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-dibromo-3-chloropropane. 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-dibromo-3-chloropropane, but may not be inclusive of the entire body of literature.

Animal inhalation studies are presented in Table 2-1 and Figure 2-2, and animal oral studies are presented in Table 2-2 and Figure 2-3. Animal dermal 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 are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an endpoint should be

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

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-dibromo-3-chloropropane have been evaluated in human and animal studies. As illustrated in Figure 2-1, most information comes from intermediate- or chronic-duration oral or inhalation studies in animals. Most human studies involved occupational exposure during production or application of 1,2-dibromo-3-chloropropane; inhalation is the presumed major exposure route for these studies. One human study evaluated effects from exposure via the drinking water. The exposure route pie chart includes the human studies. However, the lack of exposure duration data for human studies precludes inclusion in the pie chart for exposure duration. In addition to the studies summarized in Figure 2-1, another six studies only examined 1,2-dibromo-3-chloropropane lethality following inhalation, oral, or dermal exposure.

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

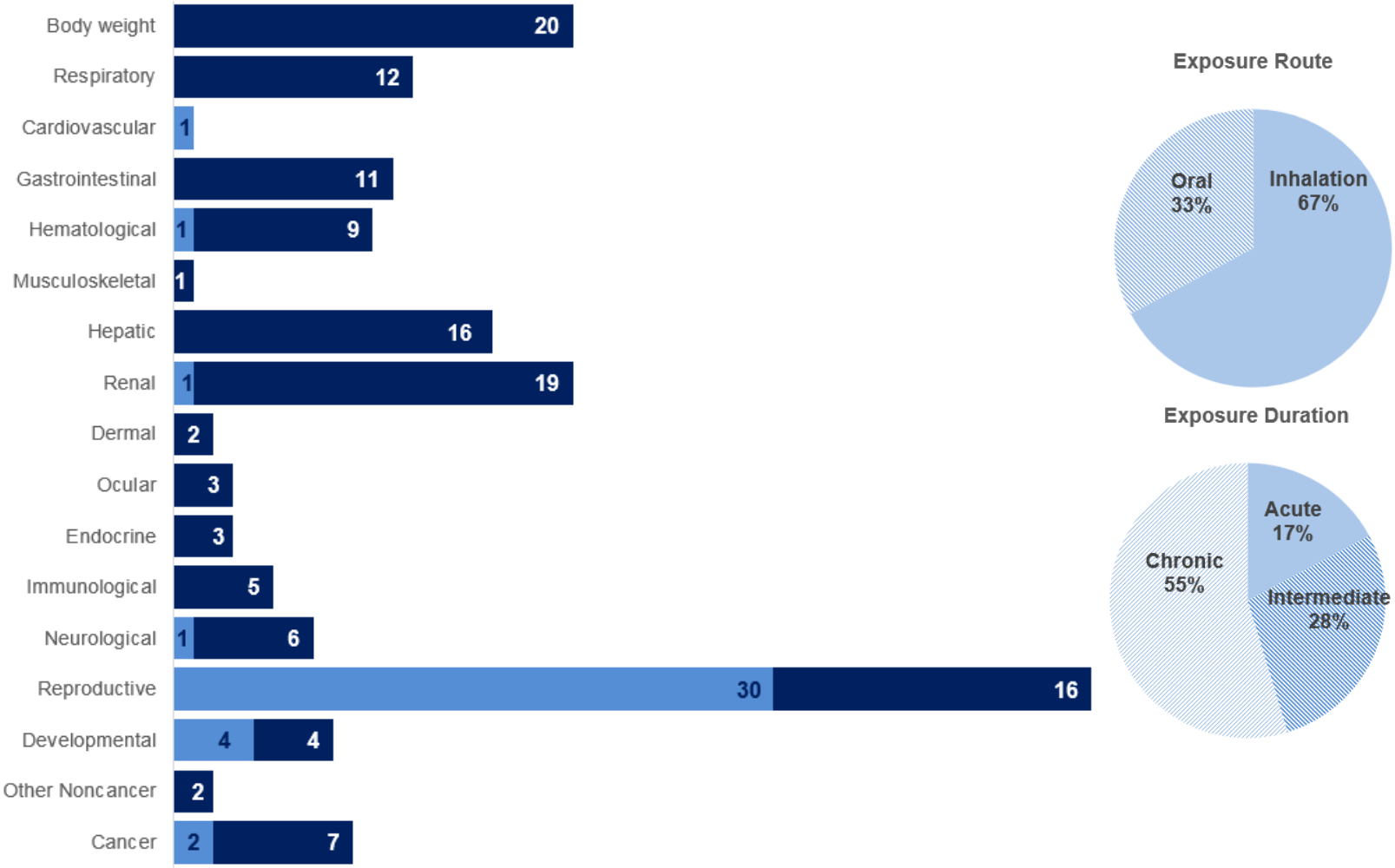
- **Respiratory Endpoint:** Inhalation exposure of laboratory animals resulted in adverse effects in in the nasal cavity, trachea, and bronchi that included inflammatory and proliferative changes and epithelial necrosis.
- **Gastrointestinal Endpoint:** Oral exposure of laboratory animals resulted in inflammatory, proliferative, and degenerative effects in the gastrointestinal tract.
- **Renal Endpoint:** Inhalation and oral exposure of laboratory animals resulted in renal effects that included nephritis and nephrosis, necrotic effects in kidney proximal tubules, and proliferative changes.

- **Reproductive Endpoint:** Male reproductive effects such as azoospermia (absence of sperm in the semen) or oligospermia (low sperm count) and depletion of germ cells in seminiferous tubules have been associated with occupational exposure to 1,2-dibromo-3-chloropropane. Testicular damage has been reported in laboratory animals exposed via inhalation or oral routes.

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

Most studies examined the potential reproductive, body weight, and renal effects of 1,2-dibromo-3-chloropropane

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



*Includes studies discussed in Chapter 2. A total of 64 studies include those finding no effect. Most animal studies examined multiple endpoints. Inhalation is the presumed exposure route for occupational studies. Human studies are not included in the pie chart for exposure duration due to lack of exposure duration data.

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
ACUTE EXPOSURE									
1	Rat (NS)	8 hours	NS	CS, LE	Death			103	8-Hour LC_{50}
					Resp		60		Respiratory tract irritation
					Ocular		60		Ocular irritation
Torkelson et al. 1961									
2	Rat (NS)	7 hours	50, 100, 190, 290	CS, GN, LE	Death			100	7-Hour exposure caused 4/5 deaths
					Renal		50		Kidney scarring
Torkelson et al. 1961									
3	Rat (Sprague-Dawley) 11 M	14 days	0, 10	GN, HP	Resp			10	Histopathologic bronchial and pulmonary lesions persisting for at least 16 days following cessation of exposures
					Renal			10	Multiple histopathologic renal lesions; some recovery by postexposure day 16
					Immuno			10	Atrophy of splenic white pulp and decreased lymphocytes in red pulp at postexposure day 1; no effects at postexposure day 16
					Repro			10	Irreversible aspermatogenesis, testicular atrophy; histopathologic testicular lesions
Saegusa et al. 1982									

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Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
INTERMEDIATE EXPOSURE									
4	Rat (F344) 5 M 5 F	13 weeks 5 days/week 6 hours/day	0, 1, 5, 25	BW, CS, HP, LE	Death			25	1/5 males and 4/5 females died
					Bd Wt	5		25	Weight loss of 0.4 g among 25 ppm males versus 190.6 g weight gain among control males; only one 25 ppm female survived
					Resp		1	25	Exposure concentration-related increasing frequency and severity of upper and lower respiratory tract lesions (necrotic and proliferative)
					Gastro	25			
					Hemato	5	25		Hypocellularity of bone marrow
					Hepatic		1	25	Hydropic changes of hepatocytes at 1 and 5 ppm; focal necrosis at 25 ppm
					Renal		1	25	Nephrosis at 1 and 5 ppm; tubular nephrosis accompanied by megalocytosis at 25 ppm
					Endocr	5	25		Adrenal vacuolation or necrosis
					Immuno	5	25		Thymic atrophy with lymphoid depletion
					Neuro	5		25	Meningoencephalitis
					Repro	5		25	Testicular atrophy and hypospermatogenesis
					Other non-cancer	5		25	Severe hair loss (33–95% of body)

NTP 1982; Reznik et al. 1980a

Table 2-1. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – 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
5	Rat (Sprague-Dawley) 30 M 30 F	4 or 14 weeks 5 days/week 6 hours/day; terminal sacrifice at weeks 40 (females) and 46 (males)	0, 0.1, 1, 10	BC, BW, CS, DX, EA, GN, HE, HP, LE, OF, OW, UR	Bd Wt	10			
					Hemato	10			
					Hepatic	10			
					Renal	10			
					Endocr	0.1 F 1 M	1 F 10 M		At terminal sacrifice, hyperplastic nodules in adrenal gland of 7/20 females at 1 ppm and 19/20 males and 18/20 females at 10 ppm
					Neuro	1	10		Focal mineralization in the cerebrum at terminal sacrifice only (15/18 males, 5/17 females)
					Repro	1		10	Testicular atrophy; decreased male fertility; increased numbers of ovarian cysts
Rao et al. 1983									
6	Rat (NS) 15 M	10 weeks 5 days/week 7 hours/day	0, 5, 10, 20, 40	GN, HE, HP, LE, OW	Death			10	Increasing rate of mortality: 0/15, 0/15, 2/15, 10/15 and 13/50 at 0, 5, 10, 20, and 40 ppm, respectively
					Bd Wt			5	24% depressed body weight gain
					Resp		5	20	5 ppm: unspecified focal changes in bronchiolar epithelium 20 ppm: lung atelectasis and emphysema; bronchopneumonia
					Gastro	10	20		Unspecified gross lesions in intestinal mucosa
					Hemato	10	20		Depressed white blood cell count
					Hepatic		5		Increased relative liver weight
					Renal		5		Unspecified epithelial changes in renal collecting tubules

Table 2-1. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – 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
					Ocular		5	10	Irritation at 5 ppm, corneal cloudiness at ≥10 ppm
					Repro			5	Increasing severity of testicular atrophy
Torkelson et al. 1961									
7	Rat (NS) 20 M 20 F	92 days 5 days/week 7 hours/day	0, 12	BW, CS, GN, HP, LE, OW	Death			12	8/20 males, 10/20 females died
					Resp			12	Pneumonia; lung infection
					Hemato		12		Increased neutrophils (likely secondary to pulmonary infection); decreased WBCs, increased packed cell volume
					Hepatic		12		Sinusoidal dilation, centrilobular congestion
					Renal		12		Cloudy swelling of tubular epithelial lining
Torkelson et al. 1961									
8	Mouse (B6C3F1) 8–10 M 10 or 12 F	13 weeks 5 days/week 6 hours/day	0, 1, 5, 25	BW, CS, HP, LE	Death			25	4/10 males died
					Bd Wt			25	Actual body weight loss
					Resp	1	5	25	Exposure concentration-related increasing frequency and severity of upper and lower respiratory tract lesions (necrotic and proliferative)
					Gastro	25			
					Hepatic	5	25		Hydropic changes in hepatocytes
					Renal	5		25	Nephrosis
NTP 1982; Reznik et al. 1980a									

Table 2-1. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – 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
9	Rabbit (New Zealand White) 10 M	14 weeks 5 days/week 6 hours/day	0, 0.1, 1, 10	BW, CS, GN, HP, OF, OW	Death			10	3/10 died during or following 8 weeks of exposures
					BW	10			
					Hemato	10			
					Hepatic	10			
					Renal	10			
					Neuro	10			
					Repro	0.1[b]	1	10	Exposure concentration-related testicular atrophy, increased sperm abnormalities and serum FSH; decreased fertility at 10 ppm
Rao et al. 1982									
10	Rabbit 3 M 3 F	92 days 5 days/week 7 hours/day	0, 12	BW, CS, GN, HE, HP, OW	Repro			12	Severe testicular atrophy and degeneration
Torkelson et al. 1961									
11	Guinea pig (NS) 10 M 10 F	92 days 5 days/week 7 hours/day	0, 12	BW, CS, GN, HE, HP, LE, OW	Bd Wt	12			
					Resp	12			
					Hepatic		12		Slight cloudy swelling and fatty changes in liver
					Renal	12			
					Repro			12	34% decreased relative testes weight
Torkelson et al. 1961									

