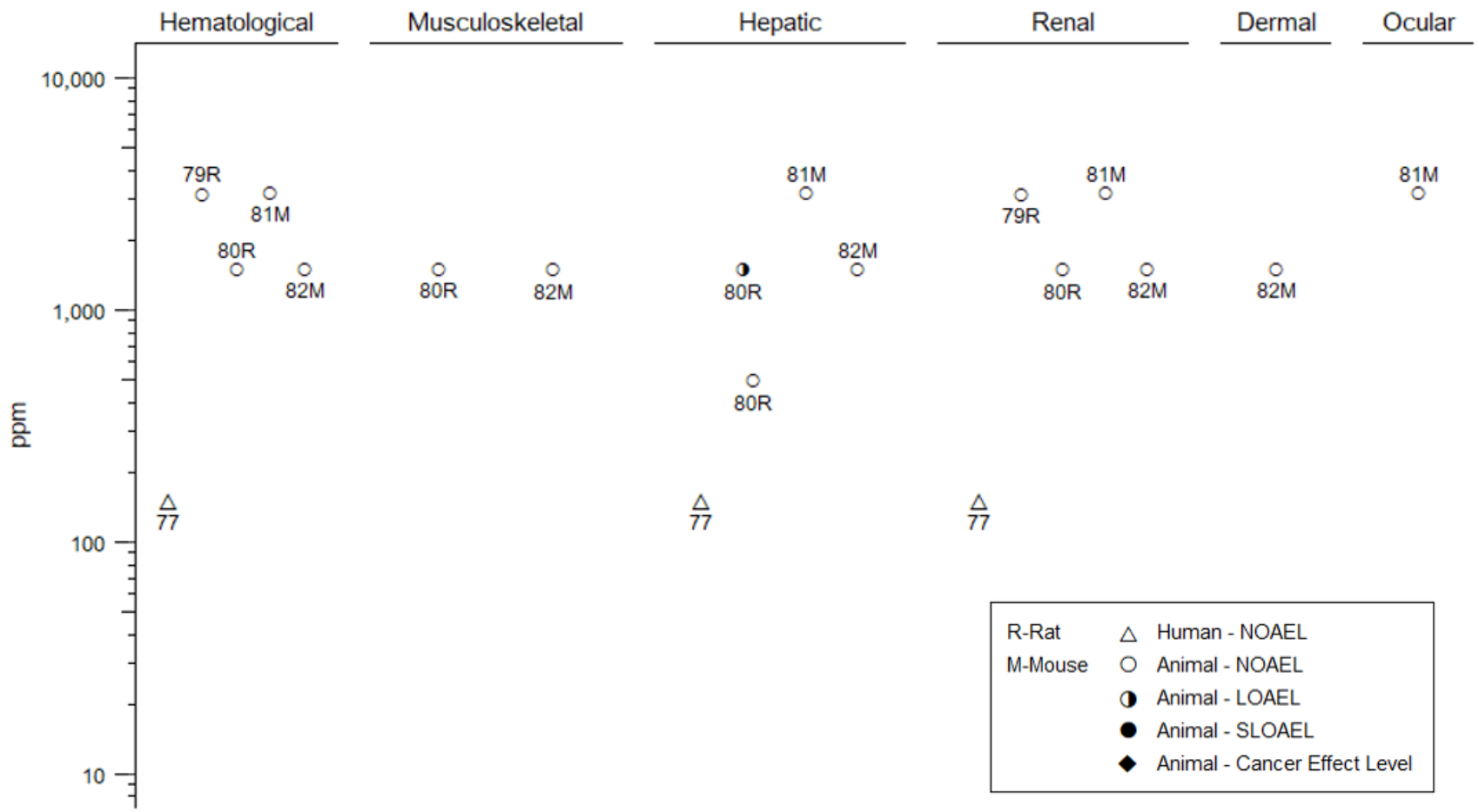


Figure 2-2. Levels of Significant Exposure to 1,1,1-Trichloroethane – Inhalation
Chronic (≥365 days)

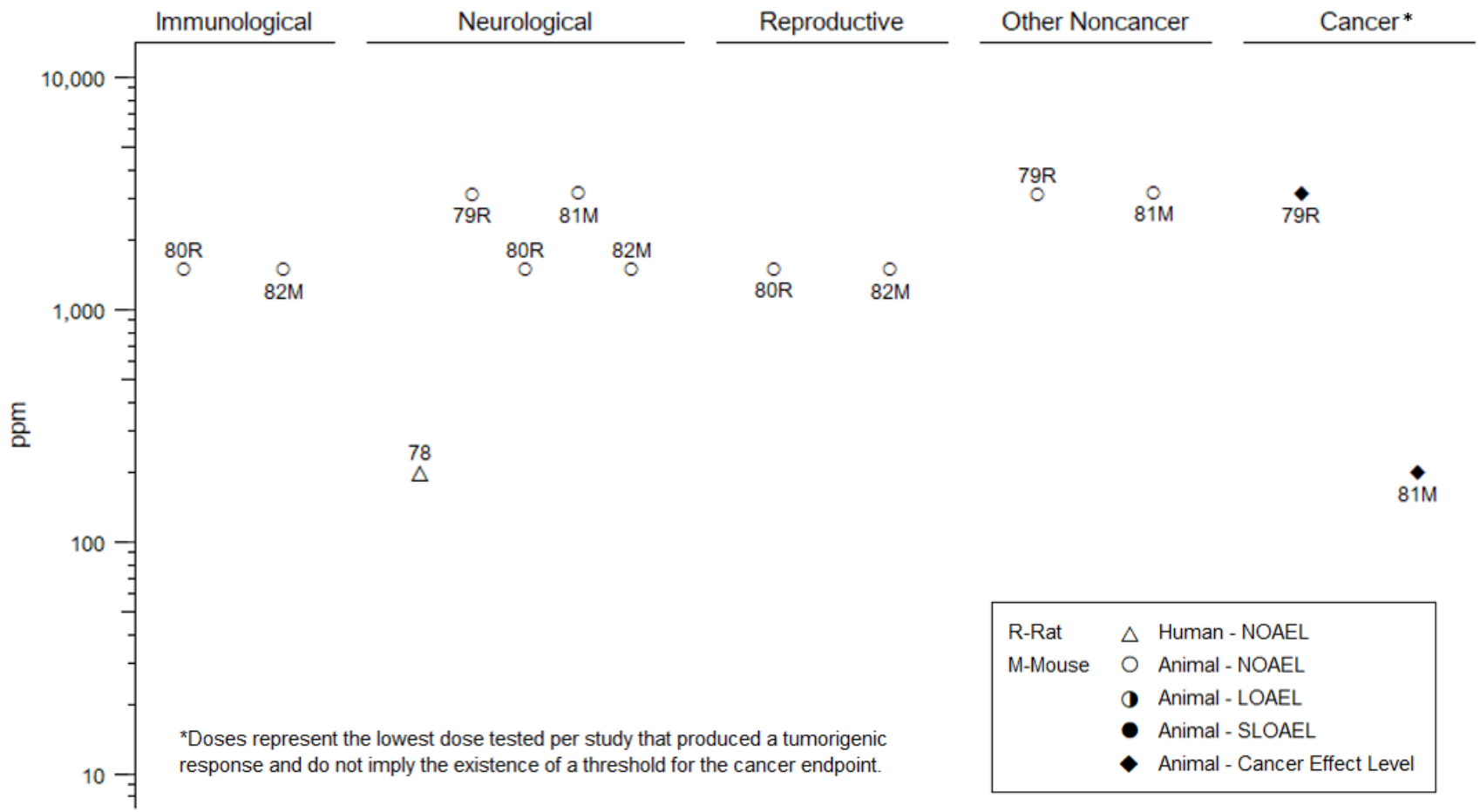


Table 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Bruckner et al. 2001									
1	Rat (Sprague-Dawley) 4–6 M	Once (GO)	0, 500, 1,000, 2,000, 4,000	BC, BI, GN, HP, LE, OF	Bd wt	4,000			
					Hepatic	4,000			
					Renal	4,000			
Bruckner et al. 2001									
2	Rat (Sprague-Dawley) 15–20 M	11 days 1 time/day; days 1–5 and days 8–11 (GO)	0, 500, 5,000, 10,000	BC, BI, GN, HP, LE, NX, OW	Death			5,000	3/15 died
					Bd wt	500	5,000		17% decrease in final body weight
					Hepatic	10,000			
					Neuro	500		5,000	Hyperexcitability followed by narcosis
Platt and Cockrill 1969									
3	Rat (NS) 4–5 NS	7 days once/day (GO)	0, 1,650	BI, BW, CS, OW	Bd wt	1,650			
					Hepatic	1,650			
Spencer et al. 1990									
4	Rat (Fischer 344) 11–12 F	4 days once/day (GO)	0, 705	CS, NX	Bd wt	705			
					Neuro		705		Increased latency in FEPs by 5.2 milliseconds; EEG changes (292% decrease in amplitude in the low frequency band)
Torkelson et al. 1958									
5	Mouse (NS) 16 F	Once (G)		CS	Death			11,240	LD_{50}
Torkelson et al. 1958									
6	Guinea pig (NS) 16 M	Once (G)		CS	Death			9,470	LD_{50}

Table 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
INTERMEDIATE EXPOSURE									
Bruckner et al. 2001									
7	Rat (Sprague-Dawley) 15–20 M	7–13 weeks 5 days/week (GO)	0, 500, 2,500, 5,000	BC, BI, BW, GN, HP, LE, NX, OW	Death			2,500	5/15 rats died
					Bd wt	500		2,500	19% decrease in final body weight
					Resp	500		2,500	Pulmonary congestion in deceased animals
					Hepatic	5,000			
					Renal	5,000			
					Neuro	500		2,500	Hyperexcitability followed by hours of narcosis after daily dosing
Dow Chemical 1993; Maurissen et al. 1994									
8	Rat (Fischer-344 25 F	GDs 6–21 LDs 1–10 (GO)	0, 75, 250, 750	BW, CS, DX, GN, HP, NX, RX	Develop	750			
George et al. 1989									
9	Rat (Sprague-Dawley) 150 M, 150 F	27 days (males and nonbreeding females) *ad libitum*; 70 days pregnant females *ad libitum* (W)	0, 0.3, 0.9, 2.60, M: 0.3, 0.9, 2.6; F (premating): 0.3, 1.3, 3.3; F (gestation): 0.3, 1.2, 3.5 F(postnatal): 0.6, 2.0, 5.9	BW, FI, WI, RX, DX	Bd wt	3.5			
					Repro	3.5 F			
					Develop	5.9			

Table 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
George et al. 1989; NTP 1988a									
10	Rat (CD) 36 M, 36 F	70 days *ad libitum* (W)	M: 0, 0.3, 0.9, 2.6 F (pre-mating): 0.3, 1.3, 3.3 F (gestation): 0.3, 1.2, 3.5; F (postnatal): 0.6, 2.0, 5.9	BW, CS, DX, FI, OW, RX, WI	Repro Develop	3.3 F 3.5			
NTP 1988b									
11	Rat (Sprague-Dawley) 37 M, 37 F	40 days *ad libitum* (W)	0 M: 0.26, 0.64, 2.0; F (premating): 0.30, 0.79, 2.0; F (gestation): 0.34, 0.84, 2.4	BW, CS, DX, FI, OW, RX, WI	Repro Develop	2 F 2.4 F			
NTP 2000									
12	Rat (F344/N) 10 M, 10 F	13 weeks *ad libitum* (F)	M: 0, 290, 600, 1,200, 2,400, 4,800; F: 0, 310, 650, 1,250, 2,500, 5,000	BC, BW, CS, FI, GN, HE, HP, OW, UR	Bd wt	4,800 F 2,400 M	4,800 M		10% decrease in final body weight
					Hepatic	2,500 F	5,000 F		Decrease in absolute and relative liver weights
						2,400 M	4,800 M		Decrease in absolute liver weights
					Renal	5,000 F 4,800 M			

Table 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Repro	2,400 M	4,800 M		10% reduction in epididymal spermatozoa concentration
Lane et al. 1982									
13	Mouse (Swiss ICR) 10 M, 30 F	25 weeks *ad libitum* (W)	0, 100, 300, 1,000	BW, CS, DX, GN, RX, WI	Repro	1,000 F			
					Develop	1,000			
NTP 2000									
14	Mouse (B6C3F1) 10 M, 10 F	13 weeks *ad libitum* (F)	M: 0, 850, 1,750, 3,500, 7,370, 15,000; F: 0, 1,340, 2,820, 5,600, 11,125, 22,900	BC, BW, CS, FI, GN, HE, HP, LE, OW, UR	Bd wt	2,820 F	850 M[b]	5,600 F	LOAEL: 9% decrease in final body weight; 18% decrease in body weight gain $BMDL_{10}$ = 208 mg/kg/day SLOAEL: 11% decreased final body weight; 33% decreased body weight gain
					Cardio	22,900 F			
						15,000 M			
					Hepatic	22,900 F			
						15,000 M			
					Renal	22,900 F			
						15,000 M			
					Repro	22,900 F			
						15,000 M			

Table 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
CHRONIC EXPOSURE									
Maltoni et al. 1986									
15	Rat (Sprague-Dawley) 40 M, 40 F	104 weeks 4–5 days/week (GO)	0, 500	GN, HP, BW	Bd wt		500 F		12% decrease in final body weight
					Cancer			500	CEL: Leukemia (total leukemias in 9/40 males, 4/40 females and 13/80 combined)
NCI 1977									
16	Rat (Osborne-Mendel) 50 M, 50 F	78 weeks 5 days/week (GO)	0, 750, 1,500	BW, FI, GN, HP, CS	Death			750	41/50 females died. 49/50 males died
					Bd wt	1,500			
					Resp	1,500			
					Cardio	1,500			
					Gastro	1,500			
					Hemato	1,500			
					Musc/skel	1,500			
					Hepatic	1,500			
					Renal	1,500			
					Dermal	1,500			
					Immuno	1,500			
					Neuro	1,500			
					Repro	1,500			
NCI 1977									
17	Mouse (B6C3F1) 50 M, 50 F	78 weeks 5 days/week (GO)	0, 2,807, 5,615	GN, HP, BW, CS	Death			2,807	22/50 females died: 29/50 males died
					Bd wt		2,807		~18% decrease in final body weight for males; ~10% decrease in final body weight for females

Table 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Resp	5,615			
					Cardio	5,615			
					Gastro	5,615			
					Hemato	5,615			
					Musc/skel	5,615			
					Hepatic	5,615			
					Renal	5,615			
					Dermal	5,615			
					Immuno	5,615			
					Neuro	5,615			
					Repro	5,615			

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive an intermediate-duration oral MRL of 2 mg/kg/day based on decreased body weight. See Appendix A for more detailed information regarding the MRL.

