CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of 1,2,3-trichloropropane. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

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

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

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to 1,2,3-trichloropropane, but may not be inclusive of the entire body of literature.

Human and animal inhalation studies are presented in Table 2-1 and Figure 2-2, animal oral studies are presented in Table 2-2 and Figure 2-3, and animal dermal/ocular studies are presented in Table 2-3.

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

endpoint should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of 1,2,3-trichloropropane are indicated in Table 2-2 and Figure 2-3.

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

The health effects of 1,2,3-trichloropropane have been primarily evaluated in experimental animal studies. As illustrated in Figure 2-1, approximately half of the health effects data come from oral exposure studies in animals. Animal data are available for each health effect category and exposure duration category. The most examined endpoints in inhalation and oral studies were hepatic, body weight, respiratory, and renal; approximately 40% of the studies examine each of these endpoints. Dermal/ocular exposure studies primarily focused on portal-of-entry effects. Human data are limited to three studies examining portal-of-entry effects following exposure to airborne 1,2,3-trichloropropane, developmental toxicity in the general population, and a case report of liver effects following ingestion. Based on these data, the following targets of toxicity have been identified:

- **Respiratory Endpoints:** Damage to the nasal olfactory epithelium has been observed in rats and mice following acute and intermediate inhalation exposures. Necrosis has also been observed in the nasal cavity following oral exposure. Throat irritation was reported in humans following a short exposure to a relatively high concentration of 1,2,3-trichloropropane. Peribronchial hyperplasia, bronchiolar epithelial regenerative hyperplasia, and lung hemorrhages have been observed in experimental animals following inhalation, oral, and dermal exposure, respectively.

- **Hepatic Endpoints:** Hepatic effects have been observed in a case study of an individual ingesting 1,2,3-trichloropropane and in experimental animal studies following acute and intermediate inhalation exposure and acute, intermediate, or chronic oral studies. Increases in liver weight, hepatocellular vacuolization, and bile duct hyperplasia were observed in these studies.

- **Renal Endpoints:** Renal effects have been observed in experimental animals following acute, intermediate, and chronic oral exposure. Effects included increases in kidney weight,

regenerative tubular hyperplasia, tubular necrosis, and increases in the severity of chronic nephropathy.

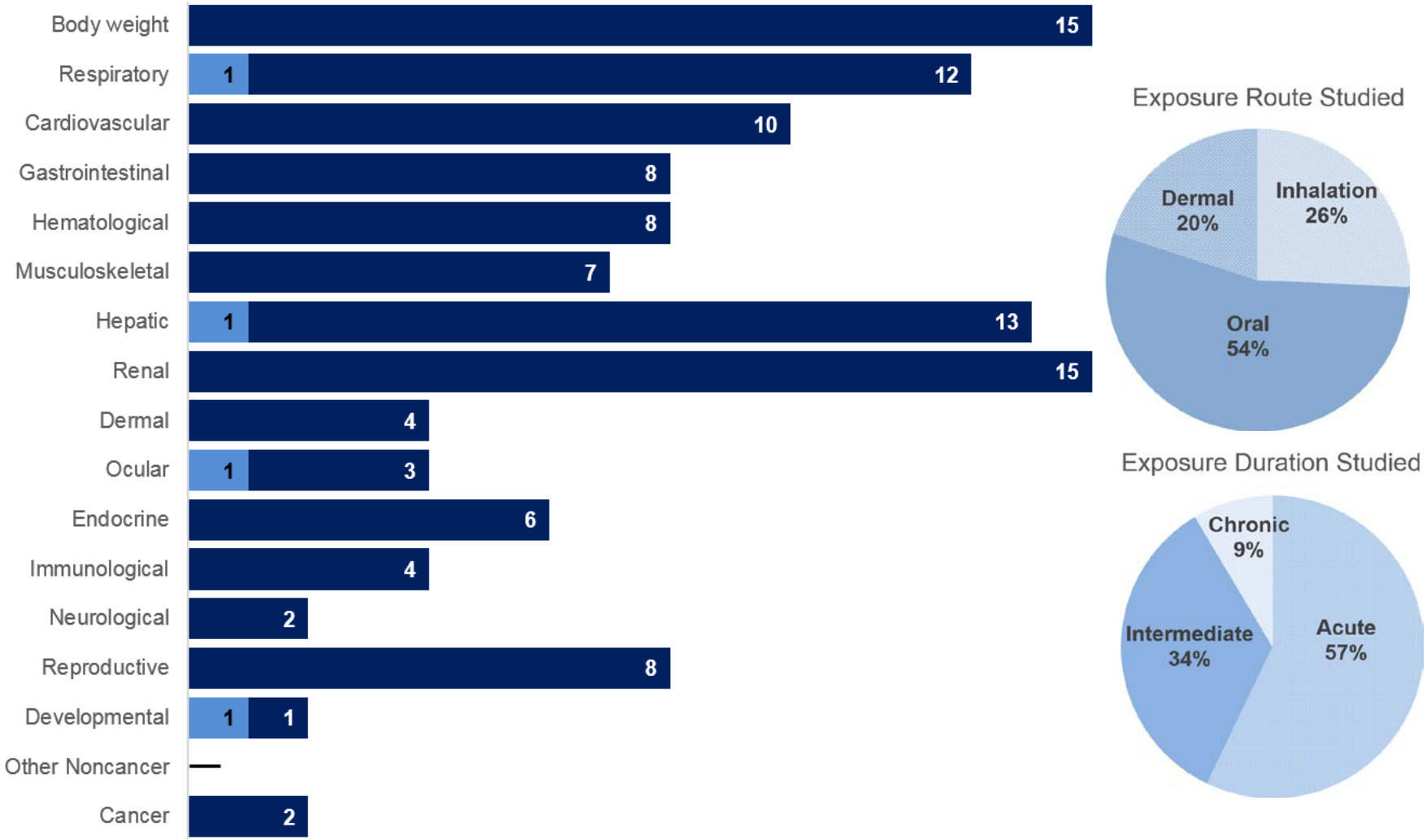
- **Hematological Endpoints:** Anemia, as evidenced by decreases in hematocrit, hemoglobin, and erythrocyte levels, and/or splenic extramedullary hematopoiesis have been observed in experimental animals following inhalation and oral exposure.

- **Cancer Endpoints.** Chronic oral exposure resulted in increases in neoplastic lesions in multiple sites in rats and mice. The most sensitive target tissue appears to be the forestomach; squamous cell papillomas and carcinomas in the forestomach were observed at the lowest doses tested. Other targets included the oral mucosa, liver, and kidneys.

- **Other Endpoints.** Alterations in body weight, lacrimation, impaired reproduction, and developmental toxicity have also been observed in inhalation and/or oral exposure studies in experimental animals; however, these do not appear to be sensitive targets of 1,2,3-trichloro-propane toxicity.

Figure 2-1. Overview of the Number of Studies Examining 1,2,3-Trichloropropane Health Effects

Most studies examined the potential hepatic, respiratory, body weight, and renal effects of 1,2,3-trichloropropane.
Fewer studies evaluated health effects in **humans** than **animals** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 32 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to 1,2,3-Trichloropropane – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
ACUTE EXPOSURE									
1	Human 12	1 days 15 minutes/day	50, 100	CS	Resp		100		Throat irritation
					Ocular		100		Eye irritation
Silverman et al. 1946									
2	Rat (F344) 6 M	1 day 4 hours/day	0, 126, 343, 697, 2,160	CS, GN	Death			697	100% death at 697 and 2,160 ppm
					Ocular		126		Eye irritation
Gushow and Quast 1984									
3	Rat (CD) 5 M, 5 F	1 day 6 hours/day	0, 888	CS	Death			888	9/10 died
Johannsen et al. 1988									
4	Rat (F344) 5 M, 5 F	11 days 9 exposures 6 hours/day	0, 13, 40, 132	HP, BC, BI, OW, BW	Death				No deaths observed
					Bd wt	40	132		10–15% decrease in body weight gain
					Resp		13		Degeneration and inflammation of nasal olfactory epithelium at ≥13 ppm; multifocal fibrosis in nasal submucosa at 132 ppm
					Cardio	132			
					Gastro	132			
					Hemato	132			
					Musc/skel	132			
					Hepatic	40	132		Very slight hepatocellular necrosis
					Renal	132			
					Endocr	132			
					Immuno	132			No histological alterations in thymus or lymphoid tissue

Table 2-1. Levels of Significant Exposure to 1,2,3-Trichloropropane – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
					Neuro	132			No histological alterations in brain, spinal cord, or peripheral nerves
					Repro	132			No histological alterations in reproductive tissues
Miller et al. 1986a									
5	Rat (F344) 5 M, 5 F	11 days 9 exposures 6 hours/day	0, 1, 3, 10	HP, OW, GN, BW	Resp	1[b]	3		Decreased thickness of olfactory epithelium
Miller et al. 1986b									
6	Rat (Carworth-Wistar) 6 NS	1 day 4 hours/day	1,000	CS	Death			1,000	5/6 died within 14-day observation period
Smyth et al. 1962									
7	Rat (NS) 6 F	1 day 1–4 hours/day	500, 1,000, 2,000, 5,650	CS	Death			500	4/6 died
Union Carbide 1958									
8	Mouse (B6C3F1) 6 M	1 day 4 hours/day	0, 126, 343, 697, 2,160	CS, GN	Death			343	100% death at 697 and 2,160 ppm
Gushow and Quast 1984									
9	Mouse (B6C3F1) 6 M	11 days 9 exposures 6 hours/day	0, 13, 40, 132	CS, GN	Death				No deaths observed
					Bd wt	132			
					Resp		13		Decreased thickness of olfactory epithelium at 13 ppm and subacute inflammation of olfactory epithelium at ≥40 ppm
					Cardio	132			
					Gastro	132			
					Hemato	132			

Table 2-1. Levels of Significant Exposure to 1,2,3-Trichloropropane – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
					Musc/skel	132			
					Hepatic	40	132		Hepatocellular vacuolization
					Renal	132			
Miller et al. 1986a									
10	Mouse (B6C3F1) 5 M, 5 F	11 days 9 exposures 6 hours/day	0, 1, 3, 10	HP, OW, GN, BW	Resp	3	10		Nasal olfactory inflammation
Miller et al. 1986b									
INTERMEDIATE EXPOSURE									
11	Rat (CD) 5 M, 5 F	4 weeks 5 days/week 6 hours/day	0, 95, 297, 579	BW, OW, GN, CS	Death			579	3/10 rats died
					Bd wt	297			Decreased weight gain
					Resp	597			
					Hepatic		95		Increased liver weight
					Renal	579			
					Immuno		579		Decreased spleen weight
					Neuro	579			No histological alterations
					Repro	579			No histological alterations
Johannsen et al. 1988									
12	Rat (CD) 15 M, 15 F	13 weeks 5 days/week 6 hours/day	0, 0.5, 1.54, 4.5, 15, 49	OW, GN, HP, BC, UR, CS	Resp	1.54	4.5		Peribronchial hyperplasia
					Cardio	49			
					Gastro	49			
					Hemato		4.5F		Extramedullary hematopoiesis in spleen
					Musc/skel	49			
					Hepatic	1.54M	4.5M		Midzonal hepatocellular hypertrophy
					Renal	49			
					Ocular	4.5	15		Excessive lacrimation
Johannsen et al. 1988									

Table 2-1. Levels of Significant Exposure to 1,2,3-Trichloropropane – Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
13	Rat (CD) 10 M, 20 F	10 weeks premating period, 30–40-day mating period, and GDs 0–14 5 days/week 6 hours/day	0, 0.49, 1.47, 4.5, 15	OW, CS, OF, GN, HP, DX	Repro	15			
Johannsen et al. 1988									

[a]The number corresponds to entries in Figure 2-2.
[b]Used to derive an acute inhalation Minimal Risk Level (MRL) of 0.001 ppm; based on a NOAEL of 1 ppm, adjusted to continuous duration exposure and converted to a human equivalent concentration ($NOAEL_{HEC}$) of 0.03 ppm, and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments, and 10 for human variability).

