Toxicological Profile for 1,2-Dibromo-3-Chloropropane

April 2018

U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

CS274127-A

FOREWORD

This toxicological profile is prepared in accordance with guidelines* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance due to associated acute, intermediate, and chronic exposures;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, intermediate, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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*Legislative Background

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

VERSION HISTORY

Date	Description
April 2018	Update of data in Chapters 2, 3, and 7
September 1992	Final Toxicological profile released

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ATSDR, Division of Community Health Investigations; ATSDR, Office of Science; NCEH, Division of Laboratory Science; NCEH, Division of Environmental Health Science and Practice.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

ATSDR's *Toxicological Profile for 1,2-Dibromo-3-chloropropane* was released in 1992. In order to update the literature in this profile, ATSDR conducted a literature search focused on health effects information as described in Appendix B. Chapters 2, 3, and 7 were revised to reflect the most current health effects data. In some cases, other sections of the profile were updated as needed or for consistency with the updated health effects and regulations/guidelines. However, the focus of the update to this profile is on health effects information.

The major sources of 1,2-dibromo-3-chloropropane ($C_3H_5Br_2Cl$; CAS Number 96-12-8) in the environment are from its former use as a soil fumigant (fumes that rid vermin or disinfect) and nematocide (worm killer) on a variety of crops and from unintentional release from hazardous waste sites that contain the chemical. There have been no recent reportable releases of 1,2-dibromo-3-chloropropane to the air, water, or soil (TRI16 2017) because all registered uses as a pesticide were canceled by the U.S. Environmental Protection Agency (EPA) in 1985.

The most likely sources of exposure of the general population to 1,2-dibromo-3-chloropropane are from drinking water that may have been contaminated in areas where the chemical was used for agricultural purposes or from food sources grown in soil that may still contain residues. However, it is not likely that the general population would be exposed to 1,2-dibromo-3-chloropropane levels in drinking water or food sources that would be high enough to cause adverse health effects.

1.2 SUMMARY OF HEALTH EFFECTS

As illustrated in Figures 1-1 and 1-2, the most sensitive effects associated with inhalation and oral exposure are testicular, renal, liver, body weight, gastrointestinal, and respiratory effects.

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to 1,2-Dibromo-3-Chloropropane

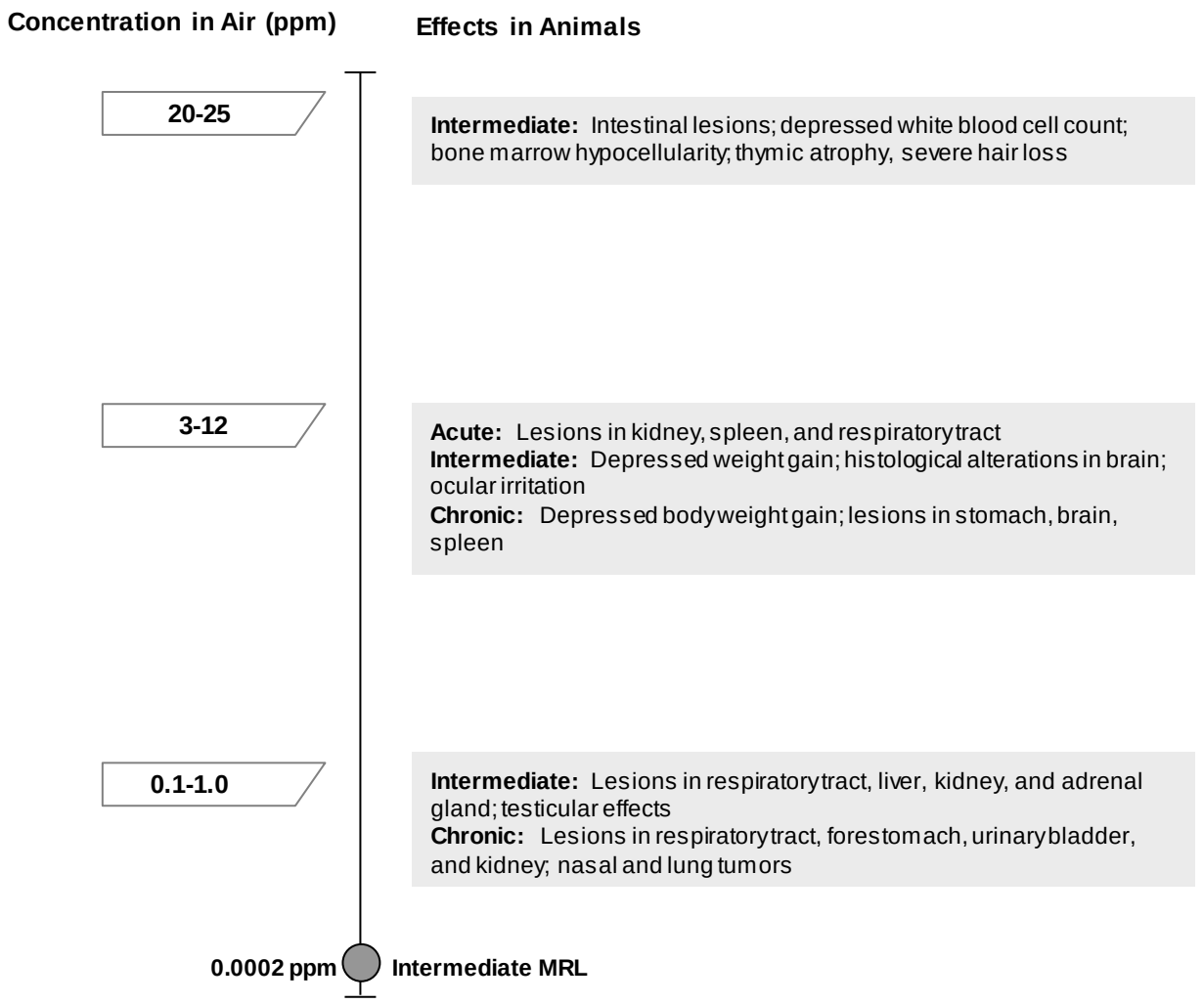
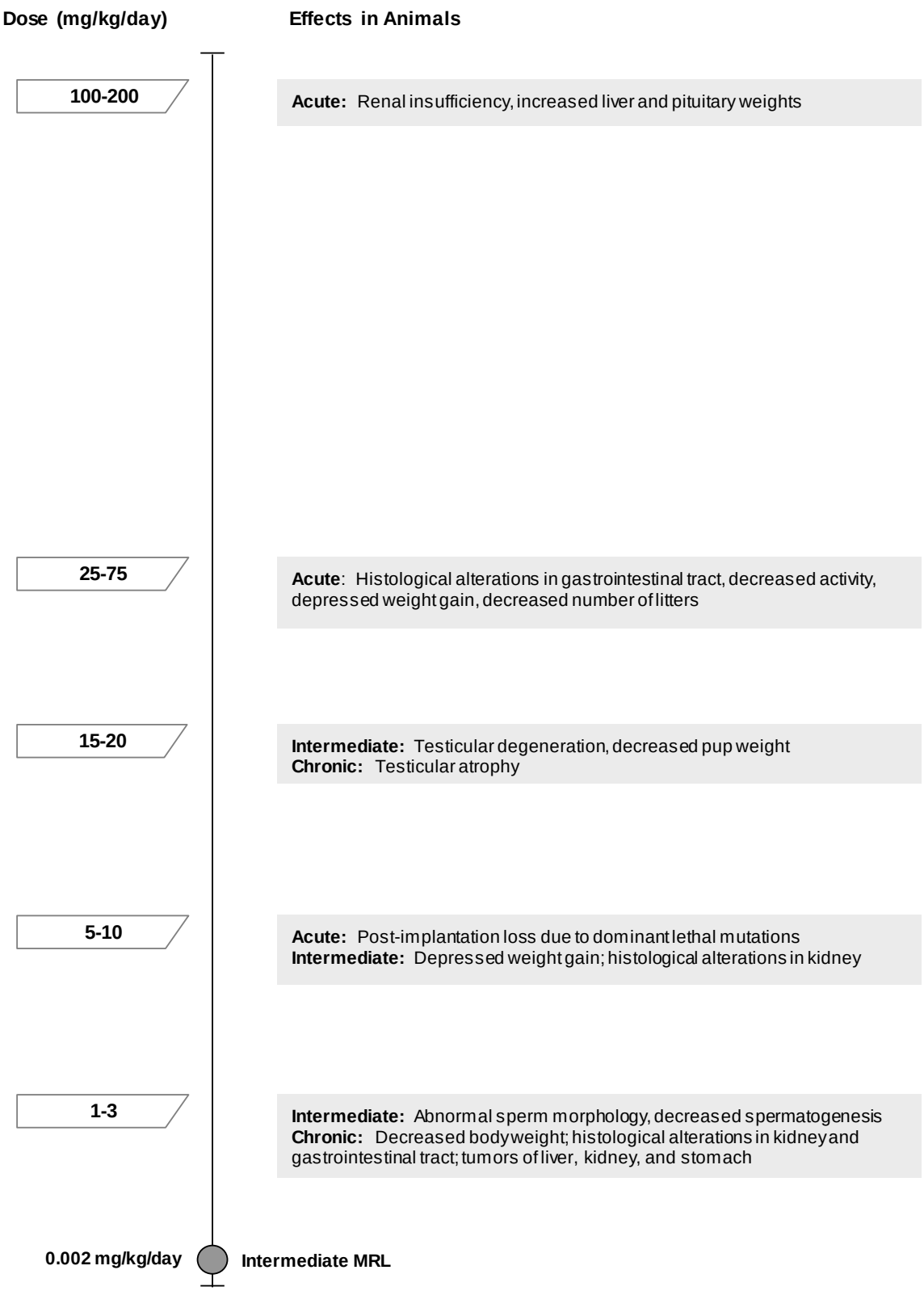


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to 1,2-Dibromo-3-Chloropropane



1.3 MINIMAL RISK LEVELS (MRLs)

As presented in Figure 1-3, limited inhalation data from animals indicate the respiratory, renal, and gastrointestinal systems as particularly sensitive targets of 1,2-dibromo-3-chloropropane toxicity. The MRL value for intermediate-duration inhalation exposure to 1,2-dibromo-3-chloropropane is summarized in Table 1-1 and discussed in greater detail in Appendix A. As presented in Figure 1-4, available oral data from animals indicate the gastrointestinal, male reproductive, and renal systems as particular sensitive targets of 1,2-dibromo-3-chloropropane toxicity. The MRL value for intermediate-duration oral exposure to 1,2-dibromo-3-chloropropane is summarized in Table 1-1 and discussed in greater detail in Appendix A. The databases were considered inadequate for derivation of acute- or chronic-duration inhalation or oral MRLs; see Appendix A for more details.

Figure 1-3. Summary of Sensitive Targets of 1,2-Dibromo-3-Chloropropane -- Inhalation

The renal system, respiratory tract, gastrointestinal tract, and liver are the most sensitive targets of 1,2-dibromo-3-chloropropane.

Numbers in circles are the lowest LOAELs (ppm) among health effects in animals; no human data were identified.

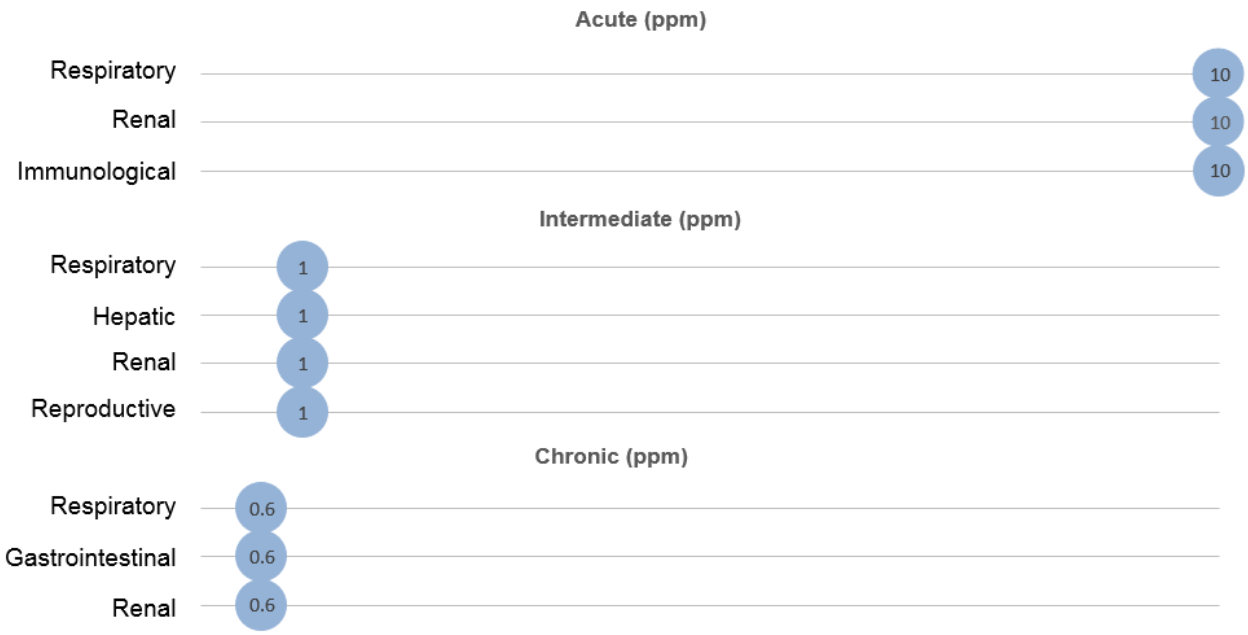


Figure 1-4. Summary of Sensitive Targets of 1,2-Dibromo-3-Chloropropane -- Oral

The gastrointestinal tract and male reproductive system are the most sensitive targets of 1,2-dibromo-3-chloropropane.

Numbers in circles are the lowest LOAELs (mg/kg/day) among health effects in animals; no reliable dose response data were available for humans.

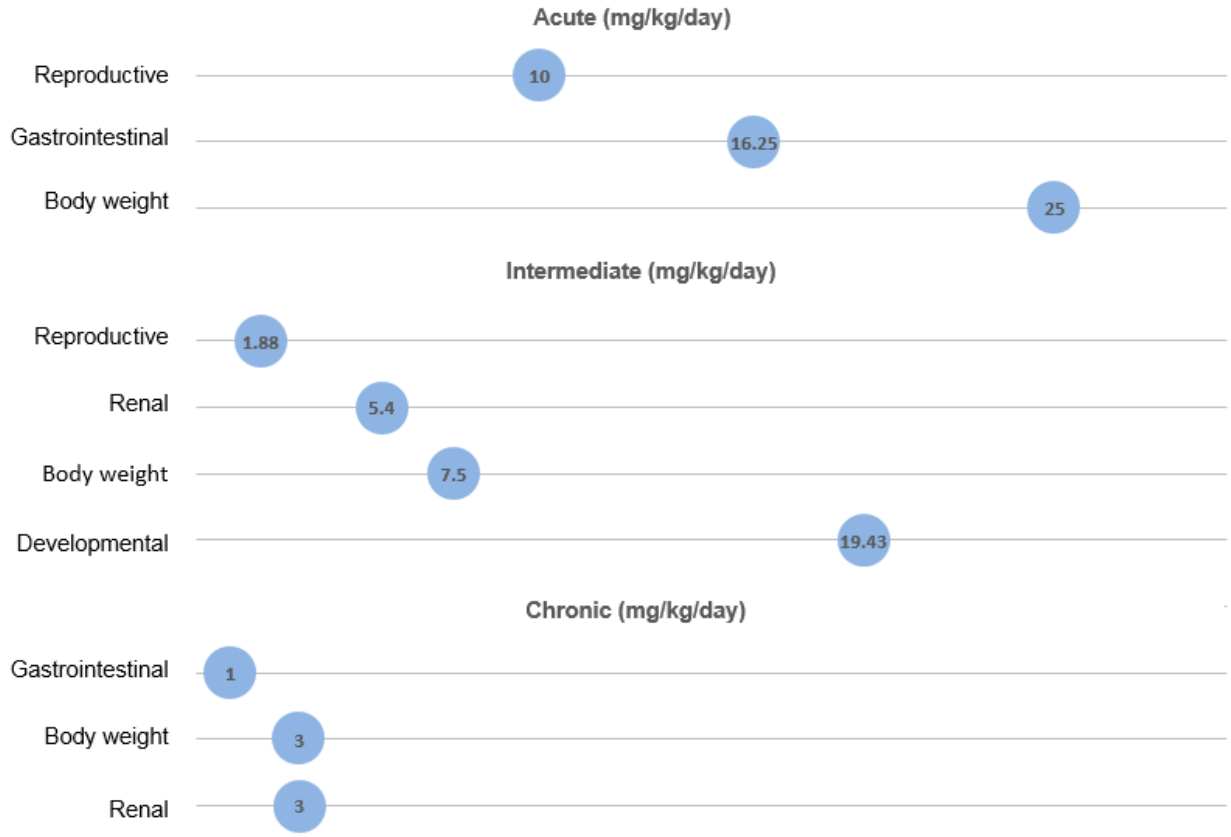


Table 1-1. Minimal Risk Levels (MRLs) for 1,2-Dibromo-3-Chloropropane[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute	Insufficient data for MRL derivation				
Intermediate	0.0002	Impaired spermatogenesis; testicular atrophy	0.1 (NOAEL)	100	Rao et al. 1982
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	Insufficient data for MRL derivation				
Intermediate	0.002	Impaired spermatogenesis and sperm morphology	1.88 (LOAEL)	1,000	Foote et al. 1986a, 1986b
Chronic	Insufficient data for MRL derivation				

[a]See Appendix A for additional information.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

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:

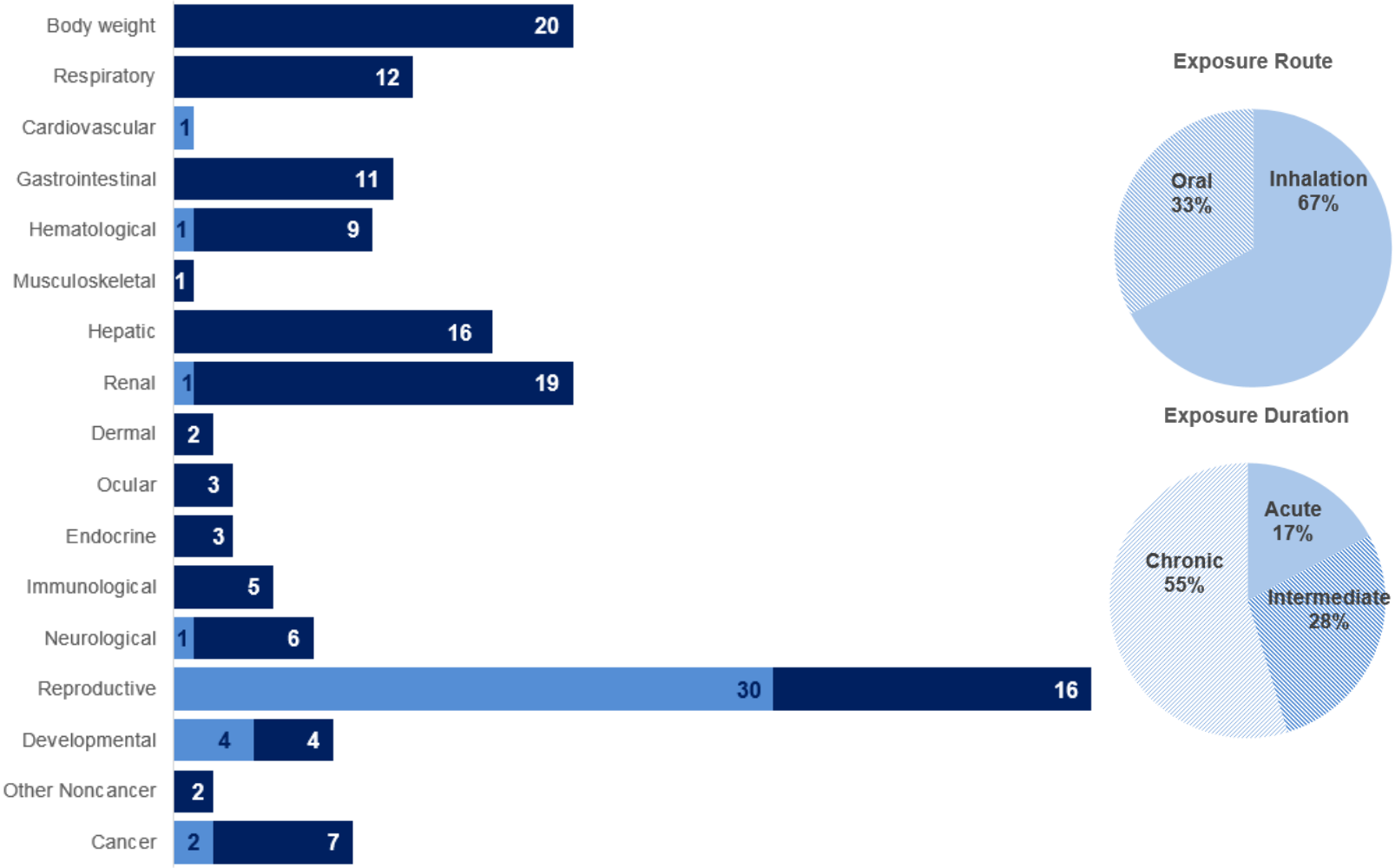
- **Respiratory Endpoint:** Inhalation exposure of laboratory animals resulted in adverse effects in in the nasal cavity, trachea, and bronchi that included inflammatory and proliferative changes and epithelial necrosis.
- **Gastrointestinal Endpoint:** Oral exposure of laboratory animals resulted in 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									

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
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)

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
					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)