BI = biochemical changes; BC = blood chemistry; Bd wt or BW = body weight; $BMDL_{10}$ = benchmark dose lower confidence limit 10%; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; EEG = electroencephalograph; (F) = food F = female(s); FEP = flashed evoked potential; FI = food intake; (G) = gavage; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; (GO) = gavage in oil; HE = hematology; Hemato = hematological; HP = histopathological; Immuno = immunological; LD = lactation day; LD_{50} = median lethal dose; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; NX = neurological function; OF = organ function; OW = organ weight; Repro = reproductive; Resp = respiratory; RX = reproductive toxicity; SLOAEL = serious LOAEL; UR = urinalysis; (W) = water; WI = water intake

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

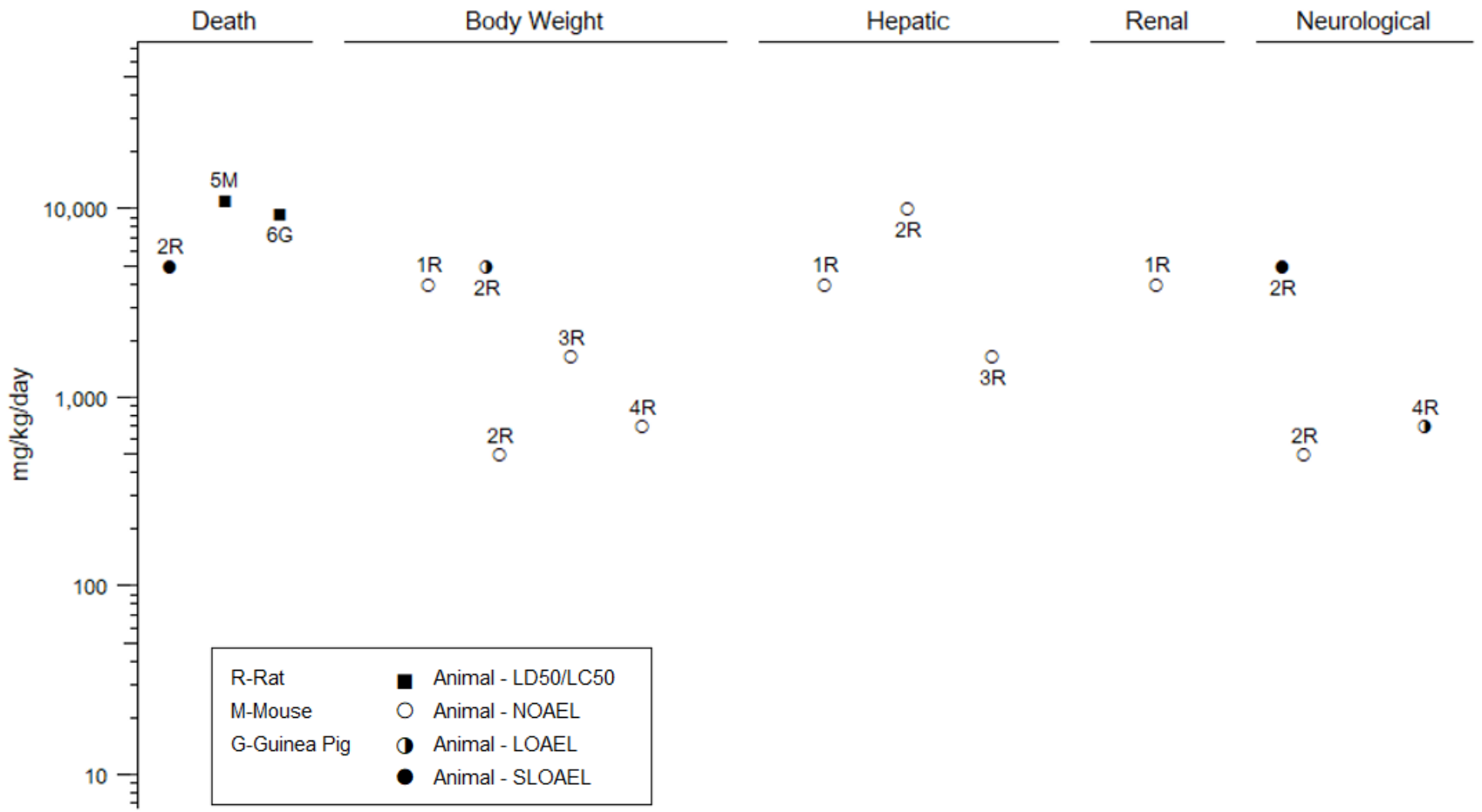


Figure 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral
Intermediate (15–364 days)

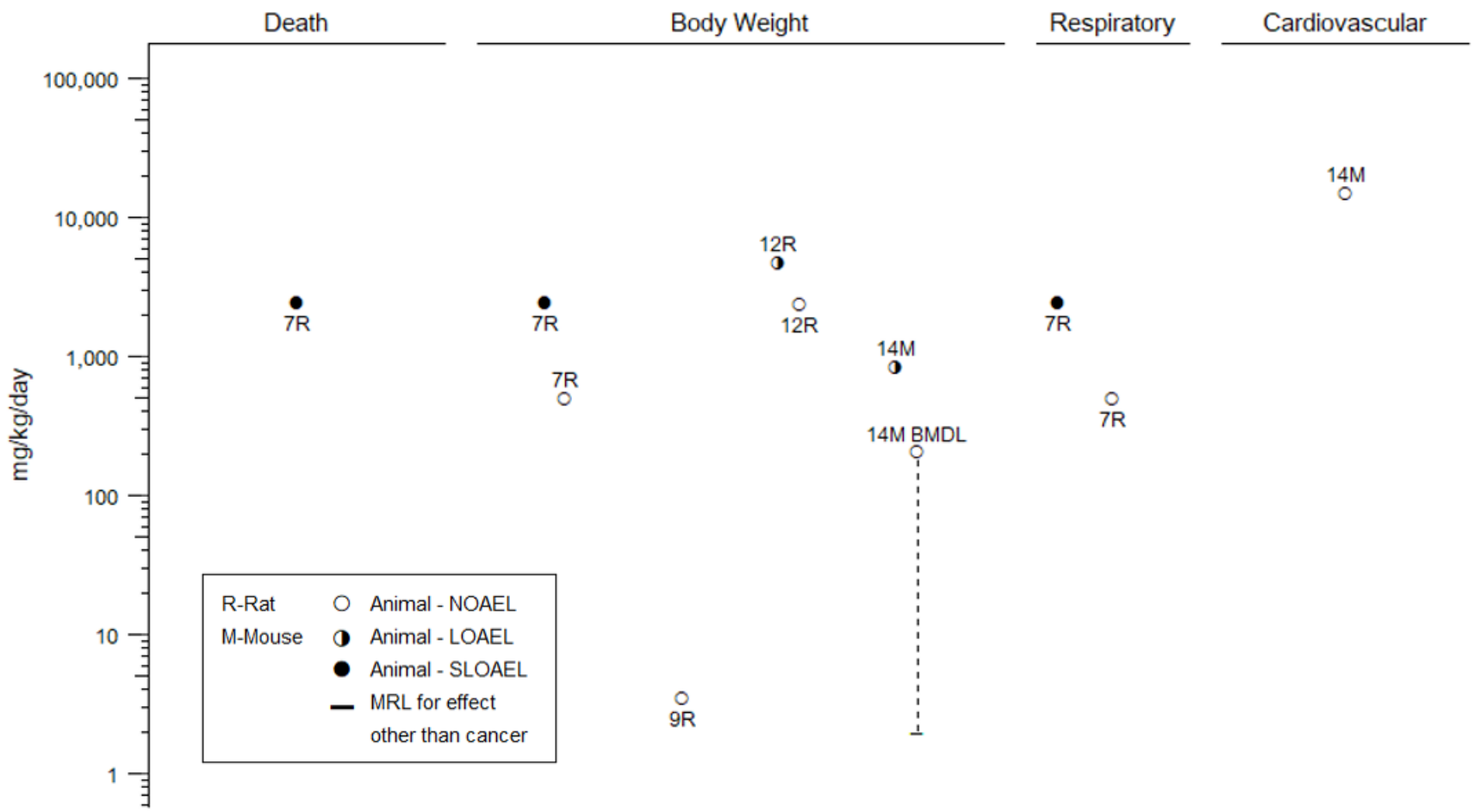


Figure 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral
Intermediate (15–364 days)

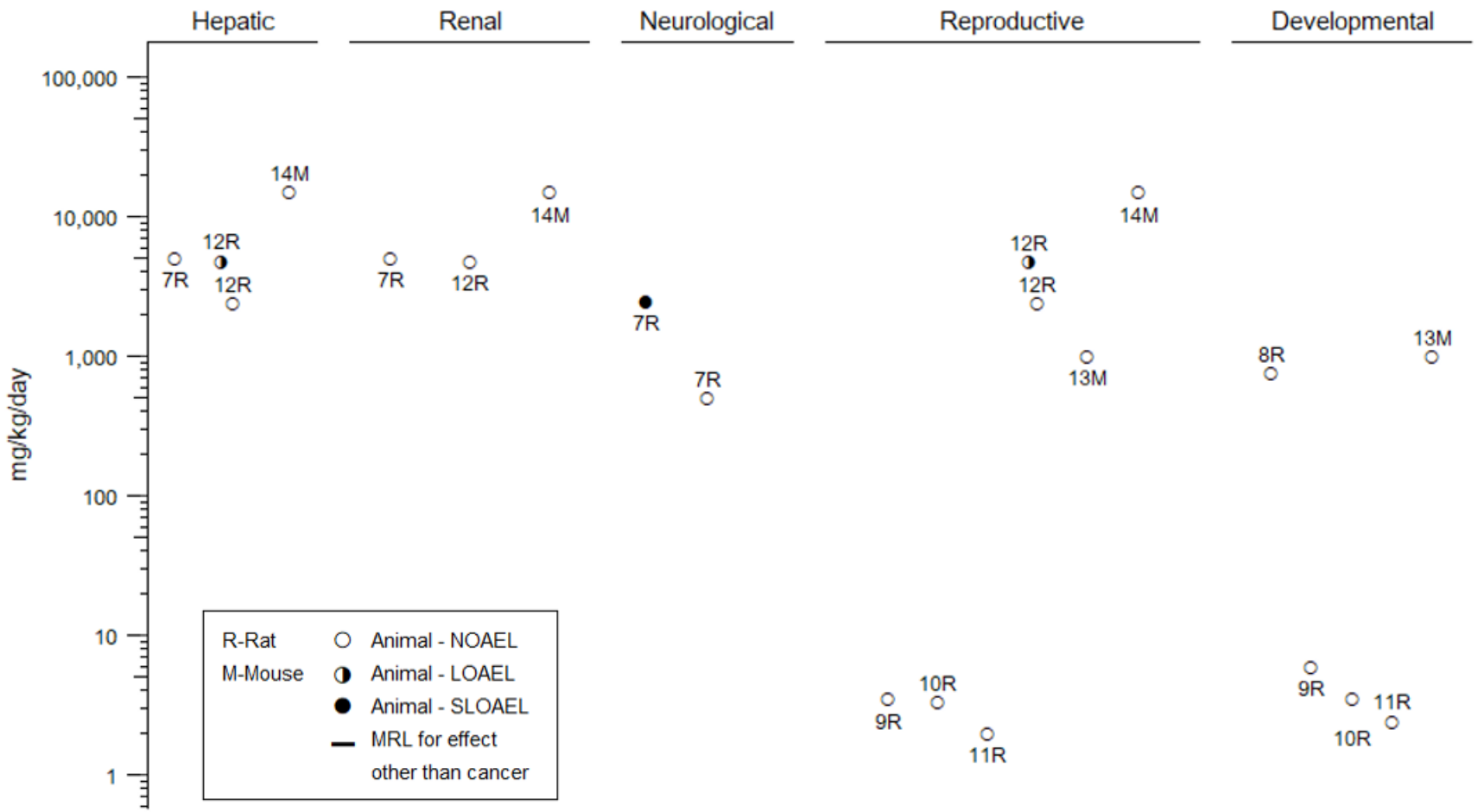


Figure 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral
Chronic (≥365 days)

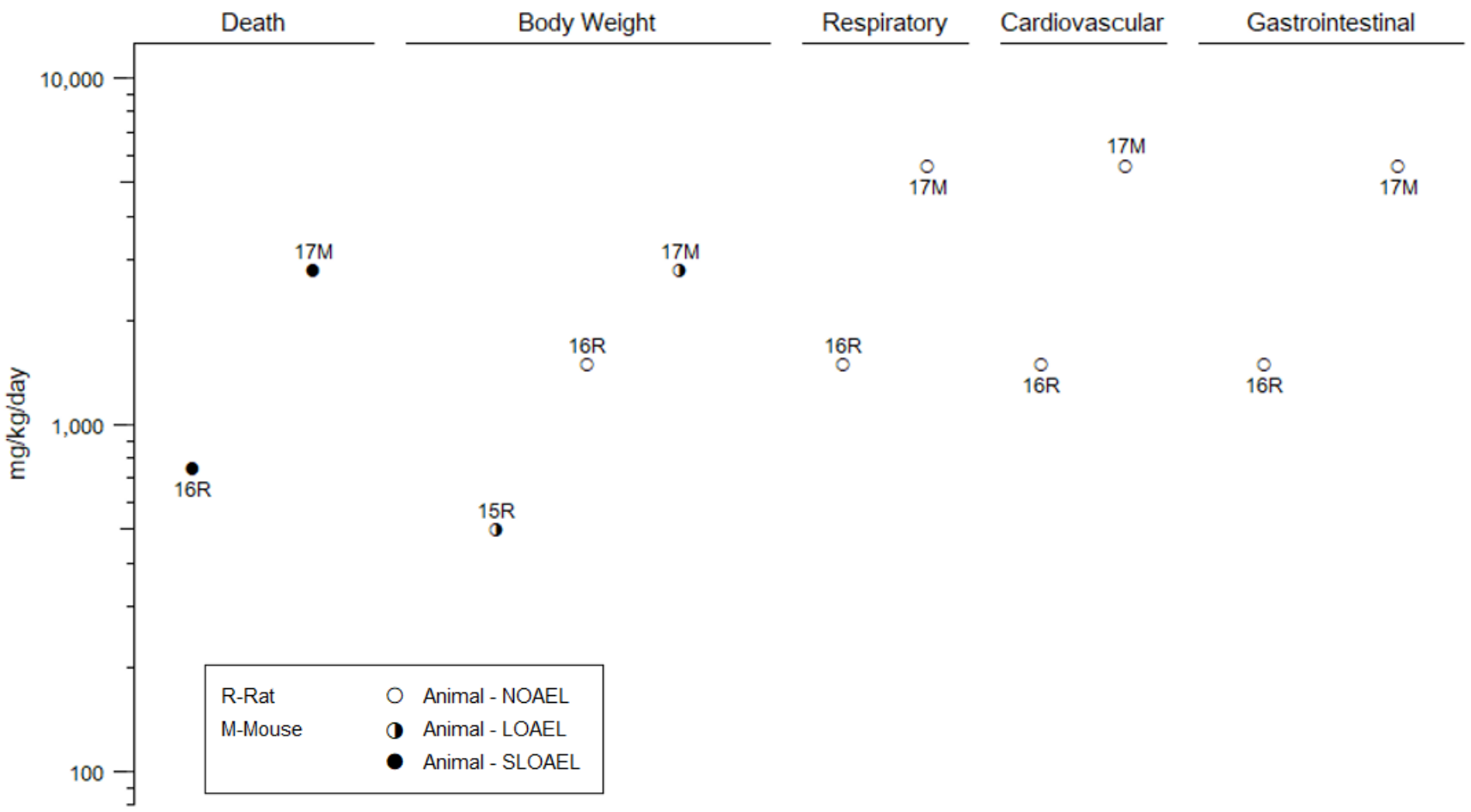


Figure 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral
Chronic (≥365 days)