BC = blood chemistry; Bd Wt or BW = body weight; BI = biochemical changes; Cardio = cardiovascular; CS = clinical signs; DX = developmental toxicity; Endocr = endocrine; F = female(s); Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; Hemato = hematological; HP = histopathology; Immuno = immunological; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OW = organ weight; Resp = respiratory; UR = urinalysis

Highlighted rows indicate MRL principal study.

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

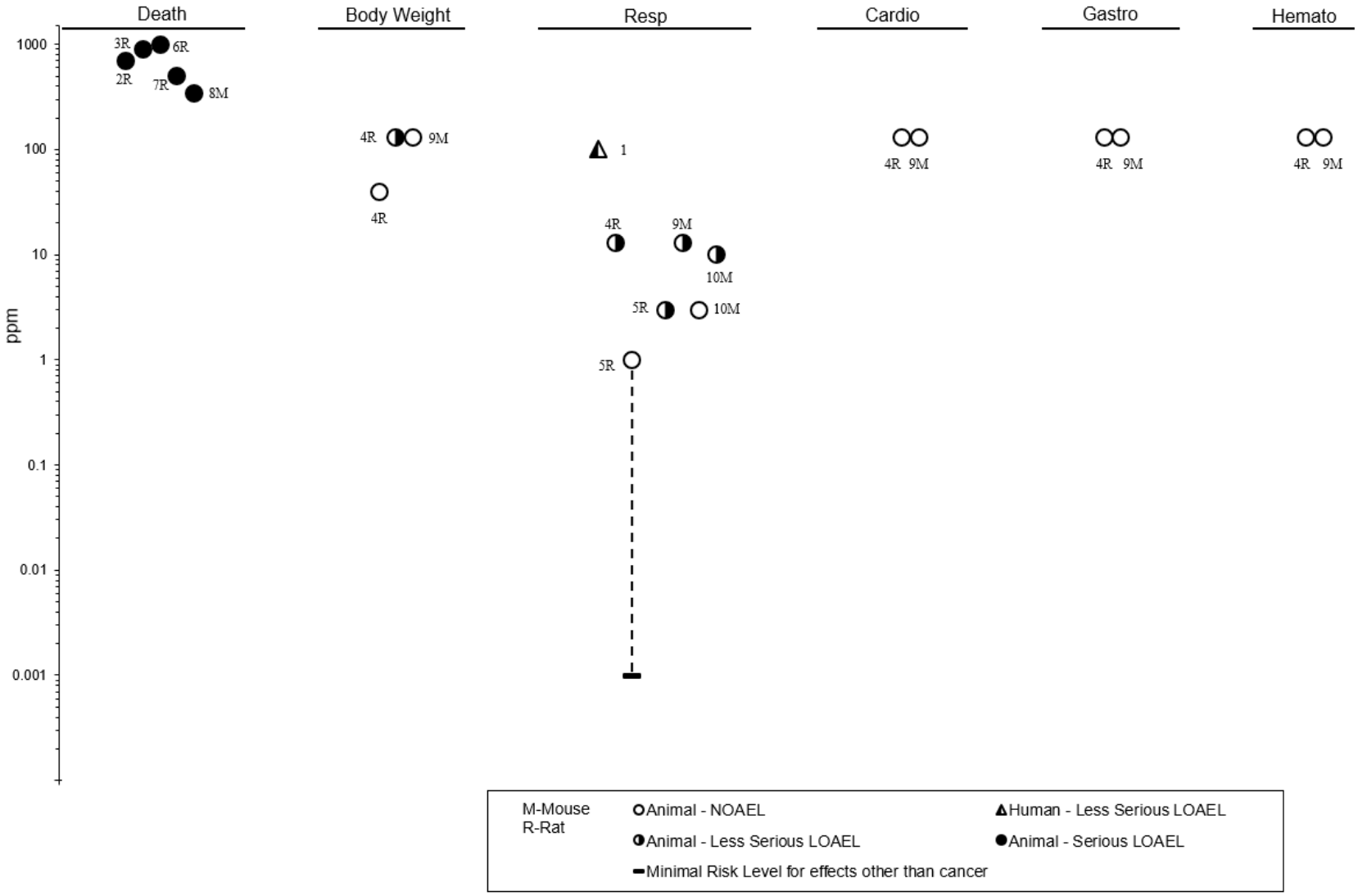


Figure 2-2. Levels of Significant Exposure to 1,2,3-Trichloropropane – Inhalation
Acute (≤14 days)

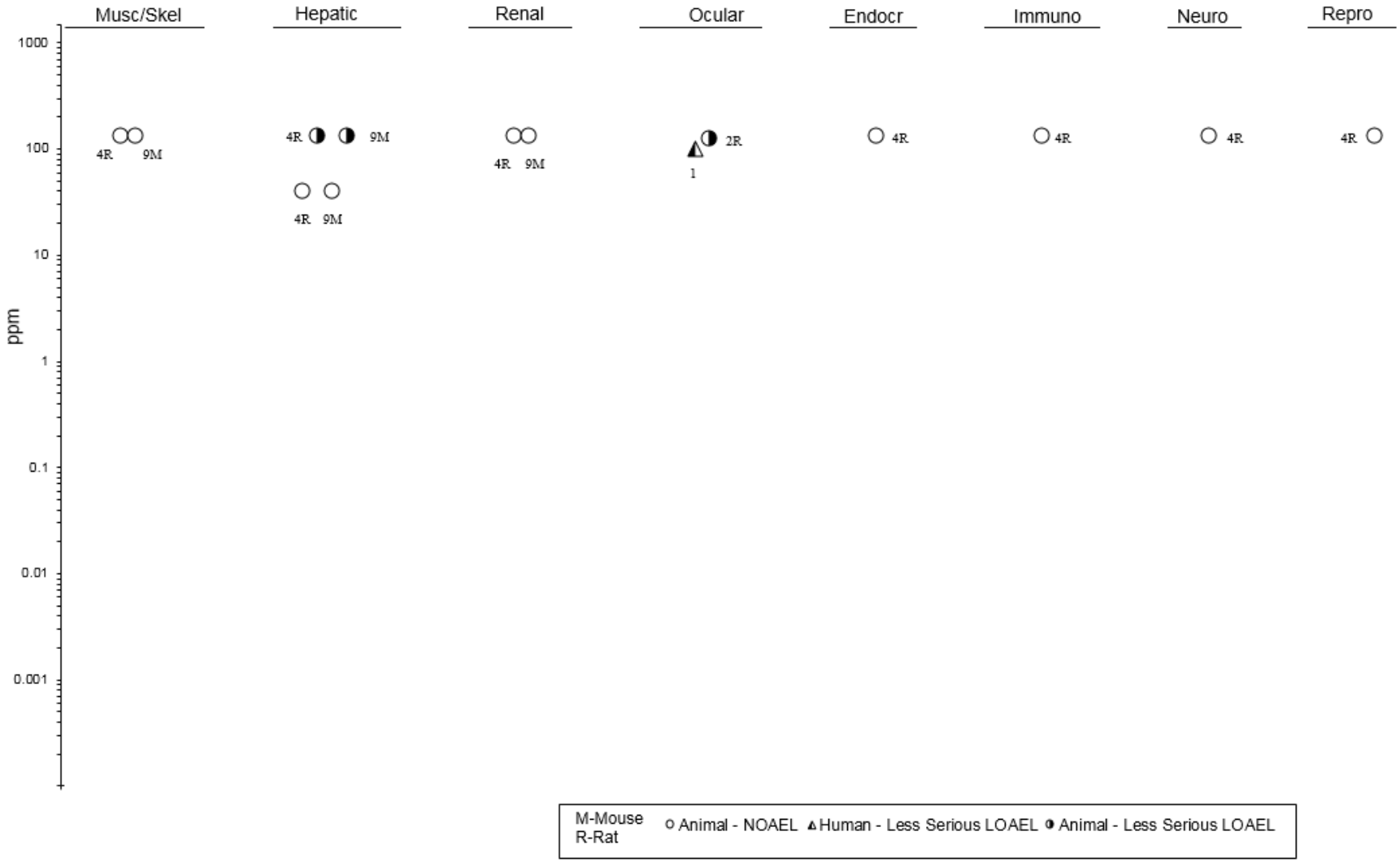


Figure 2-2. Levels of Significant Exposure to 1,2,3-Trichloropropane – Inhalation
Intermediate (15-364 days)

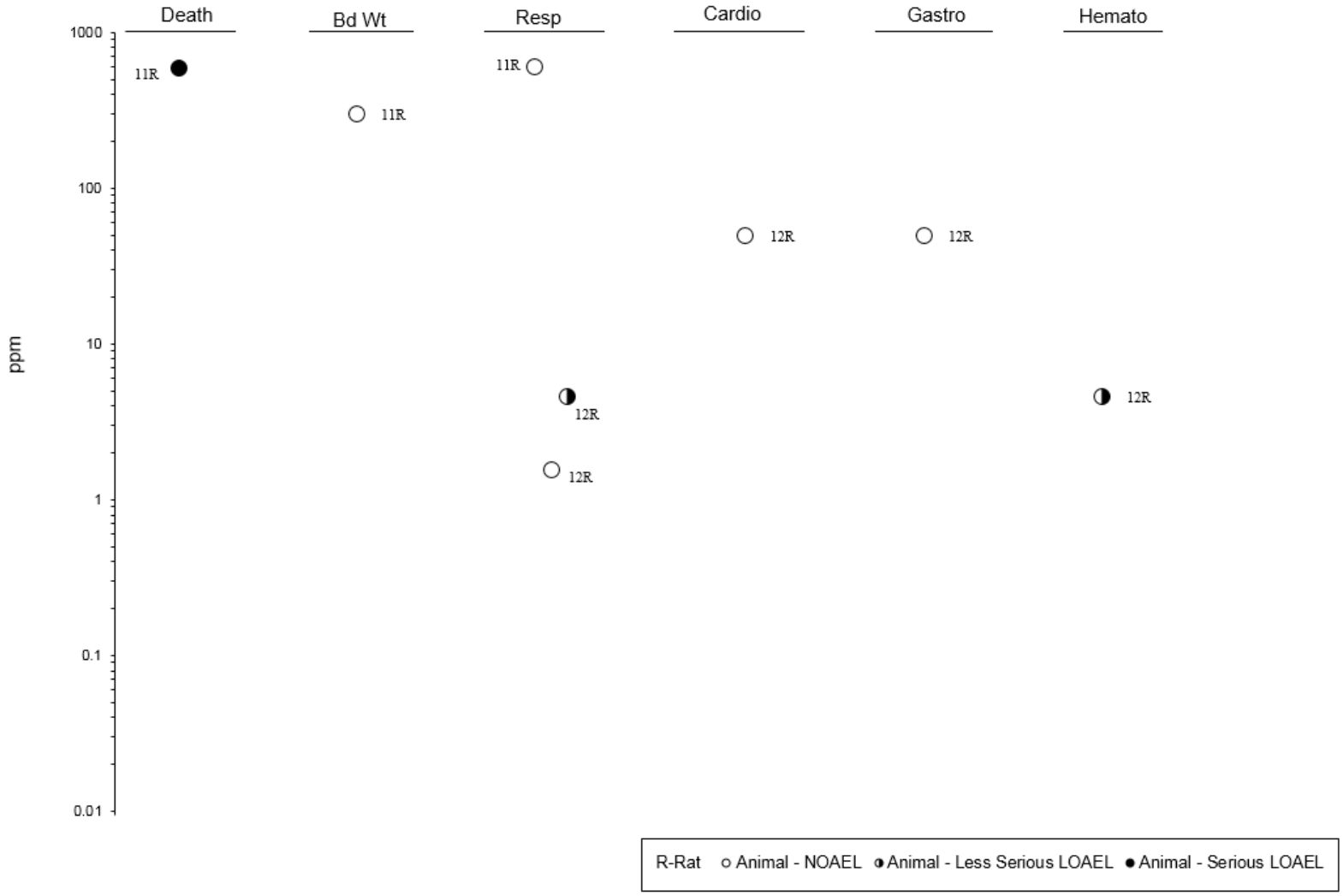


Figure 2-2. Levels of Significant Exposure to 1,2,3-Trichloropropane – Inhalation
Intermediate (15-364 days)