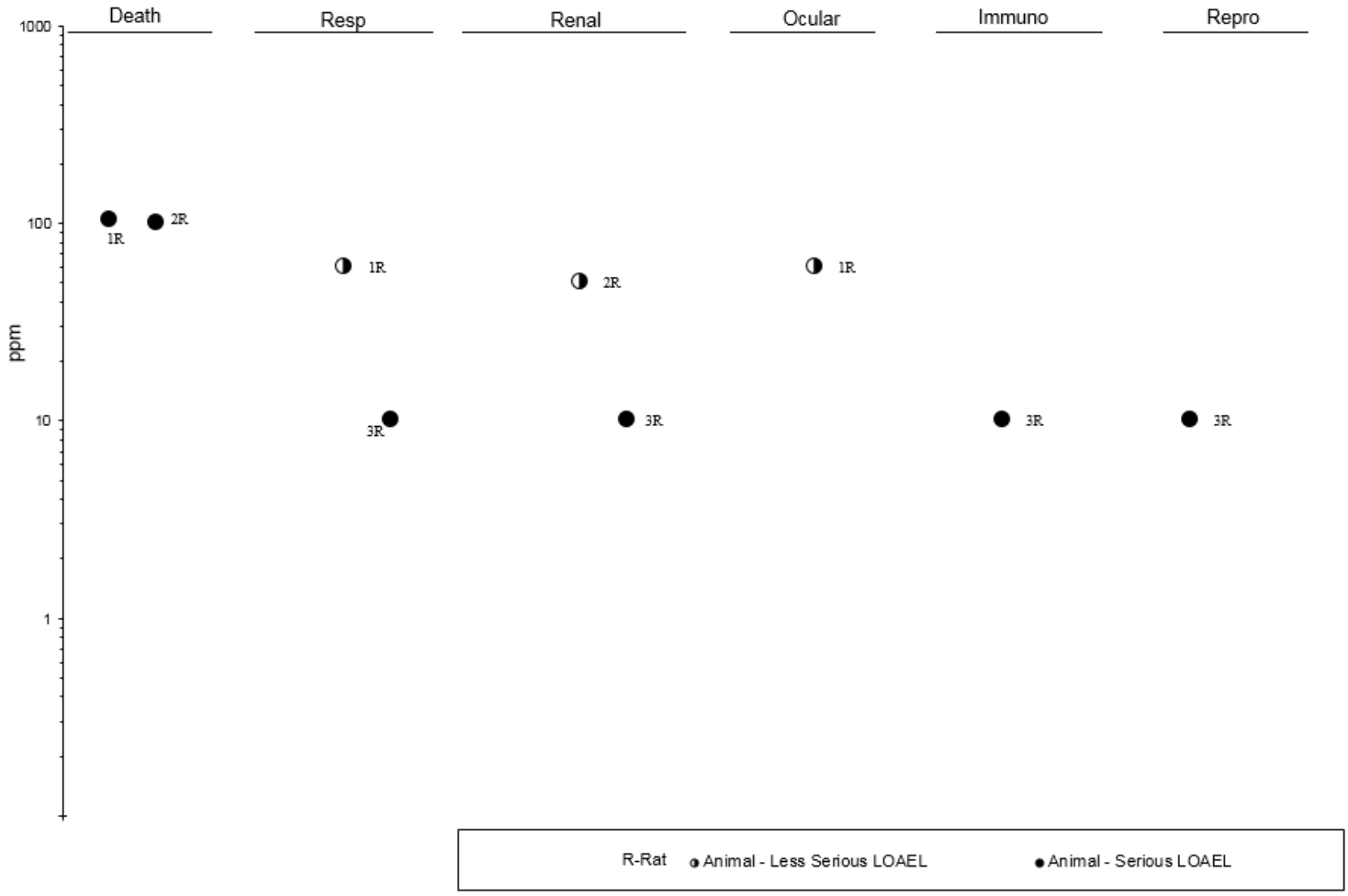


Figure 2-2. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – Inhalation
Intermediate (15-364 days)

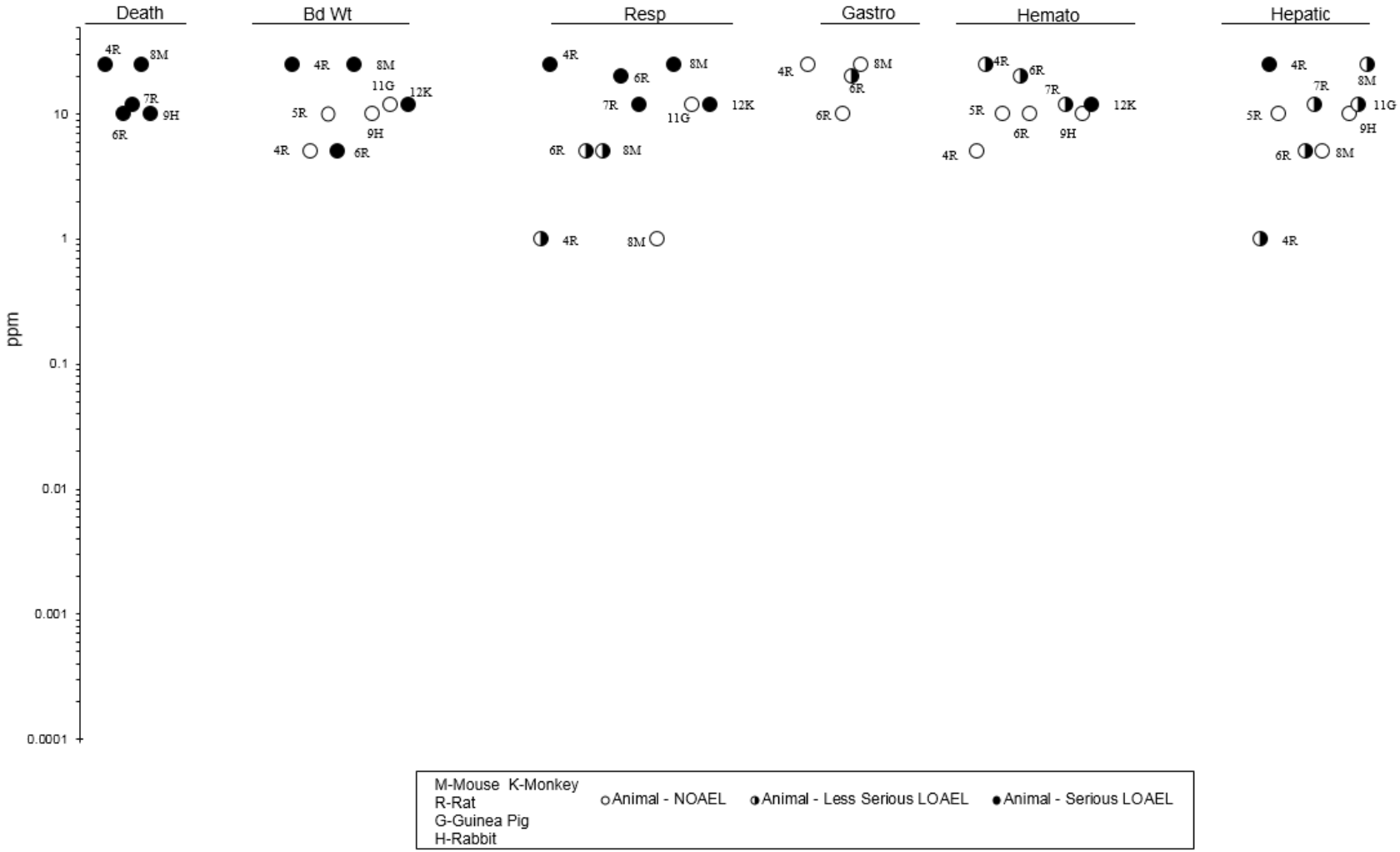


Figure 2-2. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – Inhalation
Intermediate (15-364)

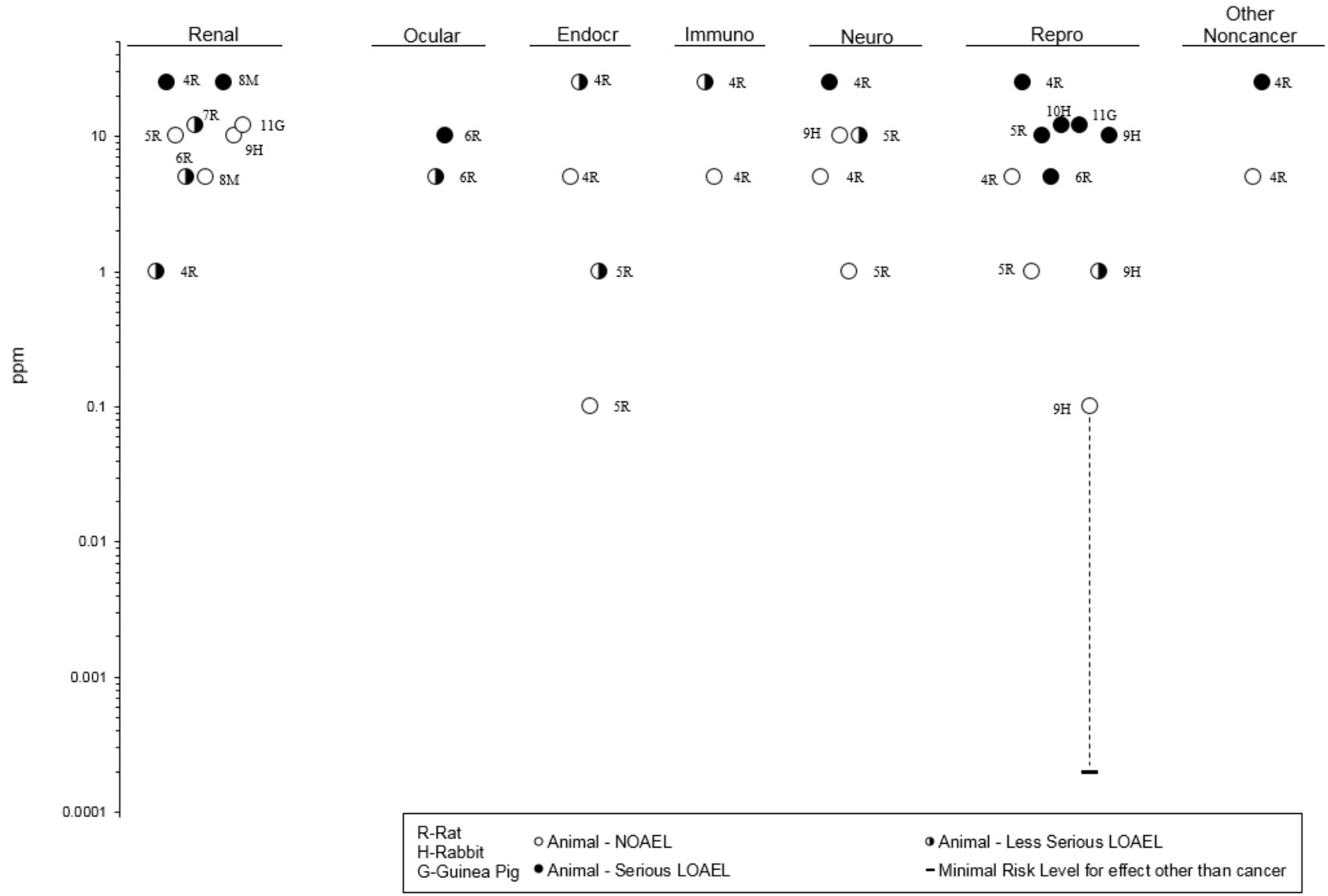


Figure 2-2. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – Inhalation
Chronic (≥365 days)

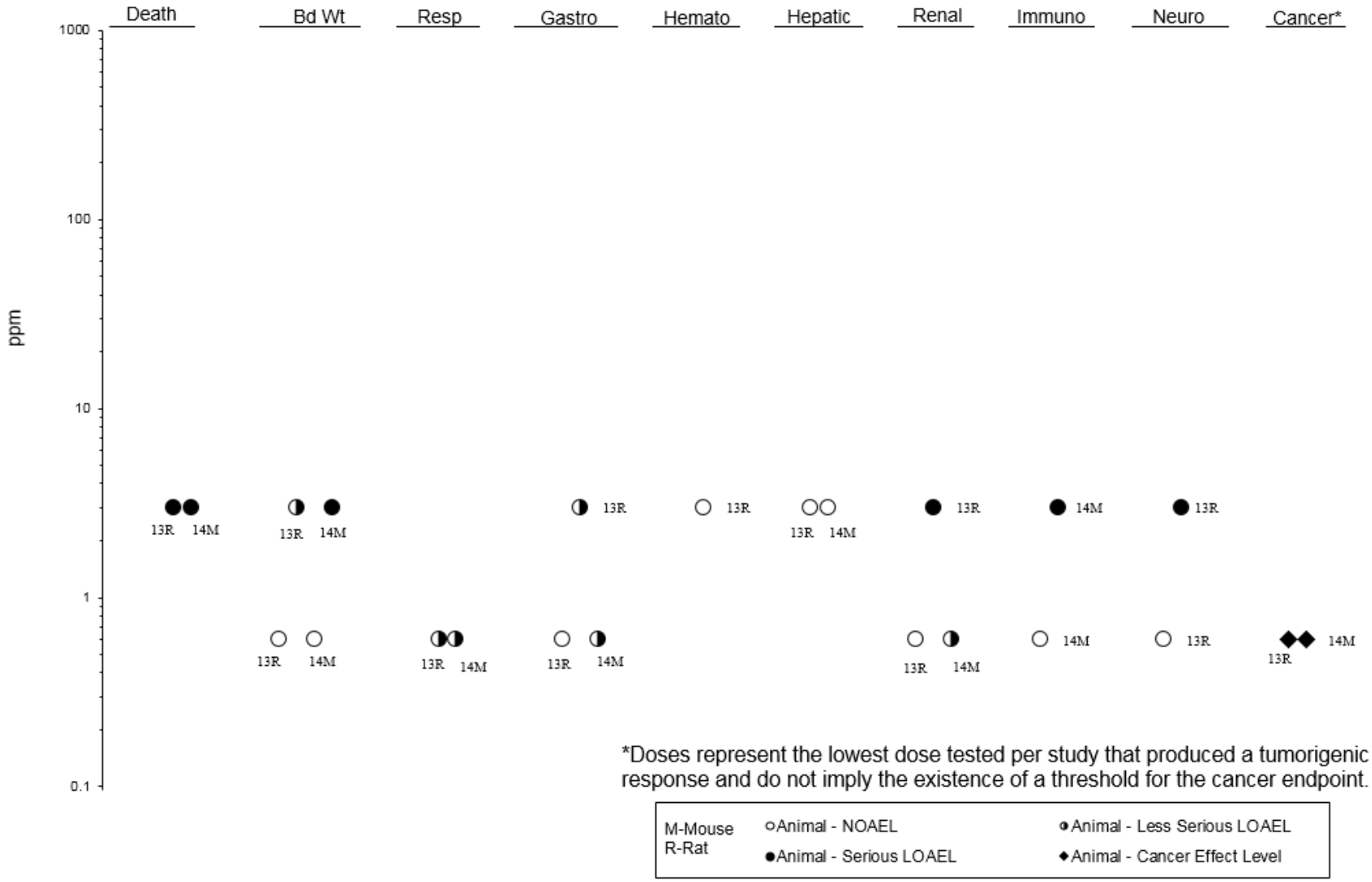


Table 2-2. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – Oral

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)

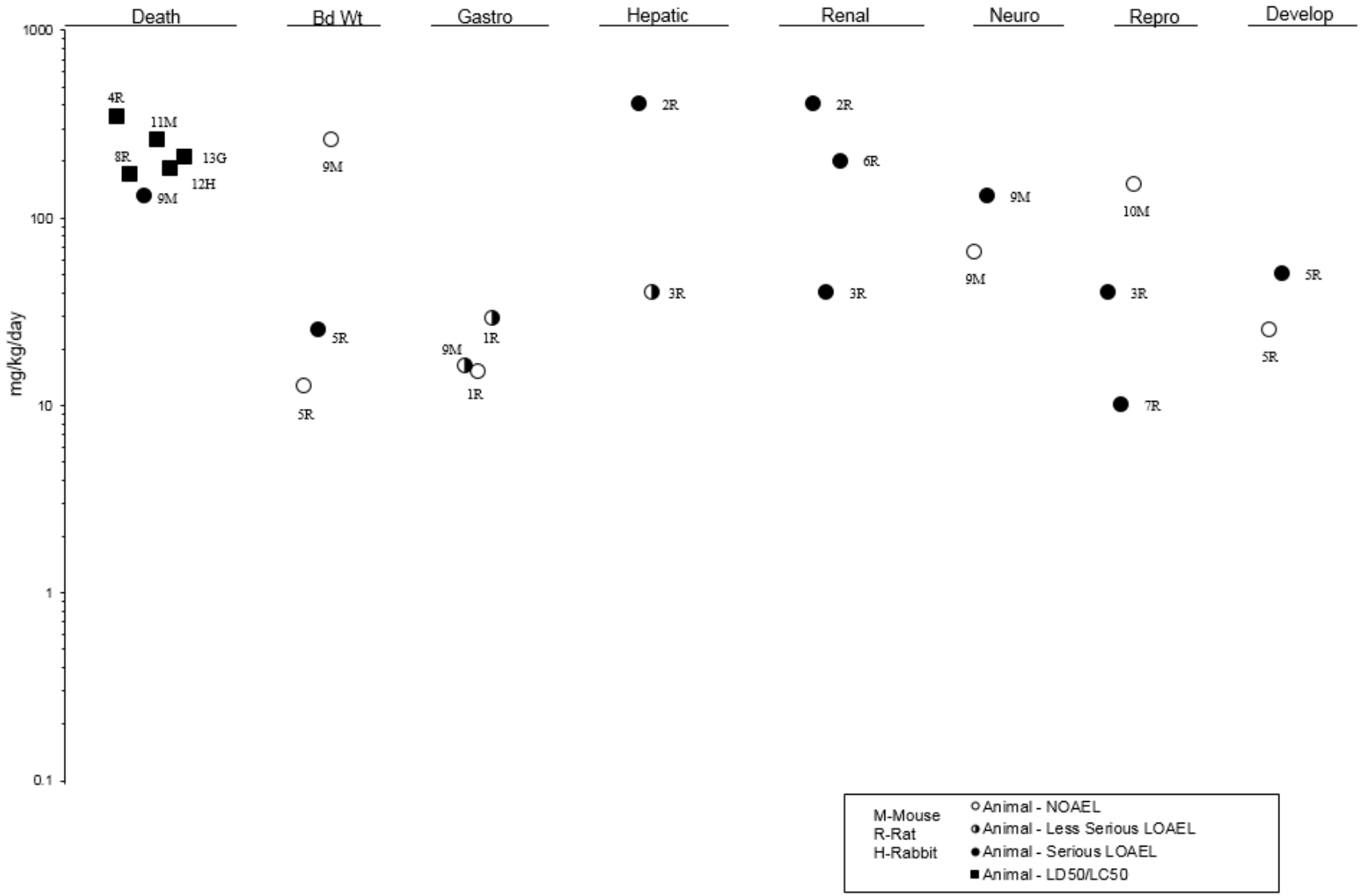


Figure 2-3. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – Oral
Intermediate (14-364 days)

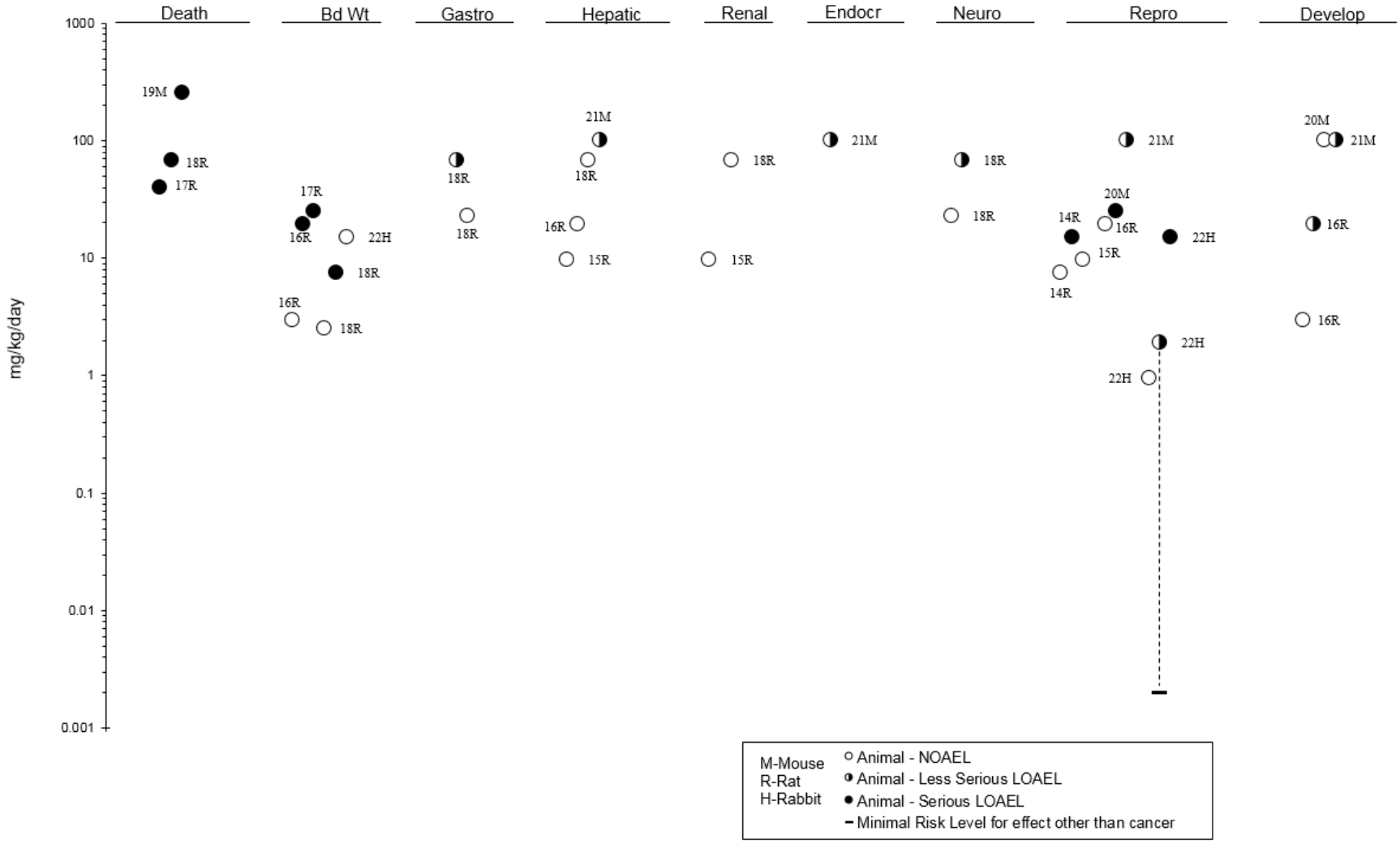


Figure 2-3. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – Oral
Chronic (≥365 days)