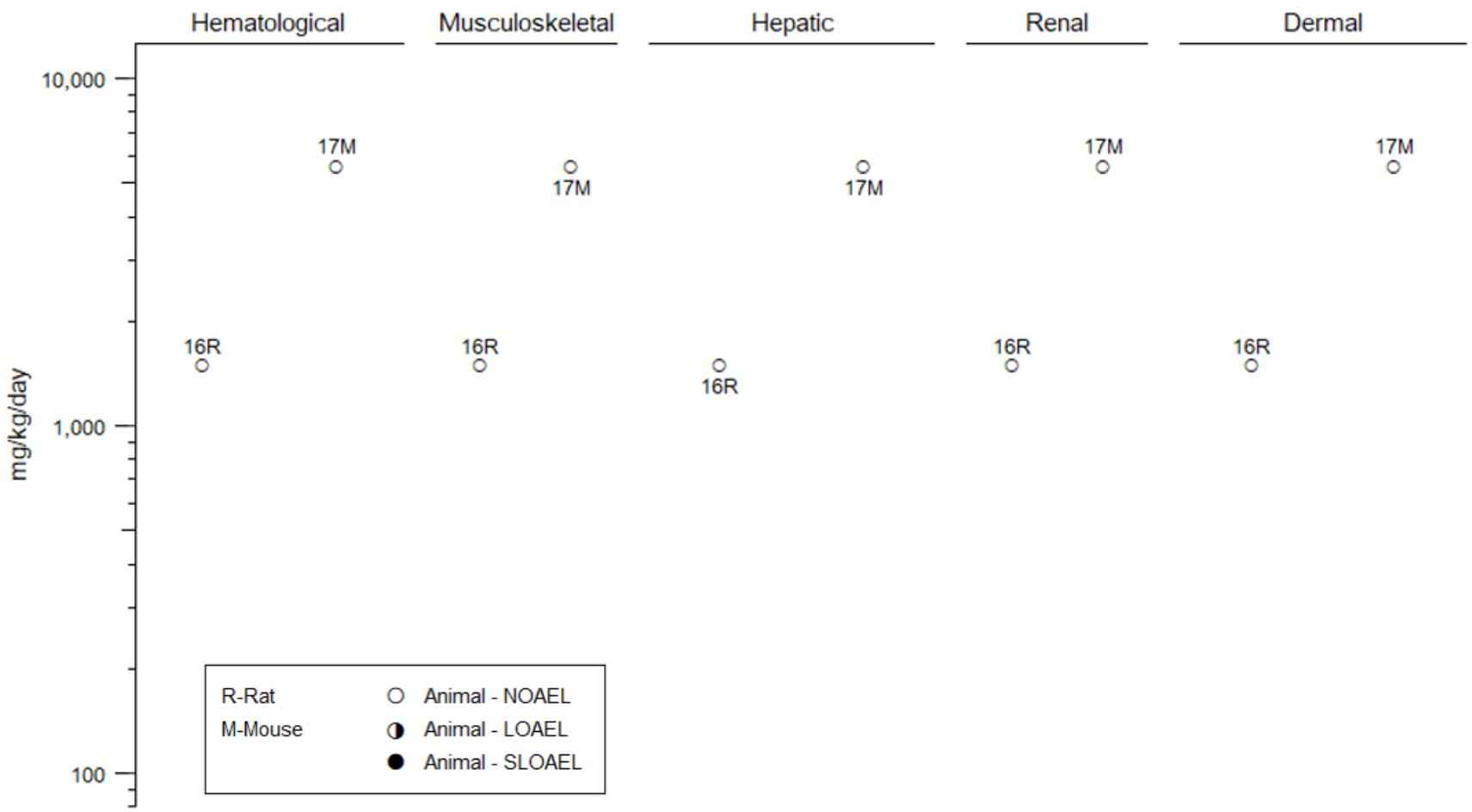


Figure 2-3. Levels of Significant Exposure to 1,1,1-Trichloroethane – Oral
Chronic (≥365 days)

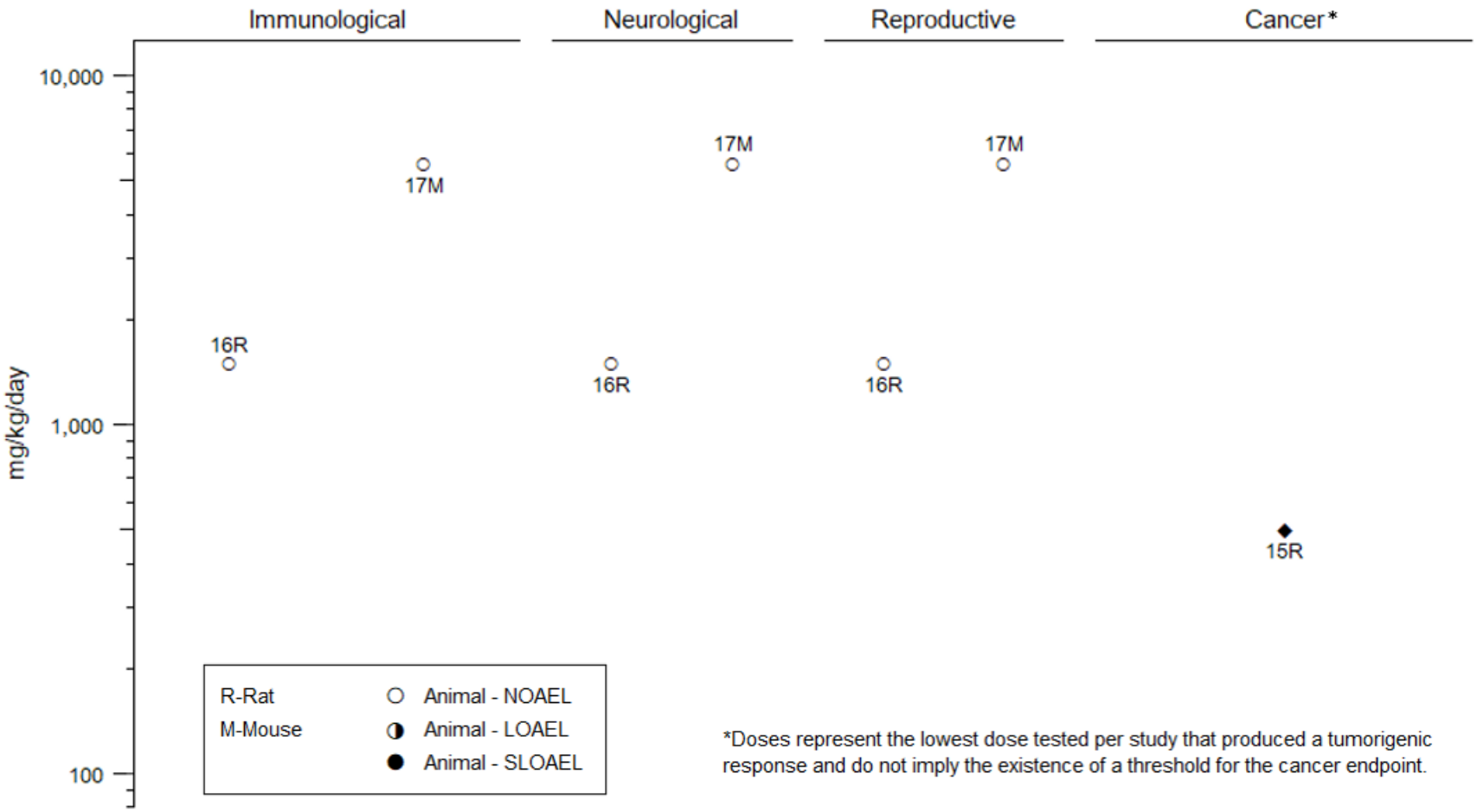


Table 2-4. Levels of Significant Exposure to 1,1,1-Trichloroethane – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE								
Marzulli and Ruggles 1973								
Rabbit (NS) 6 B	Once	50	GN, HP, CS	Ocular	50			
INTERMEDIATE EXPOSURE								
Viola et al. 1981								
Rat (Wistar) 8–10 M	22 days: 8 days once/day, 6 days 0/day, 8 days once/day	0, 280	BC, BW, HP, UR	Bd wt			280	60% decrease in body weight gain
				Gastro	280			
				Hepatic		280		Hepatocellular alterations that included small focal intralobular inflammatory infiltrates; within the hepatocytes, swollen mitochondria and microvacuoles of fatty degeneration; disruption in other cytoplasmic organelles: 650% increase in CPK, 260% increase in OCT, 80% increase in GGT
				Renal	280			
Torkelson et al. 1958								
Rabbit (Albino) 4 M	90 days 5 days/week	0, 15, 50, 100, 200, 500	BC, BW, CS, FI, GN, HP, OW	Bd wt	500			
				Resp	500			
				Cardio	500			
				Gastro	500			
				Hemato	500			
				Hepatic	500			
				Renal	500			
				Dermal		15		Mild skin irritation (not otherwise described)
				Immuno	500			

Table 2-4. Levels of Significant Exposure to 1,1,1-Trichloroethane – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
				Neuro	500			
				Repro	500			

B = both males and females; BC = blood chemistry; Bd wt or BW = body weight; Cardio = cardiovascular; CPK = creatine phosphokinase; CS = clinical signs; FI = food intake; Gastro = gastrointestinal; GGT = gamma-glutamyl transferase; GN = gross necropsy; Hemato = hematological; HP = histopathological; Immuno = immunological; LOAEL = lowest-observed-adverse-effect level; M = male(s); Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OCT = organic cation transporter; OW = organ weight; Repro = reproductive; Resp = respiratory; UR = urinalysis

2.2 DEATH

Lethal effects of 1,1,1-trichloroethane were seen in case studies where individuals were exposed to 1,1,1-trichloroethane through inhalation (Jones and Winter 1983; Northfield 1981; Silverstein 1983). Simulation of the circumstances of deaths in two people exposed while using 1,1,1-trichloroethane as a solvent, showed that concentrations up to 6,410 ppm may have been generated in one case (Jones and Winter 1983), and a concentration of 9,000 ppm was estimated in the other (Silverstein 1983). Northfield (1981) reported a case in which a worker, whose death was attributed to respiratory failure, may have been exposed to 1,1,1-trichloroethane concentrations of 6,000 ppm or higher, depending on distance from the source.

1,1,1-Trichloroethane is one of many solvents that could be intentionally inhaled to alter mood or consciousness. Solvent abuse of this type is associated with "sudden sniffing death" syndrome. In a survey of sudden sniffing deaths across the United States in the 1960s, 29 of the 110 deaths in the survey were attributed to inhalation of 1,1,1-trichloroethane (Bass 1970). Case reports of individuals who died following intentional inhalation of 1,1,1-trichloroethane are readily available (D'Costa and Gunasekera 1990; Droz et al. 1982; Guberan et al. 1976; Hall and Hine 1966; MacDougall et al. 1987; Ranson and Berry 1986; Travers 1974; Winek et al. 1997). 1,1,1-Trichloroethane was previously a widely used industrial solvent. Although mortality due to accidental exposure from its use as a solvent was not common, a number of cases have been reported (Caplan et al. 1976; Commission of the European Communities 1981; Jones and Winter 1983; McCarthy and Jones 1983; Northfield 1981; Silverstein 1983; Stahl et al. 1969; Sullivan 1994).

In mice, reported LC_{50} values ranged from 3,911 to 22,241 ppm, with higher values associated with shorter exposure durations (Gradiski et al. 1978; Horiguchi and Horiuchi 1971; Moser and Balster 1985; Woolverton and Balster 1981). For example, Moser and Balster (1985) reported LC_{50} values of 29,492, 20,616, and 18,358 ppm for 10-, 30-, and 60-minute exposures, respectively. Clark and Tinston (1982) reported an LC_{50} of 38,000 ppm in rats following a 15-minute exposure. Gehring (1968) reported an LT_{50} of 595 minutes following exposure to 1,1,1-trichloroethane at a concentration of 13,500 ppm. Two out of six male rats died after exposure to 11,550 ppm for up to 4 hours (Mullin and Krivanek 1982).

Mortality was not reported in intermediate-duration studies where exposure was up to 5,000 ppm (Prendergast et al. 1967; Rosengren et al. 1985) or in a chronic-duration study where exposures were up to 1,750 ppm (Quast et al. 1988). There were no significant differences in the survival rates of F344 rats

of both sexes after exposure to concentrations up to 3,181 ppm for 6 hours/day, 5 days/week, for 104 weeks (Ohnishi et al. 2013). In the same study, decreased survival rates were observed in male BDF1 mice exposed to 3,204 ppm; however, there were no dose-related differences in survival in female BDF1 mice at concentrations up to 3,204 ppm with the same exposure schedule.

No studies were identified regarding the lethal effects in humans after oral exposure to 1,1,1-trichloroethane.

Kinkead and Wolfe (1992) reported oral LD_{50} values of 17,148 and 12,996 mg/kg for male and female mice, respectively, after acute-duration exposures to 1,1,1-trichloroethane. In an earlier study, Torkelson et al. (1958) reported acute oral LD_{50} values in several animal species: 12,300 and 10,300 mg/kg for male and female rats, 11,240 mg/kg for mice, 9,470 mg/kg for guinea pigs, and 5,660 mg/kg for rabbits. Three of 15 Sprague-Dawley rats died after oral exposure to 5,000 mg/kg/day for 11 days (Bruckner et al. 2001). Gavage doses of 5,620 mg/kg/day in Osborne-Mendel rats and 10,000 mg/kg/day in B6C3F1 mice for 6 weeks resulted in lethality in 2/10 rats and 8/10 mice (NCI 1977). However, survival rates were not affected by dietary exposure to doses as high as 5,000 mg/kg/day in F344/N rats and 23,000 mg/kg/day in B6C3F1 mice for 13 weeks (NTP 2000). Oral exposure to 2,500 mg/kg/day for 5 days/week for 51 days resulted in death in 5/15 Sprague-Dawley rats (Bruckner et al. 2001). It is worth noting that the Bruckner et al. (2001) study mentioned that surviving rats of the 2,500 and 5,000 mg/kg/day groups were mistakenly killed on day 51 of the 13-week study. There was no effect on mortality in the control or 500 mg/kg/day group that continued for the full 13 weeks. Decreased survival was observed in Osborne-Mendel rats exposed to 750 mg/kg/day by gavage and B6C3F1 mice exposed to 2,807 mg/kg/day in a chronic-duration study (NCI 1977). Chronic-duration exposure to 500 mg/kg/day by gavage did not have any impact on survival rates in Sprague-Dawley rats (Maltoni et al. 1986).

No studies were identified regarding the lethal effects in humans after dermal exposure to 1,1,1-trichloroethane.

A 24-hour application 15,800 mg/kg/day of 1,1,1-trichloroethane to the skin of rabbits resulted in <50% mortality of eight rabbits (incidence not reported), whereas a lower dose of 3,980 mg/kg/day had no effect on mortality (Torkelson et al. 1958). No mortality was noted in rabbits exposed to 2 mL/kg for 24 hours or guinea pigs exposed to 2 mL for 35 days (AAMRL 1987; Wahlberg and Boman 1979). Mortality rates in rats and rabbits were not affected by intermediate-duration dermal application of doses up to 280 mg/kg/day (covered) or 500 mg/kg/day (uncovered) (Torkelson et al. 1958).

2.3 BODY WEIGHT

No inhalation studies were identified that investigated body weight changes in humans, but studies in several animal species consistently showed decreased mean body weight.

Several acute-duration studies reported no effects on final body weight up to 8,000 ppm in mice (Calhoun et al. 1981; Jones et al. 1996; Schwetz et al. 1975), up to 18,000 ppm in rats (Adams et al. 1950; BRRC 1987b; Calhoun et al. 1981; Cornish and Adefuin 1966), or up to 6,000 ppm in rabbits (BRRC 1987a). In mice, continuous exposures to a concentration of 4,000 ppm over 4 days caused a 25% reduction in mean body weight measured 96 hours after exposure (Evans and Balster 1993). Despite having no effects on final body weights, animals in these studies sometimes exhibited a decrease in body weight gain.

Body weight remained unaffected in most intermediate-duration studies across animal species at concentrations up to 2,210 ppm as shown in Table 2-2. In multiple studies, Adams et al. (1950) exposed guinea pigs to different concentrations of 1,1,1-trichloroethane for 7 hours/day, 5 days/week for multiple intermediate durations resulting in decreased final body weights for the following exposures: 3,000 ppm exposure for 29 days (12–13% decrease); 5,000 ppm for 45 days (10–11% decrease); 650 ppm for 58 days (11% decrease in females, but not males); and 650 ppm for 93 days (10% decrease in males, but not females). However, exposure of guinea pigs to 1,500 ppm for 60 days had no effect on final body weights. These studies showed decreases in body weight gains ranging from 17 to 53% over the course of the study, which is commonly seen when there is an initial, transient decrease in food consumption correlating with the start of exposure. There were no significant differences in terminal body weight between any of the 1,1,1-trichloroethane-exposed groups and the controls in either male or female F344 rats exposed to concentrations up to 3,181 ppm, or in BDF1 mice exposed to concentrations up to 3,204 ppm for 6 hours/day, 5 days/week, for 104 weeks (Ohnishi et al. 2013).

No oral studies were identified that investigated body weight changes in humans, but studies in multiple animal species showed decreased final body weight.

There were no effects on mean body weights in acute-duration oral studies up to 5,000 mg/kg/day in rats (Bruckner et al. 2001; Platt and Cockrill 1969; Spencer et al. 1990). Acute-duration, 11-day oral exposure to 5,000 mg/kg/day of 1,1,1-trichloroethane caused a 17% decrease in final body weights in Sprague-Dawley rats (Bruckner et al. 2001).