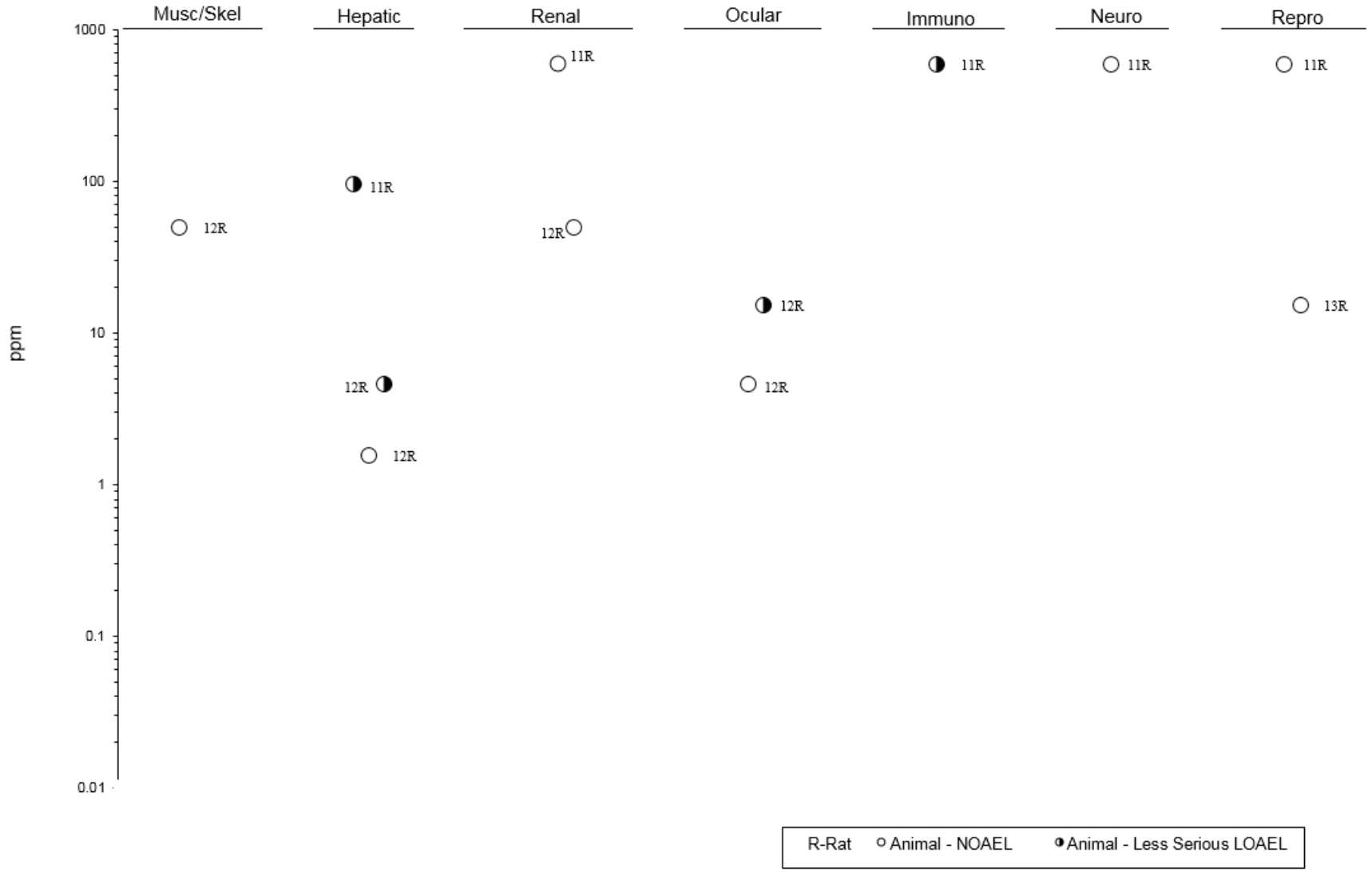


Table 2-2. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
ACUTE EXPOSURE									
1	Rat (Sprague-Dawley) 5 M, 5 F	1 time (G)	78, 139, 250, 445, 778, 1,390, 2,500	GN, CS	Death			150	LD_{50}
Albert 1982									
2	Rat (Wistar) 10 M	14 days 1 time/day (GO)	0, 15, 60	HP	Bd Wt	60			
					Renal	60			
					Repro	60			No histological alterations in male reproductive tissues
Dix 1979									
3	Rat (Sprague-Dawley) 10 M, 10 F	10 days (GO)	0, 1.5, 7.4, 29.5, 118	BW, OW, HP	Bd wt	29.5	118		22–25% decrease body weight gain
					Cardio	29.5	118		Heart inflammation, degeneration, and necrosis
					Hepatic	7.4	29.5		Increased relative liver weight
					Immuno	29.5	118		Diffuse thymic atrophy
Merrick et al. 1991									
4	Rat (F344) 20 M, 20 F	2 weeks 5 days/week (GO)	0, 8, 16, 32, 63, 125, 250	GN, CS, HP	Death			250	100% mortality
					Resp		250		Nasal necrosis
					Hepatic			250	Necrosis
					Renal			250	Necrosis
NTP 1993									
5	Rat (NS) 15 M	5 days 1 time/day (GO)	0, 80	HP, OF, FX	Repro	80			No evidence of dominant lethality or histological alterations in testes
Saito-Suzuki et al. 1982									

Table 2-2. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
6	Rat (Carworth-Wistar) 5 M	1 time (G)		CS	Death			444	LD_{50}
Smyth et al. 1962									
7	Mice (Swiss) 8 M, 8 F	14 days (GO)	0, 12.5, 25.0, 50.0, 100.0, 200.0	CS, BW	Bd wt	200			
NTP 1990									
INTERMEDIATE EXPOSURE									
8	Rat (Sprague-Dawley) 10 M, 10 F	90 days (GO)	0, 1.5, 7.4, 14.7, 58.9	BW, OW, HP	Bd wt	14.7	58.9		14–20% decrease in body weight gain
					Cardio	14.7	58.9		Heart inflammation, degeneration, and necrosis
					Hepatic	7.4	14.7		Increased relative liver weight at ≥14.7 mg/kg/day; bile duct hyperplasia at 58.9 mg/kg/day
					Immuno	14.7	58.9		Plasma cell hyperplasia in mandibular lymph nodes
Merrick et al. 1991									
9	Rat (F344) 20 M, 20 F	17 weeks 5 days/week (GO)	0, 8, 16, 32, 63, 125, 250	OW, GN, HP, BC, FI	Death			125	One male and five females died
					Bd Wt	32 M	63 M		11 and 21% decreases in body weight gain in males at 63 and 125 mg/kg; 24% decrease in females at 125 mg/kg
					Resp	63	125		Necrosis in nasal turbinates
					Cardio	125			
					Gastro	125			

Table 2-2. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
					Hemato		8[b] F		Decreases in hematocrit, and erythrocyte levels after 8 weeks ($BMDL_{1SD}$=4.03 mg/kg for hematocrit changes)
					Musc/skel	125			
					Hepatic	8 F	16 F		Increases in liver weight in females at ≥16 mg/kg; hepatocellular necrosis and hemorrhage and bile duct hyperplasia in females at ≥125 mg/kg
					Renal	16 M	32 M		Increases in absolute and relative kidney weights in males at ≥32 mg/kg; Regenerative hyperplasia after 8 weeks of exposure at ≥63 mg/kg
					Endocr	125			
NTP 1993									
10	Rat (Sprague-Dawley) 10 M,10 F	13 weeks 7 days/week (W)	M: 0, 0.17, 1.7, 17, 113; F: 0, 0.26, 2.6, 17.6, 149	OW, BC, GN, HP, BI, WI	Death				No deaths were observed
					Bd Wt	17	113		Reduced body weight gain
					Cardio	149			
					Hemato	149			
					Hepatic	17 M	113 M		Anisokaryosis, accentuated zonation and fatty vacuolation
					Hepatic	17.6 F	149 F		Biliary hyperplasia in females only

Table 2-2. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
					Renal	17	113		Eosinophilic inclusions, pyknosis, nuclear displacement, fine glomerular adhesions, interstitial reactions, and histologic proteinuria
					Endocr	17	113		Angular collapse of some follicles, reduced colloid density, increased epithelial height in thyroid
Villeneuve et al. 1985									
11	Mouse (B6C3F1) 20 M, 20 F	17 weeks 5 days/week (GO)	0, 8, 16, 32, 63, 125, 250	HP, OW, BC, BI, GN, OF, FI	Death			250	Majority of deaths occurred by week 2 in females and week 4 in males
					Bd Wt	250			
					Resp	32 F	63 F		Regeneration of bronchiolar epithelium in the lungs of males at ≥125 mg/kg and females at ≥63 mg/kg
					Cardio	250			
					Gastro	32 F	63 F		Hyperkeratosis and acanthosis of forestomach
					Hemato	250			
					Musc/skel	250			
					Hepatic	63	125		Increased liver weights at ≥125 mg/kg; focal hepatocellular necrosis at 250 mg/kg
					Renal	125		250	Multifocal tubular necrosis in animals dying early
					Endocr	125			
NTP 1993									

Table 2-2. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
12	Mice (Swiss) 20 M, 20 F	98 days (GO)	0, 30.0, 60.0, 120.0	CS, BW, FX	Repro	30	60		Decreased number of live pups in 5th litter and decreased fertility; at 120 mg/kg/day: decreased number of litters starting at the 3rd breeding, increased days to litter in the 4th and 5th litters, and decreased number of live pups per litter in 2–5 litters
					Repro	120 M			No alterations in epididymal sperm motility, count, or morphology
					Repro		120 F		Ovarian amyloidosis; no alterations in average estrous cycle length
NTP 1990									
13	Mice (Swiss) 20 M, 20 F	Prenatal exposure, post weaning, mating, and gestation exposure	0, 30.0, 60.0, 120.0	CS, BW, FX	Develop	60	120		Decreases in mating, fertility, and pregnancy indices.
NTP 1990									

Table 2-2. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
CHRONIC EXPOSURE									
14	Rat (F344/N) 60 M, 60 F	2 years 5 days/week (GO)	0, 3, 10, 30 mg/kg	CS, BW, HE, BC, OW, HP	Death			10	Decreased survival
					Bd wt	10 F	30 F		15% decrease in body weight gain in females
					Resp	30			
					Cardio	30			
					Gastro	3	10		Hyperkeratosis of esophagus and acute inflammation of tongue in females at ≥10 mg/kg and males at 30 mg/kg
					Hemato	3	10		Hematopoietic cell proliferation in spleen at ≥10 mg/kg; decreased hemoglobin, increased leukocytes, increased segmented neutrophils (measured after 15 months) at 30 mg/kg
					Musc/skel	30			
					Hepatic	3 M[c]	10 M		Bile duct hyperplasia in males at 10 mg/kg at 15 months (at 30 mg/kg after 2 years); increased liver weight at ≥10 mg/kg ($BMDL_{10}$=1.94 mg/kg)
					Renal		3 M		Increased absolute kidney weight at ≥3 mg/kg; renal tubular hyperplasia at ≥10 mg/kg (males only) and increased severity of nephropathy (males only); renal tubular hyperplasia in females at 30 mg/kg