Table 2-1. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – 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
12	Monkey (NS) 2 F	10 or 12 weeks 5 days/week 7 hours/day	0, 12	BW, CS, GN	Bd Wt			12	Extreme emaciation
					Resp			12	Infection, probably due to weakened condition
					Hemato			12	Severe anemia, probably secondary to infection from weakened condition
Torkelson et al. 1961									
CHRONIC EXPOSURE									
13	Rat (F344) 50 M 50 F	103 weeks 5 days/week 6 hours/day	0, 0.6, 3	BW, CS, GN, HP, LE	Death			3	44/49 males and 44/50 females died prior to termination at week 84
					Bd Wt	0.6	3		Up to 22 and 12% depressed body weight gain
					Resp		0.6		Inflammation, hyperplasia, hyperkeratosis in nasal cavity
					Gastro	0.6	3		Hyperkeratosis, acanthosis, chronic inflammation in stomach
					Hemato	3			
					Hepatic	3			
					Renal	0.6		3	Toxic tubular nephropathy in 49/49 males and 46/49 females
					Neuro	0.6		3	Cerebral necrosis
					Cancer			0.6	CEL; variety of tumors in nasal cavity
NTP 1982									
14	Mouse (B6C3F1) 50 M 50 F	103 weeks 5 days/week 6 hours/day	0, 0.6, 3	BW, CS, GN, HP, LE	Death			3	Death of 43/50 females between exposure weeks 51 and 74
					Bd Wt	0.6		3	Depressed body weight gain (17–28% in males, as much as 25% in females)

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Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
					Resp		0.6		Inflammation and hyperplasia in nasal cavity; hyperplasia in lungs
					Gastro		0.6		Hyperkeratosis and acanthosis in forestomach
					Hepatic	3			
					Renal		0.6		Hyperplasia in the urinary bladder and inflammation in the kidney of males
					Immuno	0.6		3	Splenic atrophy
					Cancer			0.6	CEL; variety of tumors in nasal cavity and lung of females
NTP 1982									

[a]The number corresponds to entries in Figure 2-2.
[b]Used to derive an intermediate inhalation MRL of 0.0002 ppm; exposure concentration adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

BC = serum (blood) chemistry; Bd Wt or BW = body weight; CEL = cancer effect level; CS = clinical signs; DX = developmental toxicity; EA = enzyme activity; Endocr = endocrine; F = female(s); FSH = follicle stimulating hormone; Gastro = gastrointestinal; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LC_{50} = lethal concentration; 50% kill; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OW = organ weight; Repro = reproductive; Resp = respiratory; UR = urinalysis; WBC = white blood cell

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

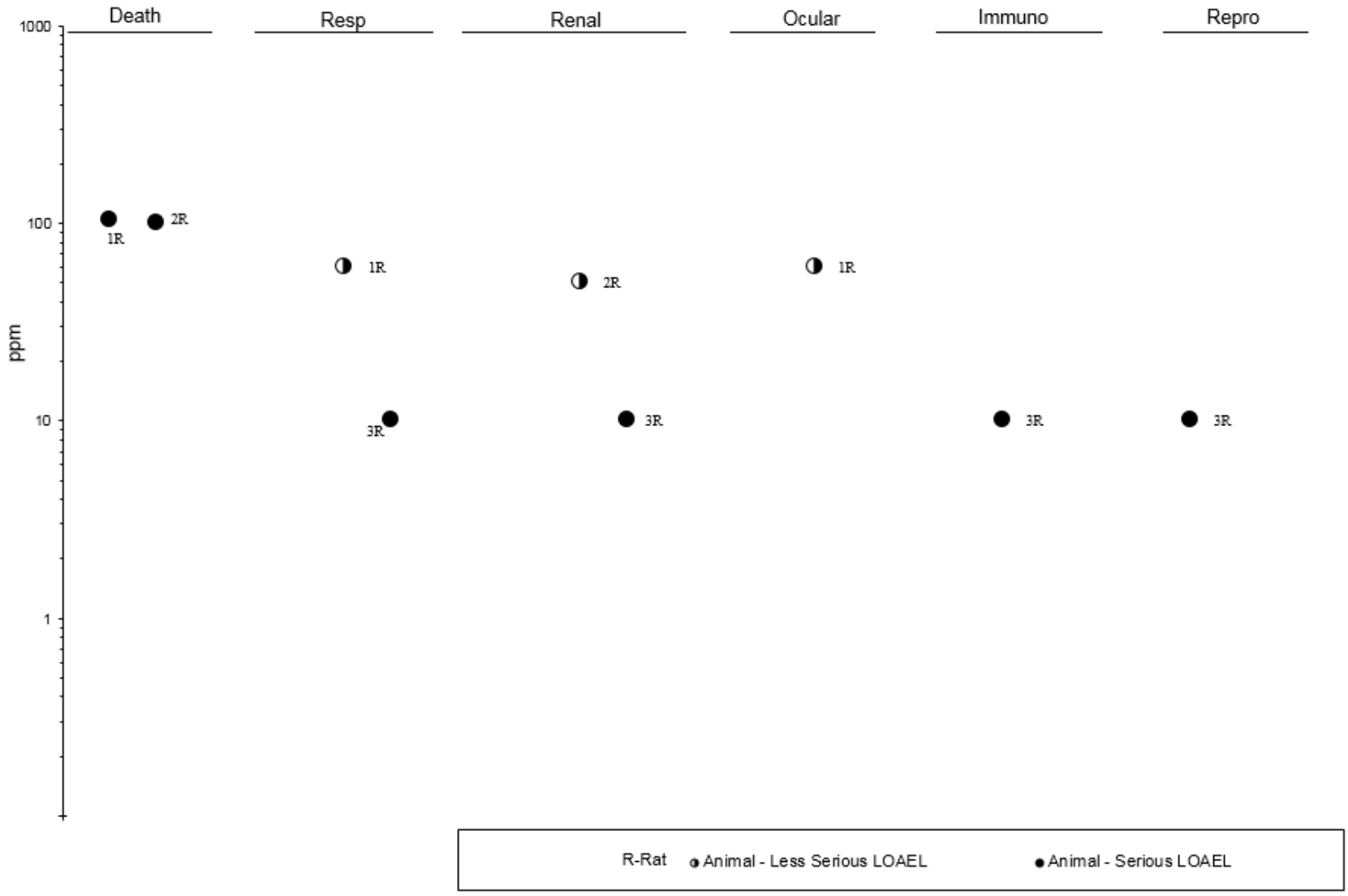

Figure 2-2. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – Inhalation
Intermediate (15-364 days)

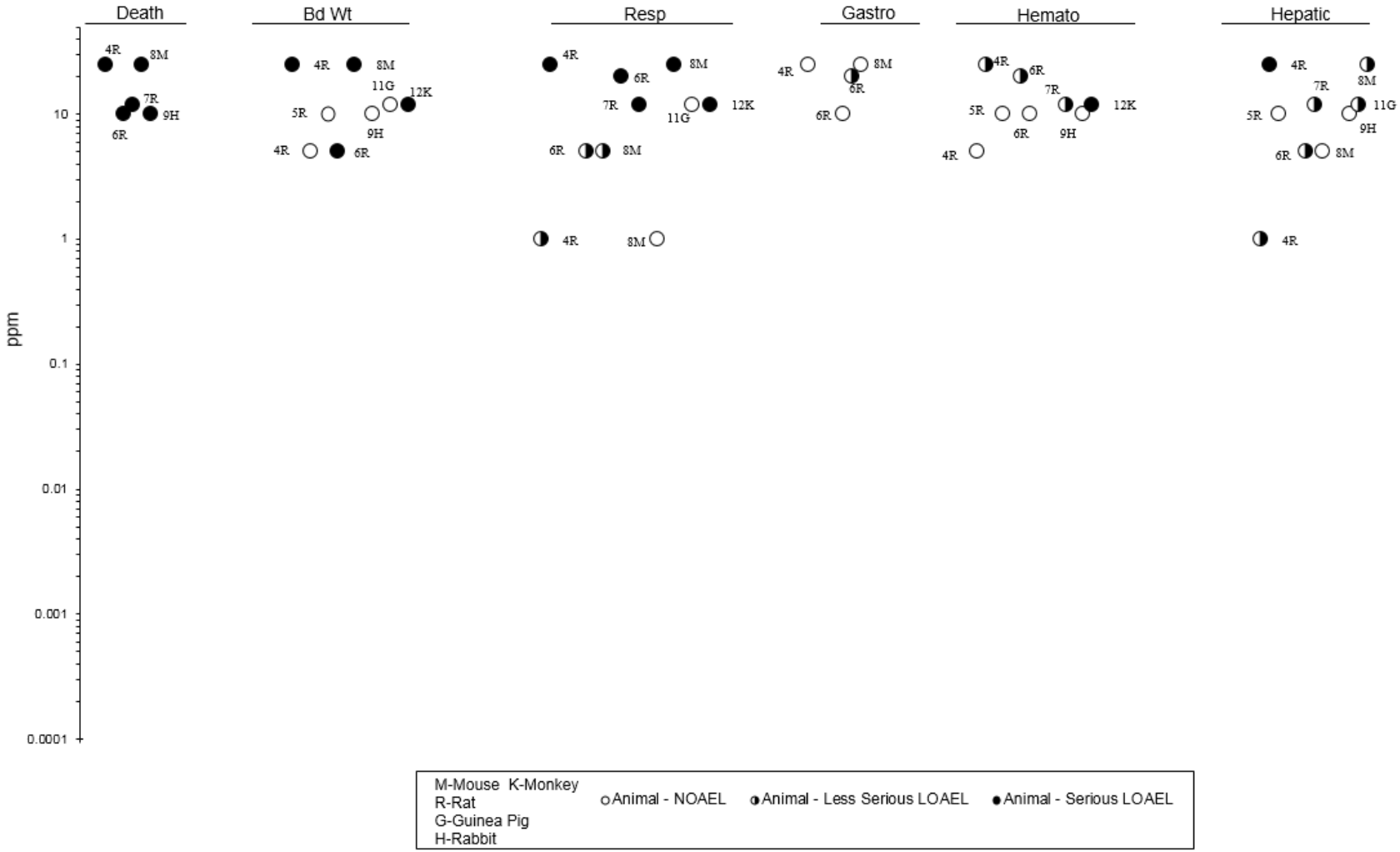

Figure 2-2. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – Inhalation
Intermediate (15-364)

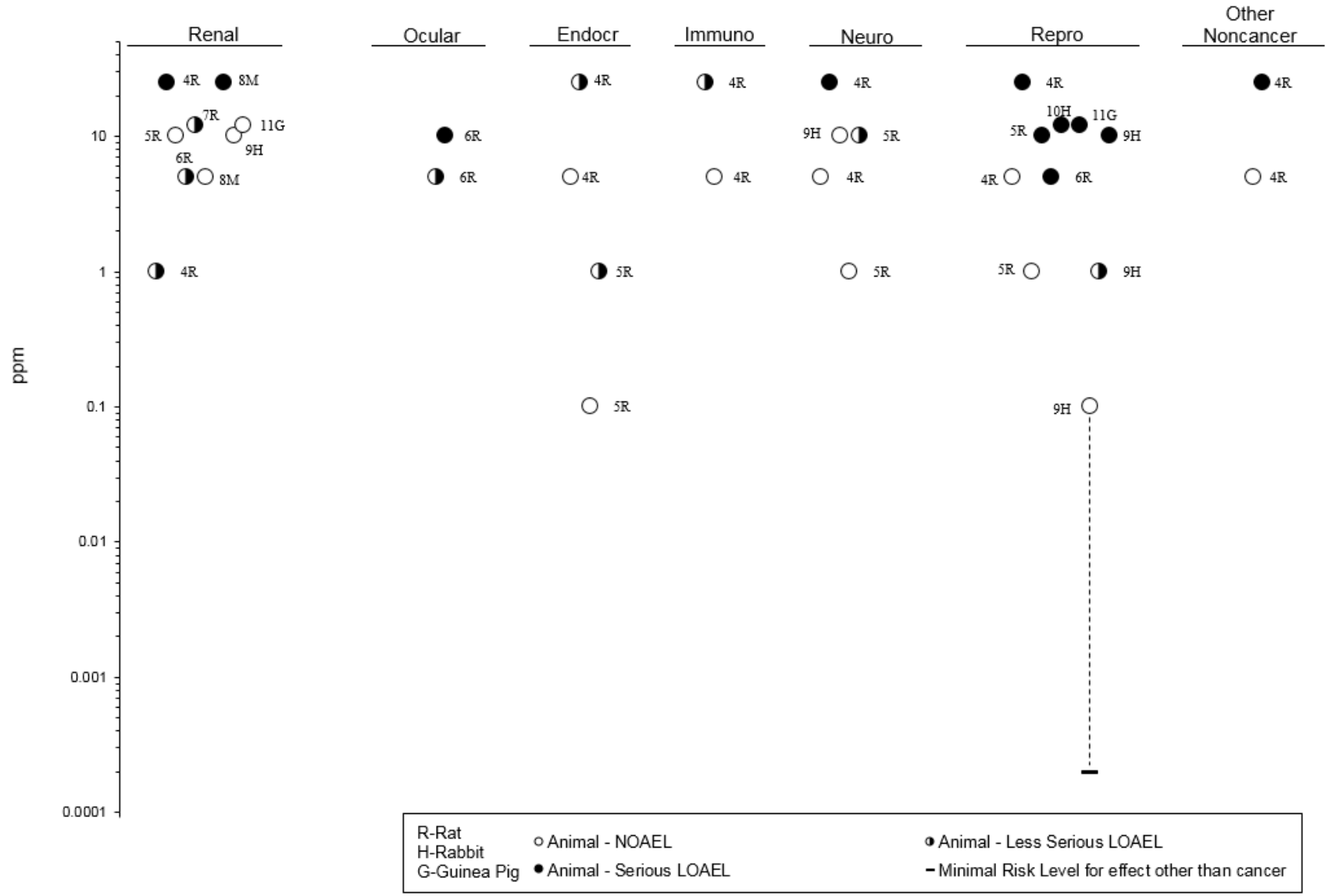

Figure 2-2. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – Inhalation
Chronic (≥365 days)