Intermediate- and chronic-duration oral studies in animals show adverse effects of exposure to 1,1,1-trichloroethane on body weight. A decrease of final body weights by 19% was seen after oral exposure to 2,500 mg/kg/day for 13 weeks (5 days/week) (Bruckner et al. 2001). In a 13-week study, NTP (2000) reported reductions in final body weight and body weight gain in rats and mice of both sexes exposed to microencapsulated 1,1,1-trichloroethane in feed. Final body weight was reduced by 10% in male rats exposed to 4,800 mg/kg/day compared to the vehicle controls. Female rats exposed to 5,000 mg/kg/day had no change in body weight. There was no difference in body weights when compared to untreated controls. In male and female mice, a 10–11% reduction in final body weight occurred at doses of 3,500 and 5,600 mg/kg/day, respectively (NTP 2000). No effects on final body weights were reported in a 78-week study in rats exposed to 1,500 mg/kg/day or mice exposed to 5,615 mg/kg/day (NCI 1977). This study reported that the body weight gain was reduced; however, the size of reduction was not quantified and in the absence of changes reflected in final body weights, it is of unclear significance (NCI 1977). A 12% reduction in final body weight occurred in female rats, but not in male rats, exposed to 500 mg/kg/day of 1,1,1-trichloroethane over 104 weeks (Maltoni et al. 1986).

No dermal studies were identified that investigated body weights in humans after exposure to 1,1,1-trichloroethane.

Four studies examined the effects of dermal exposure to 1,1,1-trichloroethane on body weight in animals; however, none of these studies reported food consumption, possibly confounding the occurrence or magnitude of body weight reduction due to 1,1,1-trichloroethane exposure. In an acute-duration study in guinea pigs, no effects on mean body weights were observed through day 35 following dermal exposure to 7,360 mg/kg for 5–7 days (Wahlberg and Boman 1979). Additionally, no effect on mean body weight was reported in rabbits exposed to a dose of 2,680 mg/kg for 24 hours 14 days after exposure (AAMRL 1987). In an intermediate-duration study where 1,1,1-trichloroethane was applied to the skin of rats for 8 days, then 6 days untreated, followed by a second 8-day exposure at doses ranging from 240 to 320 mg/kg (middle of range: 280 mg/kg), a 10% reduced final body weight was reported, with a 60% decrease in body weight gain (Viola et al. 1981). Torkelson et al. (1958) applied 1,1,1-trichloroethane to the uncovered skin of rabbits at doses up to 500 mg/kg for 90 days with no apparent effect on mean body weight.

2.4 RESPIRATORY

Little information on acute-duration exposure of humans to inhaled 1,1,1-trichloroethane is available. In humans, acute-duration exposure to high concentrations of 1,1,1-trichloroethane can produce respiratory depression (Kelly and Ruffing 1993), leading to death (Hall and Hine 1966; Jones and Winter 1983; Stahl et al. 1969; Winek et al. 1997). Six out of seven men exposed to 2,650 ppm (progressive exposure from 0 to 2,650 ppm) for up to 186 minutes reported throat irritation (self-reported) (Stewart et al. 1961). Respiratory inflammation indicated by increased concentrations of proinflammatory cytokines was reported in 12 male subjects following exposure to 200 ppm 1,1,1-trichloroethane for 4 hours (Muttray et al. 1999).

Respiratory failure as a cause of death has been reported in several species of animals acutely exposed to high 1,1,1-trichloroethane concentrations (248–657 mg/kg) (Krantz et al. 1959). Respiratory distress was reported in rats exposed to 6,100 ppm for up to 4 hours (Mullin and Krivanek 1982). However, no histopathological changes were reported in the lungs after acute-duration exposures up to 15,000 ppm in rats or 25,000 ppm in dogs (Cornish and Adefuin 1966; Herd et al. 1974).

Torkelson et al. (1958) reported lung irritation and inflammation in Guinea pigs exposed to 1,000 ppm for 3 months. Degenerative changes in the olfactory epithelium of the nasal turbinates were present in 10/10 male and 10/10 female CDF rats after a 13-week (5 days/week, 6 hours/day) exposure to 1,976 ppm 1,1,1-trichloroethane (Calhoun et al. 1981). However, some intermediate-duration exposures did not produce any histopathological changes in mice, rats, guinea pigs, rabbits, dogs, or monkeys at exposures up to 2,210 ppm (MacEwen and Vernot 1974; Prendergast et al. 1967; Torkelson et al. 1958; Truffert et al. 1977). No histopathological changes were reported in rats and mice exposed to concentrations up to 3,204 ppm for 2 years (Ohnishi et al. 2013; Quast et al. 1988).

No studies were identified regarding respiratory effects after oral exposure in humans to 1,1,1-trichloroethane.

There were no acute-duration oral studies found that identified adverse respiratory effects. Oral exposure to 2,500 mg/kg/day for 13 weeks (5 days/week) in water resulted in pulmonary congestion as the cause of death in Sprague-Dawley rats (Bruckner et al. 2001). There were no lesions observed in the lungs, trachea, or nasal passages of mice and rats exposed to 1,1,1-trichloroethane by gavage at doses up to 5,615 mg/kg/day (mice) or 1,500 mg/kg/day (rats) for 78 weeks (NCI 1977).

No studies were identified regarding respiratory effects after dermal exposure in humans to 1,1,1-trichloroethane.

Dermal exposure to 500 mg/kg/day of 1,1,1-trichloroethane (uncovered) for 90 days had no effect on lung weight or gross or microscopic lung lesions in rabbits (Torkelson et al. 1958).

2.5 CARDIOVASCULAR

Acute-duration exposure to a lower concentration (506 ppm for 450 minutes or 566 ppm for four exposures of 30 minutes) of 1,1,1-trichloroethane did not affect clinical cardiovascular parameters such as blood pressure or pulse rate in the humans tested (Gamberale and Hultengren 1973; Torkelson et al. 1958).

In a matched pair epidemiological study, workers exposed to 1,1,1-trichloroethane at concentrations <250 ppm over 6 years had no differences in blood pressure, heart rate, or electrocardiogram compared to the unexposed group (Kramer et al. 1978). When estimating a regression of the cumulative dose, there was a positive association between 1,1,1-trichloroethane exposure and P-wave duration. In a matched-pair analysis of 151 textile workers, cumulative dose exposure to 1,1,1-trichloroethane (stratified by quintiles: 1–14, 15–49, 50–99, 100–149, and 150–249 ppm) estimated by job exposure index and body burden (measured by breath analysis) was positively correlated with P-wave duration as a cardiac outcome, although correlation was unquantified (Kramer et al. 1978).

Acute-duration exposure to 1,1,1-trichloroethane at concentrations of ≥5,000 ppm produced sensitization of the heart to epinephrine-induced arrhythmias in both rabbits and dogs (Carlson 1981; Clark and Tinston 1973; Reinhardt et al. 1973). The arrhythmias occurred after only a few minutes of exposure, and they quickly disappeared after the end of exposure. In rabbits, there was evidence that susceptibility to arrhythmia increased with exposure duration, and that 1,1,1-trichloroethane itself, not its metabolites, produced the sensitizing effect (Carlson 1981). Mean arterial blood pressure was reduced by 29% (41 mmHg) in rats exposed to 8,000 ppm for up to 60 minutes (Folbergrova et al. 1984). Herd et al. (1974) reported that mean blood pressure decreased by up to 50 mmHg in dogs exposed to 8,000–25,000 ppm 1,1,1-trichloroethane beginning within 15 seconds of the start of exposure and becoming more pronounced as exposure continued for 5 minutes. Decreased mean blood pressure at both 8,000 and 15,000 ppm (change not reported) was due to a decrease in total peripheral resistance; in addition, an

increase in myocardial contractility and cardiac output was observed. The decrease in blood pressure at 20,000 and 25,000 ppm was caused by reductions in myocardial contractility and cardiac output. Blood pressure returned to pre-exposure values within 15 minutes after termination of exposure, but indices of cardiac output and contractility required 45 minutes to recover. No histopathological changes in the heart were found upon necropsy (Herd et al. 1974).

There were no reported cardiovascular lesions in several animal species (monkeys, rats, mice, guinea pigs) following exposures to concentrations up to 5,000 ppm 1,1,1-trichloroethane for up to 6 months (Adams et al. 1950; Calhoun et al. 1981; Prendergast et al. 1967; Torkelson et al. 1958). Chronic-duration inhalation of up to 2,000 ppm 1,1,1-trichloroethane did not produce cardiovascular lesions in rats or mice (Quast et al. 1988).

No cardiovascular effects were reported in a man who accidently ingested an estimated 600 mg/kg of 1,1,1-trichloroethane in a single dose (Stewart and Andrews 1966).

No cardiovascular lesions were observed in mice exposed to up to 22,900 mg/kg/day or rats exposed to up to 5,000 mg/kg/day in a 13-week repeated-dose study (NTP 2000). In a 78-week oral study, exposure of rats to 1,500 mg/kg/day and mice to 5,615 mg/kg/day did not affect the incidence of cardiac lesions (NCI 1977).

No studies were identified regarding cardiovascular effects in humans after dermal exposure to 1,1,1-trichloroethane.

Torkelson et al. (1958) conducted a 90-day dermal study in rabbits where exposure to 1,1,1-trichloro-ethane in doses up to 500 mg/kg/day resulted in no changes to heart weight or incidence of heart lesions at any dose level.

2.6 GASTROINTESTINAL

Nausea, vomiting, and diarrhea have been reported in humans exposed to high 1,1,1-trichloroethane concentrations by inhalation (Jones and Winter 1983; McCarthy and Jones 1983; Stewart 1971).

In animals, no gastrointestinal lesions were observed among rats, mice, guinea pigs, or dogs exposed to concentrations as high as 5,615 ppm 1,1,1-trichloroethane for intermediate (Calhoun et al. 1981; MacEwen and Vernot 1974; Torkelson et al. 1958) or chronic durations (Quast et al. 1988).

Vomiting and diarrhea were reported in a man who accidently ingested an estimated 600 mg/kg of 1,1,1-trichloroethane in a single dose (Stewart 1971). Vomiting ensued approximately 1 hour after ingestion with severe and incapacitating diarrhea approximately 2.5 hours after ingestion, with both continuing for 6 hours.

In oral studies, gastrointestinal endpoints examined in animals were limited to histology. In chronic-duration studies, exposures in mice to up to 5,615 ppm and rats to up to 1,500 ppm resulted in no histopathological lesions (NCI 1977).

No studies were identified regarding gastrointestinal effects in humans after dermal exposure to 1,1,1-trichloroethane.

There were no gastrointestinal effects observed in animals dermally exposed to 1,1,1-trichloroethane. Histopathological examination and serum lipase and amylase levels indicated no gastrointestinal or pancreatic damage in rats dermally exposed to 280 mg/kg/day of 1,1,1-trichloroethane under an occlusive dressing for 3 weeks (Viola et al. 1981). Rabbits exposed dermally to 500 mg/kg/day without occlusion for 90 days had no gross or microscopic lesions in the stomach or intestines (Torkelson et al. 1958).

2.7 HEMATOLOGICAL

No evidence was identified that 1,1,1-trichloroethane produces hematological effects in humans after inhalation exposure. Acute-duration inhalation exposures to 1,1,1-trichloroethane at 920 ppm did not adversely affect red or white blood cell counts or hemoglobin levels in humans (Torkelson et al. 1958). In a matched-pair occupational study in textile workers, chronic-duration exposure to up to 249 ppm 1,1,1-trichloroethane did not affect hematological parameters (red blood cells, white blood cells, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and mean corpuscular volume) (Kramer et al. 1978).

No adverse effects were reported for hematological parameters in animals exposed to moderate to high levels of 1,1,1-trichloroethane for any duration (acute, intermediate, or chronic) (Horiguchi and Horiuchi

1971; Koizumi et al. 1983; MacEwen and Vernot 1974; Ohnishi et al. 2013; Prendergast et al. 1967; Quast et al. 1988; Torkelson et al. 1958; Truffert et al. 1977). No consistent changes in hematological parameters were observed in rats exposed to concentrations of 1,1,1-trichloroethane up to 1,976 ppm for 85 days (Calhoun et al. 1981).

No adverse effects were observed on hematological parameters in a man 4 hours after accidentally drinking a single 600 mg/kg dose of 1,1,1-trichloroethane (Stewart and Andrews 1966).

No hematological effects were reported following a 13-week oral exposure to 1,1,1-trichloroethane in the diet at doses up to 5,000 mg/kg/day in rats or 22,900 mg/kg/day in mice (NTP 2000). Chronic-duration gavage exposure to 1,1,1-trichloroethane at doses of 1,500 mg/kg/day in rats and 5,615 mg/kg/day in mice did not affect the incidence of non-neoplastic lesions in bone marrow (NCI 1977), relative to control.

No studies were identified regarding hematological effects in humans after dermal exposure to 1,1,1-trichloroethane.

In rabbits, hematological parameters, including red blood cell count, white blood cell count, and hemoglobin were unaffected by dermal exposure to 500 mg/kg/day of 1,1,1-trichloroethane (uncovered) for 90 days (Torkelson et al. 1958).

2.8 MUSCULOSKELETAL

No studies were identified regarding musculoskeletal effects in humans after inhalation, oral, or dermal exposure to 1,1,1-trichloroethane.

No lesions were found in the muscles or bones of rats and mice exposed to concentrations up to 1,500 ppm for 2 years via inhalation (Quast et al. 1988).

No reported non-neoplastic lesions in muscle or bone were observed in rats exposed to 1,500 mg/kg/day or mice to 5,615 mg/kg/day by gavage in corn oil for 78 weeks (NCI 1977).

No studies were identified regarding the musculoskeletal effects in animals after dermal exposure.

2.9 HEPATIC

Although there were no indications of liver effects in studies of occupational or controlled human exposure to 1,1,1-trichloroethane, data from case reports of humans exposed to high 1,1,1-trichloroethane concentrations suggest that this chemical may produce hepatic effects.

Serum liver enzymes were normal in individuals acutely exposed by inhalation to 1,1,1-trichloroethane at concentrations up to 10,000 ppm (Stewart et al. 1961; Torkelson et al. 1958). In a matched-pair occupational study of textile workers, exposure to 1,1,1-trichloroethane levels <250 ppm did not affect serum liver enzymes in individuals (Kramer et al. 1978). Results from tests for hepatic function (not described) were within the normal range in 28 workers exposed to unspecified concentrations of 1,1,1-trichloroethane for an average of approximately 17.6 years (Kelafant et al. 1994). Some case studies of individuals exposed to high 1,1,1-trichloroethane concentrations did report elevated hepatic serum enzyme levels. Three individuals who had substantial occupational exposure to 1,1,1-trichloroethane had elevated (>2-fold) serum alanine aminotransferase (ALT) levels (Hodgson et al. 1989). An individual studied by Halevy et al. (1980) had elevated levels of serum bilirubin, lactate dehydrogenase (LDH), alkaline phosphatase, and aspartate aminotransferase (AST). Elevated serum AST (5-fold), ALT (3-fold), LDH (2-fold), gamma-glutamyl transpeptidase (GGT) (2-fold), and pathologic signs of progressive liver disease (fibrosis, nodule formation, regeneration, and granulomas) were noted in a patient who was occupationally exposed to unknown concentrations of 1,1,1-trichloroethane for several years (Cohen and Frank 1994). Removal of the patient from exposure resulted in improvement of the impaired liver function, although the serum levels of LDH, GGT, AST, and ALT remained higher than normal as long as 14 months following cessation of exposure. Other exposed individuals did not have elevated serum hepatic enzyme levels (Stewart 1971; Wright et al. 1984). In some cases, histopathological examination revealed mild fatty changes in the liver of individuals exposed to high 1,1,1-trichloroethane concentrations (Caplan et al. 1976; Hall and Hine 1966; Hodgson et al. 1989). In another case, cholestasis was observed (Halevy et al. 1980). Pathological liver effects were observed in two separate case reports of repeated exposure to 1,1,1-trichloroethane in poorly ventilated work areas (Croquet et al. 2003; Texter et al. 1979).

In several studies, acute-duration exposure to high 1,1,1-trichloroethane concentrations did not affect serum enzyme levels, liver weights, or histopathology in rats, mice (Carlson 1973; Cornish and Adefuin 1966; Gehring 1968; Savolainen et al. 1977), dogs (Herd et al. 1974), or rabbits (BRRC 1987b). Rats exposed to 2,500 ppm for 24 hours had increased absolute and relative liver weights (Fuller et al. 1970).