Table 2-2. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
					Endocr		3		Focal hyperplasia of pancreatic acini
					Repro	10	30		Interstitial cell hyperplasia in testes
					Cancer			3	CEL: squamous cell papillomas or carcinomas in forestomach and adenomas of the pancreas; at ≥10 mg/kg: squamous cell papillomas or carcinomas in oral mucosa, adenoma in renal tubules, adenoma or carcinoma of the clitoral gland, and adenocarcinoma of the mammary gland (females only); at 30 mg/kg: adenoma or carcinoma in preputial gland, carcinoma in Zymbal's gland (females only)
NTP 1993									

Table 2-2. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
15	Mouse (B6C3F1) 60 M, 60 F	2 years 5 days/week (GO)	0, 6, 20, 60 mg/kg	CS, BW, HE, SC, OW, HP	Death			6	Decreased survival
					Bd wt	20	60		12–18% decrease in body weight gain
					Resp	20	60		Bronchiole hyperplasia
					Cardio	60			
					Gastro		6		Squamous hyperplasia in forestomach in females
					Hemato		6		Hematopoietic cell proliferation in spleen at ≥6 mg/kg; decreased erythrocyte, hematocrit and hemoglobin and increased leukocyte and segmented neutrophil counts at 60 mg/kg
					Musc/skel	60			
					Hepatic	20	60		Hepatocellular necrosis and increases in relative liver weight
					Renal	60			
					Ocular	60			No histological alterations were observed in the eye
					Endocr	60			
					Repro	60			No histological alterations

Table 2-2. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
					Cancer			6	CEL 6 mg/kg: squamous cell papilloma or carcinoma in forestomach, hepatocellular adenoma or carcinoma in males; 20 mg/kg: harderian gland adenoma in males; 60 mg/kg: squamous cell papilloma or carcinoma in oral mucosa in females, harderian gland adenoma in females; uterine stromal polyps and endometrial adenoma or adenocarcinoma

NTP 1993

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[b]Used to derive an intermediate oral Minimal Risk Level (MRL) of 0.03 mg/kg/day based on $BMDL_{1SD}$, adjusted to continuous duration exposure ($BMDL_{ADJ}$ of 2.9 mg/kg/day), and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[c]Used to derive a chronic oral MRL of 0.01 mg/kg/day based on a $BMDL_{10}$ of 1.94 mg/kg, adjusted to continuous duration exposure ($BMDL_{ADJ}$ of 1.38 mg/kg/day, and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Bd Wt = body weight; BI = biochemical changes; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Endocr = endocrine; F = female(s); FI = food intake; FX = fetal toxicity; (G) = gavage, not specified; GN = gross necropsy; (GO) = gavage in oil vehicle; Gastro = gastrointestinal; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LD_{50} = lethal dose; 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; No = number; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OW= organ weight; Repro = reproductive; Resp = respiratory; (W) = drinking water; WI = water intake

Highlighted rows indicate MRL principal study.

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

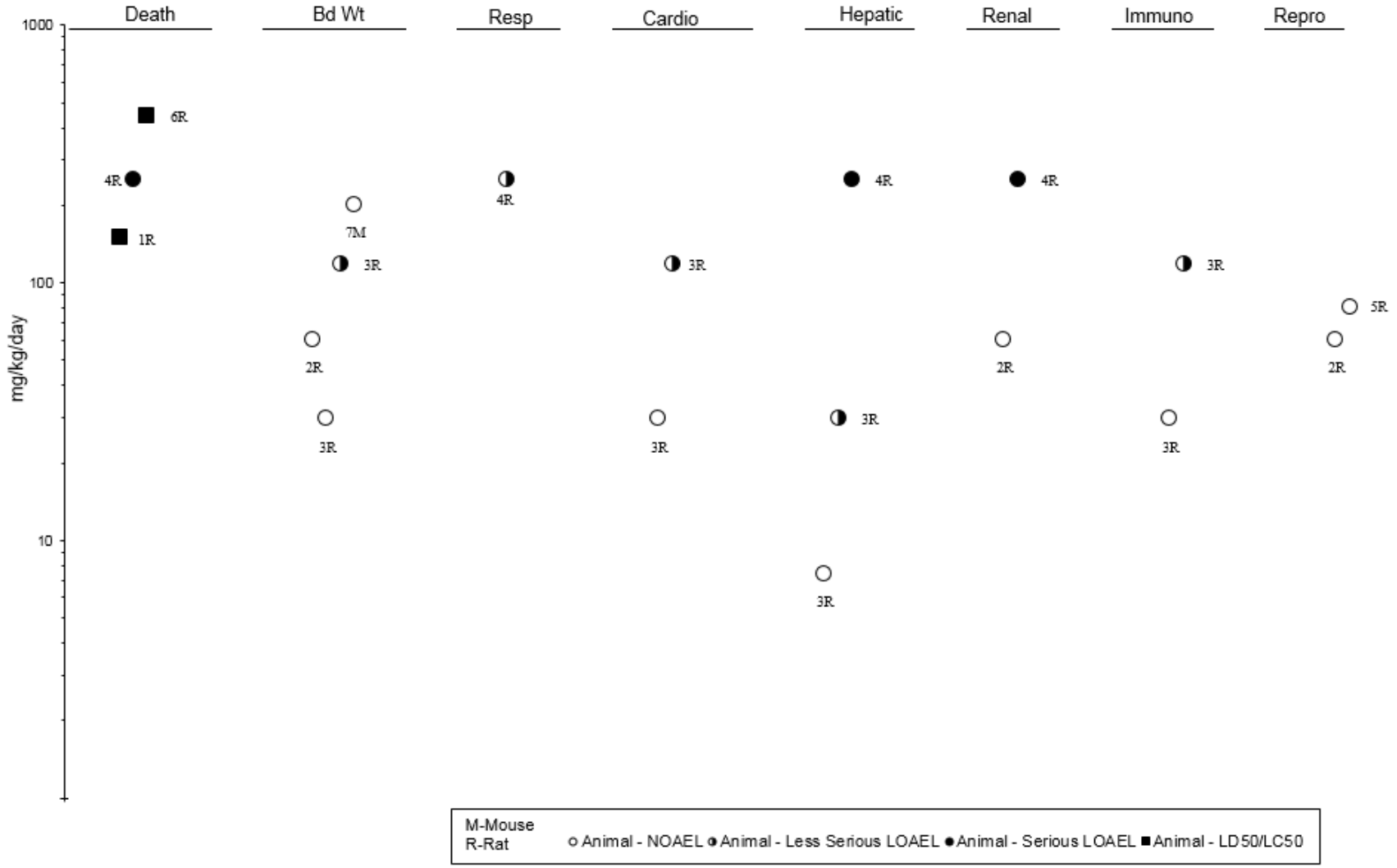


Figure 2-3. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral
Intermediate (15-364 days)

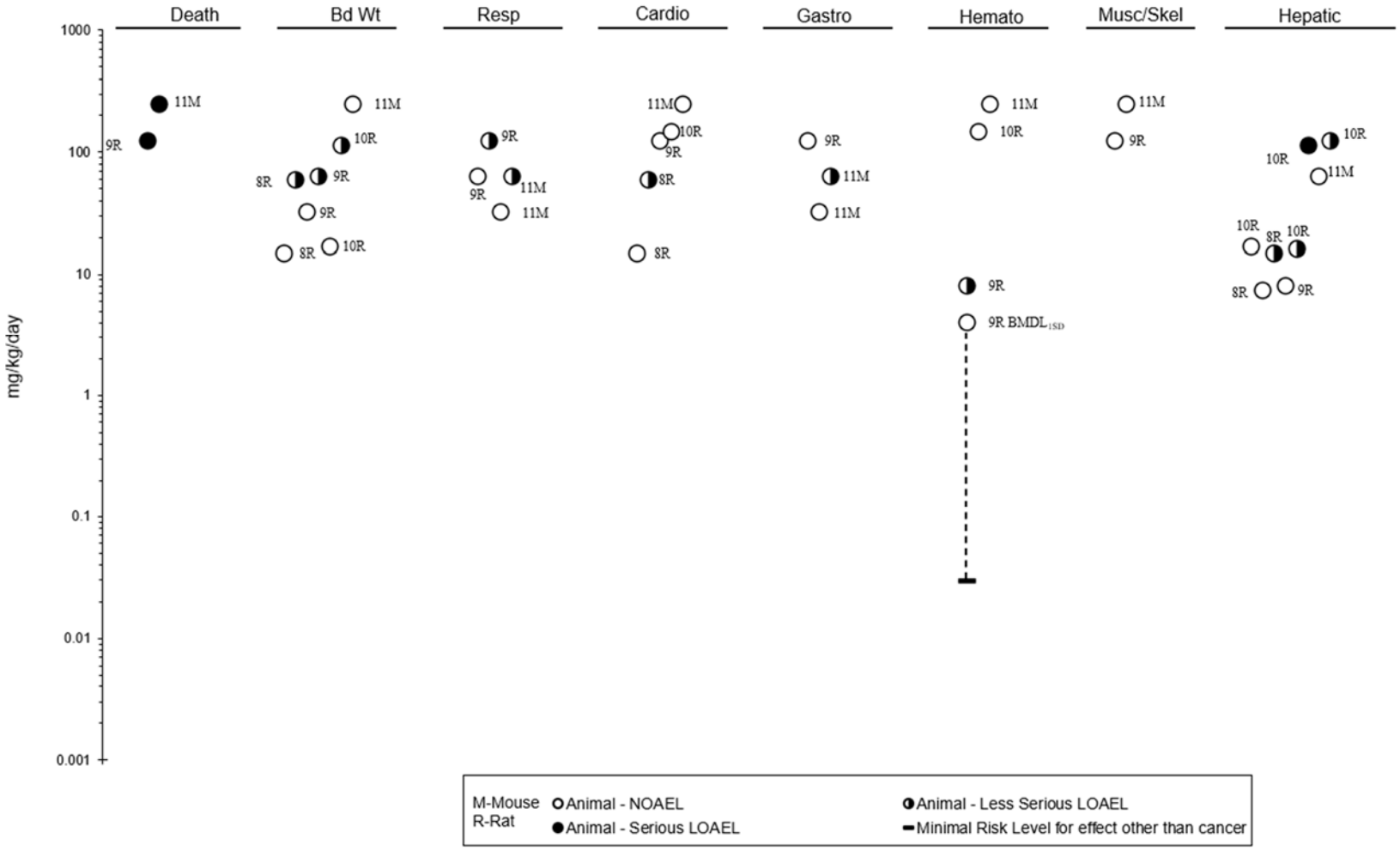


Figure 2-3. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral
Intermediate (15-364 days)