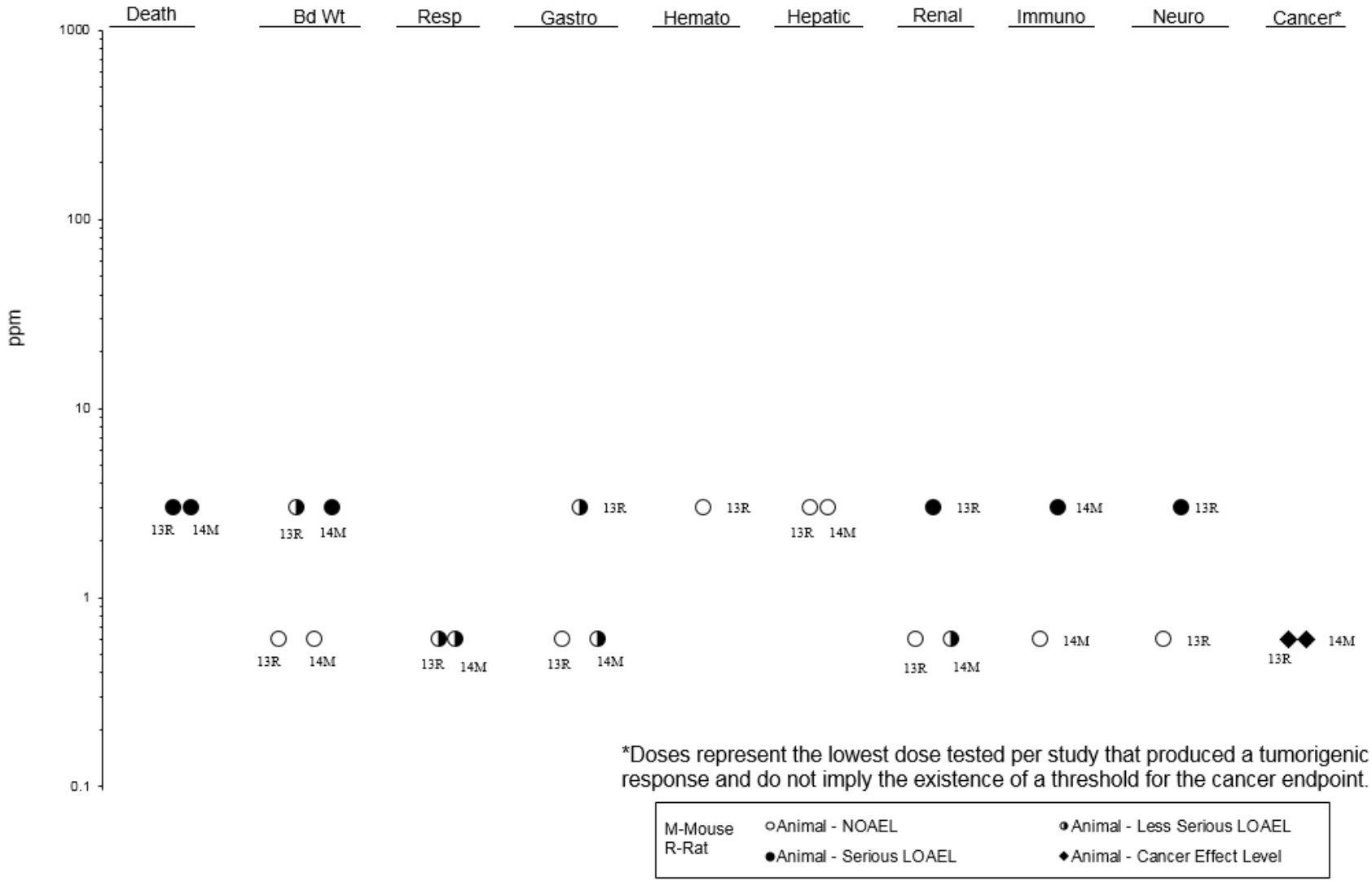

Table 2-2. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – Oral

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 (Fischer 344) 8 M (16 controls)	2 weeks 5 days/week (GO)	0, 15, 29	GN, HP	Gastro	15	29		Cell proliferation, hyperkeratosis
Ghanayem et al. 1986									
2	Rat (Wistar) NS/M	1 day 1 time/day (G)	400	GN, HP	Hepatic			400	Focal necrosis
					Renal			400	Tubular degeneration
Kato et al. 1980									
3	Rat (F344) 6 M	4 days 1 time/day (GO)	0, 40	BC, BW, CS, HP, OF, OW, UR	Hepatic		40		Hepatocellular hypertrophy
					Renal			40	Increased BUN, increased relative kidney weight, degenerative changes in renal tubular epithelia
					Repro			40	Degenerative changes in seminiferous tubules, decreased sperm density
Kluwe 1981									
4	Rat (Sprague-Dawley) NS/M	1 day 1 time/day (GO)	340	LE	Death			340	LD_{50}
Moody et al. 1984									

Table 2-2. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – 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
5	Rat (Wistar) 15 F	10 days GDs 6–15 1 time/day (GO)	0, 12.5, 25, 50	BW, DX, FX, TG	Bd Wt	12.5		25	33% depressed maternal body weight gain
					Develop	25		50	Embryonic lethality and depressed fetal body weight at maternally toxic dose level
Ruddick and Newsome 1979									
6	Rat (Fisher 344) NS/M	1 day 1 time/day (GO)	0, 200	BC, GN, HP, BC, UR	Renal			200	Renal insufficiency
Russell 1989									
7	Rat (Sprague-Dawley) 15 M	5 days 1 time/day (GO)	0, 10, 50		Repro			10	Increased post-implantation loss due to dominant lethal mutations
Teramoto et al. 1980									
8	Rat (NS) NS/M	1 day 1 time/day (G)	NS	LE	Death			170; 300	LD_{50} = 170 mg/kg (one laboratory) LD_{50} = 300 mg/kg (a separate laboratory)
Torkelson et al. 1961									

Table 2-2. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – 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
9	Mouse (CD-1) 8 M 8 F	14 days 1 time/day (GO)	0, 16.25, 32.5, 65, 130, 260	BW, CS, LE	Death			130	Death of 2/8 and 8/8 males at 130 and 260 mg/kg/day, respectively, and 5/8 females at 260 mg/kg/day
					Bd Wt	260			
					Gastro		16.25		Diarrhea in 6/8 male mice on treatment day 2
					Neuro	65		130	Ataxia, dyspnea, convulsions, lethargy in males that subsequently died; similar effects in females at 260 mg/kg/day
Reel et al. 1984									
10	Mouse (C57BLxDBA/2) 16 M	5 days 1 time/day (GO)	0, 50, 150		Repro	150			
Teramoto et al. 1980									
11	Mouse (MS) NS/M	1 day 1 time/day (G)	NS	LE	Death			260; 410	LD_{50} = 260 mg/kg (one laboratory) LD_{50} = 410 mg/kg (a separate laboratory)
Torkelson et al. 1961									
12	Rabbit (NS) NS/M	1 day 1 time/day (G)	NS	LE	Death			180	LD_{50}
Torkelson et al. 1961									
13	Guinea pig (NS) NS/M	1 day 1 time/day (G)	NS	LE	Death			210	LD_{50}
Torkelson et al. 1961									

Table 2-2. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – 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
INTERMEDIATE EXPOSURE									
14	Rat (Sprague-Dawley) 15 M	77 days 1 time/day (GO)	0, 0.94, 1.88, 3.75, 7.5, 15	BW, HP, OF	Repro	7.5		15	Decreased diameter of seminiferous tubules; decreased ratio of leptotene spermatocytes to Sertoli cells
Amann and Berndtson 1986									
15	Rat (Sprague-Dawley) 20 M	64 days (W)	0, 0.4, 3.3, 5.4, 9.7	BC, BW, CS, EA, GN, HP, OF, OW, WI	Hepatic	9.7			
					Renal	9.7			
					Repro	9.7			
Heindel et al. 1989									
16	Rat (Sprague-Dawley) 10 M 10 F	60 days (W)	0, 0.015, 0.26, 2.96, 19.43	BW, CS, FI, HP, LE, OF, OW, WI	Bd Wt	2.96		19.43	>60% depressed body weight gain accompanied by decreased food and water intakes
					Hepatic	19.43			
					Repro	19.43			
					Develop	2.96	19.43		Decreased pup weight at dose levels resulting in >60% depressed maternal body weight gain accompanied by decreased food and water intake
Johnston et al. 1986									
17	Rat (Osborne-Mendel) 5 M 5 F	6 weeks 5 days/week 1 time/day (GO)	0, 25, 40, 63, 100, 160	BW, LE	Death			40	Death among unspecified numbers of males and females at ≥63 and ≥40 mg/kg/day, respectively
					Bd Wt			25	22 and 33% depressed body weight gain among males and females, respectively
NCI 1978									

Table 2-2. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – 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
18	Rat (NS) 10–14 M 10–14 F	90 days (F)	0, 0.25, 1, 2.5, 7.5, 22.5, 67.5	CS, BW, OW, GN, HP	Death			67.5	6/28 died
					Bd Wt	7.5 M 2.5 F		22.5 M 7.5 F	Depressed weight gain (28% males, 22% females)
					Gastro	22.5	67.5		Intestinal edema
					Hepatic	67.5			
					Renal	67.5			
					Neuro	22.5	67.5		Decreased activity
Torkelson et al. 1961									
19	Mouse (B6C3F1) 5 M 5 F	6 weeks 5 days/week 1 time/day (GO)	0, 100, 160, 251, 398, 631	LE	Death			251	1/5 of each sex died; 100% mortality at ≥398 mg/kg/day
NCI 1978									
20	Mouse (CD-1) Controls: 40/sex; Dosed: 20/sex	126 days 1 time/day (GO)	0, 25, 50, 100	DX, HP, OF	Repro			25	Reduced number of litters
					Develop	100			
Reel et al. 1984									

Table 2-2. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – 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
21	Mouse (CD-1) 20 F1 M 20 F1 F	98 days 1 time/day (GO) after gestational and lactational exposure via their mothers	0, 100	DX, HP, OF, OW	Hepatic	100 F	100 M		Males: 16% increased liver weight
					Endocr		100		Increased pituitary weight
					Repro		100		Decreased epididymis and prostate weight, decreased sperm concentration in absence of adverse effects on fertility
					Develop		100		6% depressed live male pup weight
Reel et al. 1984									
22	Rabbit (Dutch) 6 M	10 weeks 5 days/week (W)	0, 0.94, 1.88, 3.75, 7.5, 15	BW, CS, FI, HP, OF	Bd Wt	15			
					Repro	0.94[b]	1.88[c]	15	Abnormal sperm morphology and decreased spermatogenesis at 1.88 mg/kg; testicular atrophy and increased serum FSH levels at 15 mg/kg
Foote et al. 1986b									
CHRONIC EXPOSURE									
23	Rat (NS)	104 weeks 7 days/week (F)	NS		Death			3	Survival was 38% in males and 40% in females at week 104 (compared to 62% in controls)
					Bd Wt	1		3	48% decreased body weight gain in males at lethal dose
					Resp	3			
					Gastro	0.3	1		Hyperkeratosis, acanthosis
					Hemato	3			
					Renal	1	3		Epithelial hyperplasia
					Ocular	3			
					Immuno	3			

Table 2-2. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – 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
					Neuro	3			
					Repro	3			
					Cancer			3	Liver, kidney, and stomach tumors
Hazleton 1977, 1978a									
24	Rat (Osborne-Mendel) 50 M 50 F	64–78 weeks 5 days/week 1 time/day (GO)	0, 15, 29	BW, CS, FI, GN, HP, LE	Death			15	Decreased survival
					Bd Wt		15		Depressed weight gain (up to 13–20 and 39–61% less than controls at 15 and 29 mg/kg/day, respectively)
					Gastro		15		Hyperkeratosis, acanthosis
					Renal			15	Toxic nephropathy characterized by degenerative changes
					Repro			15	Testicular atrophy
					Cancer			15	CEL; forestomach carcinomas in males and females; mammary gland carcinomas in females; pulmonary metastases
NCI 1978									