Continuous exposure to 1,1,1-trichloroethane at concentrations up to 400 ppm for 10 days resulted in increased relative liver weights in rats (Koizumi et al. 1983); however, in the absence of data on hepatic serum enzymes or histopathological assessments, the toxicological significance of this finding is uncertain. Acute-duration inhalation exposure to 8,000 ppm 1,1,1-trichloroethane for up to 7 hours resulted in a 12% increase in relative liver weights and slight fatty changes of the liver in male Wistar rats (Adams et al. 1950). No adverse effects on the liver (liver weights, serum enzymes, histopathology) were observed in rats exposed to up to 500 ppm for acute durations (Savolainen et al. 1977; Schwetz et al. 1975).

Intermediate-duration exposure to 1,1,1-trichloroethane produced hepatic effects in animals including mild histopathological changes in the liver and effects on liver enzymes. Intermediate-duration exposure to 800 ppm 1,1,1-trichloroethane resulted in increased liver weights by 15% and liver-to-body-weight ratios by 16% (Toftgard et al. 1981); however, in the absence of data on hepatic serum enzymes or histopathological assessments, the toxicological significance of these findings is uncertain. Increased centrilobular fat accumulation and hepatic triglycerides were reported in mice exposed to 1,000 ppm for 14 weeks (MacEwen and Vernot 1974). Histopathological effects in mice exposed to 1,000 ppm 1,1,1-trichloroethane continuously for 14 weeks included hepatocyte vacuolation, degeneration, and necrosis (McNutt et al. 1975). Necrosis was first observed after 10 weeks of exposure and was observed in 40% of exposed mice after 12 weeks. McNutt et al. (1975) also reported increased liver triglycerides and an increase in relative liver weights at all time points (weeks 1–14) and increased absolute liver weights at week 12. Torkelson et al. (1958) reported increased relative liver weights and centrilobular fatty changes in guinea pigs exposed to 1,000 ppm for 3 months. Exposure to 5,000 ppm 1,1,1-trichloroethane for 45 days resulted in slight to moderate central fatty degeneration in the liver of guinea pigs (Adams et al. 1950). However, no effects were observed in guinea pigs exposed to 650 ppm for 58 or 93 days, 1,500 ppm for 60 days, or 3,000 ppm for 29 days (Adams et al. 1950). No adverse effects on the liver were noted in several species (monkeys, rats, mice, guinea pigs) exposed to up to 5,000 ppm for up to 6 months (Adams et al. 1950; Calhoun et al. 1981; MacEwen and Vernot 1974; Prendergast et al. 1967; Torkelson et al. 1958; Truffert et al. 1977; York et al. 1982).

Rats exposed to 1,500 ppm for 2 years exhibited a reduction in hepatocyte size, accentuated lobular pattern, and altered centrilobular cytoplasmic staining (Quast et al. 1988). No effects were observed in mice exposed similarly in the same study. No hepatic effects were observed in mice or rats exposed to approximately 3200 ppm for 104 weeks (Ohnishi et al. 2013)

In a case in which a man who ingested an estimated dose of 600 mg/kg/day of 1,1,1-trichloroethane, serum bilirubin levels became slightly elevated after 48 hours but serum aminotransferase levels (i.e., ALT, AST) remained within normal limits (Stewart and Andrews 1966).

No changes in serum hepatic enzymes were observed in rats given a single oral dose of 13 mg/kg 1,1,1-trichloroethane (Tyson et al. 1983). Similarly, in rats orally exposed for 11 days to doses up to 10,000 mg/kg/day 1,1,1-trichloroethane, no toxicologically significant increases were observed on serum ALT or AST (Bruckner et al. 2001). There were no changes in serum enzymes or liver weights in rats exposed to 1,1,1-trichloroethane at a dose of 1,650 mg/kg/day for 7 days (Platt and Cockrill 1969).

No hepatic effects were observed in rats administered gavage doses of up to 5,000 mg/kg/day for 7–13 weeks (Bruckner et al. 2001). Decreased absolute (17%) and relative (12%) liver weights in female rats administered 4,800 mg/kg/day and decreased absolute (13%) liver weights in male rats administered 5,000 mg/kg/day of 1,1,1-trichloroethane in the diet for 13 weeks were observed but were attributed to reduced body weights, rather than adverse liver effects (NTP 2000). No effects on hepatic serum enzyme levels, liver weights, or histology were seen in male or female mice receiving doses up to as high as 15,000 and 23,000 mg/kg/day, respectively, for 13 weeks (NTP 2000).

Chronic-duration gavage administration of 1,1,1-trichloroethane up to 1,500 mg/kg/day did not affect the incidence of nonneoplastic lesions in the livers of rats or mice (NCI 1977).

No studies were identified regarding hepatic effects in humans after dermal exposure to 1,1,1-trichloroethane.

In rats dermally exposed to 280 mg/kg/day of 1,1,1-trichloroethane under occlusion for 3 weeks, no effect on serum levels of hepatic enzymes AST, ALT, and ALP were observed (Viola et al. 1981). Histopathological effects observed included fatty degeneration, mitochondrial swelling in hepatocytes, and inflammatory infiltrates (Viola et al. 1981). A study in which rabbits were dermally exposed without occlusion to 500 ppm 1,1,1-trichloroethane for 90 days did not reveal histopathological effects in the liver or changes in liver weight (Torkelson et al. 1958).

Mechanism of Action. 1,1,1-Trichloroethane causes mild to moderate hepatotoxic effects in humans and animals through cytochrome P-450-mediated dechlorination, which leads to liver injury (Plaa 1986). This mechanism of toxicity hypothesizes that the production of free radicals via the homolytic cleavage of the

carbon-chlorine bond in these hepatotoxic chlorinated alkanes occurs in the endoplasmic reticulum of hepatocytes and that the free radicals react with unsaturated lipids and proteins in the endoplasmic reticulum, producing lipid peroxidation and covalent binding, which leads to morphological and functional changes in the organelle eventually leading to cellular dysfunction and necrosis (Plaa 1986). Two studies evaluating the ability of 1,1,1-trichloroethane to induce hepatic drug metabolism reported induced activity of liver microsomal enzymes (e.g., cytochrome P-450, nicotinamide adenine dinucleotide phosphate, reduced form [NADPH], cytochrome c reductase) in rats and mice (Fuller et al. 1970; Lal and Shah 1970). Exposure to up to 400 ppm for 10 days also increased microsomal enzyme activity in rats but exposure to 800 ppm 1,1,1-trichloroethane suppressed hepatic mixed-function oxidative system after 48 hours (Koizumi et al. 1983). A 5-day repeated exposure to 500 ppm 1,1,1-trichloroethane decreased microsomal cytochrome P-450 levels in rats (Savolainen et al. 1977). Intermediate-duration exposure to 800 ppm 1,1,1-trichloroethane had no effect on microsomal enzyme levels in rats (Toftgard et al. 1981). Reduced levels of cytochrome P-450 and epoxide hydratase in rats suggests inhibition of these enzymes (Vainio et al. 1976).

2.10 RENAL

No adverse effects on kidneys, as measured by serum levels of blood urea nitrogen (BUN), uric acid, and creatinine, were reported in a matched pair occupational study of textile workers chronically exposed to <250 ppm 1,1,1-trichloroethane (Kramer et al. 1978). In a retrospective cohort study of aircraft workers, those exposed to 1,1,1-trichloroethane had a >2.37-fold risk of end-stage renal disease (odds ratio [OR] 2.37, 95% confidence interval [CI] 1.02, 5.49) compared to unexposed workers (Radican et al. 2006).

Acute-duration inhalation exposure to 1,1,1-trichloroethane concentrations up to 12,000 ppm did not affect kidney weights or histology in rats (Adams et al. 1950; Cornish and Adefuin 1966).

Exposure of several animal species to moderate to high concentrations of 1,1,1-trichloroethane for intermediate durations had no apparent effect on relevant serum chemistry parameters, kidney weight, or histopathology (Adams et al. 1950; Calhoun et al. 1981; Eben and Kimmerle 1974; Kjellstrand et al. 1985b; MacEwen and Vernot 1974; Prendergast et al. 1967; Torkelson et al. 1958; Truffert et al. 1977).

Chronic-duration inhalation of 1,1,1-trichloroethane did not affect the kidneys of rats or mice (Quast et al. 1988). However, female F344 rats exhibited increased relative, but not absolute, kidney weights after exposure to 3,181 ppm 1,1,1-trichloroethane for 6 hours/day, 5 days/week for 104 weeks (Ohnishi et al.

2013). The effect on relative kidney weights were observed only in the female rats, which were also the only group to have a decrease in body weight, and were not observed in male F344 rats, nor in male or female BDF1 mice exposed to 3,204 ppm 1,1,1-trichloroethane for the same duration (Ohnishi et al. 2013).

Normal BUN levels were reported in the case of a man who accidently ingested approximately 600 mg/kg 1,1,1-trichloroethane (Stewart and Andrews 1966).

No effects on kidney weights or histology were found in rats given a single gavage dose of 4,000 mg/kg/day or repeated doses of 10,000 mg/kg/day for 11 days (Bruckner et al. 2001). There was no histopathological evidence of renal damage in male rats administered 165 mg/kg/day of 1,1,1-trichloroethane by gavage for 21 days (NTP 1996). Urinalysis results showed increases in mean urinary protein; however, the statistical significance of this finding is questionable since it was based on only four surviving rats.

No effects on kidney weight or histology were found in rats with 13-week exposure to 5,000 mg/kg/day (Bruckner et al. 2001). In another study, similarly exposed rats had no treatment-related kidney effects (NTP 2000). Male rats in this study exhibited kidney lesions indicative of hyaline droplet formation; however, this effect is specific to male rats and is not a human health concern.

Chronic-duration oral exposure to 1,1,1-trichloroethane in rats and mice at doses of 1,500 and 5,615 mg/kg/day, respectively, had no effect on the incidence of nonneoplastic lesions in the kidneys (NCI 1977).

No studies were identified regarding renal effects in humans after dermal exposure to 1,1,1-trichloroethane.

No kidney lesions were reported for intermediate-duration dermal exposure to 1,1,1-trichloroethane at doses of 280 mg/kg/day in rats or 500 mg/kg/day rabbits (Torkelson et al. 1958; Viola et al. 1981).

2.11 DERMAL

No information on dermal effects in humans exposed to inhaled 1,1,1-trichloroethane were evaluated. Case-control studies on scleroderma are discussed in Section 2.14.

Whole-body exposure to 4,000 ppm 1,1,1-trichloroethane in the air for 4 hours caused the fur coat of mice to become dull (Evans and Balster 1993). Rats and mice exposed to 2,000 ppm 1,1,1-trichloroethane for 90 days did not have any dermal effects (Calhoun et al. 1981). Dermal lesions were not reported in mice exposed to 1,1,1-trichloroethane via inhalation for 2 years at a concentration of 1,500 ppm (Quast et al. 1988).

No studies were identified regarding dermal effects of oral exposure to 1,1,1-trichloroethane in humans. No non-neoplastic lesions were reported in rats or mice exposed to 1,1,1-trichloroethane at concentrations of 1,500 or 5,615 mg/kg/day, respectively, for 78 weeks (NCI 1977).

Dermal exposure to 1,1,1-trichloroethane in humans causes dermal effects that are reversible upon cessation of exposure. Stewart and Dodd (1964) had volunteers immerse their thumbs in a beaker of 1,1,1-trichloroethane for 30 minutes. After 10 minutes of exposure, subjects reported a mild burning sensation and post-exposure, erythema and fine scaling were observed on the thumbs. Symptoms resolved after an hour. Similar results were reported when the subjects immersed their entire hand into the beaker, with a more intense and rapid onset. Walhberg (1984b) reported similar symptoms after a 5-minute dermal exposure to 30 mg/kg 1,1,1-trichloroethane along with an increase in blood to the skin, which subsided after an hour. A subsequent experiment where subjects were dermally exposed to 2 mg/kg 1,1,1-trichloroethane for 10 days reported no adverse effect on skin-fold thickness or any apparent skin reactions (Wahlberg 1984a). In a case study, a 30-year-old man developed contact dermatitis, identified using skin patch testing, after occupational exposure to 1,1,1-trichloroethane for 3 years (Ingber 1991).

Dermal effects from 1,1,1-trichloroethane exposure in animals are mild and transient. Torkelson et al. (1958) reported slight reddening and scaliness of the skin of rabbits after a 1-day exposure to 3,980 mg/kg and slightly worse irritation after 10-day repeated exposures. Symptoms quickly resolved once exposure ceased. Histological examination noted degenerative changes in the epidermis (karyopyknosis, karyolysis, perinuclear edema, and spongiosis) in the skin of guinea pigs following exposure to undiluted 1,1,1-trichloroethane under a cover glass for durations ranging from 15 minutes to 16 hours (Kronevi et al. 1981). In addition, the upper part of the dermis had focal junctional separation and cellular infiltration. Effects were seen within 15 minutes of exposure and were still present 16 hours later. Skin sensitization assays are reviewed in Section 2.14.

Slight skin irritation was also reported in rabbits following a 13-week exposure to 1,1,1-trichloroethane at doses ranging from 15 to 500 mg/kg/day (Torkelson et al. 1958). Skin-fold thickness increased by 81% in rabbits and 41% in guinea pigs exposed to dermal applications of 1,1,1-trichloroethane at concentrations of 35 and 220 mg/kg/day, respectively, for 10 days (Wahlberg 1984a). Visible erythema and edema were present within 24–72 hours of the original exposure (Wahlberg 1984a).

2.12 OCULAR

Mild eye irritation was reported in volunteers exposed to 1,1,1-trichloroethane at air concentrations >1,000 ppm for durations ranging from 15 to 73 minutes (Stewart et al. 1961). Eye irritation, hyperemia, and photophobia were observed in "some" volunteers exposed to 450 ppm for 8 hours; incidence and severity were not reported (Salvini et al. 1971). In contrast, no eye irritation was reported when the 1,1,1-trichloroethane concentration was 500 ppm for 186 minutes (Stewart et al. 1961).

No treatment-related ocular effects were observed in mice or rats after a 6-hour inhalation exposure to 4,946 ppm 1,1,1-trichloroethane (Calhoun et al. 1981); however, periocular porphyrin pigmentation was observed transiently. Eye irritation was reported in rabbits continuously exposed to 4,000 ppm 1,1,1-trichloroethane for 4 days (Evans and Balster 1993). The eye irritation may be the result of direct chemical contact with the eye. There were no effects observed in rats or mice after exposure to concentrations of 2,000 ppm 1,1,1-trichloroethane for 90 days (Calhoun et al. 1981). No ocular lesions were observed in rats exposed to 1,1,1-trichloroethane at a concentration of 1,500 ppm for 2 years (Quast et al. 1988).

No studies were identified regarding ocular effects of oral exposure to 1,1,1-trichloroethane in humans or animals.

Individuals briefly exposed to 1,1,1-trichloroethane vapor concentrations of 2,650 ppm (progressive exposure from 0 to 2,650 ppm) reported mild eye irritation likely due to ocular direct contact (Stewart et al. 1961).

Ocular administration of 1,1,1-trichloroethane caused only mild eye irritation in rabbits (Krantz et al. 1959; Marzulli and Ruggles 1973; Torkelson et al. 1958). Marzulli and Ruggles (1973) conducted Draize eye testing in rabbits in 10 laboratories; little to no eye irritation was observed following exposure to 0.1 mL undiluted 1,1,1-trichloroethane. Although eye irritation produced by direct application of

1,1,1-trichloroethane seems to be minor, mice exposed continuously to 4,000 ppm 1,1,1-trichloroethane in the air for 4 hours exhibited eye irritation during exposure (Evans and Balster 1993).

2.13 ENDOCRINE

No studies were identified regarding endocrine effects in humans following inhalation exposure to 1,1,1-trichloroethane.

Information on endocrine effects in animals is limited. In an acute-duration study, no histopathological changes were seen in the adrenal glands of male rats after a single 2-hour exposure to up to 15,000 ppm 1,1,1-trichloroethane (Cornish and Adefuin 1966). Plasma corticosterone levels were significantly decreased in male rats after inhalation exposure to 1,1,1-trichloroethane at a concentration of 3,500 ppm for 30 minutes (30%) or 5,000 ppm for 10 (25%) or 30 minutes (50%) (Pise et al. 1998). Plasma adrenocorticotropic hormone was decreased by 50 and 60% at 5,000 ppm after 10 and 30 minutes, respectively.