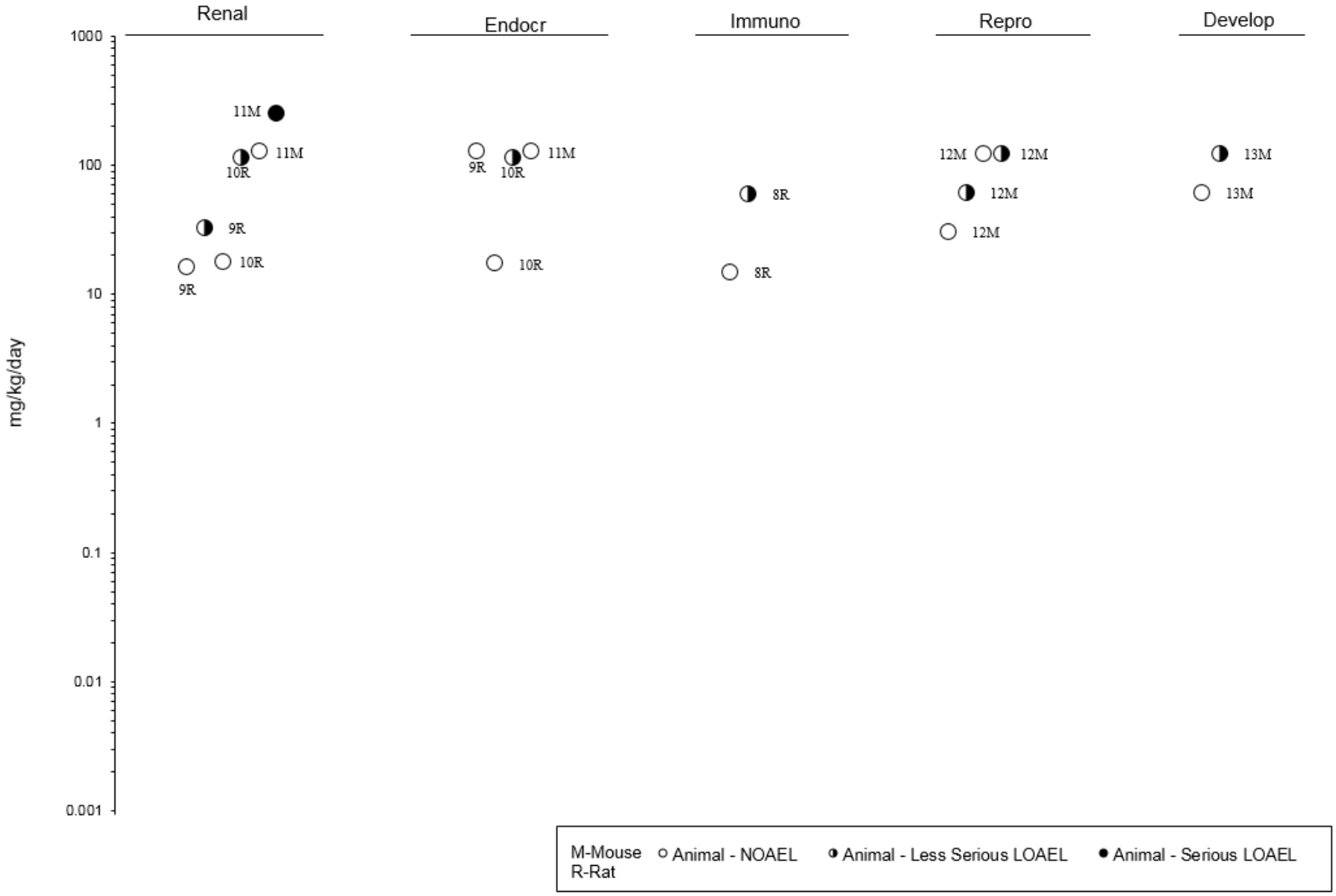


Figure 2-3. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral
Chronic (≥365 days)

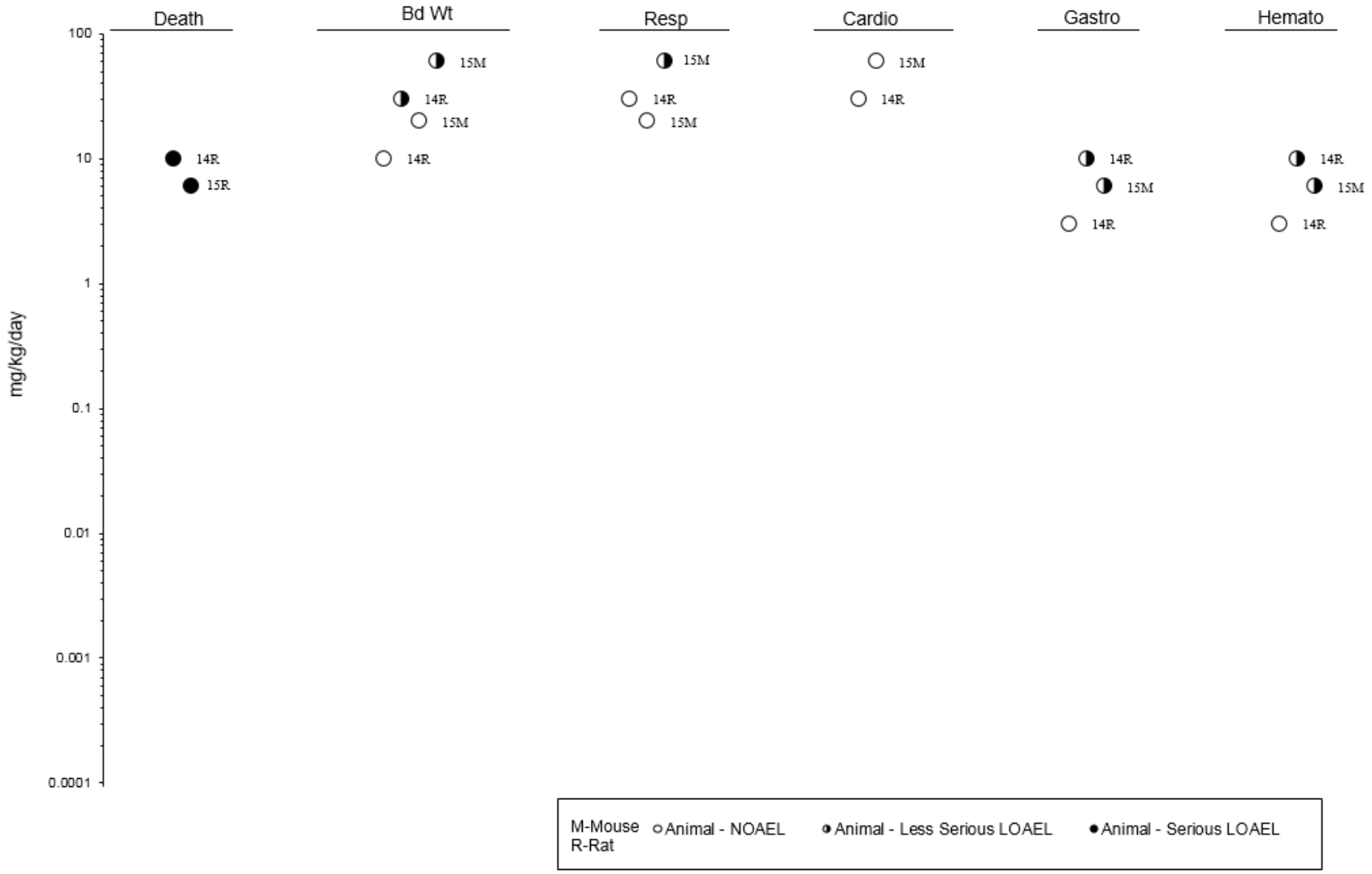


Figure 2-3. Levels of Significant Exposure to 1,2,3-Trichloropropane – Oral
Chronic (≥365 days)

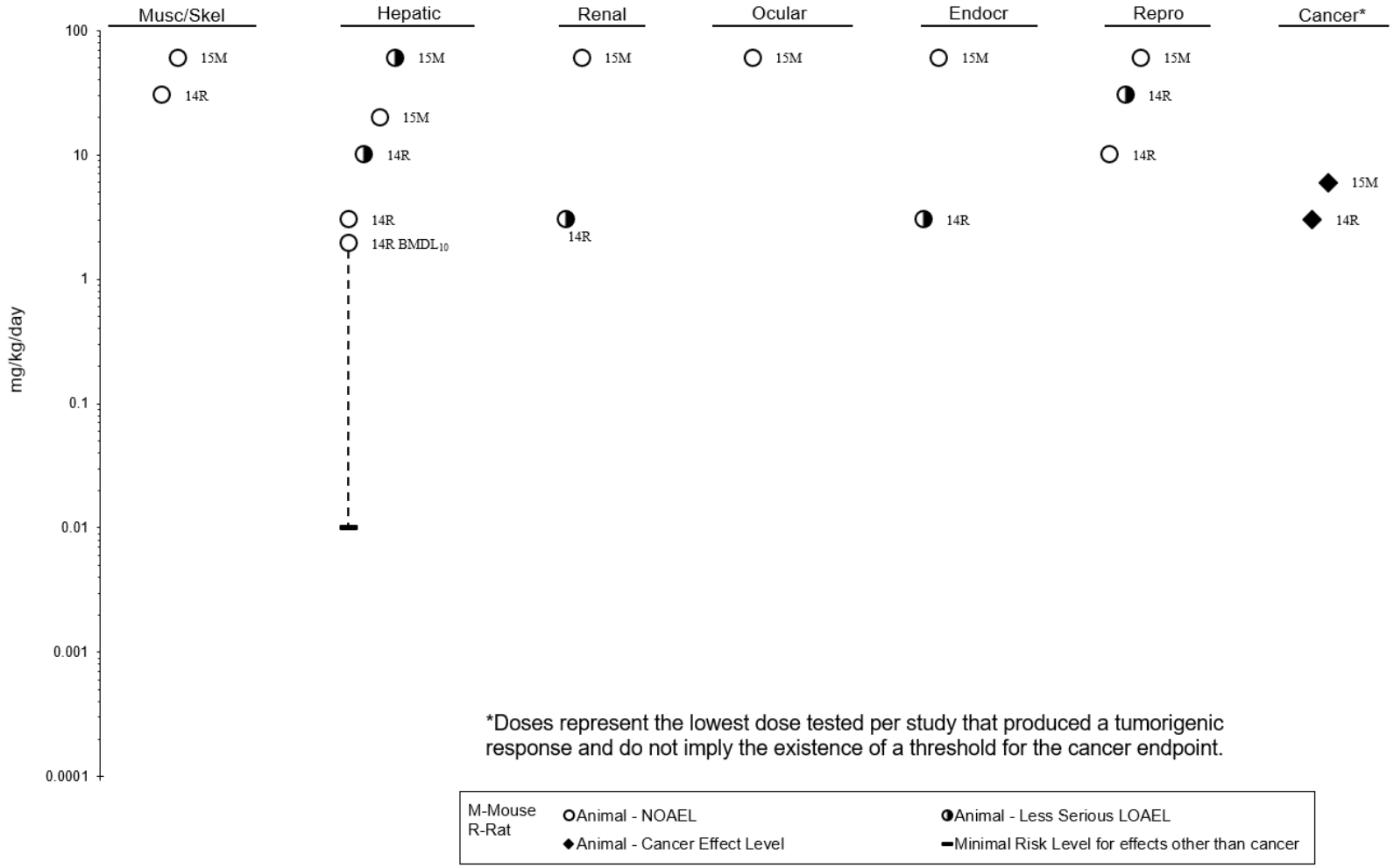


Table 2-3. Levels of Significant Exposure to 1,2,3-Trichloropropane – Dermal

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effect
ACUTE EXPOSURE								
Rat 4 M, 4 F	24 hours	278, 556, 695, 1,112, 1,390 mg/kg	CS	Death			836 mg/kg	LD_{50}
Clark 1977								
Rabbit (New Zealand white) 6 M,6 F	24 hours	250, 445, 723, 1,084, 1,390, 2,500, 4,450 mg/kg	CS	Death			250 mg/kg	2/6 males died
				Resp			250 mg/kg	Lung discoloration
				Gastro			250 mg/kg	Stomach ulceration
				Hepatic			250 mg/kg	Liver discoloration
				Renal			250 mg/kg	Discoloration of kidneys and bladder contents
Albert 1982								
Rabbit (New Zealand white) 6 M,6 F	24 hours	278 mg/kg	CS	Dermal		278 mg/kg		Skin irritation
Albert 1982								
Rabbit (New Zealand white) 6 M,3 F	1 time	0.1 mL	CS	Ocular		0.1 mL		Eye irritation
Albert 1982								
Rabbit (NS) 4M,4F	24 hours	0, 174 mg/cm^2	GN, CS	Dermal		174 mg/cm^2		Severe skin irritation
Clark 1977								
Rabbit (NS) 4 NS	1 time	NS	CS	Ocular		0.1 mL		Eye irritation
Clark 1977								

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

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effect
Rabbit (NS) 7 NS	10 times in 15 minutes	2 mL	GN, CS	Dermal		2 mL		Intense skin irritation, subdermal bleeding
McOmie and Barnes 1949								
Rabbit (NS) 4 M	1 day 24 hours/day	Log series	CS	Death			2,458 mg/kg	LD_{50}
Smyth et al. 1962								
INTERMEDIATE EXPOSURE								
Guinea pig (Duncan-Hartley) 5 M, 5 F	3 weeks 1 days/week 6 hours/day	0, 1.83	CS	Dermal	0.51 mL[a]			
Albert 1982								

[a]Challenge dose applied to sensitized and virgin skin for 6 hours 14 days after the last sensitizing dose. Both sensitizing and challenge doses were covered.