Table 2-2. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – 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
25	Mouse (CD-1) 50 M 50 F	78 weeks 7 days/week (F)	0, 0.3, 1, 3 for weeks 1–27; 0, 0.6, 2, 6 for weeks 27–78 (TWA doses 0, 0.5, 1.65, 5)	BW, CS, FI, GN, HP, LE	Resp	5			
					Gastro	1.65	5		Hyperkeratosis, acanthosis
					Hemato	5			
					Hepatic	5			
					Renal	5			
					Repro	5			
					Other non-cancer (not specified)	5			
					Cancer			5	Stomach tumors

Hazleton 1978b

Table 2-2. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – 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
26	Mouse (B6C3F1) 50 M 50 F	47–60 weeks 5 days/week 1 time/day (GO)	M: 0, 114, 219 F: 0, 110, 209	BW, CS, GN, HP, LE	Death			110	Decreased survival
					Bd Wt	110			
					Renal			110	Toxic nephropathy
					Repro	219 M			
					Cancer			110	CEL; stomach carcinoma

NCI 1978

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive gender are presented.
[b]The study authors stated the following: "The no effect level for DBCP administered to male rabbits in drinking water appears to be about 0.94 mg/kg for the most sensitive indicators of testicular function measured, if one accepts the null hypothesis at p=0.05. Because means were slightly higher for controls, on this basis the no effect level is <0.94 mg/kg of body weight." For this reason, the 0.94 mg/kg/day dose level is not used as the basis for deriving an intermediate-duration oral MRL for 1,2-dibromo-3-chloropropane.
[c]Used to derive an intermediate oral MRL of 0.002 mg/kg/day; dose adjusted for uncertainty factor of 1,000 (10 for use of LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

BC = biochemistry; Bd Wt or BW = body weight; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; DBCP = 1,2-dibromo-3-chloropropane; Develop = developmental; DX = developmental toxicity; EA = enzyme activity; Endocr = endocrine; F = female(s); (F) = feed; FI = food intake; FSH = follicle stimulating hormone; FX = fetal toxicity; (G) = gavage, not specified; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; (GO) = gavage, oil; Hemato = hematological; HP = histopathology; Immuno = immunological; LD_{50} = lethal dose; 50% kill; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OW = organ weight; PPD = postpartum day; Repro = reproductive; Resp = respiratory; TG = teratogenicity; TWA = time-weighted average; UR = urinalysis; (W) = water; WI = water intake

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

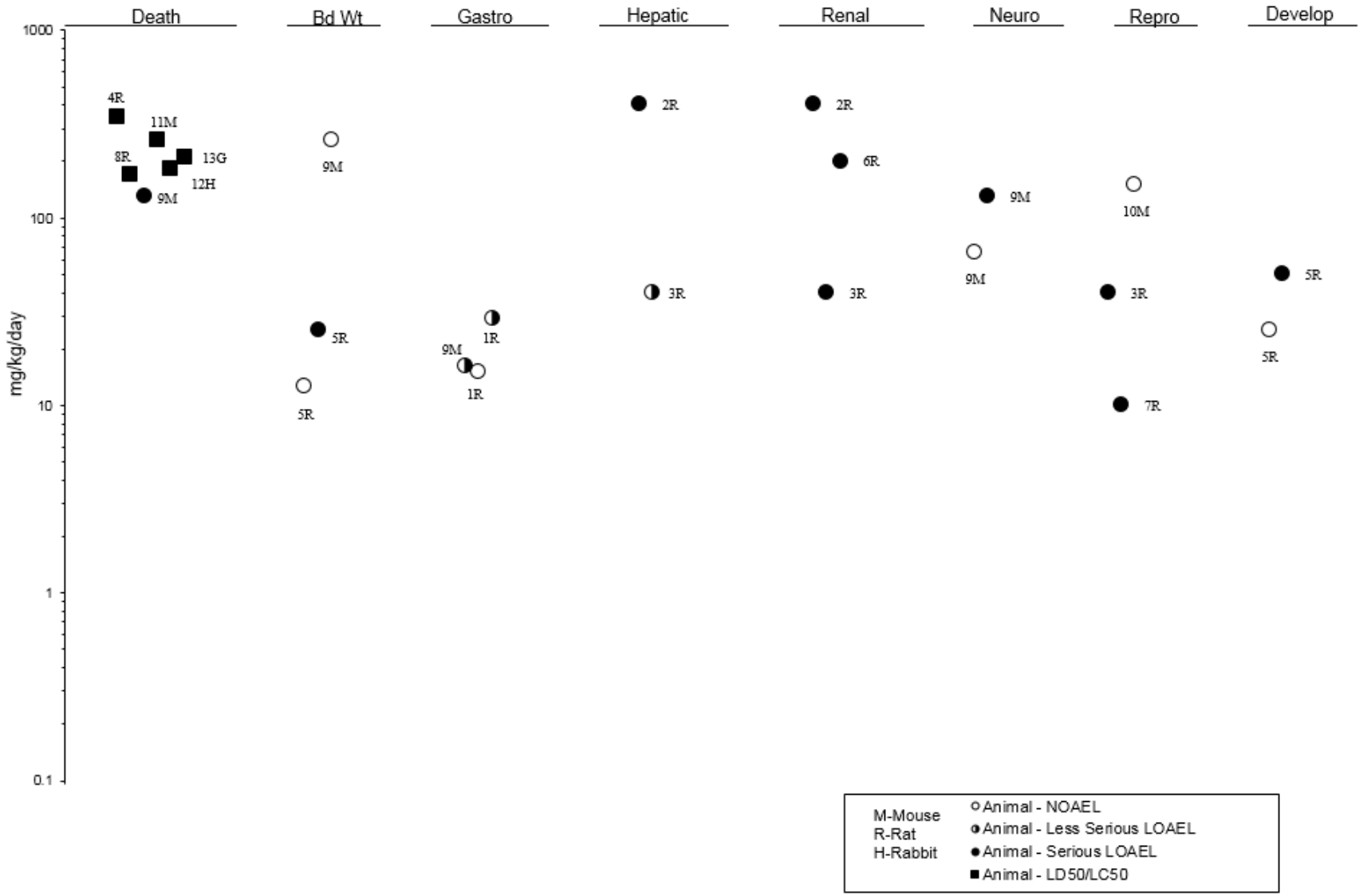

Figure 2-3. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – Oral
Intermediate (14-364 days)

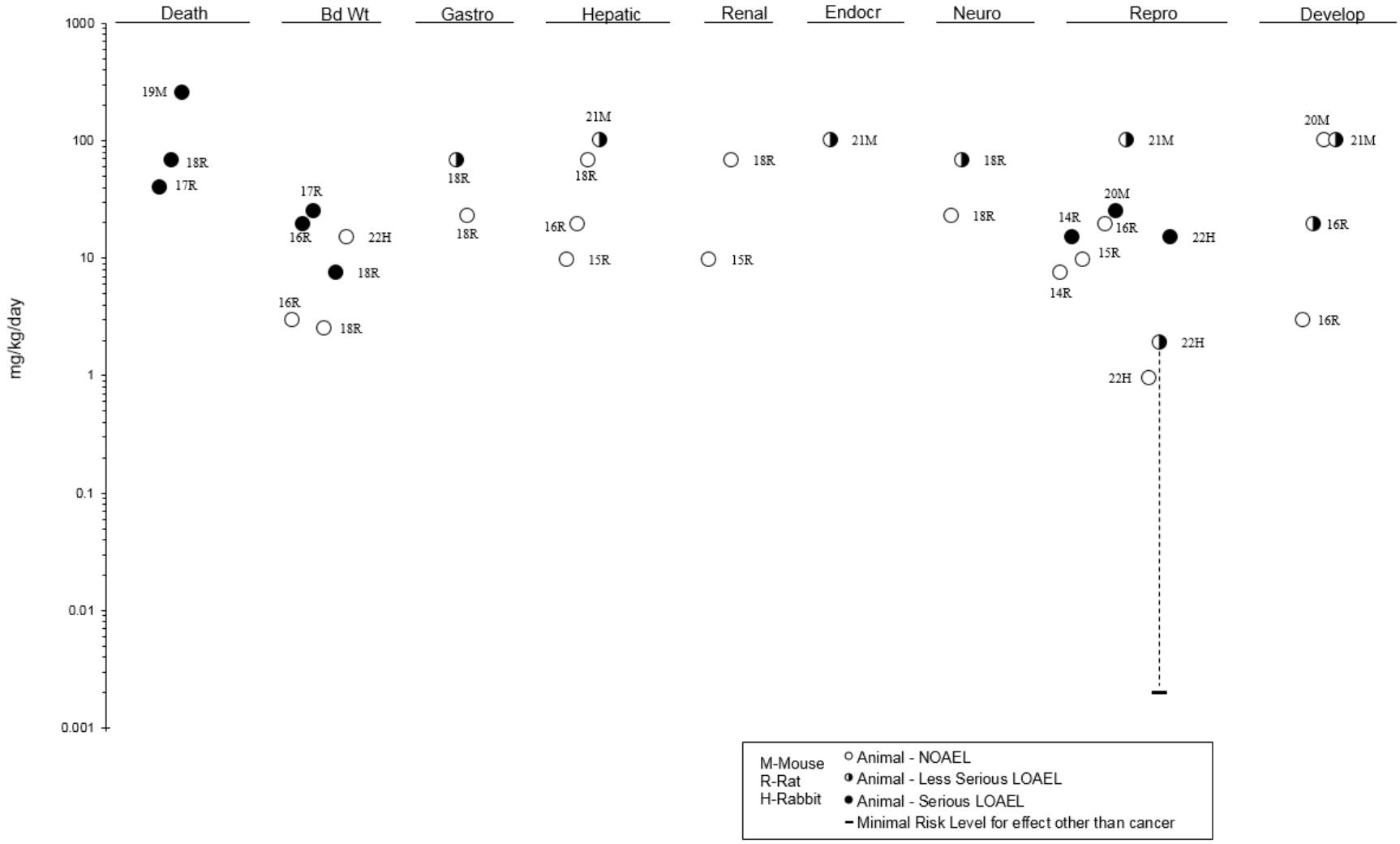

Figure 2-3. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – Oral
Chronic (≥365 days)

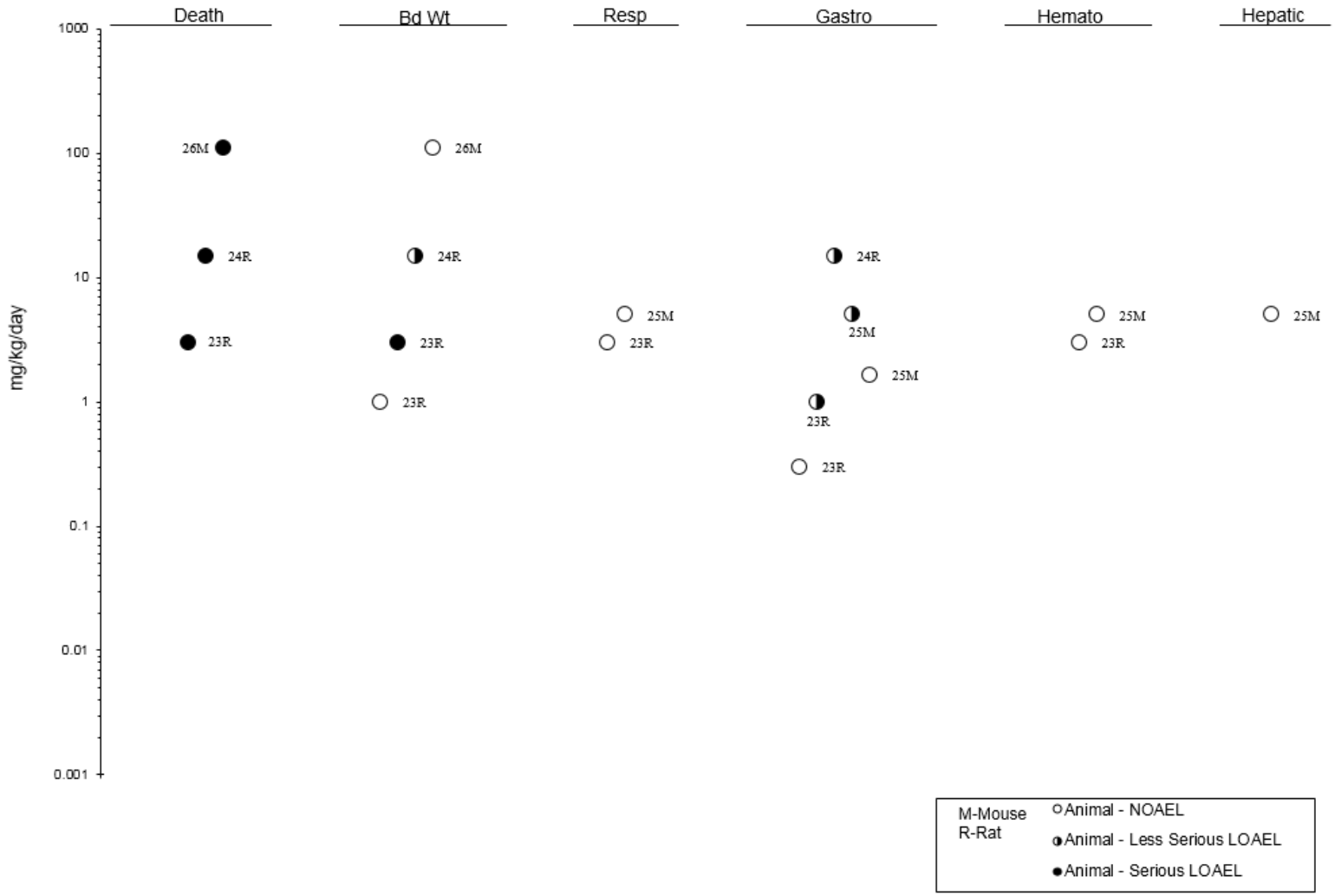

Figure 2-3. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – Oral
Chronic (≥365 days)