No studies were identified regarding endocrine effects in humans or animals following oral or dermal exposure to 1,1,1-trichloroethane.

2.14 IMMUNOLOGICAL

Available information on immunological effects of 1,1,1-trichloroethane in humans is limited to two case-control studies. Dow Corning Corp (1994) reported a positive association between purported exposure to 1,1,1-trichloroethane and increased risk of systemic sclerosis (scleroderma) in 377 Michigan women. Controlling for confounding was limited. A larger, follow-up case-control study conducted on 660 women diagnosed with scleroderma between 1980 and 1992 in Michigan and Ohio found no association between exposure to 1,1,1-tricloroethane and scleroderma (Garabrant et al. 2003). In both case-control studies, 1,1,1-trichloroethane exposure could not be quantified.

Acute-duration exposure to 1,1,1-trichloroethane for 2 hours at concentrations up to 15,000 ppm did not result in any histopathological changes to the spleen in Sprague-Dawley rats (Cornish and Adefuin 1966). A 3-hour exposure to 350 ppm 1,1,1-trichloroethane did not have immunological effects on lung host defense (as measured by susceptibility to infection with *Streptococcus zooepidemicus* challenge and

bactericidal activity of alveolar macrophages) in CD-1 mice (Aranyi et al. 1986). Mice exposed under similar conditions for 5 days produced similar results.

Intermediate-duration exposures did not result in any changes in spleen weight or any histopathological changes in several animal species at concentrations up to 2,210 ppm (Prendergast et al. 1967; Torkelson et al. 1958). Similarly, no histopathological changes in the spleen and thymus were reported in rats or mice exposed to 1,1,1-trichloroethane at concentrations up to 1,500 ppm for 2 years (Quast et al. 1988).

There was no effect on the incidence or type of non-neoplastic lesions in the thymus or spleen in rats or mice after 1,1,1-trichloroethane administration via gavage to 1,500 or 5,615 mg/kg/day, respectively, for 78 weeks (NCI 1977).

A single application of 1,1,1-trichloroethane to the mouse ear resulted in significantly increased ear thickness approximately 2 hours following treatment (Iyadomi et al. 2000). Dermal exposure to 500 mg/kg/day without occlusion in a 90-day study did not result in changes to spleen weight or histopathology in rabbits (Torkelson et al. 1958).

2.15 NEUROLOGICAL

Results of acute-duration inhalation studies in humans showed impaired performance in tests designed to measure cognitive and psychomotor skills with variables such as manual dexterity, eye-hand coordination, perceptual speed, and reaction time at concentrations as low as 175 ppm (Gamberale and Hultengren 1973; Mackay et al. 1987). Syntactic reasoning was unaffected by 1,1,1-trichloroethane exposure, but distractibility, as measured by the Stroop test, was improved in the study by Mackay et al. (1987), suggesting that impairment produced by 1,1,1-trichloroethane may be task-specific. Mackay et al. (1987) exposed 12 men to concentrations of 0, 175, or 350 ppm of 1,1,1-trichloroethane for 3.5 hours, administering three psychomotor (simple reaction time, choice reaction time, and tracking ability) and two cognitive (syntactic reasoning and concentration) tasks immediately before entering the exposure chamber, and 20, 60, 120, and 180 minutes after entry. The tests for simple reaction time, choice reaction time, and tracking ability all showed impaired psychomotor performance in volunteers exposed to 1,1,1-trichloroethane concentrations of 175 and 350 ppm. Effects were detected as soon as 20 minutes after the start of exposure at both concentrations. The test for simple reaction time appeared to be the most sensitive, exhibiting a 10–15% increase over baseline values. Observed performance changes correlated with 1,1,1-trichloroethane absolute blood levels. Performance in the cognitive tasks was not

adversely affected by exposure, and neither was the self-reported mood of the volunteers. In males exposed to 500 ppm for 5 days, alterations were observed in electroencephalograph (EEG) tracings; no changes were observed in females exposed to 350 ppm under the same exposure conditions (NIOSH 1975). In other studies, exposures up to 450 ppm for up to 6 hours did not produce significant psychomotor effects (Salvini et al. 1971) or produced only weak effects (Savolainen et al. 1981). Note that Savolainen et al. (1981) exposed some subjects to a single exposure of xylene 1 week before exposure to 1,1,1-trichloroethane. Although these studies examined some of the same parameters, such as reaction time, different analytical methods were used, and different subpopulations were tested. In another study using nine healthy, male volunteers who were exposed to a time-weighted average concentration of 200 ppm 1,1,1-trichloroethane for 5 hours, including six 10-minute periods of exercise, Laine et al. (1996) found no significant effects on electroencephalogram or visual evoked potentials and no subjective symptoms. However, Muttray et al. (2000) reported significantly increased subjective tiredness scores and electroencephalogram changes consistent with increased drowsiness following a 4-hour inhalation exposure of 12 healthy male volunteers to 200 ppm of 1,1,1-trichloroethane. Each of the studies described above have various limitations, including the use of small sample sizes, use of healthy volunteers, and use of only male subjects.

Gross neurobehavioral effects, such as disturbances of equilibrium and coordination, have been observed in humans following acute-duration exposure to 1,1,1-trichloroethane. Torkelson et al. (1958) reported adverse changes in equilibrium and coordination (Rhomberg test and self-reported lightheadedness) in volunteers exposed to 900 ppm for 75 minutes. Stewart et al. (1961) also reported lightheadedness in two of six volunteers exposed to 900 ppm for 3 hours. Later, two volunteers exposed to 500 ppm for 3 hours experienced disequilibrium; however, reports in two subjects were confounded by reports of disequilibrium in the same subjects prior to exposure, and some volunteers reported “feeling sleepy” while performing repetitive tests (Stewart et al. 1969). Laine et al. (1996) found no significant effects on equilibrium after 200 ppm of 1,1,1-trichloroethane exposure for 5 hours.

No exposure-related effects were found, based on the results of subjective questionnaires, neurological examinations, and psychological tests, in an occupational study with exposures from 200 to 990 ppm and an average duration of 6.7 years (Maroni et al. 1977). Maroni et al. (1977) suggested that no definitive conclusions can be drawn due to the small sample size of six to seven subjects per group and short duration of exposure. However, a study of 28 workers occupationally exposed to high “near anesthetic levels” of unspecified concentrations of 1,1,1-trichloroethane over an average period of 17.6 years revealed deficits in memory and in several components of balance (Kelafant et al. 1994). Deficits in

memory, attention, and concentration were also diagnosed in a 45-year-old man who had been heavily exposed to 1,1,1-trichloroethane, as well as dichloromethane, for 15 years (Garnier et al. 1991). Although the patient's brain function slowly improved following removal from exposure, lingering memory deficits were noted in a follow up 5 years later.

The principal neurological effects observed in animals exposed to 1,1,1-trichloroethane are signs of central nervous system depression, ataxia, unconsciousness, and impaired performance in behavioral tests; these are summarized below.

Neuromotor. Clinical signs of ataxia, narcosis, and unconsciousness were commonly observed in several acute-duration studies. Acute-duration exposure to concentrations up to 7,800 ppm produced intoxication and incoordination in rats (Clark and Tinston 1982; Hougaard et al. 1984). Clinical signs of narcosis were observed in rats exposed to 5,000 ppm for up to 7 hours, with unconsciousness observed at doses of 18,000 ppm (Adams et al. 1950). Ataxia, narcosis, and unconsciousness have been reported in rats following acute-duration exposures to 1,1,1-trichloroethane at concentrations of 23,000 ppm for 30 minutes (Woolverton and Balster 1981), 3,080 ppm for up to 4 hours (Mullin and Krivanek 1982), 7,800 ppm for up to 2 hours (Hougaard et al. 1984), and 8,000 ppm 3 times/day for 1 hour on gestation days (GDs) 12–17 (Jones et al. 1996). Jones et al. (1996) also reported mild tremors and gait abnormalities in dams. Dams exposed to 7,000 ppm 1,1,1-trichloroethane 3 times/day for 1 hour on GDs 13–19 exhibited clinical signs that included salivation, lacrimation, and abnormal gait (Coleman et al. 1999). Sprague-Dawley rats had clinical signs of somnolence after exposure to 10,000 ppm for 6 hours, compared with pre-exposure (Bonnet et al. 1980). Impaired placing, grasping, lift, and righting reflexes were reported in rats exposed to 3,080 ppm for up to 4 hours (Mullin and Krivanek 1982). Impaired righting reflex, motor coordination, and/or strength, measured by an inverted screen test, were observed in mice exposed to 5,173 ppm 1,1,1-trichloroethane for 30 minutes (Woolverton and Balster) and 10,000 ppm 1,1,1-trichloroethane for 20 minutes (Bowen et al. 1996b). Motor incoordination was reported following a 6-hour inhalation exposure to 4,946 ppm 1,1,1-trichloroethane in male CDF rats (Calhoun et al. 1981). Bowen and Balster (2006) observed increased locomotor activity (by 70–250%) following a 30-minute exposure to 6,000 ppm 1,1,1-trichloroethane in male mice. Increased motor activity was observed in several studies in mice exposed to 1,250 to 4,000 ppm 1,1,1-trichloroethane for 30 minutes/day for 2–5 days (Balster et al. 1997; Bowen and Balster 1996, 1998). Increased motor activity was also reported in mice and rats after acute exposures to concentration ranges of 1,800–8,000 ppm (Horiguchi and Horiuchi 1971; Kjellstrand et al. 1985a; Moser and Balster 1985; Moser et al. 1985).

Ataxia and narcosis were reported in rats following exposures to concentrations of 10,000 ppm 1,1,1-trichloroethane for 3 months (Torkelson et al. 1958). Increased locomotor activity was reported in a 15-day study of daily 30-minute exposures to 6,000 ppm (Bowen and Balster 2006). Mattsson et al. (1993) conducted a 13-week study in rats that underwent functional observational battery and foregrip strength testing pre-exposure and monthly thereafter during exposure, and functional observational battery (FOB), neurophysiological testing, and neuropathology after exposure. No adverse effects were noted other than a deficit in forelimb grip performance at 2,210 ppm in both male and female rats, which persisted for 7 weeks beyond the end of the exposure period (Mattsson et al. 1993). Histopathological and electrophysiological evaluation found no evidence of neuropathy in the forelimb that might account for this result and the study authors hypothesized that sedative properties of 1,1,1-trichloroethane may have been responsible by allowing the animals to become more relaxed and, consequently, more habituated to the test procedure (Mattsson et al. 1993).

Neurosensory. No ototoxic effects were observed in rats exposed to up to 2,210 ppm 1,1,1-trichloroethane for 13 weeks (Mattsson et al. 1993; Vyskocil et al. 2010). No ototoxic effects were reported in a weight-of-evidence study in which data from the Quebec occupational health regulation were compiled and evaluated (Vyskocil et al. 2012). In total, 44 articles, including human and animal studies evaluating the combined exposure to noise and chemicals, were compiled. No nystagmus prolongation or reduction of saccades were reported in rats exposed to up to 1,500 ppm (Niklasson et al. 1993).

Neurobehavioral. Impaired performance in behavioral tests has been reported for acute-duration inhalation exposures. Baboons exposed to 1,800 ppm for 4 hours exhibited impaired learning and memory performance as measured by a match to sample test (Geller et al. 1982). Mice exposed to 8,000 ppm for 30 minutes exhibited reduced anxiety in conditioned defensive burying task (Paez-Martinez et al. 2003). CD-1 mice exposed to 2,000 ppm for 20 minutes exhibited impaired operant learning with a 30% decrease in correct response rate (Balster et al. 1982). Inhalation of 4,000 ppm 1,1,1-trichloroethane for 30 minutes/day for 2 days decreased lever pressing in operant tasks in male albino mice by 22% (Bowen and Balster 1998). In male albino mice, exposure to 10,000 ppm for 30 minutes resulted in increased time spent in open arms (500%) and an increase in total arm entries (150%) in a radial arm maze; however, this is likely a result of hyperactivity (Bowen et al. 1996a). De Ceaurriz et al. (1983) evaluated rats in a forced swim test and found a reduced duration of immobility, which could suggest reduced behavioral despair; however, the known hyperactivity effect of 1,1,1-trichloroethane exposure makes this test difficult to interpret.

Neurophysiology. Neurophysiological changes have also been reported during acute-duration inhalation exposure to 1,1,1-trichloroethane. Continuous exposure of CFW Swiss mice to 500 ppm 1,1,1-trichloroethane for 4 days resulted in a withdrawal syndrome characterized by handling-induced seizures in 5/10 mice and reduced threshold to pentylenetetrazol-induced seizures after exposure ceased (Evans and Balster 1993). Conversely, De Ceaurriz et al. (1981) reported an EC_{50} of 6,644 ppm after a 4-hour exposure to 1,1,1-trichloroethane for elevation of the threshold for pentetrazole-induced seizures in Swiss OF1 mice.

Neuropathology. Histopathological changes in the brain and spinal cord tissues have been evaluated in rats and mice, but abnormalities have not been observed. Sprague-Dawley rats exposed to 2,210 ppm 1,1,1-trichloroethane intermittently for 8 hours/day, 5 days/week for 6 weeks did not show any histopathological abnormalities in the brain (Prendergast et al. 1967). F344 and CDF rats exposed to concentrations up to 2,000 ppm 1,1,1-trichloroethane vapors for 6 hours/day, 5 days/week, for 13 weeks did not show any brain histopathologic changes (Mattsson et al. 1993; Calhoun et al. 1981). F344 rats and B6C3F1 mice exposed to up to 3,200 ppm 1,1,1-trichloroethane for 6 hours/day, 5 days/week for 2 years also did not show any histopathological changes in the brain (Ohnishi et al. 2013; Quast et al. 1988).

Neurochemistry. Changes in brain metabolism have been reported in rats and mice after acute-duration inhalation exposure to 1,1,1-trichloroethane; however, the toxicological significance of these findings is unclear. Cerebral glucose consumption was decreased by 14–55% in rats exposed to 6,000 ppm for 2 hours (Hougaard et al. 1984). There were reported decreases in expression levels of cyclic nucleotides (cGMP and cAMP) in rats and mice exposed to up to 5,000 ppm for up to 4 hours (Nilsson 1986a, 1986b; You and Dallas 2000). While the protein levels of cyclic nucleotides were evaluated, enzyme activity was not; therefore, these are of unclear relevance. The only effect observed in rats exposed to 8,000 ppm for up to 60 minutes was increased lactate expression in the brain, suggesting possible energy dysfunction; however, in isolation, the toxicological significant of this finding is uncertain (Folbergrova et al. 1984). Páez-Martinez et al. (2008) observed a decrease in mu-opioid receptor binding in the thalamus and periaqueductal gray, as well as an increase in benzodiazepine receptor binding in the caudate putamen, in Swiss-Webster mice after a 30-minute exposure to 12,000 ppm 1,1,1-trichloroethane. Savolainen et al. (1977) did not report any adverse effects on the levels of protein, glutathione, acid proteinase, or ribonucleic acid (RNA) in the brain in rats acutely exposed to 500 ppm 1,1,1-trichloroethane. Continuous exposure to 1,200 ppm 1,1,1-trichloroethane for 30 days altered the fatty acid

composition of ethanolamine phosphoglyceride isolated from the cerebral cortex in rats (Kyrklund and Haglid 1991). No effects on brain fatty acid composition were reported in a similar study with exposure to 320 ppm (Kyrklund et al. 1988).

Markers of damage to neurological tissues have been observed in intermediate-duration studies. In an intermediate-duration study, brain injury resulting in reactive gliosis was evaluated by examining the number and/or size of astrocytes in the area as measured by the quantification of the proteins, glial fibrillary acid protein (GFAP) and astroglial protein S-100. A significant increase in GFAP was observed in the sensorimotor cerebral cortex in gerbils 4 months after exposure to 210 ppm 1,1,1-trichloroethane (Rosengren et al. 1985). Rosengren et al. (1985) did not report any increase in the levels of S-100 after exposure to this dosing regimen.

There were no neurological abnormalities reported in a man who ingested an estimated 600 mg/kg of 1,1,1-trichloroethane 4 hours earlier (Stewart and Andrews 1966).