CS = clinical signs; F = female(s); GN = gross necropsy; LOAEL = lowest-observed-adverse-effect level; LD_{50} = lethal dose, 50% kill; M = male(s); NOAEL = no-observed-adverse-effect level; NS = not specified

2.2 DEATH

No studies were located regarding death in humans after exposure to 1,2,3-trichloropropane.

Inhalation exposure to 1,2,3-trichloropropane for 4–6 hours caused death in mice at concentrations as low as 343 ppm (Gushow and Quast 1984) and rats at concentrations as low as 500 ppm (Gushow and Quast 1984; Johannsen et al. 1988; Smyth et al. 1962; Union Carbide 1958). In a repeated-exposure studies, no deaths were observed in rats or mice exposed to concentrations as high as 132 ppm (Miller et al. 1986a) for 11 days or in rats exposed to 49 ppm for 13 weeks (Johannsen et al. 1988). The cause of death in the acute studies is unclear, but signs suggestive of central nervous system (CNS) impairment (e.g., incoordination and convulsions) have been observed prior to death in both species.

Oral LD_{50} values of 150 mg/kg (Albert 1982) and 444 mg/kg (Smyth et al. 1962) have been determined for rats. Variations in LD_{50} values are apparent, which could be due to differences in animal strain, sex, fed/fasted state, or compound purity. The cause of death is unclear, but signs suggestive of CNS impairment (e.g., piloerection, salivation, ataxia, coma) prior to death and hemorrhagic damage in visceral tissues (e.g., liver, kidney) were observed. Repeated gavage administration (5 days/week) of 1,2,3-trichloropropane caused death due to liver and kidney toxicity in 15% of female rats by the 13^{th} week at a dose of 125 mg/kg, in 100% of female rats by week 2 at 250 mg/kg, and in 80% of female mice by week 4 at 250 mg/kg (NTP 1993). In another study, doses as high as 149 mg/kg/day were not lethal in rats when administered in drinking water for the 13 weeks (Villeneuve et al. 1985). Although absorption of 1,2,3-trichloropropane from drinking water could have been decreased due to use of a solubilizer, this suggests that 1,2,3-trichloropropane may be less toxic when ingested gradually throughout the day than when administered as a bolus. In chronic studies, decreases in survival were observed in rats and mice administered via gavage 10 or 6 mg/kg, respectively, 5 days/week for 2 years (NTP 1993); the early deaths were likely secondary to neoplastic lesions.

Single dermal doses as low as 250 mg/kg caused death in rabbits (Albert 1982). Dermal LD_{50} values of 836 mg/kg in rats (Clark 1977) and 2,458 mg/kg in rabbits (Smyth et al. 1962) have been identified. The treated skin of the animals in these studies was covered with an impervious barrier for 24 hours to prevent evaporation of the volatile compound. The cause of death is unclear, but symptoms suggestive of CNS impairment (e.g., ataxia, tremors, coma) and internal hemorrhage were observed.

2.3 BODY WEIGHT

Intermittent exposure to 1,2,3-trichloropropane concentrations as high as 132 ppm for 11 days did not adversely affect body weight gain in rats or mice (Miller et al. 1986a). Body weight gain was decreased in rats that were intermittently exposed to lethal concentrations (≥297 ppm) of 1,2,3-trichloropropane for 4 weeks and concentrations as low as 15 ppm 1,2,3-trichloropropane for 13 weeks (Johannsen et al. 1988). The decreased weight gain was more severe at higher concentrations and there was initial weight loss at 600 ppm in the 4-week study.

Reduced body weight gain occurred in rats treated with 1,2,3-trichloropropane by gavage at doses ≥58.9 mg/kg for acute- (Kimura et al. 2016) or intermediate-durations (Kimura et al. 2016; Merrick et al. 1991; NTP 1993; Villeneuve et al. 1985). No effect on body weight gain was observed in mice administered 250 mg/kg (5 days/week) for 17 weeks (NTP 1993). Less than 20% decreases in body weight gain were observed in rats and mice administered 30 or 60 mg/kg, respectively, 5 days/week for 2 years (NTP 1993).

2.4 RESPIRATORY

Limited information indicates that brief exposure (15 minutes) to 100 ppm 1,2,3-trichloropropane (purity unknown) can cause throat irritation in humans (Silverman et al. 1946). Repeated exposure of animals to 1,2,3-trichloropropane concentrations much lower than 100 ppm causes respiratory system effects that are indicative of irritant action. Intermittent 6-hour exposures for 11 days produced alterations in nasal tissues, particularly of the olfactory epithelium, of rats and mice (Miller et al. 1986a, 1986b). These changes included decreased thickness of the olfactory epithelium in rats and mice at 3 ppm, degeneration of the olfactory epithelium in rats at ≥13 ppm concentrations, and inflammation and decreased thickness of the olfactory epithelium in mice at 3–13 ppm with degeneration at higher concentrations. At 132 ppm, nasal submucosal fibrosis was observed in rats (Miller et al. 1986a). Intermittent exposure to ≥4.5 ppm for 13 weeks caused focal peribronchial hyperplasia in rats (Johannsen et al. 1988).

Nasal effects have also been observed in rats and mice orally administered 1,2,3-trichloropropane. These changes were produced by daily doses of 250 mg/kg (rats and mice) for 2 weeks and 125 mg/kg (rats) or 250 mg/kg (mice) for up to 17 weeks. Effects were similar in both species; these typically included inflammation, attenuation of the epithelial lining, and necrotic alterations, and principally occurred in the dorsal posterior areas of the nasal passages. The oral doses that produced the nasal alterations were in the near lethal range. Repeated daily exposure of mice to lower doses of 1,2,3-trichloropropane (as low as

63 mg/kg) by oral intubation over a period of 17 weeks or 60 mg/kg for 2 years caused regenerative changes (e.g., hyperplasia) in the bronchiolar epithelium (NTP 1993).

Lung hemorrhage and apparently related effects (e.g., discoloration of the lungs and liquid in the thoracic cavity) have been observed in rabbits exposed to lethal dermal doses of 1,2,3-trichloropropane (Albert 1982; Union Carbide 1958).

2.5 CARDIOVASCULAR

No studies were located regarding cardiovascular effects in humans after exposure to 1,2,3-trichloropropane. There were no histopathological changes in the hearts of rats and mice that were intermittently exposed to concentrations as high as 132 ppm 1,2,3-trichloropropane for 11 days (Miller et al. 1986a) or rats that were similarly exposed to up to 49 ppm 1,2,3-trichloropropane for 13 weeks (Johannsen et al. 1988).

Animal studies found that administration by gavage of 1,2,3-trichloropropane resulted in heart inflammation, degeneration, and necrosis in rats administered 118 mg/kg/day for 10 days (Merrick et al. 1991) or 58.9 mg/kg/day for 90 days (Merrick et al. 1991). In contrast, other studies have not found histological alterations in the heart of rats administered 125 mg/kg by gavage 5 days/week for 17 weeks (NTP 1993), 149 mg/kg/day by drinking water for 13 weeks (Villeneuve et al. 1985), or 30 mg/kg administered by gavage 5 days/week for 2 years (NTP 1993), or in mice administered 250 mg/kg 5 days/week for 17 weeks (NTP 1993) or 60 mg/kg 5 days/week for 2 years (NTP 1993).

2.6 GASTROINTESTINAL

No studies were located regarding gastrointestinal effects in humans after exposure to 1,2,3-trichloropropane.

There were no histopathological changes in the stomach and intestines of rats and mice that were intermittently exposed to airborne concentrations as high as 132 ppm 1,2,3-trichloropropane for 11 days (Miller et al. 1986a) or rats that were similarly exposed to up to 49 ppm 1,2,3-trichloropropane for 13 weeks (Johannsen et al. 1988).

In mice administered 63 mg/kg 1,2,3-trichloropropane for 17 weeks (5 days/week), hyperkeratosis and acanthosis of the forestomach were observed (NTP 1993). Chronic exposure also resulted in

gastrointestinal lesions. Hyperkeratosis of the esophagus and acute inflammation of the tongue were observed in female rats administered via gavage (5 days/week) 10 mg/kg and in male rats administered 30 mg/kg (NTP 1993). In female mice, squamous hyperplasia was observed in the forestomach following 5 days/week administration of 6 mg/kg (NTP 1993). Ulceration of the stomach wall was observed in rabbits dermally exposed to lethal dermal doses of 1,2,3-trichloropropane (Albert 1982).

2.7 HEMATOLOGICAL

No studies were located regarding hematological effects in humans after exposure to 1,2,3-trichloropropane. Hematological evaluations were normal in rats and mice that were intermittently exposed to inhalation concentrations as high as 132 ppm 1,2,3-trichloropropane for 11 days (Miller et al. 1986a). Hematological evaluations of rats that were similarly exposed to up to 49 ppm 1,2,3-trichloropropane for 13 weeks also were normal, but splenic extramedullary hematopoiesis was increased at ≥4.5 ppm (Johannsen et al. 1988). Although increased splenic hematopoiesis was observed, other hematology parameters were unremarkable. Spleen weights were decreased in rats that were intermittently exposed to 579 ppm 1,2,3-trichloropropane for 4 weeks, but the hematological significance of this effect cannot be determined because evaluation of hematology and histology was not performed (Johannsen et al. 1988).

An oral study found evidence of anemia, indicated by decreased hematocrit, hemoglobin, and erythrocyte counts, in rats that were administered 1,2,3-trichloropropane by gavage (5 days/week) at doses as low as 16 mg/kg over a period of 17 weeks (NTP 1993). Decreased hematocrit and erythrocyte levels were also observed in female rats administered ≥8 mg/kg for 8 weeks. The anemia was mild at the lower doses and appears to be nonregenerative and associated with depressed erythropoiesis. 1,2,3-Trichloropropane did not produce significant hematological alterations in rats when administered in the drinking water at doses as high as 149 mg/kg/day for 13 weeks (Villeneuve et al. 1985) or in mice administered up to 250 mg/kg via gavage (5 days/week) for 17 weeks (NTP 1993). Chronic administration of 10 mg/kg in rats and 6 mg/kg in mice resulted in hematopoietic cell proliferation in the spleen (NTP 1993); higher doses (30 and 60 mg/kg in rats and mice, respectively) resulted in decreased erythrocyte, hematocrit, and hemoglobin concentrations. The investigators noted that the hematological effects were likely due to depressed erythropoiesis or from blood loss associated with forestomach and/or oral mucosal neoplasms (NTP 1993). The NTP study also reported that increases in leukocyte levels, particularly segmented neutrophils, in the rats and mice were likely due to neoplasm-induced inflammation.