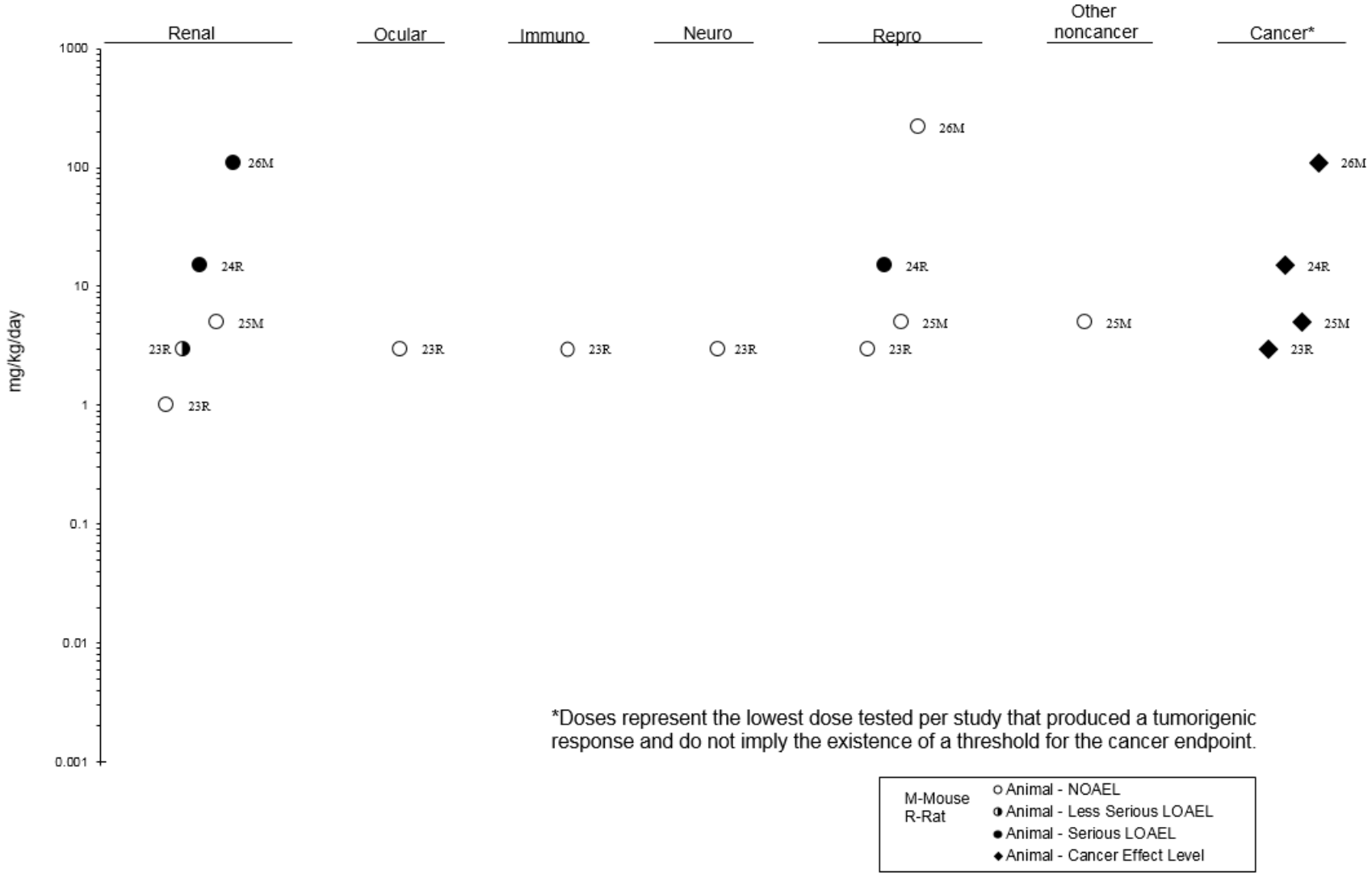

Table 2-3. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – Dermal

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								
Rabbit (NS)	24 hours	NS	LE	Death			1,400	LD_{50}
Torkelson et al. 1961								
Rabbit (NS)	1 day 1 time/day	NS	CS	Ocular		1% (solution)		Eye irritation
Torkelson et al. 1961								
Rabbit (NS) 4 NS	1 day 1 time/day	NS	CS	Dermal		0.5 mL		Slight erythema
Torkelson et al. 1961								
INTERMEDIATE EXPOSURE								
Rabbit (NS) 1 NS	20 days 1 time/day	NS	CS	Dermal		0.5 mL		Crustiness of skin
Torkelson et al. 1961								
CHRONIC EXPOSURE								
Mouse (Ha:ICR Swiss) 30 F	63–85 weeks 3 days/week 1 time/day	0, 11.7 35.0	GN, HP	Cancer			11.7[a]	CEL; stomach carcinoma
Van Duuren et al. 1979								

[a]Cumulative dose based on exposure to 390 mg/kg, 3 days/week up to 85 weeks.

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

2.2 DEATH

Mortality studies of workers occupationally exposed to 1,2-dibromo-3-chloropropane found no excesses of death from all causes or cancers at selected sites (Hearn et al. 1984; Olsen et al. 1995; Wong et al. 1984).

Single inhalation exposures of rats to 1,2-dibromo-3-chloropropane vapors (7–8 hours) at concentrations as low as 100 ppm were lethal (Torkelson et al. 1961). Repeated exposures at 10–25 ppm for up to 14 weeks were lethal to rats, mice, and rabbits (NTP 1982; Torkelson et al. 1961). Chronic-duration repeated inhalation exposures were lethal to rats and mice at exposure concentrations as low as 3 ppm (NTP 1982).

Reported single-dose oral LD_{50} values in the range of 130–410 mg/kg were reported for rats, mice, rabbits, and guinea pigs (Torkelson et al. 1961). Mortalities were observed among rats treated with 40 mg/kg/day (gavage) or 67.5 mg/kg/day (diet) for 6 and 13 weeks, respectively (NCI 1978; Torkelson et al. 1961). No deaths occurred among mice treated by gavage at 160 mg/kg/day for 6 weeks, but 100% mortality was noted at 398 mg/kg/day (NCI 1978). Decreased survival was noted among rats treated with 1,2-dibromo-3-chloropropane in the diet for 2 years at 3 mg/kg/day (Hazleton 1977, 1978a) or by gavage 15 mg/kg/day for up to 78 weeks (NCI 1978) and mice treated by gavage at 110 mg/kg/day for up to 60 weeks (NCI 1978).

A 24-hour dermal LD_{50} of 1,400 mg/kg was reported for rabbits (Torkelson et al. 1961).

2.3 BODY WEIGHT

Seriously depressed body weight gains or body weight losses were observed in some studies of rats, mice, or monkeys repeatedly exposed to 1,2-dibromo-3-chloropropane vapor for 10–13 weeks at concentrations in the range of 5–25 ppm (NTP 1982; Torkelson et al. 1961). Depressed body weight gain was also observed in rats and mice repeatedly exposed for up to 2 years at 3 ppm (NTP 1982).

Depressed body weights or body weight gains were observed in rats and rabbits administered 1,2-dibromo-3-chloropropane orally for periods of 6–13 weeks at doses as low as 7.5–25 mg/kg/day (Heindel et al. 1989; Johnston et al. 1986; NCI 1978; Torkelson et al. 1961). In the studies of Heindel et al. (1989) and Johnston et al. (1986), body weight effects were accompanied by greatly decreased food and water intake. One study reported decreased body weight among rats administered 1,2-dibromo-

3-chloropropane in the diet for 2 years at 3 mg/kg/day (Hazleton 1977, 1978a). In studies of rats and mice administered 1,2-dibromo-3-chloropropane by gavage for up to 60 or 78 weeks, respectively, adverse effects were noted in the rats at the lowest dose tested (15 mg/kg/day); there were no effects on body weight among the mice at 110–114 mg/kg/day (NCI 1978).

2.4 RESPIRATORY

1,2-Dibromo-3-chloropropane vapor was irritating to the respiratory tract of rats exposed for up to 8 hours at 60 ppm (Torkelson et al. 1961) or for 14 days continuously at 10 ppm (Saegusa et al. 1982). Pathological changes (emphysema and bronchopneumonia) were seen in lungs of rats repeatedly exposed to 1,2-dibromo-3-chloropropane at ≥10 ppm for 10–12 weeks (Torkelson et al. 1961). Cytomegaly and hyperplasia were found in the nasal cavity of rats and mice repeatedly exposed to 1 or 5 ppm, respectively, for 13 weeks (NTP 1982; Reznik et al. 1980a). Exposures at 25 ppm resulted in more severe respiratory effects, including inflammatory and proliferative changes in the nasal cavity, necrosis of the trachea, and necrosis or metaplasia of the bronchial epithelium. Chronic-duration repeated inhalation exposures at concentrations as low as 0.6 ppm resulted in respiratory tract hyperplasia, which may represent a precursor of nasal and lung tumors that were also observed at this exposure level (NTP 1982).

2.5 CARDIOVASCULAR

No conclusive evidence was located to indicate that occupational exposure to 1,2-dibromo-3-chloropropane causes cardiovascular effects in humans. Although higher mortality from arteriosclerotic heart disease was observed in workers in the production of trimethylene chlorobromide where 1,2-dibromo-3-chloropropane was a potential trace contaminant (Wong et al. 1984), it is not possible to conclude that 1,2-dibromo-3-chloropropane exposure is associated with heart disease in humans.

A few animal studies included histopathologic examination of cardiac tissue following inhalation or oral exposure to 1,2-dibromo-3-chloropropane (Hazleton 1977, 1978a; NCI 1978; NTP 1982; Rao et al. 1982; Saegusa et al. 1982); although there was no evidence of exposure-related cardiac lesions, cardiovascular function was not evaluated.

2.6 GASTROINTESTINAL

Unspecified lesions in intestinal mucosa were reported among rats repeatedly exposed to 1,2-dibromo-3-chloropropane vapor for up to 10 weeks at 20 ppm (Torkelson et al. 1961), whereas no

histopathological evidence of exposure-related gastrointestinal effects were seen in rats or mice repeatedly exposed for 13 weeks at concentrations up to 25 ppm (NTP 1982; Reznik et al. 1980a). It is unclear whether rat strain differences may have played a role in the apparent differences in response between the two rat studies because Torkelson et al. (1961) did not specify the strain of rat employed. Histopathologic lesions (hyperkeratosis, acanthosis, and/or chronic inflammation) were observed in rats and mice exposed for up to 2 years at 3.0 and 0.6 ppm, respectively (NTP 1982).

Torkelson et al. (1961) observed diarrhea among mice administered 1,2-dibromo-3-chloropropane by gavage for 14 days at 16.25 mg/kg/day, and intestinal edema in rats receiving 1,2-dibromo-3-chloropropane from the diet for 90 days at 67.5 mg/kg/day. Hyperkeratosis and acanthosis were observed in rats and mice. Oral exposure to 1,2-dibromo-3-chloropropane via the diet for 2 years at doses of 1–15 mg/kg/day (rats) and 4.6 mg/kg/day (mice) resulted in hyperkeratosis and acanthosis in the gastrointestinal tract (Hazleton 1977, 1978a, 1978b; NCI 1978).

2.7 HEMATOLOGICAL

No hematological effects were found in workers at a pesticide factory who were exposed to 1,2-dibromo-3-chloropropane (Whorton et al. 1977). Airborne concentrations, measured by personal air sampling devices at the time of the study, were approximately 0.4 ppm (averaged for an 8-hour day); however, airborne levels prior to the study were not presented.