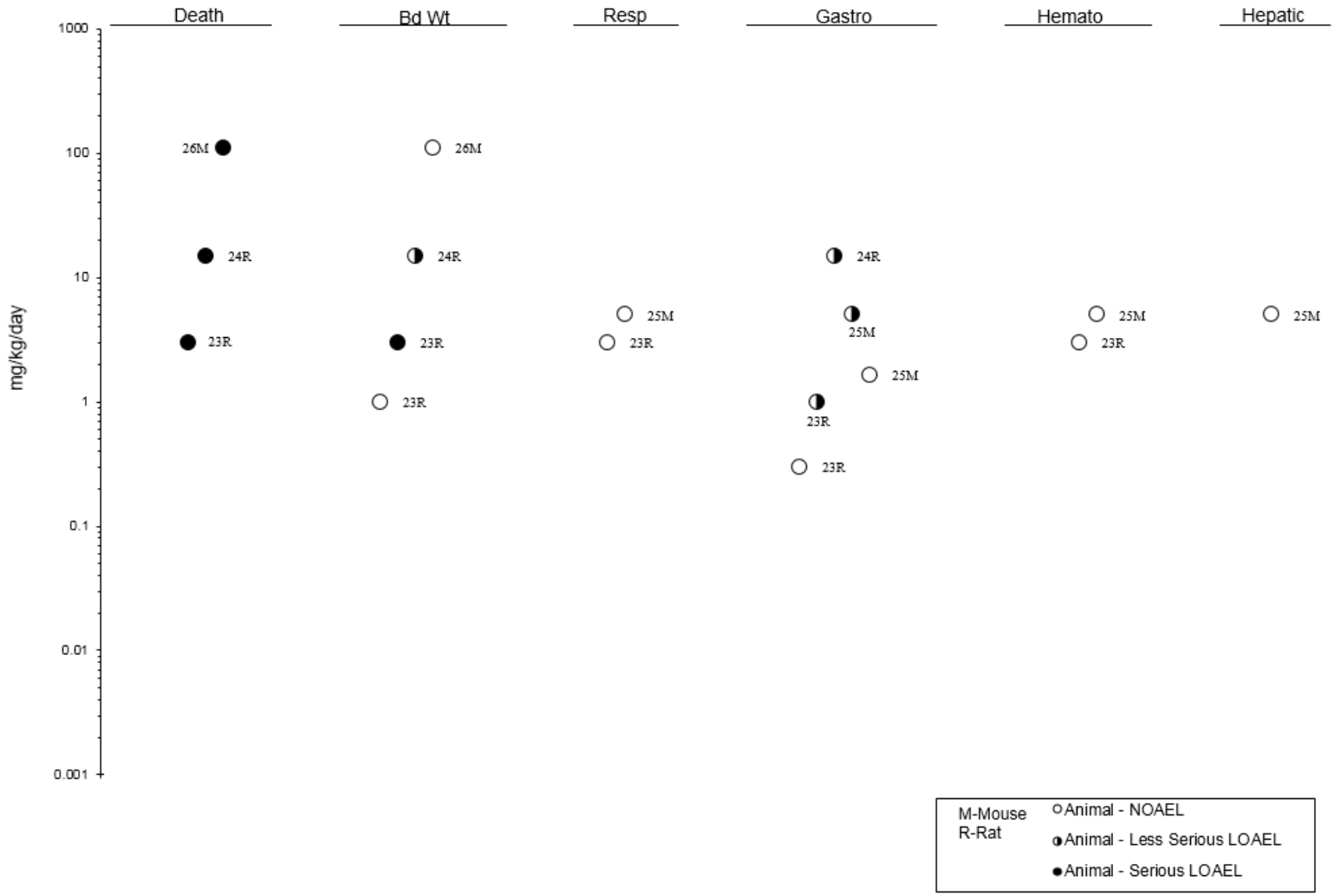


Figure 2-3. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – Oral
Chronic (≥365 days)

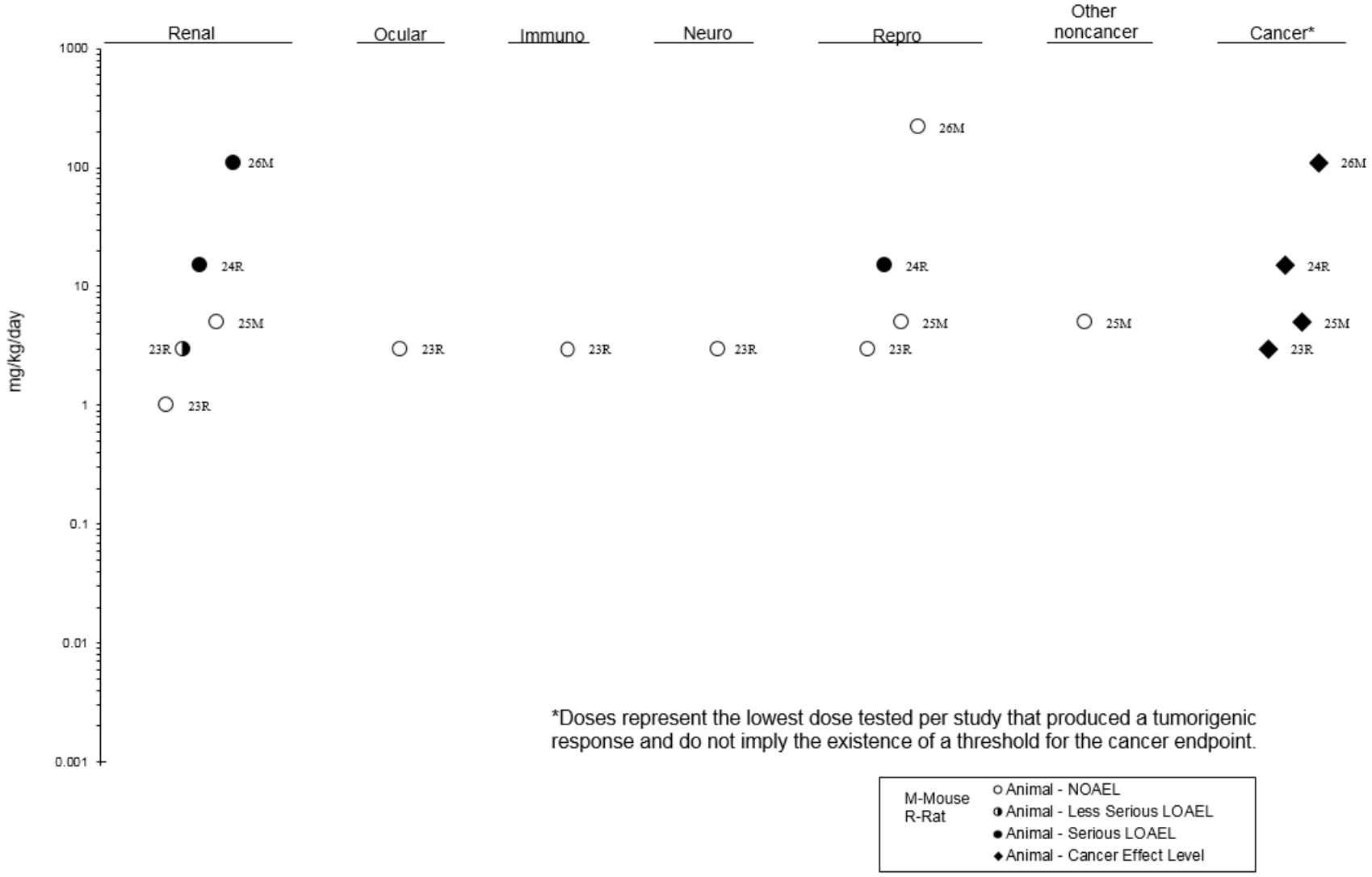


Table 2-3. Levels of Significant Exposure to 1,2-Dibromo-3-Chloropropane – Dermal

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).

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

- 1,2-Dibromo-3-chloropropane is rapidly absorbed through the gastrointestinal tract and is presumed to be readily absorbed through the respiratory tract and skin, based on systemic toxicity in animals exposed by these routes.
- Absorbed 1,2-dibromo-3-chloropropane is widely distributed to tissues and remains longer in fat than other tissues.
- The predominant pathway for 1,2-dibromo-3-chloropropane metabolism is cytochrome P450 oxidation to form epoxide intermediates, which can be further hydrolyzed and debrominated or undergo glutathione conjugation catalyzed by glutathione transferase.
- Most absorbed 1,2-dibromopropane is excreted as metabolites in the urine; lesser amounts are excreted in feces or exhaled air as carbon dioxide.

3.1.1 Absorption

No studies were located regarding absorption following occupational (predominantly inhalation, but may have included dermal and oral) exposure to 1,2-dibromo-3-chloropropane. However, reported systemic effects in laboratory animals exposed by inhalation or dermal routes provide evidence of absorption from these exposure routes. Animal studies show that 1,2-dibromo-3-chloropropane is rapidly and extensively absorbed from the gastrointestinal tract. The absorption of 1,2- dibromo-3-chloropropane followed first-order kinetics in rats after oral administration by gavage in a water vehicle. No dose dependence in absorption was observed with doses up to 10 mg/kg/day, and peak blood levels were reached within 5–40 minutes. The rate of absorption was slower and more erratic with oil vehicle, but the extent of absorption remained approximately the same (i.e., 68% with corn oil versus 78% with water) (Gingell et al. 1987a). Absorption from the gastrointestinal tract was 99% of the originally administered dose of ^{14}C-1,2-dibromo-3-chloropropane; only 0.223% of the administered radioactivity was recovered in the feces of bile duct-cannulated rats (Kato et al. 1979a).

3.1.2 Distribution

Following absorption in rats, 1,2-dibromo-3-chloropropane, which was administered by corn oil gavage for 10 consecutive days to pregnant rats, was rapidly and widely distributed to tissues, and tended to

remain longest in fat (Ruddick and Newsome 1979). The concentration of 1,2-dibromo-3-chloropropane in pooled fetuses and in spleens, brains, hearts, kidneys, and livers of dams was highest within 3 hours of the exposure to the last dose of 1,2-dibromo-3-chloropropane. The peak level in fat occurred after 6 hours, and 1,2-dibromo-3-chloropropane was still detectable after 24 hours. At 12 hours following the last dose, 1,2-dibromo-3-chloropropane was no longer detected in most other tissues. The detection in tissues of pooled fetuses provides evidence that 1,2-dibromo-3-chloropropane crossed the placenta.

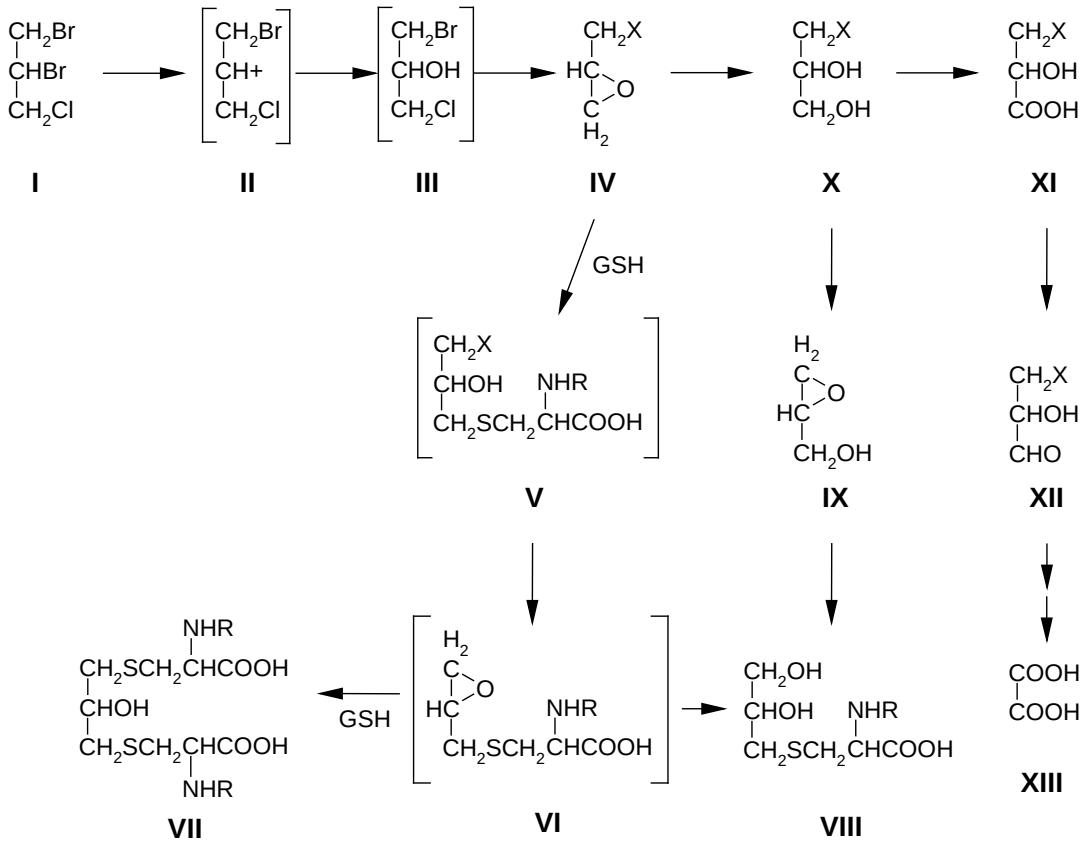
In rats administered ^{14}C-1,2-dibromo-3-chloropropane in corn oil by gavage, unchanged 1,2-dibromo-3-chloropropane accumulated only in the adipose tissues, while unextractable metabolites were found in kidneys and livers (Kato et al. 1979a). The unextractable metabolites were detected in most tissues, possibly as reactive metabolites bound to tissue macromolecules. The highest level of radioactivity was found in livers and kidneys (Kato et al. 1980) at 6 and 20 hours postexposure. As demonstrated in Sections 2.9 and 2.10, liver and kidney are targets of 1,2-dibromo-3-chloropropane toxicity.

3.1.3 Metabolism

The metabolism of 1,2-dibromo-3-chloropropane was studied in rats. The proposed metabolic pathway is shown in Figure 3-1. According to this scheme, 1,2-dibromo-3-chloropropane is converted to epoxy derivatives, which are further hydrolyzed and debrominated. Bromide accumulates in the kidneys. Beside other metabolites, epichlorohydrin and epibromohydrin were found, which can be further metabolized to oxalic acid. Mercapturic acids were detected in urine and this indicates that metabolic intermediates reacted with nonprotein sulfhydryl (NPS) groups (Jones et al. 1979).

Conjugation of the epoxide intermediates with NPS groups can occur in the liver, kidneys, lungs, stomach, and testes of rats after treatment with 1,2-dibromo-3-chloropropane (Kato et al. 1980; Kluwe et al. 1981, 1982). The greater depletion of hepatic NPS suggests that the liver is the major site of GSH conjugation with 1,2-dibromo-3-chloropropane metabolites (Kluwe et al. 1982). GSH pretreatment protected rats from 1,2-dibromo-3-propane-induced liver necrosis (Kato et al. 1980), indicating that conjugation is a detoxifying mechanism in the liver.

Figure 3-1. The Metabolism of 1,2-Dibromo-3-chloropropane in Rats



I 1,2-Dibromo-3-chloropropane
II 1-Bromo-3-chloropropylium
III 1-Bromo-3-chloropropan-2-ol
IV Epichlorohydrin or epibromohydrin
V S-[1-(2-hydroxy)propyl] cysteine
VI S-[1-(2-epoxy)propyl] cysteine
VII 1,3-(Bis-cysteine)propan-2-ol
VIII S-(2,3-dihydroxypropyl-cysteine
IX 1-Epxoy-3-hydroxypropane
X α-Chlorohydrin or α-bromohydrin
XI 3-Chloractic acid or 3-bromolactic acid
XII 3-Chlorolactadehyde or 3-bromolactaldehyde
XIII Oxalic acid
GSH Reduced glutathione

Source: Jones et al. 1979

Studies of the mechanism of 1,2-dibromo-3-chloropropane-induced testicular toxicity suggest that in the testes, conjugation with GSH with subsequent metabolism to a reactive metabolite represents a toxifying mechanism (Kluwe 1983; Omichinski et al. 1988a, 1988b).

The interspecies differences in 1,2-dibromo-3-chloropropane gonadotoxicity are probably due to interspecies differences in metabolism within the testicular cells to convert 1,2-dibromo-3-chloropropane to more reactive forms. After a single intraperitoneal injection of 1,2-dibromo-3-chloropropane, atrophy of seminiferous epithelium was more severe in rats and guinea pigs than in hamsters and mice;

furthermore, testicular DNA damage was observed only in rats and guinea pigs (Lag et al. 1989a). These findings suggest that rats and guinea pigs are sensitive to 1,2-dibromo-3-chloropropane because their testicular cells more readily activate 1,2-dibromo-3-chloropropane to a DNA-damaging intermediate(s). Species differences in metabolism were also found in *in vitro* experiments with tissues from rats and mice. Rats metabolized 1,2-dibromo-3-chloropropane in liver, kidney, testes, and stomach preparations much faster than mice, as measured by GSH-dependent debromination in cytosolic fractions (MacFarland et al. 1984). No data were located regarding potential for 1,2-dibromo-3-chloropropane to induce DNA damage in human testicular cells *in vitro*; however, effects on sperm quality and histopathological testicular changes have been associated with occupational exposure to 1,2-dibromo-3-chloropropane (see Section 2.16).

3.1.4 Excretion

Limited information was located regarding excretion following absorption of 1,2-dibromo-3-chloropropane. Excretion after administration of radioactively labeled 1,2-dibromo-3-chloropropane in rats occurred via several routes, including exhalation and biliary and urinary elimination. During 24 hours following gavage administration of ^{14}C-1,2-dibromo-3-chloropropane to male rats, captured radioactivity in urine, feces, and expired air was approximately 48, 14.4, and 17–18%, respectively, of the administered dose (Kato et al. 1979a). Expired radioactivity was primarily in the form of $^{14}CO_2$. Mercapturic acids were detected in the urine; biliary excretion accounted for approximately 23% of the administered dose. In another rat study, within 3 days of gavage administration of radioactively labeled 1,2-dibromo-3-chloropropane, 55% of the radioactivity was found in the urine, 18% in the feces, and 19.5% in the exhaled air as carbon dioxide. Less than 1% was exhaled as unchanged 1,2-dibromo-3-chloropropane (Gingell et al. 1987a).

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

No PBPK models were identified for 1,2-dibromo-3-chloropropane.

3.1.6 Animal-to-Human Extrapolations

Available information indicates significant species differences in the toxicokinetics and toxicity of 1,2-dibromo-3-chloropropane, thus precluding meaningful animal-to-human extrapolation.

Soderlund et al. (1990) reported species differences in 1,2-dibromo-3-chloropropane-induced kidney lesions and DNA damage, as well as distribution and metabolism, among rats, mice, guinea pigs, and hamsters following single intraperitoneal administration. Extensive renal tubular necrosis was observed in 5/5 rats treated at 170 or 340 µmol/kg; only slight evidence of renal tubular necrosis was observed in 3/5 mice at 340 and 680 µmol/kg, and 1/5 guinea pigs and 1/5 hamsters at 680 µmol/kg.

Rats and guinea pigs exhibited similar sensitivity to 1,2-dibromo-3-chloropropane-induced DNA damage to kidney cells, whereas a 10–50-fold higher dose was necessary to produce a similar level of DNA damage to mouse and hamster kidney cells. Bjorge et al. (1996) reported a 3-fold more rapid activation of 1,2-dibromo-3-chloropropane to covalently-bound macromolecules in rat testicular cell preparations compared to human testicular cells. Comparative evaluation of 1,2-dibromo-3-chloropropane-induced DNA damage revealed dose-related increased single-strand DNA strand breaks in rat testicular cells, but no evidence of damage in human testicular cells.

Initial 1,2-dibromo-3-chloropropane kidney concentrations were substantially higher in rats and guinea pigs, and kidney elimination occurred at a significantly lower rate in rats than mice, hamsters, and guinea pigs. Kidney preparations from rats and guinea pigs were observed to debrominate 1,2-dibromo-3-chloropropane at approximately 2–3 times the rate of preparations from mice and hamsters. These results indicate that the initial higher concentration of renal 1,2-dibromo-3-chloropropane, relatively longer retention, and increased rate of metabolism may contribute to the greater susceptibility of the rat and guinea pig to 1,2-dibromo-3-chloropropane-induced nephrotoxicity.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal

exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to 1,2-dibromo-3-chloropropane are discussed in Section 5.7, Populations with Potentially High Exposures.

No data were located regarding potential age-related differences in susceptibility to 1,2-dibromo-3-chloropropane. It is unknown whether susceptibility among children is different from that of adults. Persons with impaired kidney or lung function may also be more susceptible to the toxic effects of 1,2-dibromo-3-chloropropane because the kidney and lungs are relatively sensitive targets of 1,2-dibromo-3-chloropropane toxicity. The male reproductive system has been identified as a sensitive target of 1,2-dibromo-3-chloropropane toxicity in animals; available human data suggest that the male reproductive system is a target as well.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as biomarkers of exposure, biomarkers of effect, and biomarkers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to 1,2-dibromo-3-chloropropane are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see

http://www.cdc.gov/exposurereport/). If available, biomonitoring data for 1,2-dibromo-3-chloropropane from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by 1,2-dibromo-3-chloropropane are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

No studies were located regarding tissue, fluid, or excreta levels of 1,2-dibromo-3-chloropropane in humans.