2.8 MUSCULOSKELETAL

No studies were located regarding musculoskeletal effects in humans after exposure to 1,2,3-trichloropropane. There were no histopathological changes in the skeletal muscle or bone of rats and mice intermittently exposed via inhalation to concentrations as high as 132 ppm 1,2,3-trichloropropane for 11 days (Miller et al. 1986a) or rats that were similarly exposed to up to 49 ppm 1,2,3-trichloropropane for 13 weeks (Johannsen et al. 1988). Similarly, there were no pathological effects in bone or skeletal muscle of rats and mice that were administered via gavage 1,2,3-trichloropropane at doses as high as 125 and 250 mg/kg, respectively, over a period of 17 weeks (NTP 1993) or 30 or 60 mg/kg, respectively, for 2 years (NTP 1993).

2.9 HEPATIC

Data on the hepatic toxicity of 1,2,3-trichloropropane are limited to a case report of a man consuming 10–15 mL of an unknown liquid; 1,2,3-trichloropropane exposure was suspected based on elevated levels of 1,2,3-trichloropropane in the blood (Han 2010). Rapid progressive deterioration of liver function was noted 2 days post-exposure.

Acute- and intermediate-duration inhalation exposure to 1,2,3-trichloropropane resulted in histological alterations in the livers of rats and mice. Exposure to 132 ppm for 11 days resulted in very slight hepatocellular necrosis in rats and hepatocellular vacuolization in mice (Miller et al. 1986a). Following intermediate-duration inhalation exposure, mild hepatocellular hypertrophy was observed in rats exposed to ≥4.5 ppm in a 13-week study (Johannsen et al. 1988).

Oral studies clearly support the identification of the liver as a target of 1,2,3-trichloropropane toxicity. The most sensitive effect appears to be decreases in liver weight, which have been observed in acute studies at ≥29.5 mg/kg/day (Merrick et al. 1991), intermediate-duration studies at ≥14.7 mg/kg/day (Merrick et al. 1991; NTP 1993), and chronic studies at ≥10 mg/kg (NTP 1993). The NTP (1993) 17-week study also found decreases in pseudocholinesterase at low doses (≥8 mg/kg) in rats; the investigators noted that the decrease in pseudocholinesterase may be due to a hepatocellular damage-induced decrease in synthesis (NTP 1993). Increases in serum total bilirubin and alanine aminotransferase (ALT) have also been observed in rats exposed to ≥63 mg/kg (5 days/week) for 17 weeks (NTP 1993). Histological alterations have been observed following acute, intermediate, and chronic oral exposure. Gavage administration of 250 mg/kg (5 days/week) produced hepatocellular necrosis in rats and mice within 2 weeks; the liver effects were considered a contributing factor to the

early mortality (NTP 1993). Necrotic changes also occurred in the livers of rats and mice treated with daily gavage doses as low as 125 mg/kg over a period of 17 weeks (NTP 1993). Exposure to 113 or 149 mg/kg/day 1,2,3-trichloropropane administered in drinking water for 13 weeks produced mild hepatic changes (e.g., occasional fatty vacuolization and biliary hyperplasia) in rats (Villeneuve et al. 1985), suggesting that 1,2,3-trichloropropane may be less toxic when ingested gradually throughout the day than when administered as a bolus. Hepatocellular necrosis has also been observed in mice chronically administered 60 mg/kg 5 days/week for 2 years (NTP 1993). In addition to the reported hepatocellular effects, several oral studies have found bile duct hyperplasia in rats administered 58.9 mg/kg/day 1,2,3-trichloropropane for 90 days (Merrick et al. 1991), 113 mg/kg/day for 13 weeks (Villeneuve et al. 1985), or 30 mg/kg 5 days/week for 2 years (NTP 1993). Turgid and discolored livers were observed in rabbits exposed to lethal dermal doses of 1,2,3-trichloropropane (Albert 1982; Union Carbide 1958). These macroscopic alterations are consistent with oral and inhalation evidence of hepatotoxicity.

2.10 RENAL

No studies were located regarding renal effects in humans after exposure to 1,2,3-trichloropropane. Based on available data, the kidney does not appear to be a sensitive target following inhalation exposure to 1,2,3-trichloropropane. No histological alterations were observed in rats and mice exposed to 132 ppm for 2 weeks (Miller et al. 1986a) or 49 ppm for 13 weeks (Johannsen et al. 1988); increases in kidney weights were observed in the 13-week study, but this was not considered adverse in the absence of other indicators of renal toxicity.

In contrast to the inhalation studies, oral exposure studies have reported kidney toxicity. Daily gavage doses of 250 mg/kg produced serious renal toxicity (e.g., tubular nephropathy, necrosis) in rats and mice within 2 weeks (NTP 1993). The kidney damage in rats was severe enough to contribute to death. At a lower dose, regenerative hyperplasia in the outer medulla and proximal tubule karyomegaly were observed after 3 or 7 days of administration of 125 mg/kg/day 1,2,3-trichloropropane (Kimura et al. 2016). Increases in relative and absolute kidney weights have been observed at ≥32 and ≥64 mg/kg, respectively, following intermediate-duration exposure (Kimura et al. 2016; NTP 1993). Regenerative hyperplasia was observed in rats after 28 days of administration of 125 mg/kg/day (Kimura et al. 2016), 8 weeks of administration of 63 mg/kg 5 days/week (NTP 1993), and 17 weeks of exposure at 125 mg/kg (NTP 1993). Similar doses of 1,2,3-trichloropropane (113 or 149 mg/kg) administered in drinking water for 13 weeks produced mild renal changes (e.g., pyknosis, fine glomerular adhesions, and occasional histologic proteinuria) in rats (Villeneuve et al. 1985). The mild renal changes suggest that 1,2,3-tri-

chloropropane may be less toxic when ingested gradually throughout the day than when administered as a bolus. Necrotic changes occurred in the kidneys of mice treated with daily gavage doses of 250 mg/kg over a period of 17 weeks (NTP 1993). Chronic administration (5 days/week) resulted in several renal effects (NTP 1993): increases in absolute kidney weights in males at ≥3 mg/kg, increases in absolute kidney weight in females and relative kidney weights in males and females at ≥10 mg/kg, renal hyperplasia in rats at ≥10 mg/kg, and an increase in the severity of nephropathy in male rats, as compared to controls at 30 mg/kg. NTP (1993) noted that the renal hyperplasia was part of the continuum with renal adenomas; thus, this lesion could be considered precancerous. No renal effects were observed in mice chronically administered doses as high as 60 mg/kg 5 days/week (NTP 1993).

Limited information is available on the renal toxicity of 1,2,3-trichloropropane following oral administration. Discolored kidneys and hematuria were observed in rabbits exposed to lethal dermal doses of 1,2,3-trichloropropane (Albert 1982; Union Carbide 1958). These macroscopic alterations are consistent with oral and inhalation evidence of renal toxicity.

2.11 DERMAL

No studies were located regarding dermal or ocular effects in humans after exposure to 1,2,3-trichloropropane. Daily gavage administration of 1,2,3-trichloropropane at doses ≥63 mg/kg for up to 17 weeks caused alopecia but no gross eye irritation in rats (NTP 1993). Mice that were similarly treated with up to 250 mg/kg 1,2,3-trichloropropane had no macroscopic skin lesions or gross eye irritation (NTP 1993).

Dermal application of 1,2,3-trichloropropane causes severe skin irritation in rabbits. Evidence suggests that prolonged exposure (e.g., for 24 hours) or repeated daily application (e.g., for 2 weeks) may be necessary to cause irritation (Clark 1977; McOmie and Barnes 1949). The results of one study suggested that 1,2,3-trichloropropane in corn oil vehicle was a very mild skin sensitizer in guinea pigs (Clark 1977). Another study that used a less sensitive procedure found no evidence of skin sensitization by dermal exposure to undiluted 1,2,3-trichloropropane in guinea pigs (Albert 1982). This study also found that corn oil itself was a mild skin sensitizer in guinea pigs, indicating that there is a possibility that the vehicle may enhance the weak effect observed by Clark (1977).

2.12 OCULAR

Limited information indicates that brief (15-minute) exposure to 100 ppm 1,2,3-trichloropropane vapor causes eye irritation in humans (Silverman et al. 1946). A single 4-hour exposure to vapor concentrations

as low as 126 ppm 1,2,3-trichloropropane (Gushow and Quast 1984) caused eye irritation in rats and mice. Repeated intermittent exposure to vapor concentrations as low as 15 ppm for 13 weeks (Johannsen et al. 1988) caused eye irritation in rats. Ocular application of 1,2,3-trichloropropane caused eye irritation in rabbits (Albert 1982; Clark 1977).

2.13 ENDOCRINE

No studies were located regarding endocrine effects in humans after exposure to 1,2,3-trichloropropane. Two studies have reported effects in endocrine tissues in rats. A 13-week drinking water study reported histological alterations in the thyroid of rats exposed to 113 mg/kg/day (Villeneuve et al. 1985); alterations included reduced colloid density, increased epithelial height, and angular collapse of some follicles. NTP (1993) reported focal hyperplasia of pancreatic acini in rats administered ≥3 mg/kg 1,2,3-trichloropropane by gavage 5 days/week for 2 years. The endocrine system does not appear to be a sensitive target of 1,2,3-trichloropropane toxicity based on the inconsistency of affected tissues in the studies finding effects and that most studies examining the endocrine system, including a 2-week rat inhalation study identifying a NOAEL of 132 ppm (Miller et al. 1986a), 17-week gavage studies in rats and mice both identifying a NOAEL value of 125 ppm (NTP 1993), and a 2-year gavage study in mice with a NOAEL of 60 mg/kg (NTP 1993), have not found effects.

2.14 IMMUNOLOGICAL

No studies were located regarding immunological effects in humans after exposure to 1,2,3-trichloropropane. Information on the potential effect of 1,2,3-trichloropropane on immune function is limited to an *in vitro* assay that reported weak inhibition of B-cell lymphocyte mitogenesis and no inhibition of T-cell lymphocyte mitogenesis in C3H/He mouse splenic cells (Sakazaki et al. 2001).

There were no histopathological alterations in the thymus, spleen, lymphoid tissue, or bone marrow of rats and mice that were intermittently exposed to concentrations as high as 132 ppm 1,2,3-trichloropropane for 11 days (Miller et al. 1986a) or rats that were similarly exposed to up to 49 ppm for 13 weeks (Johannsen et al. 1988). Intermittent exposure to a higher (lethal) concentration (579 ppm) for 4 weeks caused decreased spleen weight in rats (Johannsen et al. 1988). Due to the lack of histological examinations and immunoassays, the immunological significance of the decreased spleen weight cannot be determined.

Merrick et al. (1991) reported diffuse thymic atrophy in rats administered 188 mg/kg/day for 10 days and plasma cell hyperplasia in the mandibular lymph nodes of rats administered 58.9 mg/kg/day for 90 days. NTP (1993) reported lymphoid depletion in the spleen and thymus of rats administered 1,2,3-trichloropropane at doses ≥63 mg/kg/day over 17 weeks and dying early (NTP 1993); the incidence of these lesions were not reported. Mice that were similarly treated with lethal doses (250 mg/kg) showed splenic lymphoid depletion with occasional lymphoid necrosis and increased thymus weight (incidences were not reported) (NTP 1993). The immunological significance of these effects are not known.

As indicated in the discussion of dermal effects (Section 2.11), one study provides limited evidence that 1,2,3-trichloropropane may be a very weak dermal sensitizer in animals (Clark 1977).

2.15 NEUROLOGICAL

There are limited data on the neurotoxicity of 1,2,3-trichloropropane in humans. Case reports describe neurological signs in individuals exposed to airborne 1,2,3-trichloropropane (Mi et al. 2013) or ingesting 1,2,3-trichloropropane (Han 2010). In both cases, exposure to 1,2,3-trichloropropane was assumed based on elevated levels in the blood; it was not known if they were exposed to other compounds. Observed signs included confusion and agitation (Han 2010), headache, and intermittent drowsiness (Mi et al. 2013).