Repeated exposure of rats to 1,2-dibromo-3-chloropropane vapor for 10–13 weeks at 12–25 ppm resulted in hematological changes that included hypocellularity of bone marrow, depressed white blood cell count, increased neutrophils, decreased white blood cells, and increased packed cell volume (NTP 1982; Reznik et al. 1980a; Torkelson et al. 1961). The increase in neutrophils was considered by the study authors (Torkelson et al. 1961) to result from secondary infection based on evidence of pneumonia and increased lung weight. There was no evidence of treatment-related hematological effects among rats administered 1,2-dibromo-3-chloropropane orally at 3.0 mg/kg/day for up to 2 years (Hazleton 1977, 1978a) or mice treated at 4.6 mg/kg/day for up to 78 weeks (Hazleton 1978b).

2.8 MUSCULOSKELETAL

Limited information is available regarding potential for 1,2-dibromo-3-chloropropane to cause musculoskeletal effects. No histopathological changes in skeletal muscle samples were observed following oral exposure to 1,2-dibromo-3-chloropropane for up to 2 years at 29 mg/kg/day (rats) or up to 60 weeks at 209–219 mg/kg/day (mice) (NCI 1978). Hazleton (1977, 1978a, 1978b) found no clinical signs or histopathological evidence for 1,2-dibromo-3-chloropropane-induced effects on the musculoskeletal system. However, neuromuscular function was not tested in the studies of NCI (1978) and Hazleton (1977, 1978a, 1978b); therefore, these results are not included in Table 2-2.

2.9 HEPATIC

Hydropic changes of hepatocytes were observed in rats exposed to 1,2-dibromo-3-chloropropane vapor concentrations of 1 or 5 ppm for 13 weeks; focal necrosis was noted at 25 ppm (NTP 1982; Reznik et al. 1980a). Other intermediate-duration inhalation studies found increased liver weight and/or histopathologic liver lesions (e.g., sinusoidal dilation, centrilobular congestion, hydropic changes, fatty changes) in rats, mice, or guinea pigs at exposure concentrations in the range of 5–40 ppm (NTP 1982; Reznik et al. 1980a; Torkelson et al. 1961).

Most oral studies found no evidence of treatment-related adverse nonneoplastic liver effects at the highest doses tested. However, Kluwe (1981) reported mild hepatocellular swelling and increased cytoplasmic basophilia in livers from rats administered 1,2-dibromo-3-chloropropane by daily gavage for 4 days at 40 mg/kg/day (the only dose level tested). Increased liver weight was reported in mice gavaged at 100 mg/kg/day for 98 days after having been exposed via their mothers during gestation and lactation (Reel et al. 1984). Dose-related increased incidence of peliosis hepatis (dilatation of sinusoidal blood filled spaces within the liver of uncertain toxicological significance) was reported among rats administered 1,2-dibromo-3-chloropropane in the diet for 2 years at estimated doses of 0.3–3 mg/kg/day (Hazleton 1977, 1978a). This result is not included in Table 2-2 or Figure 2-3 due to the absence of other signs of treatment-related hepatic changes.

The mechanism of 1,2-dibromo-3-chloropropane-induced hepatic toxicity has been investigated in several studies. The role of microsomal metabolism was demonstrated by the enhancement of macromolecular binding after pretreatment of rats with phenobarbital (Kato et al. 1980). However, pretreatment of rats with phenobarbital was shown to reduce 1,2-dibromo-3-chloropropane-induced hepatic toxicity (Kluwe 1983). Thus, the role of the microsomal system in the hepatic toxicity induced by 1,2-dibromo-

3-chloropropane or its metabolites is not clear. An *in vitro* study demonstrated DNA damage and a depletion of hepatocellular glutathione (GSH) after liver cells were exposed to 1,2-dibromo-3-chloropropane (Holme et al. 1989). The initial metabolism of 1,2-dibromo-3-chloropropane to reactive epoxide metabolites that bind to DNA and other macromolecules may be responsible for the hepatotoxicity.

2.10 RENAL

Urinalysis parameters were within normal limits in workers exposed occupationally to 1,2-dibromo-3-chloropropane (Whorton et al. 1977). The average airborne concentration, measured by personal air-sampling devices at the time of the study, was approximately 0.4 ppm (averaged for an 8-hour day); however, airborne levels prior to the study were not presented.

The kidney is a target organ of 1,2-dibromo-3-chloropropane toxicity in animals. Scarring of the kidney was observed in rats exposed to 1,2-dibromo-3-chloropropane vapor for several hours at 50 ppm (Torkelson et al. 1961). Histopathologic renal lesions (e.g., necrotic changes in proximal tubules, nephritis, epithelial hyperplasia) were observed among rats and mice following exposures to 1,2-dibromo-3-chloropropane vapor in the range of 1–25 ppm for 2–13 weeks (NTP 1982; Reznik et al. 1980a; Saegusa et al. 1982; Torkelson et al. 1961). No renal effects were seen in rats repeatedly exposed for 2 years at 0.6 ppm; however, at 3 ppm, most rats exhibited toxic tubular nephropathy, and tubular cell hyperplasia was observed in a few rats (NTP 1982). A few similarly-treated male mice exhibited hyperplasia in the urinary bladder and renal inflammation (NTP 1982).

Renal insufficiency was noted in rats administered 1,2-dibromo-3-chloropropane once by gavage at 200 mg/kg (Russell 1989). Tubular degeneration was reported among similarly-treated rats at 400 mg/kg (Kato et al. 1980). Kluwe (1981) reported significantly increased blood urea nitrogen (BUN), increased kidney weight (approximately 14% greater than controls), and degenerative changes in renal tubular epithelia) in rats administered 1,2-dibromo-3-chloropropane by daily gavage for 4 days at 40 mg/kg/day (the only dose level tested). Some oral studies reported treatment-related histopathologic changes (e.g., epithelial hyperplasia, toxic nephropathy) in rats treated for 64 days to 2 years at doses in the range of 3–15 mg/kg/day (Hazleton 1977, 1978a; NCI 1978). In a chronic-duration study of mice, toxic nephropathy was observed at 110 mg/kg/day, the lowest dose tested (NCI 1978).

A study in rats indicates that renal DNA damage correlates with renal necrosis after injection of 1,2-dibromo-3-chloropropane (Omichinski et al. 1987). The involvement of oxidative metabolism in

producing the nephrotoxic effect seems to be unlikely because deuteration of the parent compound did not decrease the DNA damaging effect (deuterium substitution can often decrease the extent of a compound's toxicity that is due to a reactive metabolite formed by oxidation of the carbon-hydrogen bond because of the high activation energy required to break the carbon-deuterium bond).

An accumulation of 1,2-dibromo-3-chloropropane metabolites in the kidneys was observed together with the depletion of renal GSH concentrations after oral exposure of rats (Kato et al. 1980); however, the results of experiments with modulators of nonprotein sulfhydryl (NPS) conjugate formation indicated that this mechanism is not rate-limiting in 1,2-dibromo-3-chloropropane-induced nephrotoxicity (Omichinski et al. 1987). Experiments with methylated analogs of 1,2-dibromo-3-chloropropane suggested the importance of a dibromo-ethyl group to the toxic effects. Although the mechanism is not clear, the demonstration of renal effects in rats and mice in several studies suggests the potential for renal effects in humans who are substantially exposed to 1,2-dibromo-3-chloropropane.

2.11 DERMAL

Available data are restricted to findings in animals. Piloerection was reported in mice gavaged daily for 14 days with 1,2-dibromo-3-chloropropane at 16.25 mg/kg/day (Reel et al. 1984); however, the toxicological significance of this response is uncertain. No information was located regarding dermal effects associated with inhalation or oral exposure to 1,2-dibromo-3-chloropropane. Slight erythema was observed on abraided (but not intact) skin of rabbits following a single application of 0.5 mL; following 20 repeated applications, slight crustiness was noted (Torkelson et al. 1961).

2.12 OCULAR

Ocular irritation was reported in studies of rats exposed once to 1,2-dibromo-3-chloropropane vapor for up to 8 hours at 60 ppm or repeatedly for up to 10 weeks at 5 ppm; in the repeated exposure study, corneal cloudiness was observed at 10 ppm (Torkelson et al. 1961). Ocular irritation was also noted in rabbits following ocular instillation of a 1% solution of 1,2-dibromo-3-chloropropane (Torkelson et al. 1961).

2.13 ENDOCRINE

Available information regarding possible 1,2-dibromo-3-chloropropane effects on the endocrine system is limited. Adrenal lesions (vacuolation, necrosis, and hyperplasia) were reported in rats repeatedly exposed

to 1,2-dibromo-3-chloropropane vapor for 13 weeks at 25 ppm (NTP 1982; Reznik et al. 1980a). Hyperplastic nodules were reported in adrenal cortex of rats exposed to 1,2-dibromo-3-chloropropane vapor for up to 14 weeks at 1 or 10 ppm and allowed to recover from treatment until terminal sacrifice at weeks 40 (females) and 46 (males) (Rao et al. 1983). Decreased pituitary weight (17% less than controls), in the absence of histopathological lesions, was reported in female mice orally dosed at 100 mg/kg/day for 98 days after having been exposed via their mothers during gestation and lactation (Reel et al. 1984).

2.14 IMMUNOLOGICAL

Splenic atrophy was observed in mice repeatedly exposed to 1,2-dibromo-3-chloropropane vapor for up to 2 years at 3 ppm (NTP 1982). Fourteen days of continuous inhalation exposure at 10 ppm resulted in atrophy of splenic white pulp and decreased lymphocytes in red pulp (Saegusa et al. 1982). Thymic atrophy with lymphoid depletion were reported in rats repeatedly exposed to 1,2-dibromo-3-chloropropane vapor for 13 weeks at 25 ppm (NTP 1982; Reznik et al. 1980a).

2.15 NEUROLOGICAL

Information regarding neurological effects in humans after inhalation exposure to 1,2-dibromo-3-chloropropane is limited. Subjective neurological symptoms such as headache, nausea, lightheadedness, and weakness were reported by workers occupationally exposed to 1,2-dibromo-3-chloropropane (Whorton et al. 1977). The average airborne concentration, measured by personal air sampling devices at the time of the study, was approximately 0.4 ppm (averaged for an 8-hour day); prior exposure level data were not available.

Torkelson et al. (1961) reported slight to moderate depression of the central nervous system of rats acutely exposed to 1,2-dibromo-3-chloropropane vapor; however, exposure levels resulting in this effect were not specified in the study report. Meningoencephalitis was reported in rats repeatedly exposed to 1,2-dibromo-3-chloropropane vapor for 13 weeks at 25 ppm (NTP 1982; Reznik et al. 1980a). Cerebral necrosis was observed in rats similarly exposed for up to 2 years at 3 ppm (NTP 1982). Focal mineralization in the cerebrum was reported among rats repeatedly exposed to 1,2-dibromo-3-chloropropane vapor for 14 weeks at 10 ppm (Rao et al. 1983). Ataxia, dyspnea, convulsions, and lethargy were reported among mice administered 1,2-dibromo-3-chloropropane by gavage for up to 14 days at 130 mg/kg/day (males that subsequently died) and 260 mg/kg/day (females) (Reel et al. 1984).

Decreased activity was reported for rats receiving 1,2-dibromo-3-chloropropane from the diet at 67.5 mg/kg/day (Torkelson et al. 1961).

2.16 REPRODUCTIVE

The toxicity of 1,2-dibromo-3-chloropropane to the human male reproductive system has been assessed in cohorts of occupationally exposed factory workers (Cortes-Gallegos et al. 1980; Egnatz et al. 1980; Lipshultz et al. 1980; Potashnik et al. 1978; Scharnweber 1979; Whorton et al. 1977, 1979) and in cohorts of farm workers or pesticide applicators (Coye et al. 1983; 1990; Glass et al. 1979; Sandifer et al. 1979; Slutsky et al. 1999; Takahashi et al. 1981). In these studies, inhalation was most likely the predominant exposure route. An epidemiological approach to the assessment of occupationally-linked sperm count reduction was considered in some reports (Levine et al. 1981; Milby and Whorton 1980). Follow-up studies were performed for some of the original cohorts (Eaton et al. 1986; Goldsmith et al. 1984; Lanham 1987; Lantz et al. 1981; Olsen et al. 1990; Potashnik 1983; Potashnik and Porath 1995; Potashnik and Yanai-Inbar 1987; Schenker et al. 1988).

Changes in sperm counts ranging from oligospermia (deficient or low sperm levels) to azoospermia (absence of sperm) were found among exposed workers. Histopathological changes observed after testicular biopsy revealed atrophy of the seminiferous epithelium (Biava et al. 1978; Potashnik et al. 1978) or tubular hyalinization with sparsity of germ cells; in some tubules, only Sertoli cells persisted (Lantz et al. 1981). Histopathological changes in testes were associated with elevated plasma levels of luteinizing hormone (LH) (Cortes-Gallegos et al. 1980) and follicle stimulating hormone (FSH) (Eaton et al. 1986; Lantz et al. 1981; Potashnik et al. 1978). Furthermore, decreased testicular size tended to be associated with lower sperm counts (Egnatz et al. 1980; Lantz et al. 1981; Olsen et al. 1990). In individuals whose sperm counts returned to normal, testicular atrophy was also found to be reversible (Olsen et al. 1990).