In an 11-day oral study, Sprague-Dawley rats exposed to 5,000 mg/kg/day 1,1,1-trichloroethane exhibited hyperexcitability followed by narcosis (Bruckner et al. 2001). Intermediate-duration oral exposure to 2,500 mg/kg/day for 13 weeks (5 days/week) via gavage oil in Sprague-Dawley rats caused hyper-excitability followed by hours of narcosis after dosing (Bruckner et al. 2001). There were no reported clinical signs of neurotoxicity in a 13-week study of rats and mice exposed to 1,1,1-trichloroethane at doses up to 5,000 mg/kg/day in the diet (NTP 2000).

Neurophysiological alterations were evaluated in rats exposed orally to 705 mg/kg/day of 1,1,1-trichloro-ethane for 4 days (Spencer et al. 1990). After 2 days of exposure, no behavioral or appearance changes were detected by FOB. However, after 4 days, neurophysiological alterations present including marked changes in the flash-evoked potential, electroencephalogram recordings, and smaller changes in somatosensory-evoked potential.

No changes in type or incidence of lesions of neurological tissues were reported in a 78-week gavage study of rats and mice exposed to 1,1,1-trichloroethane at doses of up to 1,500 and 5,615 mg/kg/day, respectively (NCI 1977).

Occupational exposure to 1,1,1-trichloroethane caused peripheral neuropathy in three women with the initial symptoms including numbness in their limbs, and subsequent nerve conduction studies showed

alterations in peripheral nerve activity (Howse et al. 1989; Liss 1988). Occupational exposure was likely to be a combination of inhalation and dermal exposures; however, exposure levels were not reported. Subsequent examination 3–4 years after diagnosis in the form of sural nerve biopsies in two of the women revealed chronic-duration neuropathy (axonopathy and myelinopathy) (Liss 1988). Peripheral neuropathy was also reported following exposure to 1,1,1-trichloroethane used as a degreasing agent in two additional case studies (House et al. 1994, 1996).

In animals, neurological effects of dermal exposure were limited to histopathology examination that did not find any lesions or other changes in the brains of rabbits exposed to 500 mg/kg/day of 1,1,1-trichloroethane for 90 days (Torkelson et al. 1958).

Mechanism of Action. Respiratory arrest due to central nervous system depression has been proposed as a possible explanation for sudden deaths following acute exposure to high concentrations of 1,1,1-trichloroethane (Adams et al. 1950; Jones and Winter 1983; Torkelson et al. 1958). In general, the actions of 1,1,1-trichloroethane are very similar to other central nervous system depressants. The mechanism by which acute-duration exposures to high concentrations of 1,1,1-trichloroethane depress the central nervous system is thought to involve interactions of the parent compound with lipids and/or proteins in neural membranes that lead to dysfunction (Evans and Balster 1991). The highly lipophilic nature of chlorinated hydrocarbons, such as 1,1,1-trichloroethane, allows them to cross the blood-brain barrier readily and partition into lipids in neuronal membranes. This property allows them to interfere with neural membrane function, bringing about central nervous system depression, behavioral changes, and anesthesia (Klaassen et al. 1996). It is hypothesized that trichloroethanol, a minor metabolite of 1,1,1-trichloroethane, also interacts with hydrophobic portions of cell proteins thereby altering ligand-gated channels of cell membranes, which may lead to potentiation of gamma-aminobutyric acid (GABA)-mediated responses causing inhibition of excitatory signals (Peoples and Weight 1994; Peoples et al. 1990; Savolainen et al. 1977).

2.16 REPRODUCTIVE

Limited information is available regarding the reproductive toxicity of 1,1,1-trichloroethane in humans, and exposure levels have not been quantified. Taskinen et al. (1989) conducted a case-control epidemiology study to investigate the relationship between adverse pregnancy outcomes (spontaneous abortions and congenital malformations) and occupational exposure of fathers to organic solvents, including 1,1,1-trichloroethane, during spermatogenesis for the 80 days prior to conception. No

relationship was found between exposure to 1,1,1-trichloroethane and adverse pregnancy outcomes. Other case-control studies that investigated the relationship between spontaneous abortions and maternal exposure to solvents, including 1,1,1-trichloroethane, also found no clear evidence of a relationship (Lindbohm et al. 1990). A cohort study examined decreases in fertility (as measured by number of menstrual cycles required until pregnancy achieved) involving Finnish male workers with exposure to 1,1,1-trichloroethane and found no association between the women whose partners were exposed to 1,1,1-trichloroethane and number of menstrual cycles before becoming pregnant (Sallmen et al. 1998).

In acute-duration studies, no effects on maternal body weight gain during gestation, gestation length, or litters produced were reported in CD-1 mice exposed to 2,000 ppm 1,1,1-trichloroethane for 17 hours (Jones et al. 1996). No reproductive effects (mean implantations per litter, litter size, or resorptions) were reported in mice exposed to 875 ppm during GDs 6–15 (Schwetz et al. 1975), mice exposed to 8,000 ppm for 1 hour, 3 times/day, during GDs 12–17 (Jones et al. 1996) or rabbits exposed to 1,000 ppm during GDs 6–18 (BRRC 1987b). Continuous exposure to 625 ppm of 1,1,1-trichloroethane vapor for 30 days had no effect on butyrylcholinesterase activity in mice, suggesting no effect on testosterone activity (Kjellstrand et al. 1985a). Significant increases in gestation length were noted in pregnant rats exposed to 7,000 ppm 1,1,1-trichloroethane 3 times/day for 1 hour on GDs 13–19 (Coleman et al. 1999). Litters were completely resorbed in two of nine exposed dams.

In an intermediate-duration study, Adams et al. (1950) reported that exposure to 5,000 ppm 1,1,1-trichloroethane for 45 days (5 days/week, 7 hours/day) caused testicular degeneration in guinea pigs; however, the incidences and severity were not provided; therefore, the toxicological significance is uncertain. No effects on weights or histology of reproductive organs were observed in rats exposed to up to 5,000 ppm for 44 days (testes weights) (Adams et al. 1950), 1,976 ppm for 90 days (Calhoun et al. 1981), 500 ppm for 6 months (Torkelson et al. 1958), or 1,100 for 15 weeks (Truffert et al. 1977); mice exposed to 1,976 ppm for 13 weeks (Calhoun et al. 1981); or guinea pigs exposed to up to 3,000 ppm for up to 6 months (Adams et al. 1950; Torkelson et al. 1958). No effects were observed in a comprehensive reproductive and developmental study in rats exposed to 2,100 ppm for approximately 52 days (York et al. 1982).

Histological examination of male and female reproductive tissues revealed no exposure-related changes in rats, mice, or rabbits following chronic-duration exposure to 1,1,1-trichloroethane (Quast et al. 1988).

No studies were identified regarding reproductive effects in humans exposed orally to 1,1,1-trichloroethane.

Limited information is available regarding reproductive effects in animals following oral exposure to 1,1,1-trichloroethane. Maternal survival, body weight, fertility, and duration of gestation were also not affected in a study in rats exposed to 1,1,1-trichloroethane in drinking water at doses up to 3 mg/kg/day for 27 or 70 days (George et al. 1989; NTP 1988a, 1988b). Epididymal spermatozoa concentrations were reduced by 10% in male rats after dietary exposure to 4,800 mg/kg/day for 13 weeks (NTP 2000). No other adverse male reproductive effects were reported in a 13-week study for male rats and mice fed 1,1,1-trichloroethane in the diet at doses of 4,800 and 15,000 mg/kg/day, respectively, and no signs of altered estrus were reported in female rats and mice exposed to 5,000 and 22,900 mg/kg/day, respectively (NTP 2000). Maternal survival, body weight, and reproductive performance were not adversely affected in a multigenerational study, in which male and female mice were exposed to 1,000 mg/kg/day of 1,1,1-trichloroethane in their drinking water with exposure beginning prior to mating and continuing through gestation and lactation for 3 generations (Lane et al. 1982).

In a chronic-duration study in rats and mice, there was no effect on the incidence or type of nonneoplastic lesions in the prostate, seminal vesicles, testes, or epididymides in males, or the uterus or ovary in females (NCI 1977).

No lesions or weight changes were found in the testes of rabbits exposed dermally to 500 mg/kg/day of 1,1,1-trichloroethane without occlusion for 90 days (Torkelson et al. 1958).

2.17 DEVELOPMENTAL

Taskinen et al. (1989) found no association between congenital malformations (not specified, as listed in the Finnish registry) and occupational exposure of fathers to organic solvents, including 1,1,1-trichloroethane, during spermatogenesis for the 80 days prior to conception in a case-control study.

Several animal studies have evaluated developmental effects of inhalation exposure to 1,1,1-trichloroethane. No effects of embryo- or fetotoxicity (fetal sex ratio, fetal weights, fetal body measurements, and anomalies) were observed in pregnant female rats and mice following exposure to 875 ppm 1,1,1-trichloroethane on GDs 6–15 (Schwetz et al. (1975). York et al. (1982) conducted a factorial study in which pregnant rats were either exposed to 2,100 ppm 1,1,1-trichloroethane before mating, during

gestation, or both. There were no signs of maternal toxicity or embryo toxicity in any test group. In offspring of dams exposed during premating and gestation, increased total skeletal anomalies were observed in 19/78 fetuses (8/20 litters) compared with 5/62 fetuses (4/15 litters) in controls and reduced clavicle size in 5/78 fetuses (5/15 litters) compared with none observed in controls. Increased total soft tissue anomalies were observed in 6/71 fetuses (6/18 litters). Pup survival, weight gain, and pup performance on neurobehavioral tests were not affected by any treatment and there were no gross lesions in offspring upon necropsy at 12 months. In rats exposed to 6,000 ppm for 4 hours a day during GDs 6–15, a 16% decrease in female fetal body weights and poorly or un-ossified cervical centra were observed (BRRC 1987a). Fetal malformations were observed in New Zealand rabbit pups after exposure during GDs 6–18 for 6 hours/day at 6,000 ppm. Bilateral 13th ribs were observed in 42/72 fetuses (18/20 litters) compared to 21/86 fetuses (12/21 litters) in controls (BRRC 1987b). Neurological effects observed in dams in the following studies are discussed in Section 2.15. Exposure of pregnant mice to 1,1,1-trichloroethane at a concentration of 2,000 ppm for 17 hours/day on GDs 12–17 resulted in significantly reduced litter weights, postnatal pup weights, overt developmental delays (pinnae detachment, incisor eruption, eye opening), and impaired performance in pups in behavioral tests (righting reflex, forelimb grip strength, negative geotaxis, inverted screen climbing) (Jones et al. 1996). There were no clinical signs of maternal toxicity and no statistically significant effects on litter size, number of live pups, ratio of male and female pups per litter, or spontaneous motor activity in pups. In another study, pregnant mice were exposed to 8,000 ppm 3 times/day for 1 hour on GDs 12–17 (Jones et al. 1996). Significantly reduced postnatal pup weight, developmental delays (pinnae detachment, incisor eruption, eye opening), and impaired performance in behavioral tests (righting reflex, forelimb grip strength, negative geotaxis, rooting reflex) were observed. Maternal weight gain was reduced during the exposure period in pregnant rats exposed to 7,000 ppm 1,1,1-trichloroethane 3 times/day for 1 hour on GDs 13–19 (Coleman et al. 1999). Developmental effects included increased mortality at birth, decreased litter weight, and significant deficits in coordination, muscle strength, and spontaneous motor activity.

No developmental effects have been found in humans after oral exposure based on epidemiology studies (Bove et al. 1995; Deane et al. 1989; Swan et al. 1989).

There were no developmental effects (pup body weight, physical maturation landmarks, motor activity, FOB results, brain measurements, neuropathology, learning capacity, task performance, or short-term memory) in the offspring of rats treated by gavage with 1,1,1-trichloroethane doses up to 750 mg/kg/day on GD 6 through lactation day 10 (Dow Chemical 1993; Maurissen et al. 1994). No significant developmental effects were observed in in rats administered up to 5.9 mg/kg/day 1,1,1-trichloroethane in

drinking water for 27 or 70 days (George et al. 1989; NTP 1988a, 1988b). In the NTP (1988a) study, 1,1,1-trichloroethane was added to the drinking water of male and female rats before mating and through lactation at doses up to 3.5 mg/kg/day. Exposure to 1,1,1-trichloroethane did not affect pup survival, pup body weight, incidence of malformed pups, or cardiovascular anomalies of any type. In the second NTP (1988b) study, rats were exposed to 1,1,1-trichloroethane in the drinking water from premating through gestation resulting in doses as high as 2.5 mg/kg/day. There were no observed adverse effects in fetuses or embryos, no effects on the incidence of external, visceral, or skeletal malformations, and no cardiovascular abnormalities.

There were no treatment-related developmental effects (pup body weights, pup survival, skeletal and visceral malformations) in the F1 or F2 generation in a multigenerational study, in which mice were exposed to 1,000 mg/kg/day 1,1,1-trichloroethane in their drinking water, with exposure beginning prior to mating and continuing through gestation and lactation (Lane et al. 1982). No maternal toxicity was observed.

No studies were identified regarding developmental effects of dermal exposure to 1,1,1-trichloroethane in humans or animals.

2.18 OTHER NONCANCER

No studies were identified regarding other noncancer effects of inhalation, oral, or dermal exposure to 1,1,1-trichloroethane in humans and animals.

2.19 CANCER

Several studies examined associations between exposure to 1,1,1-trichloroethane and cancer in humans as shown in Table 2-5. The most studied cancer endpoints are cancers of the hematological and neurological systems. Of the available studies, most studies reported exposure qualitatively, with only two studies reporting quantitative exposure data (Anttila et al. 1995; McLean et al. 2014), limiting interpretation of study results. Studies evaluating associations between exposure to 1,1,1-trichloroethane and all cancer reported conflicting results, with one cohort study reporting a positive association (Anttila et al. 1995) and a second cohort reporting a negative association (Spirtas et al. 1991). Anttila et al. (1995) examined both sexes in a small Finnish cohort (n=4,004), while Spirtas et al. (1991) also evaluated both sexes but included a larger population (n=14,457). In the Anttila et al. (1995) study, urinary levels of

1,1,1-trichloroethane were 6.4 and 8.4 mg/L in males and females, respectively. Studies on associations between exposure and hematological cancers also reported conflicting results, with positive associations between 1,1,1-trichloroethane exposure and multiple myeloma observed in a case-control study (Gold et al. 2011) and multiple myeloma mortality in a large cohort study (Spirtas et al. 1991); however, no association was found between 1,1,1-trichloroethane exposure and multiple myeloma in another cohort study in Finland (Anttila et al. 1995). Findings by Anttila et al. (1995) are based on only two cases of multiple myeloma. In cohort studies, Anttila et al. (1995) found a positive association between 1,1,1-trichloroethane exposure and non-Hodgkin's lymphoma (NHL), but Spirtas et al. (1991) found no association with NHL. No association between 1,1,1-trichloroethane exposure and leukemias (in adults or in children of exposed mothers) was observed in two large case-control studies (Infante-Rivard et al. 2005; Talibov et al. 2017) or cohort studies (Anttila et al. 1995; Spirtas et al. 1991). Limitations of the cohort studies include exposure to multiple chemicals and lack of quantitative exposure monitoring (air concentrations or biomarker); most exposure estimates were qualitatively described using job coding matrices and/or industrial hygiene records. Evaluation of 1,1,1-trichloroethane exposure and cancers of the nervous system show primarily no association (Heineman et al. 1994; Neta et al. 2012; McLean et al. 2014; Mulla 1996); however, Anttila et al. (1995) found a positive association between 1,1,1-trichloroethane and cancers of the central nervous system. A positive association was found between 1,1,1-trichloroethane exposure and stomach cancer in a cohort study (Anttila et al. 1995); however, no association with cancers of the stomach or esophagus were observed in a larger cohort (Rohr Indus Inc. 1986, 1987). Studies evaluating cancer of the reproductive organs were limited to a small cohort; Anttila et al. (1995) found a positive association between 1,1,1-trichloroethane exposure and cervical cancer, but no association was observed with prostate cancer. No associations were observed between 1,1,1-trichloroethane exposure and kidney cancer in a single case-control study (Purdue et al. 2017).