Toxicokinetic studies performed in animals after acute exposures to 1,2-dibromo-3-chloropropane indicate that this chemical preferentially partitions to fat; however, upon termination of exposure, the accumulated chemical is rapidly lost from this tissue (Kato et al. 1979a; Ruddick and Newsom 1979). Over 80% of adipose tissue 1,2-dibromo-3-chloropropane is lost by 24 hours postexposure. 1,2-Dibromo-3-chloropropane was lost from other tissues more rapidly. Thus, determination of tissue levels of 1,2-dibromo-3-chloropropane must be made shortly after exposure. 1,2-Dibromo-3-chloro-propane may be found in exhaled air, but <1% of an administered dose was found in exhaled air during the first 24 hours after dosing (Gingell et al. 1987a).

At least 20 metabolites were detected in the urine of rats following ingestion of radioactively labeled 1,2-dibromo-3-chloropropane (Gingell et al. 1987b). However, it is not known if these metabolites occur

in human urine following exposure to 1,2-dibromo-3-chloropropane by inhalation, oral, or dermal exposures. Also, because some of the metabolites (e.g., oxalic acid) may be produced from natural body processes, the detection of these metabolites may not be specific for 1,2-dibromo-3-chloropropane exposures. Additionally, the enzymes responsible for metabolizing 1,2 dibromo-3-chloropropane function to change many substances, not just 1,2 dibromo-3-chloropropane. Therefore, changes in enzyme activity would not be a specific biomarker of exposure for 1,2 dibromo-3-chloropropane.

3.3.2 Biomarkers of Effect

Changes in sperm parameters might be considered a biomarker of effect for 1,2-dibromo-3-chloro-propane. However, such a biomarker would not be specific to 1,2-dibromo-3-chloropropane. Several studies indicated that 1,2-dibromo-3-chloropropane induced DNA damage and changes in the activity of microsomal enzymes (Kluwe 1983; Suzuki and Lee 1981); however, these changes are not specific for 1,2-dibromo-3-chloropropane exposure and cannot be used as biomarkers. It is not likely that biomarkers specific to 1,2-dibromo-3-chloropropane exist.

3.4 INTERACTIONS WITH OTHER CHEMICALS

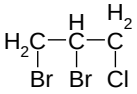
Substances such as 3-methylcholanthrene and cobalt chloride have been reported to enhance the adverse effects of 1,2-dibromo-3-chloropropane on seminiferous tubules (Kluwe 1983).

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Data pertaining to the chemical identity of 1,2-dibromo-3-chloropropane are listed in Table 4-1.

Table 4-1. Chemical Identity of 1,2-Dibromo-3-Chloropropane

Characteristic	Information	Reference
Chemical name	1,2-Dibromo-3-chloropropane	CAS 1989
Synonym(s) and registered trade name(s)	Nemagon; Nemafume; Fumazone; Fumagon; Nemabrom; Nemazon; OS 1897; and others	OHM/TADS 1989
Chemical formula	$C_3H_5Br_2Cl$	CAS 1989
Chemical structure		CAS 1989
CAS Registry Number	96-12-8	CAS 1989

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of 1,2-dibromo-3-chloropropane are presented in Table 4-2.

Table 4-2. Physical and Chemical Properties of 1,2-Dibromo-3-Chloropropane

Property	Information	Reference
Molecular weight	236.36	Windholz 1983
Color	Colorless (when pure); amber to dark brown, yellow (technical grade)	NIOSH 1985; Sax and Lewis 1987; Verschueren 1983
Physical state	Liquid	Windholz 1983
Melting point	6°C	Stenger 1978
Boiling point	196°C	Windholz 1983
Density at 20°C	2.093 g/cm^3	Windholz 1983
Odor	Pungent	Windholz 1983
Odor threshold:		
Water	No data	
Air	0.0965 mg/m^3	Ruth 1986

Table 4-2. Physical and Chemical Properties of 1,2-Dibromo-3-Chloropropane

Solubility:		
Water at 20°C	1,230 mg/L	Munnecke and VanGundy 1979
Organic solvents	Miscible with methanol, ethanol, isopropyl alcohol, hydrocarbons, halogenated hydrocarbons, and oils	Windholz 1983
Partition coefficients:		
Log K_{ow}	2.26 (estimated)	EPA 1988a
Log K_{oc}	2.17; 2.11	Sabljic 1984; Wilson et al. 1981
Vapor pressure at 20°C	0.58 mmHg	Munnecke and VanGundy 1979
Henry's law constant at 25°C	1.47×10^{-4} atm-m^3/mol[a]	Thomas 1982
Autoignition temperature	No data	
Flashpoint	76.6°C (open cup)	Sax and Lewis 1987
Flammability limits	No data	
Conversion factors	1 ppm=9.67 mg/m^3	
Explosive limits	No data	

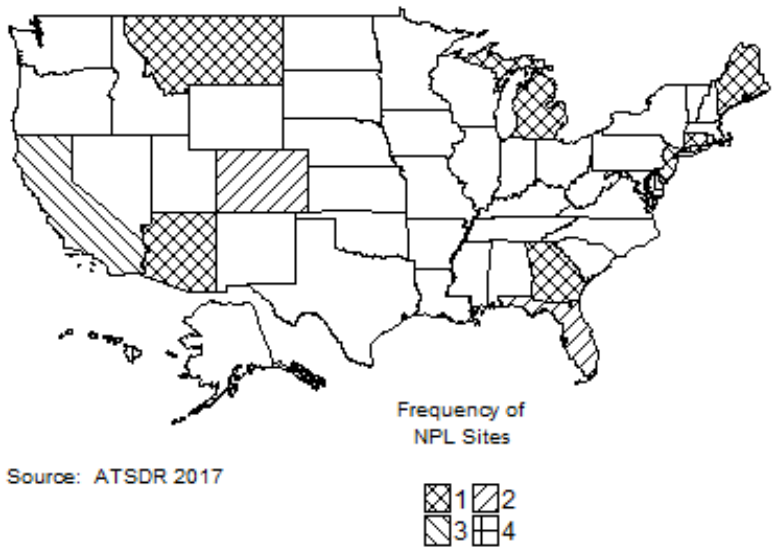
[a]Calculated from vapor pressure and water solubility using equation 15-8 in Lyman et al. (1982).

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

1,2-Dibromo-3-chloropropane has been identified in at least 18 of the 1,854 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2017). However, the number of sites in which 1,2-dibromo-3-chloropropane has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 18 are located within the United States.

Figure 5-1. Number of NPL Sites with 1,2-Dibromo-3-chloropropane Contamination



- The most likely sources of potential exposure of the general population to 1,2-dibromo-3-chloropropane are from food grown in soil that may still contain small amounts of the chemical or drinking water than may have been contaminated from 1,2-dibromo-3-chloropropane when it was used as a soil fumigant and nematocide prior to 1990.
- EPA canceled the registration of 1,2-dibromo-3-chloropropane in 1985. Only pineapple crops could use 1,2-dibromo-3-chloropropane between 1977 and 1979.
- People who live near hazardous waste sites containing 1,2-dibromo-3-chloropropane may be exposed from contaminated air, surface water or groundwater, or soil.
- Daily intakes from food or drinking water have not been estimated, based on lack of data.
- 1,2-Dibromo-3-chloropropane may be used as an intermediate in the synthesis of organic chemicals, such as brominated flame retardants.
- 1,2-Dibromo-3-chloropropane would be expected to volatilize from surface water and soil. Once in air, 1,2-dibromo-3-chloropropane is expected to degrade via a vapor-phase reaction with hydroxyl radicals. Residues in soil that do not leach or volatilize appear to be persistent.

- Estimated half-lives for 1,2-dibromo-3-chloropropane are:
  - 36 days, hydroxyl radical degradation in air
  - 13.5 hours to 8 days, volatilization from water (environmental conditions limited)
  - 140 days to 38 years, degradation (via hydrolysis) in water

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Table 5-1 summarizes information on U.S. companies that reported the manufacture or use of 1,2-dibromo-3-chloropropane in 2015 (TRI16 2017). Toxics Release Inventory (TRI) data should be used with caution since only certain types of industrial facilities are required to report. This is not an exhaustive list.

Table 5-1. Facilities that Produce, Process, or Use 1,2-Dibromo-3-Chloropropane

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
OH	1	100	999	12

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Used Processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

Source: TRI16 2017 (Data are from 2016)

1,2-Dibromo-3-chloropropane was first produced commercially in the United States in 1955 (IARC 1979). In 1969, U.S. production was 8.58 million pounds (IARC 1979). Estimates of annual production during 1974–1975 ranged from 18 to 20 million pounds (IARC 1979; NTP 1985). EPA canceled the registration of 1,2-dibromo-3-chloropropane in 1985. According to TRI (2017), a single facility was associated with 1,2-dibromo-3-chloropropane in the United States in 2016. This facility is a waste disposal company in Ohio.

5.2.2 Import/Export

No quantitative data concerning the recent import or export of 1,2-dibromo-3-chloropropane in the United States were found. Historical data indicate a single importer in 1977. It is unlikely that significant amounts of the chemical are imported or exported since its former major uses as a soil fumigant and nematocide are no longer permitted in the United States (EPA 1977, 1979, 1985b, 1985c).

5.2.3 Use

1,2-Dibromo-3-chloropropane was used as an intermediate in the synthesis of organic chemicals, such as the brominated flame retardant tris[(2,3-dibromopropyl)phosphate] (Verschueren 1983). Until 1977, 1,2-dibromo-3-chloropropane was extensively used as a soil fumigant and nematocide on over 40 different crops in the United States (Anonymous 1988). The chemical was used to protect field crops, vegetables, fruits and nuts, nursery and greenhouse crops, and turf from pests (NTP 1985). From 1977 to 1979, EPA suspended registration of products containing 1,2-dibromo-3-chloropropane except for use on pineapples in Hawaii (Anonymous 1988; EPA 1977, 1979). In 1985, EPA issued an intent to cancel all registrations for 1,2-dibromo-3-chloropropane-containing pesticide products, including use on pineapples. Subsequently, the use of existing stocks of 1,2-dibromo-3-chloropropane on pineapples was prohibited (EPA 1985b, 1985c).

Prior to the cancellation of pesticide uses, 1,2-dibromo-3-chloropropane was used extensively; 9.8 million pounds of 1,2-dibromo-3-chloropropane were applied in 1974 (NTP 1985). In California, 831,000 pounds of the chemical were applied, mainly on grapes and tomatoes, during 1977 (NTP 1985). The volume of 1,2-dibromo-3-chloropropane applied to pineapple fields in Hawaii between 1979 and 1985 was probably high, since during much of that time, the chemical was the preferred fumigant for use on pineapple fields (Albrecht 1987).

5.2.4 Disposal

1,2-Dibromo-3-chloropropane has been identified as a hazardous waste by EPA, and the disposal of this compound is regulated under the federal Resource Conservation and Recovery Act (RCRA) (EPA 1988b, 1988c). Specific information regarding federal regulations on the land disposal of 1,2-dibromo-3-chloropropane is provided in the Code of Federal Regulations (EPA 1988c). No acceptable chemical decontamination is known for 1,2-dibromo-3-chloropropane (HSDB 1989). Dilution of the chemical with

a flammable solvent is necessary for incineration to be effective, and the products must be passed through scrubbers to remove the hydrogen bromide and hydrogen chloride that is produced (HSDB 1989).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

5.3.1 Air

There were no estimated releases of 1,2-dibromo-3-chloropropane to the atmosphere from one domestic manufacturing and processing facility in 2016 required to report to the TRI (TRI16 2017; see Table 5-2).

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use 1,2-Dibromo-3-Chloropropane[a]

	Reported amounts released in pounds per year[b]								
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
OH	1	0	0	0	0	No data	0	No data	0
Total	1	0	0	0	0	0	0	0	0

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use 1,2-Dibromo-3-Chloropropane[a]

	Reported amounts released in pounds per year[b]									
								Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site

[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI16 2017 (Data are from 2016)

5.3.2 Water

There were no estimated releases of 1,2-dibromo-3-chloropropane to surface water from one domestic manufacturing and processing facility in 2016 required to report to the TRI (TRI16 2017). There were no data on releases to publicly owned treatment works (POTWs) (TRI16 2017; see Table 5-2).

5.3.3 Soil

There were no estimated releases of 1,2-dibromo-3-chloropropane to soils from one domestic manufacturing and processing facility in 2016 required to report to the TRI (TRI16 2017). There were no releases via underground injection (TRI16 2017; see Table 5-2).

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

1,2-Dibromo-3-chloropropane in soil is subject both to leaching into groundwater and to volatilization from near-surface soil. The experimental K_{oc} values of approximately 149 in Lincoln fine sand (Wilson et al. 1981) and 128 in an unspecified soil (Sabljic 1984) indicate that 1,2-dibromo-3-chloropropane is highly mobile in soil (Swann et al. 1983). Data from field and laboratory experiments confirm that 1,2-dibromo-3-chloropropane has a strong potential to leach through soil to groundwater (Bomberger et

al. 1983; Carter et al. 1984; Hodges and Lear 1974; Kloos 1983; Oki and Giambelluca 1987; Wilson et al. 1981). The rate and extent that 1,2-dibromo-3-chloropropane leaches through agricultural soil depend upon various factors that include the water-holding capacity of the soil (which is related to the size of the air spaces in the soil), the amount of organic matter in the soil, the amount of water applied, and the method of 1,2-dibromo-3-chloropropane application (Hodges and Lear 1974).

In a study using primarily clay, silt, and sandy soils, mobility was lowest in the clay soil, which had a higher content of organic matter than both sandy and silt soil and a lower amount of air space between particles of soil than was found in the silt soil (Hodges and Lear 1974). Mobility was highest in the sandy soil, which had the largest spaces between soil particles (and therefore the fastest rate of water movement) and the lowest amount of organic matter (Hodges and Lear 1974).

Application of 1,2-dibromo-3-chloropropane by either injection or application in irrigation water (flood application) led to extensive and rapid penetration of the fumigant. Application of 1,2-dibromo-3-chloropropane by injection led to greater penetration in the clay and silt soils, compared to its flood application, because it was retained near the soil surface in the latter case and was subsequently lost to the atmosphere (Hodges and Lear 1974).

An illustration of the volatilization behavior of 1,2-dibromo-3-chloropropane from soil was obtained in a study of a pineapple field that was treated with 4 gallons per acre of the chemical injected to a depth of 12 inches (Albrecht and Chenchin 1985). 1,2-Dibromo-3-chloropropane concentration in the air at ground level and at 42 inches above the ground reached peaks after 2 days (approximately 0.4 and 8 ppb, respectively), dropped off to nondetectable levels after 3 days, peaked after 6 days following a 6-mm rainfall on days 5–6 (approximately 1.2 and 0.5 ppb at ground level and 42 inches, respectively), and dropped off but remained at measurable levels for the remainder of the 30-day experiment (Albrecht and Chenchin 1985).

These data support results obtained in modeling studies that predict that volatilization of 1,2-dibromo-3-chloropropane from near-surface soil is important (Bomberger et al. 1983; Jury et al. 1987). Estimated volatilization half-lives for 1,2-dibromo-3-chloropropane that was evenly distributed in the top 10 cm of soil varied between 0.6 days in dry soil with very low soil organic content to 26.2 days in wet soil with relatively high soil organic content (Bomberger et al. 1983). The use of plastic coverings over 1,2-dibromo-3-chloropropane treated fields retards volatilization loss from soil.

Small amounts of 1,2-dibromo-3-chloropropane may be absorbed through the roots of plants growing in 1,2-dibromo-3-chloropropane contaminated soil and may be translocated to other parts of the plants (see Section 5.5.4.) (Carter and Riley 1982; Newsome et al. 1977). 1,2-Dibromo-3-chloropropane was found in peaches and in the roots and tops of carrots and radishes that were grown in 1,2-dibromo-3-chloropropane-treated soil. The generally lower amounts of the chemical found in the foliage than in the roots of the carrot and radish plants may have resulted from translocation from the roots or from absorption of 1,2-dibromo-3-chloropropane that had volatilized from the soil to the air (Newsome et al. 1977). The possibility of absorption of volatilized 1,2-dibromo-3-chloropropane by the peaches appears to be a less likely explanation than translocation because the 1,2-dibromo-3-chloropropane was applied to the fields in the fall, months before the spring harvest of the peaches (Carter and Riley 1984).

In the atmosphere, 1,2-dibromo-3-chloropropane is expected to exist predominantly in the vapor phase based upon its vapor pressure (see Table 4-2) (Eisenreich et al. 1981; Munnecke and VanGundy 1979). Because significant amounts of 1,2-dibromo-3-chloropropane are not likely to be present in the particulate phase, dry deposition to the earth's surface is not a significant removal process. Based upon its high water solubility (see Table 4-2), the small amounts of 1,2-dibromo-3-chloropropane that are present in air may be removed by wet deposition; however, much of the 1,2-dibromo-3-chloropropane removed from the atmosphere by washout is likely to reenter the atmosphere by volatilization. No experimental or predictive data were located in the literature regarding the transport of 1,2-dibromo-3-chloropropane in the atmosphere; however, the expected half-life of 36 days (see Section 5.4.2) indicates that it could be transported long distances in the atmosphere.

1,2-Dibromo-3-chloropropane that is present in water is expected to volatilize rapidly to the atmosphere. Using the Henry's law constant, a half-life of 13.5 hours was calculated for evaporation from a model river l-m deep, flowing at 1 m/second, with a wind velocity of 3 m/second, and neglecting adsorption to sediment (Thomas 1982). A volatilization half-life of 8 days from a model pond can be estimated using a three-compartment EXAMS model (EPA 1985d). 1,2-Dibromo-3-chloropropane is not expected to adsorb significantly to sediment and suspended organic matter based upon a K_{oc} ranging between 128 and 149 (Sabljic 1984; Wilson et al. 1981). It is not expected to bioconcentrate in fish and other aquatic organisms based upon an estimated bioconcentration factor (BCF) of 11.2 (calculated from water solubility; see Table 4-2) (Bysshe 1982; Munnecke and VanGundy 1979). No data were located that would indicate a potential for 1,2-dibromo-3-chloropropane to biomagnify from lower to higher trophic states of aquatic or terrestrial foodchains.

5.4.2 Transformation and Degradation

Air. The primary degradation process for 1,2-dibromo-3-chloropropane in the atmosphere is likely to be a vapor-phase reaction with photochemically produced hydroxyl radicals. The experimental rate constant for this process is $4.4x10^{-13}$ cm^3/molecule-second (Tuazon et al. 1986). This corresponds to a half-life of 36 days at an estimated atmospheric concentration of $5x10^5$ hydroxyl radicals/cm^3. Direct photolysis of 1,2-dibromo-3-chloropropane is not expected to occur in the atmosphere since the chemical lacks a chromophore that absorbs light at environmentally significant wavelengths (>290 nm) (Silverstein et al. 1974).

Water. Degradation of 1,2-dibromo-3-chloropropane in natural waters is a slow process. It volatilizes from surface waters before significant degradation can occur. Hydrolysis of 1,2-dibromo-3-chloropropane in natural waters is unlikely to be an important removal process. The base hydrolysis rate constant at 25°C of 20.6 $hour^{-1}$ M^{-1} was extracted from data obtained at 40–100°C (Burlinson et al. 1982). This rate constant corresponds to half-lives for hydrolysis of 38 years and 140 days at pH 7 and 9, respectively. Direct photolysis of 1,2-dibromo-3-chloropropane is not likely to occur in environmental waters since the chemical lacks a chromophore that absorbs light at environmentally significant wavelengths (>290 nm) (Silverstein et al. 1974).

No studies were located regarding the biodegradation of 1,2-dibromo-3-chloropropane in natural waters. 1,2-Dibromo-3-chloropropane may be susceptible to slow biodegradation in natural waters based upon the observation of biologically mediated dehalogenation in certain soils amended with a nutrient (Castro and Belser 1968). In experiments using anoxic biofilm columns that were designed to resemble groundwater environments, 1,2-dibromo-3-chloropropane was susceptible to biodegradation under conditions of methanogenesis, denitrification, and sulfate respiration (Bouwer and Wright 1988). Although data from these experiments cannot be used to predict what type of aquifer is likely to support biodegradation or the rate of biodegradation to be expected, they indicate that some biodegradation of 1,2-dibromo-3-chloropropane in groundwater may occur under anaerobic conditions.

Sediment and Soil. 1,2-Dibromo-3-chloropropane is subject to biodehalogenation in soil-water suspensions (aerobic/anaerobic conditions not specified) in the presence of an added nutrient (Castro and Belser 1968). Biodegradation did not occur in the absence of the added glycerol nutrient or in suspensions of sterilized soil. Dehalogenation occurred in approximately 75% of the soil samples that were tested. The highest rate of dehalogenation was 20% in 1 week at pH 8, which was measured by the

rate of bromide ion formation. The maximum observed yield of bromide from 1,2-dibromo-3-chloropropane was 63% of the theoretical yield in 4 weeks under unspecified conditions. The data from these experiments suggest that 1,2-dibromo-3-chloropropane may be susceptible to biodegradation in soil under certain conditions; however, it is not possible to predict the soils that will biodegrade the chemical or the rate of biodegradation (Castro and Belser 1968). In another study, it appears that no degradation of 1,2-dibromo-3-chloropropane was observed in soil columns within 25 days under aerobic conditions (Wilson et al. 1981). Based upon aqueous hydrolysis data, chemical hydrolysis is not expected to be significant except in very alkaline soils.

Based upon monitoring data obtained years after the last known application, 1,2-dibromo-3-chloropropane residues that do not leach or volatilize are very persistent in soil. For example, 1,2-dibromo-3-chloropropane residues as high as 0.5 µg/kg were found in the soil at a site 6–7 years following the last known application (Nelson et al. 1981).

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to 1,2-dibromo-3-chloropropane depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of 1,2-dibromo-3-chloropropane in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on 1,2-dibromo-3-chloropropane levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-3 shows the lowest limit of detections that are achieved by analytical analysis in environmental media.

Table 5-3. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air	0.02 ppb	Mann et al. 1980
Drinking water	0.01 µg/L	EPA 1986a
Surface water and groundwater	0.01 µg/L	EPA 1986a
Whole blood	3 ng/mL	Pellizzari et al. 1985b

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

Detections of 1,2-dibromo-3-chloropropane in air, water, and soil at NPL sites are summarized in Table 5-4.