Data on the effects of 1,2,3-trichloropropane on the nervous system is limited to studies examining histopathology; no studies tested for neurofunction. Clinical signs were observed in animals exposed to lethal airborne concentrations of 1,2,3-trichloropropane; prostration was observed in rats exposed to 888 ppm for 6 hours (Johannsen et al. 1988) and hypoactivity was observed in rats exposed to 579 ppm 6 hours/day for 4 weeks (Johannsen et al. 1988). Histopathological examination of nervous tissue was not conducted for either groups of rats.

No histopathological effects were observed in the brain, spinal cord, or peripheral nerves of rats and mice that were intermittently exposed to concentrations as high as 132 ppm 1,2,3-trichloropropane for 2 weeks (Miller et al. 1986a). No effect was observed on brain and spinal cord histology and brain weight in rats that were intermittently exposed to up to 49 ppm for 13 weeks (Johannsen et al. 1988). There were no treatment-related changes in brain weight or brain histology in rats and mice that were administered 1,2,3-trichloropropane doses as high as 250 mg/kg/day for periods as long as 17 weeks (Shell Oil 1983a, 1983b).

2.16 REPRODUCTIVE

No studies were located regarding reproductive effects in humans after exposure to 1,2,3-trichloropropane. In the only inhalation reproductive study of 1,2,3-trichloropropane, male and female rats were intermittently exposed to concentrations of 0.49–15 ppm prior to mating, during mating, and during gestation (Johannsen et al. 1988). There were no effects on mating performance or fertility in either sex, but the data for the males at ≥4.5 ppm concentrations are inconclusive because the control group for these males had low mating performance compared to another male control group. No effects on mating or fertility were found in male rats administered 80 mg/kg/day 1,2,3-trichloropropane by gavage for 5 days in a dominant lethal mutation study (Saito-Suzuki et al. 1982). In a continuous breeding study, decreases in the number of litters produced and decreases in the number of live pups per litter were observed in rats administered ≥60 mg/kg/day for five litters (approximately 98 days) (NTP 1990). An increase in the days to litter was also observed at 120 mg/kg/day. To assess whether the observed effects were due to effects in the male or female animals, a cross-over mating study was conducted after the fifth litter was born (NTP 1990). A decrease in the number of live pups was observed when females administered 120 mg/kg/day were mated with control males. In the cross-over mating study, no alterations in epididymal sperm motility, count, or morphology or estrous cycle length were observed (NTP 1990).

Other inhalation and oral studies have examined potential histological alterations in reproductive tissues. Intermittent inhalation exposure to ≤132 ppm for 2 weeks (Miller et al. 1986b) or ≤49 ppm 1,2,3-trichloropropane for 13 weeks (Johannsen et al. 1988) had no effect on the weights or histology of the reproductive organs of male and female rats. In gavage studies, no histological alterations were observed in the testes of rats administered 80 mg/kg/day 1,2,3-trichloropropane for 5 days (Saito-Suzuki et al. 1982); no alterations were observed in male or female reproductive tissues in rats or mice administered ≤125 mg/kg (5 days/week) for 17 weeks (NTP 1993), rats administered ≤30 mg/kg 5 days/week for 2 years (NTP 1993), or mice administered ≤60 mg/kg 5 days/week for 2 years (NTP 1993). In the cross-over mating study (NTP 1990), amyloidosis was observed in the ovaries of rats administered 120 mg/kg/day for at least 98 days.

2.17 DEVELOPMENTAL

One epidemiology study examined the possible association between 1,2,3-trichloropropane exposure and birth defects (Brender et al. 2014). Using data from the Texas Birth Defect Registry, the study found associations for several birth defects, including any neural tube defect, spina bifida, and septal heart

defects; the odds ratios (OR) and confidence intervals (CI) are presented in Table 2-4. Exposure was quantified based on maternal residential proximity and estimated pounds of chemical emitted. For spina bifida and cleft palate, associations were only found at the highest exposure intensity (OR 2.62, 95% CI 1.55–4.46 and OR 1.91, 95% CI 1.01–3.63, respectively). For septal heart defects, an association was found in the medium-intensity group (OR 1.31, 95% CI 1.12–1.52), but not in the high-intensity group (OR 1.02, 95% CI 0.86–1.21). Although the study found associations, it does not establish causality; it is also noted that the study found associations for a number of chemicals.

Table 2-4. Possible Associations Between Maternal Residential Proximity to 1,2,3-Trichloropropane Air Emissions and Birth Defects

Defect	Adjusted odds ratio[a]	95% Confidence interval
Any neural tube defect	1.49	1.08–2.06
Anencephaly	1.15	0.56–2.36
Spina bifida	1.78	1.22–2.59
Any oral cleft defect	1.16	0.89–1.51
Cleft palate alone	1.48	0.97–2.25
Cleft lip without cleft palate	1.03	0.73–1.44
Conotruncal heart defects	1.01	0.74–1.37
Obstructive heart defects	1.06	0.79–1.42
Septal heart defects	1.13	1.02–1.24
Any type of limb deficiency	1.10	0.72–1.67
Longitudinal limb deficiency	1.08	0.58–1.99
Transverse limb deficiency	0.95	0.53–1.71

[a]Adjustments for birth year and maternal age, education, race/ethnicity, and public health region of residence.

Source: Brender et al. 2014

Limited information regarding developmental effects of inhaled 1,2,3-trichloropropane in animals is available from a reproduction study in which male and female rats were intermittently exposed to concentrations as high as 15 ppm prior to mating, during mating, and during gestation (Johannsen et al. 1988). There were no effects on gestation length, and pup viability and weight at birth and during lactation were normal. In an oral developmental toxicity study utilizing the offspring of rats tested in the continuous breeding study (NTP 1990, see Section 2.16), decreases in mating and fertility indices were observed at 120 mg/kg/day. No alterations in the number of live pups, sex ratio, or pup body weight were observed at a dose of ≤120 mg/kg/day (NTP 1990). Increases in average estrous cycle length was observed at 30, 60, and 120 mg/kg/day, but the increase was not dose-related.

2.18 OTHER NONCANCER

No studies were located regarding other noncancer effects in humans or animals after exposure to 1,2,3-trichloropropane.

2.19 CANCER

No studies were located regarding carcinogenicity in humans after exposure to 1,2,3-trichloropropane.

Information on the carcinogenicity of 1,2,3-trichloropropane is based on chronic-duration gavage studies in rats and mice (NTP 1993). Increases in the incidence of neoplastic lesions were observed at all doses tested. In rats administered ≥3 mg/kg (5 days/week), squamous cell papillomas or squamous cell carcinomas were observed in the forestomach and adenomas were observed in the pancreas. At ≥10 mg/kg, squamous cell papillomas or squamous cell carcinomas in the oral mucosa, adenomas in renal tubules, adenoma or carcinoma of the clitoral gland, and adenocarcinomas of the mammary gland were observed. At the highest dose tested (30 mg/kg), adenoma or carcinoma in the preputial gland, and carcinoma in the Zymbal's gland (males only) were also observed. Clear evidence of carcinogenicity was also found in male and female mice treated with ≥6 mg/kg (NTP 1993). The evidence consisted of increased incidences of squamous cell papilloma or carcinoma in the forestomach and hepatocellular adenoma or carcinoma (males only) at 6 mg/kg; harderian gland adenoma in males at 20 mg/kg; and squamous cell papilloma or carcinoma of the oral mucosa (females only), harderian gland adenoma (females only), and uterine stromal polyps and endometrial adenoma or adenocarcinoma at 60 mg/kg.

The HHS has determined that 1,2,3-trichloropropane is reasonably anticipated to be a human carcinogen (NTP 2016). EPA concluded that it is likely to be carcinogenic to humans (EPA 2009a), and IARC considers it as probably carcinogenic to humans (IARC 1995).

2.20 GENOTOXICITY

The genotoxicity of 1,2,3-trichloropropane has been investigated in a small number of *in vitro* studies, which are summarized in Table 2-5. 1,2,3-Trichloropropane was mutagenic in certain strains of *Salmonella typhimurium* when assayed with exogenous metabolic activation preparation (Haworth et al. 1983; Kubo et al. 2002; Låg et al. 1994; Mersch-Sundermann et al. 1994; NTP 1993; Ratpan and Plaumann 1988; Stolzenberg and Hine 1980). It did not induce gene mutations in *Escherichia coli* (Mersch-Sundermann et al. 1994). In eukaryotic organisms, 1,2,3-trichloropropane induced gene

mutations in mouse lymphoma cells (NTP 1993), DNA damage in human lymphocytes (Tafazoli and Kirsch-Volders 1996), sister chromatid exchange in Chinese hamster V79 and ovary cells (NTP 1993; Von Der Hude et al. 1987), and chromosomal aberrations in Chinese hamster ovary cells (NTP 1993). In most cases, the positive results were only observed with activation. 1,2,3-Trichloropropane did not increase micronuclei formation in human lymphocytes (Tafazoli and Kirsch-Volders 1996).

Table 2-5. Genotoxicity of 1,2,3-Trichloropropane *In Vitro*

Species (test system)	Endpoint	Results: Activation With	Results: Activation Without	Reference
Prokaryotic organisms				
Salmonella typhimurium (plate incorporation test)	Gene mutation	+	–	Stolzenberg and Hine 1980
S. typhimurium strains (liquid preincubation test)	Gene mutation	+	–	Haworth et al. 1983
S. typhimurium TA97, TA98, TA100, and TA1535, (liquid preincubation test)	Gene mutation	+	–	NTP 1993
S. typhimurium TA1537 (liquid preincubation test)	Gene mutation	–	–	NTP 1993
S. typhimurium (plate incorporation test)	Gene mutation	+	–	Ratpan and Plaumann 1988
S. typhimurium TA98 (Ames assay)	Gene mutation	–	–	Kubo et al. 2002
S. typhimurium TA100 (Ames assay)	Gene mutation	+	–	Kubo et al. 2002
S. typhimurium TA100 (Ames assay)	Gene mutation	+	–	Låg et al. 1994
S. typhimurium TA100 (Ames assay)	Gene mutation	+	–	Mersch-Sundermann et al. 1994
Escherichia coli (SOS chromotest)	Gene mutation	–	–	Mersch-Sundermann et al. 1994
Eukaryotic organisms				
L5178Y mouse lymphoma cells	Gene mutation	+	–	NTP 1993
Human lymphocytes (comet assay)	DNA damage	+	+	Tafazoli and Kirsch-Volders 1996
Human lymphocytes	Micronuclei formation	–	–	Tafazoli and Kirsch-Volders 1996
Chinese hamster V79 cells	Sister chromatid exchange	+	–	Von Der Hude et al. 1987
Chinese hamster ovary cells	Sister chromatid exchange	+	–	NTP 1993

Table 2-5. Genotoxicity of 1,2,3-Trichloropropane *In Vitro*

		Results		
		Activation		
Species (test system)	Endpoint	With	Without	Reference
Chinese hamster ovary cells	Chromosomal aberrations	+	–	NTP 1993

+ = positive results; – = negative results

A small number of studies have evaluated the *in vivo* genotoxicity (Table 2-6). In *Drosophila*, exposure to 1,2,3-trichloropropane increased the frequency of somatic mutations and recombinations (Chroust et al. 2007). In mammalian species, 1,2,3-trichloropropane did not induce dominant lethal mutations when administered orally to rats (Saito-Suzuki et al. 1982) (see Section 2.16) or increase the frequency of micronucleated polychromatic erythrocytes in mice (Crebelli et al. 1999).

Table 2-6. Genotoxicity of 1,2,3-Trichloropropane *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Drosophila melanogaster	Somatic mutation and recombination	+	Chroust et al. 2007
CD-1 mice (intraperitoneal)	Micronucleated polychromatic erythrocytes	–	Crebelli et al. 1999

– = negative result; + = positive result