Those men who showed decreased spermatogenesis with normal FSH levels showed greater recovery of spermatogenesis during an 8-year postexposure recovery period than men whose FSH and/or LH levels were elevated throughout the 8-year period (Potashnik 1983; Potashnik and Yanai-Inbar 1987). The results suggest that 1,2-dibromo-3-chloropropane-induced sterility can persist for at least 8–17 years (Eaton et al. 1986; Potashnik 1983; Potashnik and Porath 1995). A standardized fertility ratio for the period when workers were exposed was depressed compared with the period prior to exposure (Levine et al. 1981).

Exposure levels at which sperm effects are elicited are not known because exposure levels were not clearly defined in any of the human studies. This was because either the historical data regarding workplace levels were lacking or, in the case of pineapple workers, exposure levels were so low that they were undetectable in some samples. Furthermore, most human studies were conducted in small cohorts with a low participation of exposed individuals. However, the changes in sperm count appear to be associated with workplace airborne 1,2-dibromo-3-chloropropane concentrations <1 ppm, although the Whorton et al. (1977, 1979) studies are the only ones in which airborne 1,2-dibromo-3-chloropropane concentrations were reported. A correlation was found between the severity of testicular effects and the length of exposure calculated either in years (Whorton et al. 1979) or in hours of direct 1,2-dibromo-3-chloropropane exposure (Potashnik et al. 1978). Lack of spermatogenesis recovery was found to be job (e.g., exposure) and possibly, age related (Olsen et al. 1990). In contrast, cross-sectional (Coye et al. 1983) and longitudinal (Coye et al. 1990) studies in pineapple workers who were exposed to lower levels of 1,2-dibromo-3-chloropropane (estimated at 1 ppb) did not find any effects on sperm counts.

Slutsky et al. (1999) evaluated sperm production (during the early to mid-1990s) within a cohort of more than 26,000 male applicators of 1,2-dibromo-3-chloropropane on banana and/or pineapple plantations in 12 countries where the pesticide was not banned. After an estimated median exposure period of 3 years, azoospermia or oligospermia was reported within 64.3% of the men overall and 90.1% of the men in the Philippines.

No change in male/female birth ratios was found in a population of Fresno County, California, during the years 1978–1982 when the drinking water system was contaminated with 1,2-dibromo-3-chloropropane at concentrations ranging from 0.004 to 5.75 ppb (Wong et al. 1988). However, in a 17-year follow-up of testicular function and reproductive performance among 15 production workers diagnosed with 1,2-dibromo-3-chloropropane-induced testicular dysfunction (Potashnik and Porath 1995), the study authors reported a low prevalence of male infants conceived during paternal exposure (16.9% versus 52.9% during a preexposure period). As fertility was restored among most of the exposed males following cessation of exposure, the prevalence of male infants conceived increased to 41.4%.

Effects on the male reproductive system have also been found in animals. Histopathological evidence of testicular atrophy was observed in rats continuously or intermittently exposed to 1,2-dibromo-3-chloropropane vapors for 2–14 weeks at airborne concentrations as low as 5–25 ppm (NTP 1982; Rao et al. 1983; Saegusa et al. 1982; Torkelson et al. 1961). Rao et al. (1983) also observed increased

incidences of ovarian cysts and decreased male fertility (male-mediated dominant lethality) in rats intermittently exposed to 10 ppm for 14 weeks. Increased serum FSH levels, together with testicular atrophy, were seen in rabbits intermittently exposed to 1 and 10 ppm 1,2-dibromo-3-chloropropane for 8–14 weeks (Rao et al. 1982). The changes after exposure to 1 ppm were reversible. No evidence of gonadotoxicity was found in rabbits exposed to 0.1 ppm.

Increased postimplantation loss, as a result of genetic damage to sperm, was observed in rats after males were orally treated for 5 days with 10 mg/kg/day and mated to nonexposed females (Teramoto et al. 1980). The peak incidence was observed after mating during weeks 4–5 postexposure, which suggests that the spermatids were the most likely target. In contrast, no increase in postimplantation loss was observed in mice after oral treatment of males at 150 mg/kg/day for 5 days (Teramoto et al. 1980). Kluwe (1981) reported treatment-related histopathological effects (degenerative lesions in seminiferous tubules and decreased sperm density) in rats administered 1,2-dibromo-3-chloropropane by daily gavage for 4 days at 40 mg/kg/day (the only dose level tested).

Histological evaluation of the testes from rats gavaged with 15 mg/kg/day of 1,2-dibromo-3-chloropropane for 77 days revealed a reduced ratio of leptotene spermatocytes to Sertoli cells and reduced diameter of seminiferous tubules; this is evidence of reduced production of sperm. There was an increased incidence of dead embryos when the exposed males were allowed to mate with unexposed females during the last days of exposure (Amann and Berndtson 1986).

Rats that received 0.4–9.7 mg/kg/day of 1,2-dibromo-3-chloropropane from drinking water for 64 days exhibited no treatment-related effects on testes weight; sperm count; levels of LH, FSH, or testicular testosterone in serum; histopathology of the seminiferous tubules; or spermatozoal development (Heindel et al. 1989). No changes in fertility or gestation indices were observed in rats when both males and females that consumed 1,2-dibromo-3-chloropropane from the drinking water at up to 19.43 mg/kg/day for 60 days and were then allowed to mate (Johnston et al. 1986).

Reproductive toxicity was observed in other animal species as well. Oral exposure of male and female mice at 25 mg/kg/day for 126 days resulted in reduced numbers of litters (Reel et al. 1984). Reproductive success was not adversely affected among the control and high-dose (100 mg/kg/day) F1 offspring treated for an additional 98 days to produce an F2 generation, although the treated F1 male mice exhibited significantly decreased epididymal and prostate weights (8 and 20%, respectively, less than controls). Rabbits appear to be particularly sensitive to 1,2-dibromo-3-chloropropane treatment-related testicular

effects. Abnormalities in sperm morphology and decreased spermatogenesis were observed among rabbits receiving 1,2-dibromo-3-chloropropane from the drinking water for 10 weeks at doses ≥1.88 mg/kg/day (Foote et al. 1986b). Testicular atrophy occurred at 15 mg/kg/day. Increases in serum FSH levels, which are indicative of impaired spermatogenesis, were detected at 7.5 and 15 mg/kg/day, but were significant only at the higher dose. However, fertility was not affected when the exposed males were allowed to mate during the last week of the exposure. Complete azoospermia without recovery developed in monkeys within 45 days during 1,2-dibromo-3-chloropropane treatment; the initial concentration of 650 ppm in drinking water had been gradually reduced to 10 ppm over the first 27 days of treatment (Overstreet et al. 1988).

Statistically significant increased incidences of testicular atrophy were observed in rats gavaged at time-weighted average doses ≥15 or mg/kg/day for 64–78 weeks (NCI 1978). No increase in testicular atrophy was found in mice similarly treated at 114 mg/kg/day for 60 weeks or 219 mg/kg/day for 47 weeks (NCI 1978). No testicular changes were found in rats (Hazleton 1977, 1978a) or mice (Hazleton 1978b) receiving 1,2-dibromo-3-chloropropane from the diet for 104 weeks at 3 mg/kg/day (rats) or 78 weeks at 4.6 mg/kg/day (mice).

The mechanism of 1,2-dibromo-3-chloropropane testicular toxicity has been investigated in several studies *in vitro*. The inhibition of sperm carbohydrate metabolism, probably at the step of nicotinamide adenine dinucleotide (NADH) dehydrogenase activity in the mitochondrial electron transport chain, was suggested to be the cause of the toxicity (Bartoov et al. 1987; Greenwell et al. 1987). Results from other studies indicate that the severity of testicular necrosis is directly related to DNA damage (Lag et al. 1991; Omichinski et al. 1988a, 1988b; Soderlund et al. 1988). Metabolism via a cytochrome P450-dependent pathway is probably not involved in the DNA-damaging effects because the use of deuterated analogs of the parent compound, which interfere with cytochrome P450 metabolism, did not decrease the amount of the damage. It has been suggested that the testicular genotoxicity of 1,2-dibromo-3-chloropropane may involve conjugation with GSH, with subsequent formation of a reactive episulphonium ion that can cause direct alkylation of target molecules. If so, in contrast to the apparent detoxifying role of GSH conjugation in the liver, conjugation with GSH in the testes may be a toxifying mechanism.

2.17 DEVELOPMENTAL

No increase in gross congenital malformations and no cytogenetic abnormalities were found in a cohort of 34 children conceived during or after paternal exposure to 1,2-dibromo-3-chloropropane, as compared

with the control group that was conceived before the exposure (Goldsmith et al. 1984; Potashnik and Abeliovich 1985; Potashnik and Phillip 1988). Exposure was likely through inhalation and the levels were not specified in these reports.

No correlation between low birth weights or birth defects and 1,2-dibromo-3-chloropropane contamination of drinking water was found in a population exposed in Fresno County, California, during 1978–1982 (Whorton et al. 1989). Potential exposure concentrations of 1,2-dibromo-3-chloropropane in the water system ranged from $1x10^{-7}$ to $1.6x10^{-4}$ mg/kg/day.

Depressed pup body weight was observed in a single-generation reproductive toxicity study of rat dams receiving 1,2-dibromo-3-chloropropane from the drinking water at 19.43 mg/kg/day, an exposure level resulting in >60% depressed maternal body weight gain accompanied by decreased food and water intake (Johnston et al. 1986). In another study, (Ruddick and Newsome 1979) pregnant rats were treated with 1,2-dichloro-3-bromopropane by gavage during gestation days 6–15 at up to 50 mg/kg/day. The highest dose level resulted in 33% depressed maternal weight gain, embryonic lethality, and depressed fetal body weight. There were no signs of developmental toxicity in a study of mice administered 1,2-dibromo-3-chloropropane by gavage for up to 126 days at 100 mg/kg/day (Reel et al. 1984). However, Reel et al. (1984) reported significantly depressed live pup weight (6% less than controls) among male (but not female) offspring of mice gavaged for 98 days at 100 mg/kg/day after having been exposed via their mothers during gestation and lactation.

2.18 OTHER NONCANCER

Severe hair loss (33–95% of the body) was reported in rats repeatedly exposed to 1,2-dibromo-3-chloropropane vapor for 13 weeks at 25 ppm (NTP 1982).

2.19 CANCER

In an epidemiological study of workers exposed to 1,2-dibromo-3-chloropropane, no increase in the incidence of mortality from cancer of the lungs, stomach, liver, kidney, testes, or skin was found. The workers were exposed to airborne 1,2-dibromo-3-chloropropane concentrations <1 ppm (time-weighted average exposure levels obtained via personal monitoring in the years 1974 and 1975); however, exposure levels in previous years were not known (Hearn et al. 1984).

Wong et al. (1989) performed ecological and case-control analyses of individuals in Fresno County, California, where drinking water contained 1,2-dibromo-3-chloropropane levels in the range of 0.004–5.75 ppb during the years 1978–1982. There were no significant correlations between 1,2-dibromo-3-chloropropane levels in the drinking water and incidences of gastric cancer or leukemia.

When rats were exposed by inhalation (6 hours/day, 5 days/week, for 84–103 weeks) to 0.6 or 3 ppm 1,2-dibromo-3-chloropropane, multiple-site tumors developed. The most common were carcinomas and squamous cell carcinomas of the nasal cavity (squamous cell papilloma, adenocarcinoma, and adenomatous polyps were also observed), squamous cell papillomas of the tongue in both sexes, fibroadenomas of the mammary gland and adenomas of the adrenal cortex in females, and trichoadenomas of the skin and mesotheliomas of the tunica vaginalis in males. Adenomas, squamous cell carcinomas, and carcinomas of the respiratory tract also developed in mice after intermittent chronic-duration inhalation exposure to 1,2-dibromo-3-chloropropane at 0.6 or 3 ppm (NTP 1982).

Carcinogenicity has been observed in animals following chronic-duration oral exposure to 1,2-dibromo-3-chloropropane. Multiple-site carcinomas were found in rats treated by gavage at 15 or 29 mg/kg/day (NCI 1978). An increased incidence of carcinomas, squamous cell carcinomas, and papillomas of the forestomach was observed in rats of both sexes. Hemangiomas were detected in the spleens of both sexes treated with 15 mg/kg/day, while mammary adenocarcinomas were found in both 15 and 29 mg/kg/day females. Squamous cell carcinomas of the stomach were observed in similarly-treated male and female mice at 110–114 mg/kg/day (NCI 1978). Increased incidences of squamous cell carcinoma of the forestomach, hepatocellular carcinoma, and adenoma and/or carcinoma of the kidneys were observed in rats that ingested 3 mg/kg/day 1,2-dibromo-3-chloropropane for 104 weeks from their diet (Hazleton 1977, 1978a). Squamous cell papillomas and carcinomas also developed in the stomachs of mice chronically exposed to 4.6 mg/kg/day (Hazleton 1978b). Metastatic lesions from these tumors were observed in livers, kidneys, and other viscera. Benign lung papillomas and stomach carcinomas and papillomas were found in mice after dermal application of 390 mg/kg/application, 3 days/week for up to 85 weeks (Van Duuren et al. 1979). These tumors may have resulted from ingestion of dermally-applied 1,2-dibromo-3-chloropropane during grooming activity. 1,2-Dibromo-3-chloropropane was also active as a skin-tumor initiator in a two-stage carcinogenicity assay; phorbol myristate acetate was used as a promoter. The median survival time for mice was 342–468 days (Van Duuren et al. 1979).