Table 5-4. 1,2-Dibromo-3-Chloropropane Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (ppb)	2.2	2.86	6,840	10	5
Soil (ppb)	61,000	63,000	23,700	5	3
Air (ppbv)	No data				

[a]Concentrations found in ATSDR site documents from 1981 to 2017 for 1,854 NPL sites (ATSDR 2017). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

Few data concerning the detection of 1,2-dibromo-3-chloropropane in the atmosphere were found. Ambient air surrounding bromine industry chemical plants in the vicinity of two cities in Arkansas were analyzed for the presence of 1,2-dibromo-3-chloropropane in 1976 and 1977 (Pellizzari et al. 1978). In the vicinity of Magnolia, Arkansas, the maximum concentration of the chemical found in air surrounding a Dow Chemical Company plant was 6,653 ng/m^3. The maximum concentration in the El Dorado, Arkansas, area was 187 ng/m^3 at the Velsicol Chemical Corporation (Pellizzari et al. 1978). In a study that reported data collected primarily between 1970 and 1980, the median concentration of 1,2-dibromo-3-chloropropane was 1.8 ng/m^3 in ambient air near source-dominated areas; no data were listed for rural, remote, urban, or suburban areas (Brodzinsky and Singh 1982). This study is not comprehensive since it involved only scattered sampling of bromine industry chemical plants in one state. Furthermore, the data are old and were taken when the chemical was still being manufactured and widely used as a soil fumigant. Current releases to the atmosphere from manufacturing or research-use point sources are not likely to be significant since only limited amounts are presumed to be made and used (Section 5.2). Significant concentrations of the chemical are probably not present in the ambient atmosphere at this time; therefore, the background level estimated for ambient air is expected to be less than the detection limit. Exceptions may include air near NPL sites where 1,2-dibromo-3-chloropropane has been disposed, although no data were found concerning atmospheric concentrations at these sites.

5.5.2 Water

Data concerning levels of 1,2-dibromo-3-chloropropane in water are lacking, and those available are neither current nor comprehensive. The data in Table 5-5 indicate that contamination of municipal drinking water supplies was not widespread in the past. Where contamination was found, the concentrations had been <10 µg/L; however, concentrations as high as 95 and 137 µg/L have been reported in water from drinking water wells in California and Arizona, respectively, although no information was provided on possible sources of contamination (Burmaster 1982).

In a study of water from drinking water wells in the Fresno area of California's Central Valley conducted between 1979 and 1983, the tested wells generally had seasonal concentration patterns ranging from a low in winter to highs in spring/summer months. The 1,2-dibromo-3-chloropropane concentration also changed with daily use patterns ranging from highs at the start of pumping with lower concentrations as pumping continued (Kloos 1983). In a study of various waters in South Carolina sampled between 1979 and 1980, concentrations of 1,2-dibromo-3-chloropropane in water from one of three municipal water supplies ranged from 0.008 µg/L (detection limit) to 0.05 µg/L in an area where 1,2-dibromo-3-chloropropane was not known to have been used (Carter and Riley 1981).

Few data concerning the detection of 1,2-dibromo-3-chloropropane in surface water were found. In a study of South Carolina surface waters that were sampled between 1979 and 1980, concentrations of 1,2-dibromo-3-chloropropane ranged from not detected (detection limit 0.008 µg/L) to 0.05 µg/L in areas where 1,2-dibromo-3-chloropropane usage rates ranged from non-use to scattered use (Carter and Riley 1981). In high-use areas, 18 of 48 sites had concentrations exceeding the background level of 0.05 µg/L;

Table 5-5. Levels of 1,2-Dibromo-3-chloropropane in Potable Water[a]

Location	Date of sampling	Number of samples	Number positive samples	Concentration (µg/L)		Reference
				Range	Mean	
Municipal water supplies						
United States	1981–1982	466	1	5.5	5.5	Westrick et al. 1984
Mainly rural California	1979	61	12	0.1–9.5	1.4	Peoples et al. 1980
Riverside & Stanislaus Counties (California)	1979	3	3	0.1	0.1	Kutz and Carey 1986
South Carolina DBCP nonuse area[b]	1979–1980	3	1	<0.008–0.05	No data	Carter and Riley 1981
South Carolina DBCP high-use area[b]	1979–1980	8	4	<0.05	No data	Carter and Riley 1981
Drinking water wells						
South Carolina DBCP nonuse area[b]	1979–1980	8	3	<0.008–0.05	No data	Carter and Riley 1981
South Carolina DBCP high-use area[b]	1979–1980	49	29	<0.008–>1.0[c]	No data	Carter and Riley 1981
Madera, Stanislaus, and San Joaquin Counties (California)	1979	7	7	0.1–10.8	3.2	Kutz and Carey 1986
Well water and groundwater in areas with agricultural or undefined uses						
California	1979–1984	8,190	2,522	No data[d]	No data	Cohen 1986
Fresno County, California	1979–1983	9,000–10,000	1,500[e]	0.001–32[f]	No data	Kloos 1983
Mainly rural California	1979	262	90	0.1–39.2	No data	Peoples et al. 1980
San Joaquin Valley, California	April 1980	4 sites	3 sites	0.54–12	4.6	Nelson et al. 1981
Hawaii pineapple-growing regions	1980–1983	No data	No data	0.002–11	No data	Oki and Giambelluca 1987
United States[g]	No data	No data	No data	0.02–20[h]	No data	Cohen et al. 1986

[a]Based upon positive values; if one is listed, it is a maximum.
[b]Areas of no 1,2-dibromo-3-chloropropane use (nonuse) and widespread use (high use), respectively.
[c]13 of 49 sites contained greater than the background level of 0.05 µg/L, and 5 contained >1.0 µg/L.
[d]1,455 wells contained >1.0 µg/L 1,2-dibromo-3-chloropropane.
[e]Approximate number.
[f]850 wells contained >1.0 µg/L 1,2-dibromo-3-chloropropane.
[g]Five U.S. states: Arizona, California, Hawaii, Maryland, and South Carolina.
[h]Typically positive values.

DBCP = 1,2-dibromo-3-chloropropane

concentrations as high as 0.35 µg/L were detected (Carter and Riley 1981). 1,2-Dibromo-3-chloropropane was identified, but not quantified, in surface water at a bromine industry chemical plant in the vicinity of Magnolia, Arkansas, which was sampled in 1977 (Pellizzari et al. 1978).

These data, combined with the knowledge that use of 1,2-dibromo-3-chloropropane as a soil fumigant has not been permitted in the United States for several years, suggest that widespread exposure to the chemical in drinking water is not likely. The estimated background level for groundwater in areas where the chemical has not been used or disposed of in the past and in surface water is less than the detection limit. In areas where it was used as a soil fumigant, background levels of 0.001–0.008 µg/L can be expected depending on the amount used and environmental conditions.

5.5.3 Sediment and Soil

Few data concerning the detection of 1,2-dibromo-3-chloropropane in soil were found. 1,2-Dibromo-3-chloropropane was tentatively identified, but not quantified, in sediment at a bromine industry chemical plant in the vicinity of Magnolia, Arkansas, which was sampled in 1977 (Pellizzari et al. 1978).

In a study conducted in 1980, 1,2-dibromo-3-chloropropane was analyzed in soils and subsoils from fields at four sites that were known to have been treated with 1,2-dibromo-3-chloropropane (the last application was 3–6 years prior to sampling) and where groundwater contamination with the chemical had been identified (Nelson et al. 1981). The concentrations in the soil and subsoils ranged from not detected (detection limit not stated) to 9 µg/kg (dry weight basis); higher levels were generally found in clay and silt layers. In 32 fields that had received 1,2-dibromo-3-chloropropane treatments 2–4 years prior to sampling, the surface of the topsoil contained approximately 2–5 µg/kg of the chemical (Peoples et al. 1980).

In another study, soil samples taken from two Edgefield County, South Carolina peach orchards (site 1 containing Wagram sand; site 2 containing Faceville sandy loam) with similar histories of 1,2-dibromo-3-chloropropane usage contained mostly undetectable levels (detection limit 0.025 µg/kg); the highest 1,2-dibromo-3-chloropropane concentrations were 0.095 and 0.497 µg/kg at sites 1 and 2, respectively (Carter et al. 1984). Soil profile samples indicated residues were usually found in the upper 90 cm (Carter et al.1984). A higher level of soil contamination (up to 7.84 µg/kg) was measured in soil near a well in site 2; the concentration of 1,2-dibromo-3-chloropropane was 1 µg/kg. The higher soil level in this area

was attributed to a spill in which a formulation containing 1,2-dibromo-3-chloropropane had leaked from a rusting barrel.

These data, combined with the knowledge that use of 1,2-dibromo-3-chloropropane as a soil fumigant has not been permitted in the United States for several years, suggest that widespread exposure to the chemical due to contamination of soil is unlikely. The estimated background level for ambient soil in areas where the chemical has not been used is less than the detection limit. In areas where it was used as a soil fumigant or disposed, background levels of up to 0.5 µg/kg can probably be expected.

5.5.4 Other Media

Few data concerning levels of 1,2-dibromo-3-chloropropane in other environmental media were found.

Peaches grown in soil treated by injection into the soil of 51.4 and 137.5 L/hectare of a fumigant formulation containing 1.45 kg/L of 1,2-dibromo-3-chloropropane (peaches harvested between 183 and 217 days following treatment) contained 0.13 and 0.72 ppb of 1,2-dibromo-3-chloropropane (Carter and Riley 1984). No residues were found in peaches grown in nonfumigated soil or in soil treated at or below the recommended treatment rate of 46.8 L/treated hectare (Carter and Riley 1984). In another study, Carter and Riley (1982) found levels as high as 24.7 ppb in peaches that were treated 114 days prior to harvest (application rate not reported).

Three weeks after treatment, carrots grown in soil that was injected with 12.26 pounds/acre of 1,2-dibromo-3-chloropropane contained up to 1.50 ppm and the residues persisted for 16 weeks when fumigation was at seeding (Newsome et al. 1977). Most of the residues were contained in the pulp of the carrots and two-thirds of the residues in unpeeled carrots disappeared when the carrots were boiled for 5 minutes. The maximum concentration found in radishes from treated fields (application rate of 12.26 pounds/acre of 1,2-dibromo-3-chloropropane) was 0.194 ppm (Newsome et al. 1977).

1,2-Dibromo-3-chloropropane was found at concentrations between 15 and 25 ppb in a commercial sample of sodium humate that was apparently imported from Germany (Gabbita 1986). It was not known whether the soil from which the humate was extracted was itself contaminated with the chemical.

5.6 GENERAL POPULATION EXPOSURE

The general population may be exposed to 1,2-dibromo-3-chloropropane through the ingestion of contaminated drinking water and food. Contaminated drinking water is most likely to be derived from contaminated groundwater sources at or near locations where 1,2-dibromo-3-chloropropane had been used as a soil fumigant. Not only are these areas limited in number and size, but the use of 1,2-dibromo-3-chloropropane as a soil fumigant was banned in the late 1970s and early 1980s; therefore, although no current and comprehensive data were found to calculate an estimate of general population exposure to 1,2-dibromo-3-chloropropane from drinking water, the estimate is expected to be minimal based upon older data concerning the presence of 1,2-dibromo-3-chloropropane in drinking water and groundwater in the United States (see Section 5.5).

1,2-Dibromo-3-chloropropane has been detected in some food products in the past (Carter and Riley 1982, 1984; Newsome et al. 1977). Selected food source could presently contain very small amounts of 1,2-dibromo-3-chloropropane because the chemical is persistent in soil. However, it is unlikely that food sources would contain 1,2-dibromo-3-chloropropane in amounts likely to cause adverse health effects. Although data are lacking, inhalation is not expected to contribute significantly to general population exposure to 1,2-dibromo-3-chloropropane.

Due to the lack of recent comprehensive monitoring data, the average daily intake of 1,2-dibromo-3-chloropropane and the relative significance of each source of exposure cannot be determined. Since releases of 1,2-dibromo-3-chloropropane to the environment are generally limited to areas where it was used as a soil fumigant, a use that was banned by the EPA in 1985, widespread exposure to the chemical is not likely.

The Fourth National Report on Human Exposures to Environmental Chemicals, published and updated by the Centers for Disease Control and Prevention reporting biomonitoring data from the National Health and Nutrition Examination Survey (NHANES) for survey years 2003–2010, does not include data for 1,2-dibromo-3-chloropropane (CDC 2018).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The highest levels of exposure may occur with workers who manufacture or use the compound for research or as a chemical intermediate in synthesis.

Populations with potentially higher exposure than normal for the general population include those in areas that obtain drinking water from contaminated groundwater sources. These areas are generally at or near agricultural regions where 1,2-dibromo-3-chloropropane had been used as a soil fumigant, and include, for example, the San Joaquin Valley in California (Kloos 1983), the pineapple-growing regions of Hawaii (Oki and Giambelluca 1987), and the peach-growing regions of South Carolina (Carter and Riley 1981).

Drinking water derived from contaminated groundwater at or near hazardous waste sites that contain 1,2-dibromo-3-chloropropane might contain the chemical and contribute to exposure. Inhalation of contaminated air may contribute significantly to overall exposure for those populations living at or near hazardous waste dumps where 1,2-dibromo-3-chloropropane has been found. Most, if not all, of these exposures are expected to be rare and at relatively low levels.

CHAPTER 6. ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,2-dibromo-3-chloropropane is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of 1,2-dibromo-3-chloropropane.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

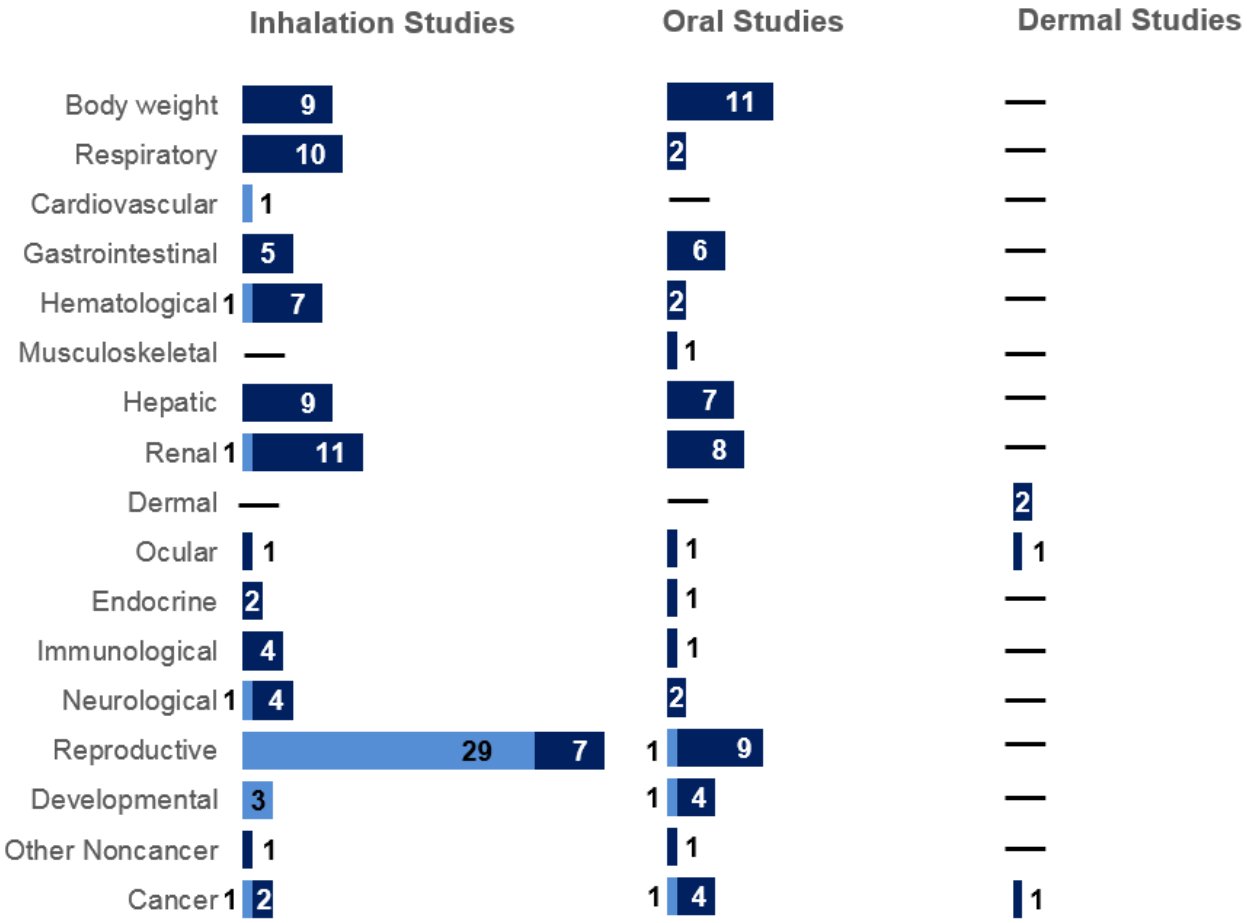
6.1 Information on Health Effects

Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to 1,2-dibromo-3-chloropropane that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of 1,2-dibromo-3-chloropropane. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

As illustrated in Figure 6-1, most of the data on the toxicity of 1,2-dibromo-3-chloropropane come from inhalation or oral studies in animals. The most commonly examined endpoints were body weight, liver, kidney, and reproductive effects. Most human data come from assessments of the male reproductive system in cohorts of occupationally exposed factory workers or cohorts of farmers or pesticide applicators. A limited number of studies evaluated the effects of dermal exposure to 1,2-dibromo-3-chloropropane.

Figure 6-1. Summary of Existing Health Effects Studies on 1,2-Dibromo-3-Chloropropane By Route and Endpoint*

The majority of the studies examined inhalation or oral exposure in animals (versus **humans**)
Potential reproductive, body weight, renal, and hepatic effects were the most studied endpoints



*Includes studies discussed in Chapter 2; the numbers of studies include those finding no effect. Occupational exposures are assumed to have been predominantly via inhalation.

6.2 Identification of Data Needs

Missing information in Figure 6-1 should not be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Acute-Duration MRLs. Sufficient information was not available on the health effects of 1,2-dibromo-3-chloropropane to derive an MRL for acute-duration inhalation exposure. In one study, reproductive effects were noted in rats following acute inhalation exposure to 1,2-dibromo-3-chloropropane (Saegusa et al. 1982). Although this is the most sensitive endpoint for 1,2-dibromo-3-chloropropane toxicity, the data are only available for rats. Intermediate-duration studies indicate that rabbits are more sensitive than rats to reproductive effects of 1,2-dibromo-3-chloropropane. Therefore, reproductive toxicity data are needed for acute inhalation exposures in rabbits and humans.

There are insufficient data for derivation of an acute-duration oral MRL. Several studies provided information on LD_{50} values and sublethal effects following acute oral exposure to 1,2-dibromo-3-chloropropane. However, among the available acute-duration oral studies, dominant lethality was observed at the lowest dose tested (10 mg/kg/day) (Teramoto et al. 1980). Additional acute-duration oral studies in the most sensitive animal species are needed to identify NOAELs and LOAELs for the most sensitive endpoint of oral 1,2-dibromo-3-chloropropane toxicity.

Intermediate-Duration MRLs. There are no data needs for intermediate-duration animal studies to serve as a basis for MRLs.

Chronic-Duration MRLs. Information regarding effects following chronic-duration exposure to 1,2-dibromo-3-chloropropane is available for rats and mice exposed by inhalation (NTP 1982) or from the diet (Hazleton 1977, 1978a; NCI 1978). The data were not suitable for MRL development because rabbits appear to be more sensitive than rats or mice to male reproductive effects (as demonstrated from intermediate-duration oral studies) and chronic-duration inhalation and oral toxicity studies are not available for rabbits. Additional chronic-duration inhalation and oral studies could be designed to establish the threshold for reproductive effects in rabbits in order to derive chronic-duration MRLs for 1,2-dibromo-3-chloropropane.

Health Effects. The toxicity of inhaled and ingested 1,2-dibromo-3-chloropropane has been assessed in laboratory animals. Although the primary use of 1,2-dibromo-3-chloropropane as a fumigant and nematocide has been cancelled, residues may still be found in soil and contaminated drinking water sources. Populations living in areas where 1,2-dibromo-3-chloropane is found in soil and/or drinking water should be monitored for potential exposure-related health effects. Since 1,2-dibromo-3-chloropropane may still be used as an intermediate in the production of other substances, workers who may be exposed should be monitored as well. Limited information was located regarding systemic effects following dermal exposure.

Respiratory. No studies were located regarding respiratory effects in humans after exposure to 1,2-dibromo-3-chloropropane by any route. Inhalation exposure of laboratory animals resulted in adverse effects in the nasal cavity, trachea, and bronchi that included inflammatory and proliferative changes and epithelial necrosis (NTP 1982; Saegusa et al. 1982; Torkelson et al. 1961). Chronic exposure of rats and mice resulted in tumors of the respiratory tract (NTP 1982). 1,2-Dibromo-3-chloropropane can volatilize from contaminated soil or surface water. Therefore, people living in areas where 1,2-dibromo-3-chloropropane may be detected in air should be monitored for possible exposure-related effects on the respiratory system.

Gastrointestinal. Available human data are limited to a single study that examined the correlation between ingestion of drinking water containing 0.004–5.75 ppb 1,2-dibromo-3-chloropropane and gastric cancer and found no correlation (Wong et a1.1989). Acute-, intermediate-, and chronic-duration oral exposure of laboratory animals to 1,2-dibromo-3-chloropropane resulted in inflammatory, proliferative, and degenerative effects in the gastrointestinal tract (Ghanayem et al. 1986; Hazleton 1977, 1978a, 1978b; NCI 1978; Torkelson et al. 1961); chronic-duration oral exposure also resulted in stomach cancer (Hazleton 1977, 1978a, 1978b; NCI 1978). Substantial oral exposure to 1,2-dibromo-3-chloropropane (from contaminated drinking water or food sources) is not likely among the general population. However, in areas where 1,2-dibromo-3-chloropropane was used as a fumigant and nematocide, food grown in the formerly-treated soil and nearby drinking water sources should be monitored and people living in such areas should be monitored for possible exposure-related effects on the gastrointestinal system.