Table 2-5. Summary of Epidemiological Studies Evaluating Possible Associations Between 1,1,1-Trichloroethane Exposure and Risk of Selected Cancer Types

Reference, study type, and population	Exposure	Cancer type	Result
All cancer			
Anttila et al. 1995 Cohort, 2,050 males, 1,924 females, Finland	Urinary 1,1,1-trichloroethane Men: mean 6.4 mg/L Women: mean 8.4 mg/L	All cancer	↑
Spirtas et al. 1991 Cohort, 14,457 Airforce base workers, Utah, United States	NR	All cancer mortality	↓

Table 2-5. Summary of Epidemiological Studies Evaluating Possible Associations Between 1,1,1-Trichloroethane Exposure and Risk of Selected Cancer Types

Reference, study type, and population	Exposure	Cancer type	Result
Hematological cancer			
Anttila et al. 1995 Cohort, 2,050 males, 1,924 females, Finland	Urinary 1,1,1-trichloroethane Men: 6.4 mg/L Women: 8.4 mgl/L	Multiple myeloma	↔
		Leukemia	↔
		NHL	↑
Gold et al. 2011 Case-control, 181 cases, 481 controls, SEER study Washington and Michigan, United States	Subjective (ever exposed versus unexposed)	Multiple myeloma	↑
Infante-Rivard et al. 2005 Case-control, 790 cases, 790 controls, Canada	Maternal exposure classified as no exposure and any exposure	Acute lymphoblastic leukemia	↔
Spirtas et al. 1991 Cohort, 14,457 Airforce base workers**,** Utah, United States	NR	Multiple myeloma mortality	↑
		NHL mortality	↔
		Leukemia mortality	↔
Talibov et al. 2017 Case-control, 20,615 cases, 103,075 controls, Nordic countries	Cumulative exposure stratified in tertiles (T) T1: ≤5.6 ppm-years T2: 5.6–12.9 ppm-years T3: >12.9 ppm-years	Leukemia (CLL)	↔
Nervous system cancer			
Anttila et al. 1995 Cohort, 2,050 males, 1,924 females, Finland	Urinary 1,1,1-trichloroethane Men: 6.4 mg/L Women: 8.4 mgl/L	Cancer of the central nervous system	↑
Heineman et al. 1994 Case-control, 741 cases, 714 controls, Louisiana, New Jersey, and Pennsylvania, United States	Qualitative exposure classified as no exposure, low, medium, and high	Astrocytic brain cancer	↔
McLean et al. 2014 Case-control, 1,906 cases, 5,565 controls, New Zealand	Mean cumulative exposure: Cases: 188 ppm Controls: 458 ppm	Meningioma	↔
Mulla 1996 Cross-sectional, 26 counties Florida, United States	NA	Brain tumors	↔
Neta et al. 2012 Case-control, 489 cases, 799 controls, Arizona, Mississippi, and Pennsylvania, United States	Classified as unexposed, possible exposure, and probably exposure	Glioma	↔
		Meningioma	↔

Table 2-5. Summary of Epidemiological Studies Evaluating Possible Associations Between 1,1,1-Trichloroethane Exposure and Risk of Selected Cancer Types

Reference, study type, and population	Exposure	Cancer type	Result
Kidney cancer			
Purdue et al. 2017 Case-control, 1,217 cases, 1,235 controls, Michigan and Illinois, United States	Stratified by probability of exposure: 0, <10, 10–49, 50–89, and ≥90%	Kidney cancer	↔
Gastrointestinal cancer			
Anttila et al. 1995 Cohort, 2,050 males, 1,924 females, Finland	Urinary 1,1,1-trichloroethane Men: 6.4 mg/L Women: 8.4 mgl/L	Stomach	↑
Rohr Indus Inc. 1986, 1987 Cohort, 14,067 workers (85% male, 15% female)	Ever versus never exposed estimated by job matrix	Esophageal or stomach cancer	↔
Reproductive organ cancer			
Anttila et al. 1995 Cohort, 2,050 males, 1,924 females, Finland	Urinary 1,1,1-trichloroethane Men: 6.4 mg/L Women: 8.4 mgl/L	Cervical	↑
		Prostate	↔

↑ = increase; ↓ = decrease; ↔ = no change; CLL = chronic lymphocytic leukemia; NA = not applicable; NHL = non-Hodgkin's lymphoma; NR = not reported; T = tertile

Cancer studies in animals exposed to 1,1,1-trichloroethane via inhalation were limited to two 2-year studies that evaluated necropsy and histopathology in all animals (Ohnishi et al. 2013; Quast et al. 1988). Multiple carcinogenic effects were observed in the chronic-duration study by Ohnishi et al. (2013), in which rats were exposed to 0, 200, 797, or 3,181 ppm and mice were exposed to 0, 201, 801, or 3,204 ppm for 6 hours/day, 5 days/week, for 104 weeks. Cancers of the respiratory tract were observed in both species. In male rats, bronchioloalveolar adenomas showed a positive trend with incidences of 0/50, 1/50, 7/50, 4/50, at 0, 200, 797, or 3,181 ppm, respectively; however, female rats showed no carcinogenic effects in the same study. In mice (both sexes), there were increased trends for bronchioloalveolar carcinomas and combined bronchioloalveolar adenomas and carcinomas in the lung. At 3,204 ppm, 7/49 female mice had combined bronchioloalveolar adenomas and carcinomas in the lung, compared with 1/50 in controls. In male F344 rats exposed to 3,181 ppm 1,1,1-trichloroethane, incidence of mesothelioma in the peritoneum was increased (16/50 compared to 1/50 in controls) and a positive trend was also observed. Mesothelioma in the peritoneum was not observed in female rats or in mice of either sex. There were no other cancer types reported in rats.

Mice exhibited additional cancer types compared to rats (Ohnishi et al. 2013). Males exhibited a positive trend in hepatocellular adenoma incidence, females exhibited a dose-dependent increase that was statistically significant in all exposed groups (2/50, 9/48, 14/50, and 19/49 at 0, 200, 797, and 3,181 ppm, respectively). Female mice also exhibited increased incidences of combined hepatocellular adenomas and carcinomas (4/50, 10/48, 16/50, 20/49, at 0, 200, 797, and 3,181 ppm, respectively), significant at concentrations of ≥797 ppm. The incidences in all exposure groups exceeded the maximum historical control values. Male mice appear to be more sensitive as the following cancer types were observed only in males. There was an increased trend for Harderian gland adenoma, with significantly increased incidence at 3,204 ppm (8/50 compared with 1/50 in controls). There was also an increased trend for malignant lymphoma of the spleen; while not statistically significant, it did exceed the maximum tumor incidence in the historical control data.

In contrast to findings in the Ohnishi et al. (2013) study, the 2-year carcinogenicity study by Quast et al. (1988) found no carcinogenic effects in rats or mice exposed to concentrations of 150–1,500 ppm 1,1,1-trichloroethane.

Isacson et al. (1985) found no association between of 1,1,1-trichloroethane in drinking water and the incidence of bladder, colon, lung, rectum, breast, or prostate cancer in people over 55 years of age. No other studies were identified regarding other cancer effects of oral exposure to 1,1,1-trichloroethane in humans.

Oral cancer studies in animals were limited to two chronic-duration studies that evaluated a comprehensive set of endpoints (Maltoni et al. 1986; NCI 1977), with conflicting results. Maltoni et al. (1986) conducted a 104-week carcinogenicity study that found an increase in the total incidence of rats with leukemias, with 13/80 (9/40 males and 4/40 females) in treated rats compared to 4/100 (3/50 males and 1/50 females) in vehicle controls. NCI (1977) conducted a 78-week (reduced duration due to early mortality) carcinogenicity bioassay, including necropsy and histological evaluation in all animals, for 1,1,1-trichloroethane in rats and mice. Gavage doses were 750 or 1,500 mg/kg/day in rats and 2,807 or 5,615 mg/kg/day in mice. The incidence and type of neoplasms observed in treated animals were comparable to untreated controls (vehicle controls were not used). There was a significant dose-related decrease in survival with a mortality rate of 100% for male rats, 96–98% for female rats, 70–78% for male mice, and 54–74% for female mice. Because the high rate of early mortality may have lowered the incidence of late-appearing tumors, the study authors did not consider this study an adequate test of 1,1,1-trichloroethane carcinogenicity in either species.

No studies were identified regarding cancer effects of dermal exposure to 1,1,1-trichloroethane in humans or animals.

The Department of Health and Human Services (NTP 2021) has not classified the carcinogenicity of 1,1,1-trichloroethane. The International Agency for Research on Cancer (IARC) has classified 1,1,1-trichloroethane as Group 2A, *probably carcinogenic to humans*, based on limited evidence for cancer in humans including positive associations with multiple myeloma, and sufficient evidence for cancer in experimental animals (IARC 2022). The EPA (2007) determined that there was inadequate information to assess carcinogenic potential of 1,1,1-trichloroethane.

2.20 GENOTOXICITY

Results of *in vivo* genotoxicity studies are summarized in Table 2-6. *In vivo* tests were negative for Basc test and mitotic recombination test in *Drosophila melanogaster,* and micronuclei tests and DNA damage tests in mice (see Table 2-6). Weakly positive results were reported for DNA adducts in mouse liver (Turina et al. 1986). No effects were observed with 1,1,1-trichloroethane in an initiation-promotion assay (Milman et al. 1988)

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

Species (test system)	Endpoint	Results	Reference
Drosophila melanogaster	Sex linked recessive lethal mutations	–	Gocke et al. 1981
D. melanogaster	Mitotic recombination	–	Vogel and Nivard 1993
Mouse erythrocytes	Micronucleus test	–	Tsuchimoto and Matter 1981
Mouse bone marrow	Micronucleus test	–	Gocke et al. 1981; Kataz et al. 1981; Mackay et al. 1987; Salamone et al. 1981
Mouse liver	DNA adducts	(+)	Turina et al. 1986
Mouse liver	DNA unwinding	–	Taningher et al. 1991
Rat liver	DNA synthesis	+	Truffert et al. 1977

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

Results of genotoxicity studies *in vitro* are summarized in Table 2-7. While the results of *in vitro* mutation testing were mostly negative, those tests that employed a system designed to minimize volatilization, likely preserving or prolonging exposure, reported positive results in mutagenic assays in

Salmonella typhimurium (Gocke et al. 1981; Nestmann et al. 1980, 1984; Simmon et al. 1977). These results suggest that exposure conditions may play a role in mutagenicity.

Table 2-7. Genotoxicity of 1,1,1-Trichloroethane *In Vitro*

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
Prokaryotic organisms				
Salmonella typhimurium on plates or in liquid	Reverse mutation	–	–	Baker and Bonin 1981; Brooks and Dean 1981; Falck et al. 1985; Ichinotsubo et al. 1981; Legault et al. 1994; MacDonald 1981; Milman et al. 1988; Nagao and Takahashi 1981; Nestmann et al. 1980; Quillardet et al. 1985; Richold and Jones 1981; Rowland and Severn 1981; Simmon and Shepherd 1981; Suovaniemi et al. 1985; Trueman 1981; Venitt and Crofton-Sleigh 1981
S. typhimurium on plates in desiccator	Reverse mutation	+	+	Gocke et al. 1981; Nestmann et al. 1980, 1984; Simmon et al. 1977
S. typhimurium	Fluctuation	–	–	Gatehouse 1981; Hubbard et al. 1981
S. typhimurium	Forward mutation	–	ND	Skopek et al. 1981
S. typhimurium	Ara test	–	–	Roldan-Arjona et al. 1991
S. typhimurium	*umu* test	–	–	Nakamura et al. 1987; Ono et al. 1991
S. typhimurium	Rec-assay for DNA repair	–	–	Kada 1981
Escherichia coli	Reverse mutation	–	–	Matsushima et al. 1981
E. coli	Differential killing	–	–	Green 1981; Tweats 1981
E. coli	Lambda prophage induction	–	–	Thomson 1981
E. coli	Gene induction	–	ND	Quillardet et al. 1985
E. coli	Growth inhibition	(+)	–	Rosenkranz et al. 1981
E. coli	DNA damage	ND	–	Legault et al. 1994
Vibrio fischeri	DNA damage	ND	–	Legault et al. 1994
Eukaryotic organisms: fungi				
Schizosaccharo-myces pombe	Forward mutation	–	–	Loprieno 1981
Aspergillus nidulans	Forward mutation	ND	–	Crebelli and Carere 1988
A. nidulans	Mitotic aneuploidy	ND	–	Crebelli and Carere 1988; Crebelli et al. 1988

Table 2-7. Genotoxicity of 1,1,1-Trichloroethane *In Vitro*

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
A. nidulans	Mitotic crossing over	ND	–	Crebelli and Carere 1988
Saccharomyces cerevisiae	Gene deletions	ND	(+)	Brennan and Schiestl 1998
S. cerevisiae	Reversion	–	–	Mehta and von Borstel 1981
S. cerevisiae	Mitotic aneuploidy	ND	–	Whittaker et al. 1990
S. cerevisiae	Mitotic aneuploidy	–	ND	Parry and Sharp 1981
S. cerevisiae	Mitotic crossing over	–	–	Kassinova et al. 1981
S. cerevisiae	Mitotic gene conversion	–	–	Jagannath et al. 1981; Sharp and Parry 1981a; Zimmermann and Scheel 1981
S. cerevisiae	DNA repair	–	–	Brennan and Schiestl 1998; Sharp and Parry 1981b
Mammalian cells				
HeLa cells	Unscheduled DNA synthesis	–	–	Martin and McDermid 1981
Rat hepatocytes	Unscheduled DNA synthesis	ND	–	Althaus et al. 1982; Milman et al. 1988; Williams et al. 1989
Rat hepatocytes	DNA repair	ND	–	Milman et al. 1988
Mouse hepatocytes	DNA repair	ND	+	Milman et al. 1988
Rat hepatocytes	Degranulation of endoplasmic reticulum	ND	+	Fey et al. 1981
Human lymphoblasts	Gene locus mutation	ND	–	Penman and Crespi 1987
L5178Y mouse lymphoma cells	Forward mutation	±	–	Myhr and Caspary 1988
L5178Y mouse lymphoma cells	Chromosomal aberrations	–	–	Mitchell et al. 1988
Chinese hamster ovary cells	Chromosomal aberrations	(+)	+	Galloway et al. 1987
Chinese hamster ovary cells	Sister chromatid exchange	–	ND	Perry and Thomson 1981
Chinese hamster ovary cells	Sister chromatid exchange	±	–	Galloway et al. 1987
Human peripheral lymphocytes	Sister chromatid exchange	ND	–	Lindahl-Kiessling et al. 1989
Hamster kidney cells	Cell transformation	–	ND	Styles 1981
Rat embryo cells F1706	Cell transformation	+	+	Daniel and Dehnel 1981
Rat embryo cells F1706	Cell transformation	ND	+	Price et al. 1978
Hamster embryo cells	Cell transformation	ND	+	Hatch et al. 1983; Hatch et al. 1982

Table 2-7. Genotoxicity of 1,1,1-Trichloroethane *In Vitro*

Species (test system)	Endpoint	Results		Reference
		With activation	Without activation	
Mice BALB/c-3T3 cells	Cell transformation	ND	+	Milman et al. 1988; Tu et al. 1985
Calf thymus	DNA Binding	–	ND	DiRenzo et al. 1982

= negative; + = positive; (+) = weakly positive; ± = equivocal; DNA = deoxyribonucleic acid; ND = no data

Chromosomal aberrations were reported in Chinese hamster ovary cells *in vitro* (Galloway et al. 1987) but not in mouse lymphoma cells (Mitchell et al. 1988). Positive or weakly positive results were reported in *in vitro* assays for DNA repair in mouse and rat hepatocytes (Milman et al. 1988).

Positive results *in vitro* were reported for degranulation of endoplasmic reticulum, a measure of the ability of a compound to displace polysomes from endoplasmic reticulum in rat hepatocytes (Fey et al. 1981) and for promoting cell transformation, a process believed to be similar to neoplastic transformation *in vivo*, in rat embryo cells, hamster embryo cells, baby hamster kidney cells, and mouse BALB/c-3T3 cells (Daniel and Dehnel 1981; Hatch et al. 1982, 1983; Milman et al. 1988; Price et al. 1978; Tu et al. 1985).

Mixed results in mutagenicity studies suggest that the volatility of 1,1,1-trichloroethane needs to be considered in exposure during mutagenicity assays. Positive results in chromosomal aberrations were observed in a Chinese hamster ovary cell assay only. 1,1,1-Trichloroethane was positive in most mammalian cell transformation assays.