The U.S. Department of Health and Human Services categorized 1,2-dibromo-3-chloropropane as reasonably anticipated to be a human carcinogen (NTP 2016). EPA's Integrated Risk Information System

(IRIS 2003) has not evaluated 1,2-dibromo-3-chloropropane for carcinogenicity. The International Agency for Research on Cancer categorized 1,2-dibromo-3-chloropropane as possibly carcinogenic to humans (Group 2B) (IARC 1999). The cancer classifications are based on sufficient evidence of carcinogenicity in animal studies and inadequate or no evidence in humans.

A genotoxic mode of action appears likely for 1,2-dibromo-3-chloropropane carcinogenicity based on positive results from a variety of *in vivo* and *in vitro* tests (see Section 2.20). 1,2-Dibromo-3-chloropropane-induced DNA damage has been observed in tissues exhibiting 1,2-dibromo-3-chloropropane-induced tumors as well.

2.20 GENOTOXICITY

1,2-Dibromo-3-chloropropane was evaluated for potential genotoxicity both *in vivo* (Table 2-4) and *in vitro* (Table 2-5).

Table 2-4. Genotoxicity of 1,2-Dibromo-3-Chloropropane *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Drosophila melanogaster (vapor exposure of adult males)	Sex-linked recessive lethal mutations in sperm cells	–	Kale and Baum 1982a
D. melanogaster (vapor exposure of male embryos)	Sex-linked recessive lethal mutations in spermatogonia	(+)	Kale and Baum 1982a
D. melanogaster (feed of adult males)	Sex-linked recessive lethal mutations	+	Zimmering 1983
D. melanogaster (feed of adult males)	Sex-linked recessive lethal mutations	+	Inoue et al. 1982
D. melanogaster (feed of adult males)	Sex-linked recessive lethal mutations	+	Yoon et al. 1985
D. melanogaster (vapor exposure of adult males)	Genetic crossing over in sperm cells	+	Kale and Baum 1982a
D. melanogaster (vapor exposure of male embryos)	Genetic crossing over in spermatogonia	–	Kale and Baum 1982a
D. melanogaster (vapor exposure of adult males)	Heritable translocations	–	Kale and Baum 1982a
D. melanogaster (feed of adult males)	Heritable translocations	+	Yoon et al. 1985
D. melanogaster (feed of adult males)	Heritable translocations	+	Zimmering 1983
D. melanogaster (feed of adult males)	Chromosome loss	+	Zimmering 1983
Muta-mouse (intraperitoneal)	Gene mutation in testicular cells	(+)	Hachiya and Motohashi 2000

Table 2-4. Genotoxicity of 1,2-Dibromo-3-Chloropropane *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Mouse (intraperitoneal)	Specific-locus gene mutations	–	Russell et al. 1986
Mouse (intraperitoneal)	Somatic cell mutagenicity (spot test)	+	Sasaki et al. 1986
Mouse (intraperitoneal)	Chromosomal aberrations in bone marrow	–	Shelby and Witt 1995
Rat (intraperitoneal)	DNA damage in cells from multiple organs	+	Brunborg et al. 1988, 1996
Rat (intraperitoneal)	DNA damage in kidney and testicular cells	+	Lag et al. 1991
Rat (intraperitoneal)	DNA damage in kidney cells	+	Omichinski et al. 1987
Rat, mouse, guinea pig, hamster (intraperitoneal)	DNA damage in kidney cells	+	Soderlund et al. 1990
Mouse (oral)	DNA damage	+	Sasaki et al. 1998
Rat (oral)	Micronuclei in bone marrow	+	Albanese et al. 1988; George et al. 1990
Mouse (oral)	Micronuclei in bone marrow, stomach, liver, kidney, lung	+	Sasaki et al. 1998
Mouse (oral)	Micronuclei in bone marrow	–	Albanese et al. 1988
Mouse (intraperitoneal)	Micronuclei in bone marrow	–	Shelby and Witt 1995; Shelby et al. 1993
Rat (oral)	Dominant lethality	+	Teramoto et al. 1980
Rat (oral)	Dominant lethality	+	Saito-Suzuki et al. 1982
Rat (inhalation)	Dominant lethality	+	Rao et al. 1983
Mouse (oral)	Dominant lethality	–	Teramoto et al. 1980
Mouse (intraperitoneal or subcutaneous)	Dominant lethality	–	Generoso et al. 1985
Rat (intraperitoneal)	Unscheduled DNA synthesis in spermatocytes	+	Bentley and Working 1988
Mouse, prepubertal males (intraperitoneal)	Unscheduled DNA synthesis in premeiotic germ cells	+	Lee and Suzuki 1979
Mouse, adult males (intraperitoneal)	Unscheduled DNA synthesis in spermatozoa	–	Lee and Suzuki 1979

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

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

Species (test system)	Endpoint	Results: Activation: With	Results: Activation: Without	Reference
Salmonella typhimurium TA98, TA100, TA1535	Gene mutation	+	+	Moriya et al. 1983
S. typhimurium TA1537, TA1538	Gene mutation	No data	–	Moriya et al. 1983
S. typhimurium TA1537, TA1538	Gene mutation	–	–	McKee et al. 1987
S. typhimurium TA98, TA100	Gene mutation	+	–	McKee et al. 1987
S. typhimurium TA1535	Gene mutation	+	+	McKee et al. 1987
S. typhimurium TA1535	Gene mutation	+	–	Biles et al. 1978
S. typhimurium TA98, TA100	Gene mutation	+	–	Stolzenberg and Hine 1979
S. typhimurium TA100, TA1535	Gene mutation	+	–	Ratpan and Plaumann 1988
S. typhimurium TA1530	Gene mutation	No data	+	Rosenkranz 1975
S. typhimurium TA1538	Gene mutation	No data	–	Rosenkranz 1975
S. typhimurium TA100	Gene mutation	+	No data	Lag et al. 1994
S. typhimurium TA100	Gene mutation	+	–	Simula et al. 1993
S. typhimurium TA100	Gene mutation	–	–	Omichinski et al. 1988b
S. typhimurium BA13	Gene mutation	+	–	Roldan-Arjona et al. 1991
Escherichia coli WP2hvr	Gene mutation	No data	+	Moriya et al. 1983
Big Blue Rat2 fibroblasts	Gene mutation	No data	(+)	Ryu et al. 2002
Chinese hamster V79 cells	Sister chromatid exchange	No data	+	Tezuka et al. 1980
Chinese hamster ovary cells	Sister chromatid exchange	+	+	Loveday et al. 1989
Chinese hamster ovary cells	Chromosomal aberrations	+	+	Loveday et al. 1989
Chinese hamster V79 cells	Chromosomal aberrations	No data	+	Tezuka et al. 1980
E. coli PQ37	DNA damage	+	No data	Ohta et al. 1984
Chinese hamster V79 cells	DNA damage	No data	+	Soderlund et al. 1991
Rat liver cells	DNA damage	No data	+	Soderlund et al. 1991
Rat liver cells	DNA damage	No data	+	Labaj et al. 2007
Rat liver cells	DNA damage	No data	+	Holme et al. 1991
Rat liver and kidney cells	DNA damage	No data	+	Kouzi et al. 1995
Rat testicular cells	DNA damage	No data	+	Soderlund et al. 1991
Rat testicular cells	DNA damage	No data	+	Omichinski et al. 1988b
Rat testicular cells	DNA damage	No data	+	Bjorge et al. 1995, 1996

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

Species (test system)	Endpoint	Results: Activation: With	Results: Activation: Without	Reference
Rat testicular cells	DNA damage	No data	+	Lag et al. 1991
Rabbit lung cells	DNA damage	No data	+	Becher et al. 1993
Pig kidney LLCPK cells	DNA damage	No data	+	Wiger et al. 1998
Human testicular cells	DNA damage	No data	–	Bjorge et al. 1996
Human renal proximal tubular cells	DNA damage	No data	+	Wiger et al. 1998
Human leukemia HL-60 cell line	DNA damage	No data	+	Wiger et al. 1998
Rat liver cells	Unscheduled DNA synthesis	No data	+	Soderlund et al. 1991

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

1,2-Dibromo-3-chloropropane was positive for genotoxicity in most *in vivo* studies. In assays of *Drosophila melanogaster*, 1,2-dibromo-3-chloropropane-induced sex-linked lethal mutations (Inoue et al. 1982; Yoon et al. 1985; Zimmering 1983), genetic crossing over in sperm cells (Kale and Baum 1982a), heritable translocations (Yoon et al. 1985; Zimmering 1983), and chromosome loss (Zimmering 1983). 1,2-Dibromo-3-chloropropane induced gene mutations in mouse somatic cells (Sasaki et al. 1986), deoxyribonucleic acid (DNA) damage in cells from selected organs of rat, mouse, guinea pig, and hamster (Brunborg et al. 1988, 1996; Lag et al. 1991; Omichinski et al. 1987; Sasaki et al. 1998; Soderlund et al. 1990), micronuclei in bone marrow from rats and mice (Albanese et al. 1988; George et al. 1990; Sasaki et al. 1998; Shelby and Witt 1995; Shelby et al. 1993), micronuclei in cells from stomach, liver, kidney, and lung of treated mice (Sasaki et al. 1998), and dominant lethality and unscheduled DNA synthesis in rats and/or mice (Bentley and Working 1988; Lee and Suzuki 1979; Rao et al. 1983; Saito-Suzuki et al. 1982; Teramoto et al. 1980).

1,2-Dibromo-3-chloropropane was positive for genotoxicity in most *in vitro* assays as well. 1,2-Dibromo-3-chloropropane-induced gene mutations were reported in several strains of *Salmonella typhimurium* in the presence of exogenous metabolic activation (Biles et al. 1978; Lag et al. 1994; McKee et al. 1987; Moriya et al. 1983; Ratpan and Plaumann 1988; Roldan-Arjona et al. 1991; Simula et al. 1993; Stolzenberg and Hine 1979). In the assay of Simula et al. (1993), 1,2-dibromo-3-chloropropane-induced mutation was potentiated in *S. typhimurium* strain TA100 expressing human GST, indicating that cytochrome P450-mediated metabolism was a prerequisite for GST-mediated potentiation. A few *S.*

typhimurium assays were positive for gene mutation in the absence of exogenous metabolic activation (McKee et al. 1987; Moriya et al. 1983; Rosenkranz 1975). However, most assays of *S. typhimurium* that evaluated gene mutation in the absence of exogenous metabolic activation provided negative results (Biles et al. 1978; McKee et al. 1987; Moriya et al. 1983; Ratpan and Plaumann 1988; Roldan-Arjona et al. 1991; Rosenkranz 1975; Simula et al. 1993; Stolzenberg and Hine 1979). In two assays, 1,2-dibromo-3-chloropropane was negative for gene mutations both with and without exogenous metabolic activation (McKee et al. 1987; Omichinski et al. 1988b). 1,2-Dibromo-3-chloropropane induced gene mutation in *Escherichia coli* strain WP2hvr in the absence of exogenous metabolic activation (Moriya et al. 1983).

1,2-Dibromo-3-chloropropane-induced gene mutations (predominant mutations indicative of a base substitution mutagen, especially at guanine bases) were reported in Big Blue Rat2 fibroblasts (Ryu et al. 2002). 1,2-Dibromo-3-chloropropane induced sister chromatid exchange and chromosomal aberrations in Chinese hamster V79 cells in the absence of exogenous metabolic activation (Tezuka et al. 1980) and ovary cells in the presence and absence of exogenous metabolic activation (Loveday et al. 1989), DNA damage in rat liver, kidney, and/or testicular cells (Bjorge et al. 1995, 1996; Holme et al. 1991; Kouzi et al. 1995; Labaj et al. 2007; Lag et al. 1991; Omichinski et al. 1988b; Soderlund et al. 1991); rabbit lung cells (Becher et al. 1993); and pig kidney cells, human renal proximal tubular cells, and human leukemia HL-60 cells (Wiger et al. 1998), in the absence of exogenous metabolic activation. No evidence of DNA damage was observed in 1,2-dibromo-3-chloropropane-exposed human testicular cells in the absence of exogenous metabolic activation (Bjorge et al. 1996). Unscheduled DNA synthesis was observed in rat liver cells incubated with 1,2-dibromo-3-chloropropane in the absence of exogenous metabolic activation (Soderlund et al. 1991).