Renal. No studies were located regarding renal effects in humans after exposure to 1,2-dibromo-3-chloropropane by the oral route. No renal effects were detected from the urinalysis of workers occupationally exposed to 1,2-dibromo-3-chloropropane (Whorton et al. 1977). 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 (Kato et al. 1980; NTP 1982; Saegusa et al. 1982; Torkelson et al. 1961). Substantial oral exposure to 1,2-dibromo-3-chloropropane (from contaminated drinking water or food sources) is not likely among the general population. However, in areas where 1,2-dibromo-3-chloropropane was used as a fumigant and nematocide, food grown in the formerly-treated soil and nearby drinking water sources should be monitored and people living in such areas should be monitored for possible exposure-related effects on the renal system. 1,2-Dibromo-3-chloropropane can volatilize from contaminated soil or surface water. Therefore, people living in areas where 1,2-dibromo-3-chloropropane may be detected in air should be monitored for possible exposure-related effects on the renal system.

Reproductive. The toxicity of 1,2-dibromo-3-chloropropane to the male reproductive system has been assessed in workers who were exposed primarily by inhalation (Biava et al. 1978; Lanham 1987; Potashnik et al. 1978, 1984; Slutsky et al. 1999). The only information on reproductive effects in low-dose orally exposed humans is that no changes in birth rates were observed in populations that were exposed to drinking water contaminated with 1,2-dibromo-3-chloropropane (Wong et al. 1988). Therefore, more studies regarding reproductive effects in humans after oral exposure from contaminated water would be useful. No data were located regarding the reproductive toxicity of 1,2-dibromo-3-chloropropane after dermal exposure.

The testicular toxicity of 1,2-dibromo-3-chloropropane after inhalation and oral exposure was demonstrated in rats and rabbits, but not in mice. More information for reproductive effects (including reproductive function) from all routes of exposure and different exposure durations, and on interspecies differences would be useful. Mostly negative results were obtained for reproductive effects in experimental animals after inhalation and oral exposure of females; however, ovarian cysts were reported in rats after inhalation exposure (Rao et al. 1983). More data about 1,2-dibromo-3-chloropropane toxicity to the female reproductive system would be useful. More data about 1,2-dibromo-3-chloropropane reproductive toxicity in human males might be helpful to correlate exposure levels with effects.

Developmental. No developmental effects were observed among workers occupationally-exposed to 1,2-dibromo-3-chloropropane (presumably by inhalation), but the cohort was not big enough to give reliable information (Goldsmith et al. 1984; Potashnik and Abeliovich 1985; Potashnik and Phillip 1988). Negative results were obtained after examination of the offspring in a population exposed to 1,2-dibromo-3-chloropropane through drinking water (Whorton et al. 1989). Reduced litter weight and size were found in rats at oral doses that caused maternal toxicity (Johnston et al. 1986; Ruddick and Newsome 1979). There is no information regarding developmental effects after dermal exposure. Additional data on developmental toxicity in experimental animals would be useful to identify possible risks for humans.

Immunotoxicity. No data were located regarding immunological effects of 1,2-dibromo-3-chloropropane in humans after inhalation, oral, or dermal exposure of any duration. Results of animal studies suggest that the spleen (NTP 1982; Reznik et al. 1980a; Saegusa et al. 1982), lymph (NTP 1982; Reznik et al. 1980a), and thymus (NTP 1982) may be targets following inhalation exposure. Hazleton (1977, 1978a) evaluated immunological endpoints in animals exposed to 1,2-dibromo-3-chloropropane in the diet. The apparent greater susceptibility of 1,2-dibromo-3-chloropropane-exposed animals to pulmonary infections also suggests a possible immunologic effect. A battery of immune function tests has not been performed in humans or in animals, but would provide valuable information to confirm or refute the suggestive evidence. Studies regarding skin sensitization with 1,2-dibromo-3-chloropropane have not been performed.

Neurotoxicity. No data were located regarding neurological effects in humans known to have been orally or dermally exposed to 1,2-dibromo-3-chloropropane. Workers occupationally exposed to 1,2-dibromo-3-chloropropane reported subjective neurological symptoms (Whorton et al. 1977). Neurological effects (e.g., meningoencephalitis, cerebral mineralization, cerebral necrosis) were observed in laboratory animals repeatedly exposed to 1,2-dibromo-3-chloropropane by inhalation (NTP 1982; Rao et al. 1983). Reduced activity was reported in rats receiving 1,2-dibromo-3-chloropropane from the diet at 67.5 mg/kg/day (Torkelson et al. 1961). Reel et al. (1984) reported depression of the central nervous system in rats receiving 1,2-dibromo-3-chloropropane from the diet, but did not indicate doses at which this effect was elicited. No data were located regarding neurotoxicity of 1,2-dibromo-3-chloropropane after dermal exposure in animals. Additional neurological and neurobehavioral tests in experimental animals would help to identify possible subtle neurological effects and the exposures associated with them.

Cancer. Well-conducted chronic inhalation, oral, and dermal exposure studies in animals demonstrate the carcinogenicity of 1,2-dibromo-3-chloropropane (NCI 1978; NTP 1982; Van Duuren et al. 1979). This is supported by the genotoxicity studies on prokaryotic and eukaryotic organisms. Further epidemiological studies of exposed workers would be useful to determine the possible risk in humans.

Genotoxicity. 1,2-Dibromo-3-chloropropane was positive for genotoxicity in most *in vivo* and *in vitro* assays (see Section 2.20). Depending on species, age, and exposure route or test system, generally negative results were observed for sperm gene crossover and heritable cross mutations (Kale and Baum 1982a), specific-locus gene mutations (Russell et al. 1986), bone marrow chromosomal aberrations (Shelby and Witt 1995) and bone marrow micronuclei (Albanese et al. 1988; Shelby and Witt 1995), human testicular DNA damage (Bjorge et al. 1996), and rat liver unscheduled DNA synthesis (Soderlund et al. 1991). Additional genotoxicity studies for 1,2-dibromo-3-chloropropane do not appear necessary.

Epidemiology and Human Dosimetry Studies. Several epidemiological studies have been conducted in humans exposed to 1,2-dibromo-3-chloropropane. Some dealt with the occurrence of cardiovascular disease and cancer in the exposed workers or in a population exposed to contaminated drinking water (Hearn et al. 1984; Wong et al. 1984, 1989). The limitations of occupational studies are coexposure to other chemicals and uncertainty about actual 1,2-dibromo-3-chloropropane concentrations in the workplace. More retrospective studies would be useful to determine possible 1,2-dibromo-3-chloropropane-induced mortality from cancer.

Other epidemiologic studies dealt with 1,2-dibromo-3-chloropropane toxicity on the reproductive system after occupational exposure or exposure via contaminated drinking water. 1,2-Dibromo-3-chloropropane-induced toxicity to the human male reproductive system was well established in several cross-sectional studies. Reliable dosimetry data on the exposed population and correlation with early signs of mild oligospermia would be useful. Follow-up studies of exposed workers would be of value to further determine the reversibility of testicular effects. The determination of 1,2-dibromo-3-chloropropane toxicity to the female reproductive system would be valuable. More data about the reproductive outcome in exposed populations and the possibility of spontaneous abortions after exposure would be useful. The inhalation and dermal routes of exposure are important for occupationally exposed individuals; inhalation, oral, and dermal exposure might be of concern to populations living near hazardous waste sites as

1,2-dibromo-3-chloropropane might get into soil and then contaminate the source of water used for bathing or drinking.

Biomarkers of Exposure and Effect. No biomarkers of exposure were identified for 1,2-dibromo-3-chloropropane. Further studies regarding possible biochemical changes after 1,2-dibromo-3-chloropropane exposure would be useful. The identification of urinary metabolites specific to 1,2-dibromo-3-chloropropane and their correlation with levels of exposure would also be useful.

No biomarkers of effect that would be specific to 1,2-dibromo-3-chloropropane have been identified. Several studies indicated that 1,2-dibromo-3-chloropropane induced DNA damage and changes in the activity of microsomal enzymes (Kluwe 1983; Suzuki and Lee 1981) or alterations in sperm parameters (Biava et al. 1978; Potashnik et al. 1978, 1984; Slutsky et al. 1999); however, these changes are not specific for 1,2-dibromo-3-chloropropane exposure and cannot be used as biomarkers. It is not likely that specific biomarkers of effect exist for 1,2-dibromo-3-chloropropane. No studies are suggested because toxicologically significant exposure to 1,2-dibromo-3-chloropropane is not likely since it was banned for use as a pesticide in the United States in 1985.

Absorption, Distribution, Metabolism, and Excretion. 1,2-Dibromo-3-chloropropane can be absorbed through the lungs, gastrointestinal tract, and skin, as indicated by toxicity studies (Gingell et al. 1987a; Kato et al. 1979a). Absorption has been studied specifically only after oral exposure (Gingell et al. 1987a; Kato et al. 1979a). The absorption followed first-order kinetics, and no saturation has been observed with concentrations tested thus far. In animals, 1,2-dibromo-3-chloropropane is quickly distributed to tissues throughout the body, with highest concentrations accumulating in adipose tissue (Kato et al. 1979a, 1980). The metabolic pathway has been well-studied in rats (e.g., Jones et al. 1979; Pearson et al. 1990; Soderlund et al. 1995). Excretion occurs mainly via urinary metabolites in exposed animals, and smaller amounts are excreted in breath and bile (Gingell et al. 1987b; Kato et al. 1979a). No comparisons have been made regarding absorption, distribution, metabolism, and excretion via different routes of exposure. Additional studies using inhalation and dermal exposure routes would be useful.

Comparative Toxicokinetics. The differences between reproductive toxicity in mice and rats were demonstrated in several studies. Similar differences were observed in toxicokinetics between rats and hamsters (with high testicular toxicity) and mice and guinea pigs (with low testicular toxicity) (Lag et al. 1989a; MacFarland et al. 1984). Also, rabbits were found to be more susceptible to reproductive effects than rats (Rao et al. 1982, 1983). The fact that reproductive toxicity of 1,2-dibromo-3-chloropropane was

also observed in humans might suggest that rabbits, and possibly rats, could serve as a model for 1,2-dibromo-3-chloropropane toxicity. Further investigation of toxicokinetics in different species and the comparison of detected metabolites with those detected in humans would be useful.

Children's Susceptibility. No information was located regarding potential age-related differences in susceptibility to 1,2-dibromo-3-chloropropane toxicity. Animals studies could be designed to evaluate potential age-related differences. Most human exposure to 1,2-dibromo-3-chloropropane in the past has involved occupational exposure via production of the pesticide, its use as an intermediate in the production of other pesticides, or exposure during mixing and application when it was registered for agricultural use. The most likely source of information regarding potential age-related differences in susceptibility among humans would be from dermal contact with contaminated soil, ingestion of contaminated water, or inhalation following volatilization from contaminated soil or water. If such populations could be identified, they should be monitored for possible age-related differences in susceptibility.

Physical and Chemical Properties. Physical and chemical property data are essential for estimating the transport and partitioning of a chemical in the environment. Most of the essential physical and chemical properties needed to estimate the environmental fate and transport of 1,2-dibromo-3-chloropropane are available (see Table 4-2).

Production, Import/Export, Use, Release, and Disposal. Data regarding the production methods for 1,2-dibromo-3-chloropropane are available; however, comprehensive data regarding current production volumes, release, and use patterns are lacking. Current levels of production, release, and use are considered relatively low due to the banning of the chemical's major use as a soil fumigant. Use, release, and disposal data can be useful for determining areas where environmental exposure to 1,2-dibromo-3-chloropropane may be high. Based upon relatively outdated data, significant concentrations are expected to be found mainly in the groundwater and drinking water near areas where 1,2-dibromo-3-chloropropane was used extensively as a soil fumigant (Burmaster 1982; Carter and Riley 1981; Cohen 1986; Kloos 1983; Kutz and Carey 1986; Nelson et al. 1981; Oki and Giambelluca 1987; Peoples et al. 1980; Westrick et al. 1984). Only general data are available on the methods of disposal of 1,2-dibromo-3-chloropropane (HSDB 1989). Specific disposal information would be useful for determining the effectiveness of the disposal methods. Regulations are available pertaining to the restrictions upon the land disposal of 1,2-dibromo-3-chloropropane.

Environmental Fate. The ultimate environmental fate of 1,2-dibromo-3-chloropropane remains unclear due to a lack of data. The chemical partitions to water and the atmosphere, volatilizes from water and soil, leaches through soil, degrades in the atmosphere, and via hydrolysis in water, and is persistent in soils (see Chapter 5). Additional experimental data concerning biodegradation in soil would aid in assessing the ultimate environmental fate of 1,2-dibromo-3-chloropropane.

Bioavailability from Environmental Media. 1,2-Dibromo-3-chloropropane can be present in water and food and it is absorbed through the gastrointestinal tract (see Section 3.1.1). This suggests that exposure to 1,2-dibromo-3-chloropropane may occur as the result of ingestion of soil by children playing near hazardous waste sites. No data were found concerning absorption through the lungs or through dermal contact. Knowledge of the bioavailability through the various exposure routes is essential in assessing the potential body burdens that may occur as a result of exposure to known environmental concentrations.

Food Chain Bioaccumulation. Experimental data regarding the bioconcentration of 1,2-dibromo-3-chloropropane in plants, aquatic organisms, and animals were not located in the literature. However, based on an estimated BCF of 11.2, 1,2-dibromo-3-chloropropane is not expected to bioconcentrate in fish and other aquatic organisms (Bysshe 1982; Munnecke and VanGundy 1979); thus, biomagnification in aquatic food chains is unlikely. Additional information on bioconcentration in plants and animals and biomagnification in terrestrial food chains would be helpful in assessing the potential for exposure of terrestrial animals at higher trophic levels.

Exposure Levels in Environmental Media. The data concerning the detection of 1,2-dibromo-3-chloropropane in the environment are limited and outdated. Current and comprehensive monitoring data, especially in areas where the chemical has been used in the past, are needed to estimate human intake. Food survey analyses are needed since it is difficult to ascertain whether previous surveys tested for the presence of 1,2-dibromo-3-chloropropane.

Exposure Levels in Humans. No monitoring data were found indicating that 1,2-dibromo-3-chloropropane has been found in human tissues or blood. Data concerning the level of 1,2-dibromo-3-chloropropane in human tissue samples would be helpful in assessing the extent of human exposure to the chemical and in estimating its body burden.

Exposures of Children. No studies are available to assess whether children are at a higher exposure risk than adults. Studies examining potential exposure sources for children would be useful.

6.3 Ongoing Studies

No ongoing studies were identified for 1,2-dibromo-3-chloropropane.

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding 1,2-dibromo-3-chloropropane in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for 1,2-dibromo-3-chloropropane.

Table 7-1. Regulations and Guidelines Applicable to 1,2-Dibromo-3-Chloropropane

Agency	Description	Information	Reference
	Air		
EPA	RfC	$2x10^{-4}$ mg/m^3 [a]	IRIS 2003
WHO	Air quality guidelines	No data	WHO 2010
	Water & Food		
EPA	Drinking water health advisories		EPA 2012
	1-Day (10 kg child)	0.2 mg/L	
	10-Day (10 kg child)	0.05 mg/L	
	mg/L at 10^{-4} cancer risk	0.003	
	National primary drinking water regulations		EPA 2009
	MCL	0.0002 mg/L[b]	
	Public health goal	Zero	
	RfD	No data	IRIS 2003
WHO	Drinking water quality guidelines		WHO 2017
	Guideline value	0.001 mg/L (1 µg/L)[c]	
FDA	EAFUS	No data[d]	FDA 2013
	Cancer		
HHS	Carcinogenicity classification	Reasonably anticipated to be a human carcinogen[e]	NTP 2016
EPA	Carcinogenicity classification	Not evaluated	IRIS 2003
IARC	Carcinogenicity classification	Group 2B[f,g]	IARC 1999
	Occupational		
OSHA	PEL (8-hour TWA) for occupational exposure	1 ppb[h]	OSHA 2016a, 2016b, 2016c
NIOSH	REL (up to 10-hour TWA)	No data	NIOSH 2016

Table 7-1. Regulations and Guidelines Applicable to 1,2-Dibromo-3-Chloropropane

Agency	Description	Information	Reference
	Emergency Criteria		
EPA	AEGLs-air	No data	EPA 2016
DOE	PACs-air		DOE 2016a
	PAC-1[i]	0.003 ppm	
	PAC-2[i]	2.2 ppm	
	PAC-3[i]	4.3 ppm	

[a]Based on testicular effects found in a 13-week subchronic rabbit inhalation study.
[b]Potential health effects from long-term exposure above the MCL: reproductive difficulties; increased risk of cancer.
[c]Derivation based on a linearized multistage model applied to the data on the incidence of stomach, kidney, and liver tumors in the male rat in a 104-week dietary study. Guideline value should be protective for reproductive toxicity.
[d]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[e]Based on sufficient evidence of carcinogenicity from studies in experimental animals.
[f]Group 2B: Possibly carcinogenic to humans.
[g]Based on sufficient evidence for carcinogenicity in experimental animals and inadequate evidence in humans.
[h]Employer shall ensure no employee is exposed to eye or skin contact with dibromochloropropane.
[i]Definitions of PAC terminology are available from the U.S. Department of Energy (DOE 2016b).

AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

*Ahmad N, Wisner JR., Warren DW. 1988. Morphological and biochemical changes in the adult male rat reproductive system following long-term treatment with 1,2-dibromo-3-chloropropane. Anat Ret 222:340-349.

*AIHA. 2015. Current ERPG Values (2015). Fairfax, VA: American Industrial Hygiene Association. https://www.aiha.org/get-involved/AIHAGuidelineFoundation/EmergencyResponsePlanningGuidelines/Documents/2015%20ERPG%20Levels.pdf. March 22, 2016.

*Albanese R, Mirkova E, Gatehouse DG, et al. 1988. Species-specific response to the rodent carcinogens 1,2-dimethylhydrazine and 1,2-dibromo-3-chloropropane in rodent bone-marrow micronucleus assays. Mutagenesis 3(1):35-38.

*Albrecht WN. 1987. Occupational exposure to 1,3-dichloropropene (TeloneII@) in Hawaiian pineapple culture. Arch Environ Health 42:286-291.

*Albrecht WN, Chenchin K. 1985. Dissipation of 1,2-dibromo-3-chloropropanecis-1',3-dichloropropene (1,3-DCP) and dichloropropenes from soil to atmosphere. Bull Environ Contam Toxicol 34:824-831.

*Albrecht WN, Hagadone MR, Chenchin K. 1986. Charcoal air sampling tube storage stability and desorption efficiencies of 1,2-dibromo-3-chloropropane (DBCP) and 1,3-dichloropropene (DCP). Bull Environ Contam Toxicol 36:629-634.

*Amann RP, Berndtson WE. 1986. Assessment of procedures for screening agents for effects on male reproduction: Effects of dibromochloropropane (DBCP) on the rat. Fundam Appl Toxicol 7:244-255.

*Anonymous. 1988. DBCP. Rev Environ Contam Toxicol 104:73-91.

*ATSDR. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles; Notice. Agency for Toxic Substances and Disease Registry. Fed Regist 54(174):37618-37634.

*ATSDR. 2017. 1,2-Dibromo-3-chloropropane. Full SPL data. Substance priority list (SPL) resource page. Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention. http://www.atsdr.cdc.gov/SPL/resources/index.html. October 6, 2017.

Axelson O. 1985. Halogenated alkanes and alkenes and cancer: Epidemiological aspects. In: Fishbein L, O'Neill I, eds. Environmental carcinogens selected methods of analysis. Lyon, France: World Health Organization, 7:5-20.

Barlow S, Sullivan F. 1982. Dibromochloropropane (DBCP). In: Reproductive hazards of industrial chemicals. London, England: Academic Press, 253-268.

*Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8(4):471-486.

*Bartoov B, Ventura V, Ailenberg M, et al. 1987. Effects of dibromochloropropane and ethylene dibromide on biochemical events and ultramorphology of ejaculated ram spermatozoa *in vitro*. Am J Ind Med 11:647658.

Beattie P, Miller G, Brabec M, et al. 1984. Dibromochloropropane and methoxyacetic-acid alter lactate metabolism by isolated rat spermatocytes. Biol Reprod 30:169.

*Becher R, Lag M, Schwarze PE, et al. 1993. Chemically induced DNA damage in isolated rabbit lung cells. Mutat Res 285(2):303-311.

*Bentley KS, Working PK. 1988. Activity of germ-cell mutagens and nonmutagens in the rat spermatocyte UDS assay. Mutat Res 203:135-142.

Berndtson W, Neefus C, Foote R, et al. 1989. Optimal replication for histometric analyses of testicular function in rats or rabbits. Fundam Appl Toxicol 12:291-302.

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*Cited in text

8. REFERENCES

*Biava CG, Smuckler EA, Whorton D. 1978. The testicular morphology of individuals exposed to dibromochloropropane. Exp Mol Pathol 29:448-458.

Biles R. 1979. The toxicology and genetic toxicology of dibromochloropropane(DBCP). Diss Abst Int 39:5817.

*Biles RW, Connor TH, Trieff NM, et al. 1978. The influence of contaminants on the mutagenic activity of dibromochloropropane (DBCP). J Environ Pathol Toxicol 2:301-312.

*Bjorge C, Wiger R, Holme JA, et al. 1995. *In vitro* toxicity of 1,2-dibromo-3-chloropropane (DBCP) in different testicular cell types from rats. Reprod Toxicol 9(5):461-473.

*Bjorge C, Wiger R, Holme JA, et al. 1996. DNA strand breaks in testicular cells from humans and rats following *in vitro* exposure to 1,2-dibromo-3-chloropropane (DBCP). Reprod Toxicol 10(1):51-59.

*Bomberger DC, Gwinn JL, Mabey WR, et al. 1983. Environmental fate and transport at the terrestrial-atmospheric interface. American Chemical Society Symp Ser 225:197-214.

Borzsonyi M, Torok G, Pinter A, et al. 1984. Agriculturally-related carcinogenic risk. Models, mechanisms and etiology of tumor promotion. Lyon, France: World Health Organization. IARC Sci Pub1 56:465-486.

*Bouwer EJ, Wright JP. 1988. Transformations of trace halogenated aliphatics in anoxic biofilm columns. J Contam Hydrol 2:155-169.

*Brodzinsky R, Singh HB. 1982. Volatile organic chemicals in the atmosphere: An assessment of available data. Atmospheric Science Center, SRI International, Menlo Park, CA, 12, 19-21, 42.

*Bronstein AC, Currance PL. 1988. Emergency care for hazardous materials exposure. Washington DC: The CV Mosby Company, 155-156.

*Brunborg G, Holme JA, Soederlund EK, et al. 1988. An automated alkaline elution system: DNA damage induced by 1,2-dibromo-3-chloropropane *in vivo* and *in vitro*. Anal Biochem 174:522-536.

*Brunborg G, Soderlund EJ, Holme JA, et al. 1996. Organ-specific and transplacental DNA damage and its repair in rats treated with 1,2-dibromo-3-chloropropane. Chem Biol Interact 101(1):33-48.

Bull R. 1982. Experimental methods for evaluating the health risks associated with organic chemicals in drinking water. Toxicol Environ Chem 6:1-17.

Burek J, Murray F, Rao K, et al. 1979. Pathogenesis of inhaled 1,2-dibromo-3-chloropropane (DBCP) induced testicular atrophy in rats and rabbits. Toxicol Appl Pharmacol 48:A121.

*Burlinson NE, Lee LA, Rosenblatt DH. 1982. Kinetics and products of hydrolysis of 1,2-dibromo-3-chloropropane. Environ Sci Technol 16:627-632.

*Burmaster DE. 1982. The new pollution-groundwater contamination. Environment 24:7-13, 33-36.

*Bysshe SE. 1982. Bioconcentration factor in aquatic organisms. In: LymanWJ, Reehl WF, Rosenblatt DH, eds. Handbook of chemical property estimation methods. Environmental behavior of organic compounds. New York, NY: McGraw-Hill Book Co., 5-5.

*Carter GE Jr., Riley MB. 1981. 1,2-Dibromo-3-chloropropane residues in water in South Carolina, 1979-80. Pest Monit J 15:139-142.

*Carter GE Jr,, Riley MB. 1982. Residues of dibromochloropropane in fresh and preserved peaches. J Agric Food Chem 30:647-649.

*Carter GE Jr., Riley MB. 1984. Dibromochloropropane residues in peaches following fall orchard fumigation. J Agric Food Chem 32:186-187.

*Carter GE Jr., Ligon JT, Riley MB. 1984. DBCP residue studies in soil and well water from two South Carolina peach orchards. Water Air Soil Pollut 22:201-208.

*CAS. 1989. Chemical Abstracts Service CAS on-line registry file. American Chemical Society, Chemical Abstracts Service, Cleveland, OH. December 18,1989.

*Castro CE, Belser NO. 1968. Biodehalogenation. Reductive halogenation of the biocides ethylene dibromide, 1,2-dibromo-3-chloropropane, and 2,3-dibromobutane in soil. Environ Sci Technol 2:779-783.

*CDC. 2018. Fourth national report on human exposure to environmental chemicals, updated tables (March 2018). Centers for Disease Control and Prevention. https://www.cdc.gov/exposurereport/. April 6, 2018.

8. REFERENCES

Chayoth R, Kaplanski J, Sror U, et al. 1988. The effect of dibromochloropropane (DBCP) on *in vitro* cyclic AMP levels and testosterone production in rat testes. Andrologia 20:232-237.

Clegg E, Sakai C, Voytek P. 1986. Assessment of reproductive risks. Biol Reprod 34:5-16.

CLPSD. 1989. Contract Laboratory Statistical Database. Viar and Company, Alexandria, VA. July 12, 1989.

*Clewell HJ, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1(4):111-131.

*Cohen D B 1986. Groundwater contamination by toxic substances: A California assessment. American Chemical Society Symp Ser 315:499-529.

*Cohen SZ, Eiden C, Lorber MN. 1986. Monitoring ground water for pesticides. American Chemical Society Symp Ser 315:170-196.

*Cooper ER, Jones AR, Jackson H. 1974. Effects of α-chlorohydrin and related compounds on the reproductive organs and fertility of the male rat. Reprod Fertil 39:379-386.

*Cortes-Gallegos V, Castaneda G, Alonso R, et al. 1980. Effects of dibromochloropropane upon diurnal variations of gonadotropins and androgens. J Androl 1:277-280.

*Coye MJ, Albrecht WB, Sinks T. 1990. NIOSH health hazard evaluation report no. 81-162, Maui Pineapple Company, Kahuli, Hawaii. HETA 81-162-1935.

*Coye MJ, Albrecht WB, Whorton DM. 1983. NIOSH health hazard evaluation report no. 81-040, Dole Pineapple Corporation, Lanai, Hawaii. HETA 81-0401315.

Crosbie E, Eisenmann C. 1986. Health effects assessment for dibromochloropropane. Prepared by Syracuse Research Corporation, Syracuse, NY for Environmental Criteria and Assessment Office, U.S. Environmental Protection Agency, Cincinnati, OH.

Curry M, Lybarger J, Meyer C. 1979. NIOSH conference on dibromochloropropane. In: Symposium on DBCP, National Institute for Occupational Safety and Health, Division of Surveillance, Hazard Evaluations and Field Studies, Cincinnati, OH, October 19-20, 1977.

*Daft JL. 1988. Rapid determination of fumigant and industrial chemical residues in food. J Assoc Off Anal Chem 71:748-760.

*Daft JL. 1989. Determination of fumigants and related chemicals in fatty and non-fatty foods. J Argic Food Chem 37:560-564.

De Serres F, Malling H, Brockman H, et al. 1982. Mutagenicity of epichlorohydrin and 1,2-dibromoethane in heterokaryon 12 of *Neurospora crassa*. Environ Mutagen 4:398-399.

*DOE. 2016a. Table 3: Protective Action Criteria (PAC) Rev. 29 based on applicable 60-minute AEGLs, ERPGs, or TEELs. The chemicals are listed by CASRN. May 2016. Oak Ridge, TN: U.S. Department of Energy. https://sp.eota.energy.gov/pac/teel/Revision_29_Table3.pdf. February 28, 2017.

*DOE. 2016b. Protective Action Criteria (PAC) with AEGLs, ERPGs, & TEELs: Rev. 29 for chemicals of concern - May 2016. Oak Ridge, TN: U.S. Department of Energy. https://energy.gov/ehss/protective-action-criteria-pac-aegls-erpgs-teels-rev-29-chemicals-concern-may-2016. February 28, 2017.

Dohn D, Graziano M, Casida J. 1988. Metabolites of [$_{3\text{-}13}$C]1,2-dibromo-3-chloropropane in male rats studied by $_{13}$C and $_{1}$H-$_{13}$C correlated two dimensional NMR spectroscopy. Biochem Pharmacol 37:3485-3495.

Dow Chemical Company. 1978. Exploratory RES Programs with transmittal letter from EPA. Dow Chemical Company, Midland, MI.

Dybing E, Omichinski J, Soderlund E, et al. 1986. Role of cytochrome P-450 metabolism in 1,2 dibromo-3-chloropropane mutagenicity and nephrotoxicity. Toxicol Lett 31(Suppl):220.

*Eaton M, Schenker M, Whorton M, et al. 1986. Seven-year follow-up of workers exposed to 1,2-dibromo-3-chloropropane. J Occup Med 28:1145-1150.

*Egnatz D, Ott M G, Townsend J, et al. 1980. DBCP and testicular effects in chemical workers: An epidemiological survey in Midland, Michigan. J Occup Med 22:727-732.

8. REFERENCES

*Eisenreich.SJ, Looney BB, Thornton JD. 1981. Airborne organic contaminants in the Great Lakes ecosystem. Environ Sci Technol 15:30-38.

*EPA. 1977. U.S. Environmental Protection Agency: Southern Agricultural Insecticides, Inc., et al. Suspension order. Fed Regist 42:57543-57548.

EPA. 1978. Occupational exposure to 1,2-dibromo-3-chloropropane (DBCP). Fed Regist 43:11514-11533.

*EPA. 1979. U.S. Environmental Protection Agency: Dibromochloropropane(DBCP); Suspension order and notice of intent to cancel. Fed Regist 44:65135-65176.

*EPA. 1985a. Drinking water criteria document for 1,2-dibromo-3chloropropane (DBCP). Prepared by Environmental Criteria and Assessment Office, Cincinnati, OH, for Office of Drinking Water, Washington, DC. EACOCIN410. NTIS 118064 PB 86-18.

*EPA. 1985b. U.S. Environmental Protection Agency: Dibromochloropropane; intent to cancel registrations of pesticide products containing dibromochloropropane (DBCP). Fed Regist 50:1122-1123.

*EPA. 1985c. U.S. Environmental Protection Agency: Dibromochloropropane; denial of use of existing stocks. Fed Regist 50:46512.

*EPA. 1985d. Exposure analysis modeling system: Reference manual for EXAMS II. Athens, GA: U.S. Environmental Protection Agency, Environmental Research Lab. EPA600385038.

*EPA. 1985e. U.S. Environmental Protection Agency. List of hazardous substances and reportable quantities. Fed Regist 50:13483.

*EPA. 1986a. Method for the determination of organic compounds in finished drinking water and raw source water. Method Nos. 504.1, 524.1 and 524.2. Cincinnati, OH: U.S. Environmental Protection Agency, Environmental Monitoring and Support Laboratory.

*EPA. 1986b. Test method for evaluating solid waste, physical/chemical methods, SW-846, Method Nos. 5030, 8010. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

*EPA. 1987a. List of hazardous substances and reportable quantities. Fed Regist 52:8152.

*EPA. 1987b. Health advisories for 16 pesticides (including alachlor, aldicarb, carbofuran, chlordane, DBCP, 1,2-dichloropropane, 2,4-D, endrin, ethylene dibromide, heptachlor/heptachlor epoxide, lindane, methoxychlor, oxamyl, pentachlorophenol, toxaphene and 2,4,5-TP). Washington, DC: U.S. Environmental Protection Agency, Office of Drinking Water.

EPA. 1987c. List (phase 1) of hazardous constituents for ground-water monitoring. Appendix IX - Ground water monitoring list. Fed Regist52:25948.

*EPA. 1988a. PC Gems CLOGP3 (Octanol/Water Partition Coefficient). Graphical Exposure Modeling Systems. Washington, DC: U.S. Environmental Protection Agency.

*EPA. 1988b. U.S. Environmental Protection Agency: Discarded chemical products, off-specification species, container residues, and spill residues thereof. Code of Federal Regulations. 40 CFR 261.33.

*EPA. 1988c. U.S. Environmental Protection Agency: Part 268 - Land Disposal Restrictions. Code of Federal Regulations. 40 CFR 261.33(f).

*EPA. 1989a. Interim methods for development of inhalation reference doses. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA600888066F.

EPA. 1989b. Computer printout (CIS): 1977 Non-confidential production data from TSCA inventory. OPTS, CID. Washington, DC: U.S. Environmental Protection Agency.

*EPA. 2005. Toxic chemical release inventory reporting forms and instructions: Revised 2004 version. Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986). U.S. Environmental Protection Agency, Office of Environmental Information. EPA260B05001.

8. REFERENCES

*EPA. 2009. National primary drinking water regulations. Washington, DC: Office of Ground Water and Drinking Water, U.S. Environmental Protection Agency. EPA816F090004. https://www.epa.gov/sites/production/files/2016-06/documents/npwdr_complete_table.pdf. February 28, 2017.

*EPA. 2012. Drinking water standards and health advisories. Washington, DC: U.S. Environmental Protection Agency, Office of Water. EPA822S12001. https://www.epa.gov/sites/production/files/2015-09/documents/dwstandards2012.pdf. February 28, 2017.

*EPA. 2016. Acute Exposure Guideline Levels (AEGLs) Values. U.S. Environmental Protection Agency. https://www.epa.gov/aegl/access-acute-exposure-guideline-levels-aegls-values#chemicals. February 28, 2017.

*FDA. 2013. Everything added to food in the United States (EAFUS). Washington, DC: U.S. Food and Drug Administration. http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting. February 28, 2017.

*Foote RH, Berndtson WE, Rounsaville TR. 1986a. Use of quantitative testicular histology to assess the effect of dibromochloropropane (DBCP) on reproduction in rabbits. Fundam Appl Toxicol 6:638-647.

*Foote RH, Schermerhorn EC, Simkin ME. 1986b. Measurement of semen quality, fertility, and reproductive hormones to assess dibromochloropropane (DBCP) effects in live rabbits. Fundam Appl Toxicol 6:628-637.

*Fredrickson S, Jackson T, Liao CL, et al. 1985. Determination of dibromochloropropane and ethylene dibromide in air. IARC Sci Pub1 68:259-268.

FSTRAC. 1988. Summary of state and federal drinking water standards and guidelines. Chemical Communication Subcommittee. Federal-State Toxicology and Regulatory Alliance Committee

*Gabbita KV. 1986. Presence of 1,2-dibromo-3-chloropropane (DBCP) residues in sodium humate and its possible significance. Toxicol Environ Chem 11:203-213.

*Garman JR, Freund T, Lawless EW. 1987. Testing for groundwater contamination at hazardous waste sites. J Chromatogr Sci 251:328-337.

*Generoso W, Cain K, Hughes L. 1985. Tests for dominant-lethal effects of 1,2-dibromo-3-chloropropane (DBCP) in male and female mice. Mutat Res 156:103-168.

*George E, Wootton AK, Gatehouse DG. 1990. Micronucleus induction by azobenzene and 1,2-dibromo-3-chloropropane in the rat: Evaluation of a triple-dose protocol. Mutat Res 234(3-4):129-134.

Getzendaner M. 1975. A review of bromine determination in foods. J Assoc Off Anal Chem 58:711-716.

*Ghanayem BI, Maronpot RR, Matthews HB. 1986. Association of chemically induced forestomach cell proliferation and carcinogenesis. Cancer Lett 321:271-278.

*Gingell R, Beatty PW, Mitschke HR, et al. 1987a. Toxicokinetics of 1,2dibromo-3-chloropropane (DBCP) in the rat. Toxicol Appl Pharmacol 91:386-394.

*Gingell R, Beatty PW, Mitschke HR, et al. 1987b. Evidence that epichlorohydrin is not a toxic metabolite of 1,2-dibromo-3-chloropropane. Xenobiotica 17:229-240.

*Glass RI, Lyness RN, Mengle DC, et al, 1979. Sperm count depression in pesticide applicators exposed to dibromochloropropane. Am J Epidemiol 109:346-351.

*Goldsmith JR, Potashnik G, Israeli R. 1984. Reproductive outcomes in families of DBCP-exposed men. Arch Environ Health 39:85-89.

*Greenwell A, Tomaxzewski KE, Melnick RL. 1987. A biochemical basis for 1,2-dibromo-3-chloropropane-induced male infertility: Inhibition of sperm mitochondrial electron transport activity. Toxicol Appl Pharmacol 91:274-280.

*Hachiya N, Motohashi Y. 2000. Examination of *lac*Z mutant induction in the liver and testis of Muta™ mouse following injection of halogenated aliphatic hydrocarbons classified as human carcinogens. Ind Health 38:213-220.

8. REFERENCES

*Hahn JD. 1970. Post-testicular anti-fertility effects of epichlorohydrin and 2,3-epoxypropanol. Nature 226:87.

Hamill P, Steinberger E, Levine R, et al. 1982, The epidemiologic assessment of male reproductive hazard from occupational exposure to TDA and DNT. J Occup Med 24:985-993.

Hawley GG. 1981. The condensed chemical dictionary. 10th ed. New York, NY: Van Nostrand Reinhold Co., 325.

*Hazleton 1977. 104-Week dietary study in rats: 1,2-Dibromo-3-Chloropropane (DBCP). Final report. Unpublished data submitted to Dow Chemical Company. Midland, Michigan. Project No. 174-122.

*Hazleton 1978a. 104-Week dietary study in Rats: 1,2-Dibromo-3-Chloropropane (DBCP): Supplementary histopathology report to final report Dated October 28, 1977. Unpublished data submitted to Dow Chemical Company. Midland, Michigan. Project No. 174-122.

*Hazleton 1978b. 78-Week toxicity and carcinogenicity study in Mice: 1,2-Dibromo-3-Chloropropane, final report. Unpublished data submitted to Dow Chemical Company. Midland, Michigan. Project No. 174-125.

*Hearn S, Ott MG, Kolesar RC, et al. 1984. Mortality experience of employees with occupational exposure to DBCP. Arch Environ Health 39:49-55.

*Heindel JJ, Berkowitz AS, Kyle G, et al. 1989. Assessment in rats of the gonadotoxic and hepatorenal toxic potential of dibromochloropropane (DBCP) in drinking water. Fundam Appl Toxicol 13:804-815.

*Ho JSY. 1989. A sequential analysis for volatile organics in water by purge-and-trap capillary column gas chromatography with photoionization and electrolytic conductivity detectors in series. J Chromatogr Sci 27:91-98.

*Hodges LR, Lear B. 1974. Persistence and movement of DBCP in three types of soil. Soil Sci 118:127-130.

*Holme JA, Soderlund EJ, Brunborg G, et al. 1989. Different mechanisms are involved in DNA damage, bacterial mutagenicity and cytotoxicity induced by 1,2-dibromo-3-chloropropane in suspensions of rat liver cells. Carcinogenesis 10:49-54.

*Holme JA, Soderlund EJ, Brunborg G, et al. 1991. DNA damage and cell death induced by 1,2-dibromo-3-chloropropane (DBCP) and structural analogs in monolayer culture of rat hepatocytes: 3-aminobenzamide inhibits the toxicity of DBCP. Cell Biol Toxicol 7(4):413-432.

Hooper K, Gold L. 1986. Ranking the carcinogenic hazards of occupational exposures: Exposure-Potency Index (EPI) values for nine volatile industrial chemicals. Prog Clin Biol Res 207:217-228.

*HSDB. 1989. Hazardous Substances Data Bank. National Library of Medicine, National Toxicology Information Program, Bethesda, MD.

Huff J. 1983. 1,2-dibromo-3-chloropropane. Environ Health Perspect 47:365-369.

IARC. 1977. IARC monographs on the evaluation of the carcinogenic risk of chemicals to man. Some fumigants, the herbicides 2,4-D and 2,4,5-T, chlorinated dibenzodioxins and miscellaneous industrial chemicals. Lyon, France: World Health Organization. Vol 15:83-96.

*IARC. 1979. Monograph on the evaluation of the carcinogenic risk of chemicals to humans. Vol. 20: Some halogenated hydrocarbons. Lyon, France: World Health Organization. Vol 20:l-40, 83-96.

IARC. 1987. IARC monographs on the evaluation of carcinogenic risks to humans. Supplement 7: Overall evaluations of carcinogenicity: An updating of IARC monographs volumes 1 to 42. Lyon, France: World Health Organization. Suppl 7.

*IARC. 1999. 1,2-Dibromo-3-chloropropane. IARC Monographs on the evaluation of carcinogenic risks to humans. Volume 71. Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. Lyon, France: International Agency for Research on Cancer. http://monographs.iarc.fr/ENG/Monographs/vol71/mono71-20.pdf. June 29, 2017.

*Inoue TI, Miyazawa T, Tanahashi N, et al. 1982. Induction of sex-linked recessive lethal mutations in *Drosophila melanogaster* males by gaseous 1,2-dibromo-3-chloropropane (DBCP). Mutat Res 105:89-94.

Inskeep PB, Guengerich FP. 1984. Glutathione-mediated binding of dibromoalkanes to DNA: Specificity of rat glutathione-S-transferases and dibromoalkane structure. Carcinogenesis 5:805-808.

*IRIS. 1991. Integrated Risk Information System (database). Washington, D.C.: U.S. Environmental Protection Agency.

*IRIS. 2003. 1,2-Dibromo-3-chloropropane (DBCP); CASRN 96-12-8. Chemical assessment summary. Integrated Risk Information System. Washington, DC: U.S. Environmental Protection Agency. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0414_summary.pdf. June 29, 2017.

Irvin T, Sawin V. 1986. Characterization of DNA reaction products formed by *in vitro* activation of 14^{C}-DBCP by microsomes or GSH. Environ Mutagen 8(Suppl6):39.

*Johnston RV, Mensik DC, Taylor HW, et al. 1986. Single-generation drinking water reproduction study of 1,2-dibromo-3-chloropropane in Sprague-Dawley rats. Bull Environ Contam Toxicol 37:531-537.

*Jones A, Fakhouri G, Gadiel P. 1979. The metabolism of the soil fumigant 1,2-dibromo-3-chloropropane in the rat. Experientia 35:1432-1434.

*Jury WA, Winer AM, Spencer WF, et al. 1987. Transport and transformation of organic chemicals in the soil-air-water ecosystem. Rev Environ Contam Toxicol 99:119-164.

*Kale PG, Baum JW. 1982a. Genetic effects of 1,2-dibromo-3-chloropropane(DBCP) in drosophila. Environ Mutagen 4:681-687.

*Kale PG, Baum JW. 1982b. Genetic effects of strong magnetic fields in *Drosophila melanogaster*. III. Combined treatment with homogeneous fields and gaseous DBCP. Mutat Res 1051:79-83.

Kapp R. 1979. Evaluation of the genetic toxicity of 1,2-dibromo-3-chloropropane in humans and rats. Diss Abstr Int 40:1516-1660.

Kapp RW, Picciano DJ, Jacobson CB. 1979. Y-chromosomal nondisjunction in dibromochloropropane-exposed workmen. Mutat Res 64:47-51.

*Kastl PE, Hermann EA, Braun WH. 1981. Quantitative determination of 1,2-dibromo-3-chloropropane in whole rat blood and drinking water by gas chromatography. J Chromatogr 213:156-161.

*Kato Y, Sato K, Maki S, et al. 1979a. Metabolic fate of 1,2-dibromo-3chloropropane (DBCP) in rats. J Pestic Sci 4:195-203.

*Kato Y, Matano O, Goto S. 1979b. Covalent binding of DBCP to proteins *in vitro*. Toxicol Lett 3:299-302.

*Kato Y, Sato K, Harada T, et al. 1980. Correlation between macromolecular binding of DBCP-metabolite and pathogenicity of necrosis. J Pestic Sci 5:81-88.

*Kawabata A. 1981. Studies on the carcinogenic activity of epichlorohydrin by oral administration in male Wistar rats. J Nara Med Assoc 32:270-280.

Kemper J, Bernstein M. 1978. Dibromochloropropane (DBCP: Final position document). Environmental Protection Agency, Arlington, VA. EPASPRD8020.

*Kloos H. 1983. DBCP pesticide in drinking water wells in Fresno and other communities in the Central Valley of California. Ecol Disease 2:353-367.

*Kluwe WM. 1981. Acute toxicity of 1,2-dibromo-3-chloropropane in F344 male rat. I. Dose-response relationships and differences in routes of exposure. Toxicol Appl Pharmacol 59:71-83.

*Kluwe WM. 1983. Chemical modulation of 1,2-dibromo-3-chloropropanetoxicity. Toxicology 27:287-299.

*Kluwe WM, McNish R, Smithson K, et al. 1981. Depletion by 1,2-dibromoethane, 1,2-dibromo-3-chloropropane, tris(2,3-dibromopropyl)phosphate, and hexachloro-1,3-butadiene of reduced non-protein sulfhydryl groups in target and non-target organs. Biochem Pharmacol 30:2265-2271.

*Kluwe WM, Greenwell A, Harrington F. 1982. Relationship of tissue nonprotein sulfhydryls to the acute toxic effects of 1,2-dibromo-3-chloropropane. J Pharmacol Exp Ther 220:399-405.

Kluwe WM, Lamb JC IV, Greenwell A, et al. 1983. 1,2-dibromo-3-chloropropane(DBCP)-induced infertility in male rats mediated by a post-testicular effect. Toxicol Appl Pharmacol 71:294-298.

*Kluwe WM, Weber H, Greenwell A, et al. 1985. Initial and residual toxicity following acute exposure of developing male rats to dibromochloropropane. Toxicol Appl Pharmacol 79:54-68.

Kodama J, Dunlap M. 1956. Toxicity of 1,2-dibromo-3-chloropropane. Fed Proc 15:448.

*Kouzi SA, Soderlund EJ, Dybing E, et al. 1995. Comparative toxicity of (+)-(R)- and (-)-(S)-1,2-dibromo-3-chloropropane. Chirality 7(5):359-364. 10.1002/chir.530070509.

*Krishnan K, Anderson ME, Clewell HJ, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang RSH, ed. Toxicology of chemical mixtures. Case studies, mechanisms, and novel approaches. San Diego, CA: Academic Press, 399-437.

*Kutz FW, Carey AE. 1986. Pesticides and toxic substances in the environment. J Arboric 12:92-95.

*Labaj J, Slamenova D, Lazarova M, et al. 2007. Induction of DNA-lesions in freshly isolated rat hepatocytes by different genotoxins and their reduction by lignin given either as a dietary component or in *in vitro* conditions. Nutr Cancer 57(2):209-215. 10.1080/01635580701277643.

*Lag M, Omichinski JG, Dybing E, et al. 1994. Mutagenic activity of halogenated propanes and propenes: Effect of bromine and chlorine positioning. Chem Biol Interact 93(1):73-84.

*Lag M, Omichinski JG, Soderlund EJ, et al. 1989a. Role of P-450 activity and glutathione levels in 1,2-dibromo-3-chloropropane tissue distribution, renal necrosis and *in vivo* DNA damage. Toxicology 56:273-288.

Lag M, Soderlund EJ, Brunborg G, et al. 1989b. Species differences intesticular necrosis and DNA damage, distribution and metabolism of 1,2-dibromo-3-chloropropane (DBCP). Toxicology 58:133-144.

Lag M, Soderlund E, Omichinski J, et al. 1989c. Metabolism of selectively methylated and deuterated analogs of 1,2-dibromo-3-chloropropane: Role in organ toxicity and mutagenicity. Chem Biol Interact 69:33-44.

*Lag M, Soderlund EJ, Omichinski JG, et al. 1991. Effect of bromine and chlorine positioning in the induction of renal and testicular toxicity by halogenated propanes. Chem Res Toxicol 4(5):528-534.

*Lanham J. 1987. Nine-year follow-up of workers exposed to 1,2-dibromo-3chloropropane [letter]. J Occup Med 29:488-490.

*Lantz GD, Cunningham GR, Huckins C, et al. 1981. Recovery from severe oligospermia after exposure to dibromochloropropane. Fertil Steril 35:46-53.

*Laskin S, Sellakumar AR, Kuschner M, et al. 1980. Inhalation carcinogenicity of epichlorohydrin in noninbred Sprague-Dawley rats. J Natl Cancer Inst 65:751-757.

*Lee IP, Suzuki K. 1979. Induction of unscheduled DNA synthesis in mouse germ cells following 1,2-dibromo-3-chloropropane (DBCP) exposure. Mutat Res 68:169-173.

Legator M, Kapp R Jr. 1984. Detection of chemically induced y-chromosomal nondisjunction in human spermatozoa. Topics in Chemical Mutagenesis 2:265-277.

Leroith D, Potashnik G, Dunn J, et al. 1981. The exaggerated prolactin response to thyrotropin-releasing hormone and metoclopramide in 1,2-dibromo-3-chloropropane-induced azoospermia. J Clin Endocrinol Metab 52:38-41.

Levine RJ, Symons MJ, Balogh SA, et al. 1980. A method for monitoring the fertility of workers: 1. Method and pilot studies. J Occup Med 22:781-791.

*Levine RJ, Symons MJ, Balogh SA, et al. 1981. A method for monitoring the fertility of workers. 2. Validation of the method among workers exposed to dibromochloropropane. J Occup Med 23:183-188.

Levine R, Blunden P, DalCorso R, et al. 1983. Superiority of reproductive histories to sperm counts in detecting infertility at a dibromochloropropane manufacturing plant. J Occup Med 25:591-597.

*Lipshultz LI, Ross CE, Whorton D, et al. 1980. Dibromochloropropane and its effects on testicular function in man. J Urol 124:464-468.

Loveday KS, Morris M, Zeiger E. 1986. *In-vitro* cytogenetic testing using sister chromatid exchange and chromosome aberration end point in CHO cells. Environ Mutagen 8(Suppl 6):48.

*Loveday KS, Lugo MH, Resnick MA, et al. 1989. Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells *in vitro*: II. Results with 20 chemicals. Environ Mol Mutagen 13:60-94.

8. REFERENCES

*Lui EMK; Wysocki GP. 1987. Reproductive tract defects induced in adult male rats by postnatal 1,2-dibromo-3-chloropropane exposure. Toxicol Appl Pharmacol 90:299-314.

*MacFarland RT, Gandolfi AT, Sipes IC. 1984. Extra-hepatic GSH-dependent metabolism of 1,2-dibromoethane (DBE) and 1,2-dibromo-3-chloropropane (DBCP) in the rat and mouse. Drug Chem Toxicol 7:213-227.

*Mann JB, Freal JJ, Enos HF, et al. 1980. Development and application of methodology for determining 1,2-dibromo-3-chloropropane (DBCP) in ambient air. J Environ Sci Health B15:519-528.

Marsden P, Casida J. 1982. 2-Haloacrylic acids as indicators of mutagenic 2-haloacrolein intermediates in mammalian metabolism of selected promutagens and carcinogens. J Agric Food Chem 30:627-631.

Mayaudon EM. 1978. 1,2-Dibromo-3-chloropropane (DBCP), a nematocide with sterilizing action in humans. Salud Publica de Mexico 5(20):195-200.

*McKee RH, Phillips RD, Traul KA. 1987. The genetic toxicity of 1,2-dibromo-3-chloropropane, 1,2-dibromo-3-chloro-2-methylpropane, and 1,2,3-tribromo-2-methylpropane. Cell Biol Toxicol 3(4):391-406. http://www.ncbi.nlm.nih.gov/pubmed/3333733.

Meyer C. 1984. Critical review of studies relating occupational exposures of males and reproductive capacity. In: Lackey J, Lemasters G, Keye W, ed. Reproduction: The new frontier in occupational and environmental health research. New York, NY: Alan R Liss, Inc., 375-384.

*Milby T, Whorton D. 1980. Epidemiological assessment of occupationally-related, chemically induced sperm count suppression. J Occup Med 22:77-82.

*Milby TH, Whorton HA, Stubbs HA, et al. 1981. Testicular function among epichlorohydrin workers. Br J Ind Med 38:372-377.

Miller G. 1986. *In vitro* toxicity of 1,2-dibromo-3-chloropropane to isolated testicular cells. Diss Abstr Int B 47:1007-1128.

Moody D, Smuckler E. 1979. Decrease in hepatic microsomal cytochromes P-450 and b, after treatment with 1,2-dibromo-3-chloropropane (DBCP). Effect on synthesis of protein and heme moieties. Fed Proc 38:845.

Moody D, James J, Clawson G, et al. 1981. Correlations among the changes in hepatic microsomal components after intoxication with alky halides and other hepatotoxins. Mol Pharmacol 20:685-693.

Moody D, Clawson G, Woo C, et al. 1982. Cellular distribution of cytochrome P-450 loss in rats of different ages treated with alkyl halides. Toxicol Appl Pharmacol 66:278-289.

*Moody D, Clawson G, Piper W, et al. 1984. Effects of 1,2-dibromo-3-chloropropane on hepatic heme synthesis. Toxicol Appl Pharmacol 75:561-570.

Moody D, Head B, Woo C, et al. 1986. NADPH-dependent and -independent loss of cytochrome P-450 in control and phenobarbital-induced rat hepatic microsomes incubated with carbon tetrachloride. Exp Mol Pathol 44:318-328.

Moody D, Clawson G, Geller D, et al. 1988. Sodium cholate extraction of rat liver nuclear xenobiotic-metabolizing enzymes. Biochem Pharmacol 37:1331-1341.

*Moriya M, Ohta T, Watanabe K, et al. 1983. Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat Res 116:185-216.

*Munnecke DE, VanGundy SD. 1979. Movement of fumigants in soil, dosage responses, and differential effects. Ann Rev Phytopathol 17:405-429.

*NAS/NRC. 1989. Report of the oversight committee. Biologic markers in reproductive toxicology. Washington, DC: National Academy of Sciences, National Research Council, National Academy Press. 15-35.

*NATICH. 1988. NATICH database report on state, local and EPA air toxic activities. National Air Toxics Information Clearinghouse, EPA Office of Air Quality Planning and Standards, Research Triangle Park, NC. 109.

National Research Council. 1986. Drinking water & health. Vol. 6. Board on Toxicology and Environmental Health Hazards, Commission on Life Sciences, National Research Council, 314-236.

8. REFERENCES

*NCI. 1978. Bioassay of dibromochloropropane for possible carcinogenicity. Prepared by Carcinogenesis Program, Division of Cancer Cause & Prevention, National Cancer Institute, Bethesda, MD. NTIS PB277472. NIH 78-828.

*Nelson SJ, lskander M, Volz M, et al. 1981. Studies of DBCP in subsoils. In: Van Dujvenbooden W, et al., eds. Stud Environ Sci 17:169-174.

*Newsome WH, Iverson F, Panopio LG, et al. 1977. Residues of dibromochloropropane in root crops grown in fumigated soil. J Agric Food Chem 25:684-685.

NIOSH. 1978. Criteria document on dibromochloropropane. U.S. Department of Health, Education, and Welfare, Center for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, OH. DHEW publ. no. 78-115.

*NIOSH. 1979. Health hazard evaluation determination report no. 77-126-646. Prepared by Shell Chemical Company, Rocky Mountain Arsenal, Denver, CO for the U.S. Department of Health, Education, and Welfare, Center for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, OH.

*NIOSH. 1985. NIOSH pocket guide to chemical hazards. U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health, Washington, DC. DHHS (NIOSH) publ.no. 85-114, 240-241.

*NIOSH. 1988. Occupational safety and health guideline for dibromochloropropane potential human carcinogen. In: Occupational safety and health guidelines for chemical hazards. U.S. Department of Health, Education, and Welfare, Center for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, OH. Publ. no. 89-104, Suppl. II-OHG, 1-5.

*NIOSH. 1989. National Occupational Exposure Survey (NOES) database. US Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, OH. March 29, 1989.

*NIOSH. 1990. NIOSH pocket guide to chemical hazards. U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health, Washington, D.C. DHHS (NIOSH) pub1 no. 90-117, 82-83 and App. A.

*NIOSH. 2016. 1,2-Dibromo-3-chloropropane. NIOSH pocket guide to chemical hazards. Atlanta, GA: National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. https://www.cdc.gov/niosh/npg/npgd0184.html. June 29, 2017.

NIOSH/OSHA. 1981. Occupational safety and health guideline for dibromochloropropane: Potential human carcinogen. In: Occupational health guidelines for chemical hazards. U.S. Department of Health, Education, and Welfare, Center for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, OH. DHHS (NIOSH) pub1 no. 81-123.

*NTP. 1982. NTP technical report on the carcinogenesis bioassay of 1,2dibromo-3-chloropropane (CAS no. 96-12-8) in F344 rats and B6C3Fl mice (inhalation study). National Toxicology Program, Research Triangle Park, NC and Bethesda, MD. NTP-81-21.

*NTP. 1985. Fourth annual report on carcinogens. National Toxicology Program, 179-182.

*NTP . 1991. NTP Chemtrack System (database). National Toxicology Program, Division of Toxicology Research and Testing, Central Data Management, Research Triangle Park, NC.

*NTP. 2016. 1,2-Dibromo-3-chloropropane. Report on carcinogens, Fourteenth Edition. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. https://ntp.niehs.nih.gov/ntp/roc/content/profiles/dibromochloropropane.pdf. June 29, 2017.

*Oakberg E, Cummings C. 1984. Lack of effect of dibromochloropropane on the mouse testis. Environ Mutagen 6:621-625.

*OHM/TADS. 1989. Oral and Hazardous Material Technical Data System. On-line database. Accession No. 7216513. December 12, 1989.

*Ohta T, Nakamura N, Moriya M, et al. 1984. The SOS-function-inducing activity of chemical mutagens in *Escherichia coli*. Mutat Res 131:101-109.

8. REFERENCES

*Oki DS, Giambelluca TW. 1987. DBCP, EDB, and TCP contamination of groundwater in Hawaii. Ground Water 25:693-702.

*Olsen GW, Bodner KM, Stafford BA, et al. 1995. Update of the mortality experience of employees with occupational exposure to 1,2-dibromo-3-chloropropane (DBCP). Am J Ind Med 28(3):399-410.

*Olsen GW, Laham JM, Bodner KM, et al. 1990. Determinants of spermatogenesis recovery among workers exposed to 1,2-dibromo-3-chloropropane. J Occup Med 32:979-984.

Olson W, Habermann R, Weisburger E, et al. 1973. Induction of stomach cancer in rats and mice by halogenated aliphatic fumigants. J Natl Cancer Inst 51:1993-1995.

*Omichinski JG, Brunborg G, Soderlund EJ, et al. 1987. Renal necrosis and DNA damage caused by selectively deuterated and methylated analogs of 1,2dibromo-3-chloropropane in the rat. Toxicol Appl Pharmacol 91:358-370.

*Omichinski JG, Brunborg G, Holme JA, et al. 1988a. The role of oxidative and conjugative pathways in the activation of 1,2-dibromo-3-chloropropane to DNA-damaging products in rat testicular cells. Mol Pharmacol 34:74-79.

*Omichinski JG, Soderlund EJ, Dybing E, et al. 1988b. Detection and mechanism of formation of the potent direct-acting mutagen 2-bromoacrolein from 1,2-dibromo-3-chloropropane. Toxicol Appl Pharmacol 92:286-294.

OPD. 1989. OPD chemical buyers directory. 76th ed. New York, NY: Schnell Publishing Co. Inc., 235, 696.

*OSHA. 1988. 1,2-Dibromo-3-chloropropane. Code of Federal Registration. Ch.XVII:940-951.

*OSHA. 2016a. Part 1915 - Occupational safety and health standards for shipyard employment. Subpart Z - Toxic and hazardous substances. Section 1915.1044 - 1,2-dibromo-3-chloropropane. Occupational Safety and Health Standards. Code of Federal Regulations 29 CFR 1915.1044. https://www.gpo.gov/fdsys/pkg/CFR-2016-title29-vol7/pdf/CFR-2016-title29-vol7-sec1915-1044.pdf. June 29, 2017.

*OSHA. 2016b. Part 1926 - Safety and health regulations for construction. Subpart Z - Toxic and hazardous substances. 1,2-dibromo-3-chloropropane. Occupational Safety and Health Standards. Code of Federal Regulations 29 CFR 1926.1144. https://www.gpo.gov/fdsys/pkg/CFR-2016-title29-vol8/pdf/CFR-2016-title29-vol8-sec1926-1144.pdf. June 29, 2017.

*OSHA. 2016c Subpart Z - Toxic and hazardous substances. 1,2-Dibromo-3-chloropropane. Code of Federal Regulations. Occupational Safety and Health Standards. 29 CFR 1910.1044. https://www.gpo.gov/fdsys/pkg/CFR-2016-title29-vol6/pdf/CFR-2016-title29-vol6-sec1910-1044.pdf. June 29, 2017.

*Overstreet JW, Samuels SJ, Day P, et al. 1988. Early indicators of male reproductive toxicity. Risk Anal 8:21-26.

*Pellizzari ED, Zweidinger RA, Erickson MD. 1978. Environmental monitoring near industrial sites: Brominated chemicals. Part I. Washington, DC: U.S. Environmental Protection Agency, Office of Toxic Substances, 59, 82, 86, 127,132, 133, 172, 211, 212, 221, 222, 239, 243, 270, 273, 275.

*Pellizzari ED, Zweidinger RA, Sheldon LS. 1985a. GC/MS determination of volatile hydrocarbons in breath samples. In: Fishbein L, O'Neill I, eds. Environmental carcinogens selected methods of analysis. Lyon, France: World Health Organization Vol 7:413-431.

*Pellizzarri ED, Sheldon LS, Bursey JT. 1985b. BC/MS determination of volatile halocarbons in blood and tissue. In: Fishbein L, O'Neill I, eds. Environmental carcinogens selected methods of analysis, Lyon, France: World Health Organization, Vol 7:435-444.

*Peoples SA, Maddy KT, Cusick W, et al. 1980. A study of samples of well water collected from selected areas in California to determine the presence of DBCP and certain pesticide residues. Bull Environ Contam Toxicol 24:611-618.

*Potashnik G. 1983. A four-year reassessment of workers with dibromochloropropane-induced testicular dysfunction. Andrologia 15:164-170.

8. REFERENCES

*Potashnik G, Abeliovich D. 1985. Chromosomal analysis and health status of children conceived to men during or following dibromochloropropane-induced spermatogenic suppression. Andrologia 17:291-296.

*Potashnik G, Phillip M. 1988. Lack of birth defects among offspring conceived during or after paternal exposure to dibromochloropropane (DBCP). Andrologia 20:90-94.

*Potashnik G, Porath A. 1995. Dibromochloropropane (DBCP): A 17-year reassessment of testicular function and reproductive performance. J Occup Environ Med 37(11):1287-1292.

*Potashnik G, Yanai-Inbar I. 1987. Dibromochloropropane (DBCP): An 8-year re-evaluation of testicular function and reproductive performance. Fertil Steril 47:317-323.

*Potashnik G, Ben-Aderet N, Israeli R, et al: 1978. Suppressive effect of 1,2-dibromo-3-chloropropane on human spermatogenesis. Fertil Steril 30:444-447.

*Potashnik G, Goldsmith J, Insler V. 1984. Dibromochloropropane-induced reduction of the sex-ratio in man. Andrologia 16:213-218.

Powers M, Voelker R, Page N, et al. 1975. Carcinogenicity of ethylenedibromide (EDB) and 1,2-dibromo-3-chloropropane (DBCP) after oral administration in rats and mice. Toxicol Appl Pharmacol 33:171-172.

Rao K, Murray F, Crawford A, et al. 1979. Effects of inhaled 1,2-dibromo-3-chloropropane (DBCP) on the semen of rabbits and the fertility of male and female rats. Toxicol Appl Pharmacol 48:A137.

*Rao KS, Burek JD, Murray FJ, et al. 1982. Toxicologic and reproductive effects of inhaled 1,2-dibromo-3-chloropropane in male rabbits. Fundam Appl Toxicol 2:241-251.

*Rao K, Burek J, Murray F, et al. 1983. Toxicologic and reproductive effects of inhaled 1,2-dibromo-3-chloropropane in rats. Fundam Appl Toxicol 3:104-110.

Ratpan F, Plaumann H. 1985. Mutagenicity of halogenated three-carbon compounds and their methylated derivatives. (Meeting Abstract). Environ Suppl 3:15.

*Ratpan F, Plaumann H. 1988. Mutagenicity of halogenated propanes and their methylated derivatives. Environ Mol Mutagen 12:253-259.

*Reel JR, Wolkowski-Tyl R, Lawton AD. 1984. Dibromochloropropane: Reproduction and fertility assessment in CD-1 mice when administered by gavage. National Toxicology Program, Research Triangle Park, NC. NTIS PB85118644. NTP 84-263.

*Reznik G, Stinson S, Ward J. 1980a. Respiratory pathology in rats and mice after inhalation of 1,2-dibromo-3-chloropropane or 1,2-dibromoethane for 13weeks. Arch Toxicol 46:233-240.

Reznik G, Reznik-Schuller H, Ward J, et al. 1980b. Morphology of nasal cavity tumours in rats after chronic inhalation of 1,2-dibromo-3-chloropropane. Br J Cancer 42:772-781.

Reznik G, Stinson S, Ward J. 1980c. Lung tumors induced by chronic inhalation of 1,2-dibromo-3-chloropropane in BCF, mice. Cancer Lett 10:339-342.

*Roldan-Arjona T, Garcia-Pedrajas MD, Luque-Romero FL, et al. 1991. An association between mutagenicity of the Ara test of *Salmonella typhimurium* and carcinogenicity in rodents for 16 halogenated aliphatic hydrocarbons. Mutagenesis 6(3):199-206.

Rosenberg M, Feldblum P, Marshall E. 1987. Occupational influences on reproduction: A review of recent literature. J Occup Med 29:584-591.

*Rosenkranz HR. 1975. Genetic activity of 1,2-dibromo-3-chloropropane, a widely-used fumigant. Bull Environ Contam Toxicol 14(1):8-12.

*RTECS. 1984. Registry of Toxic Effects of Chemical Substances. Current Awareness File. U.S. Department of Human Services, Public Health Service, Centers for Disease Control, National Institute of Occupational Safety and Health, Research Triangle Park, NC. March 1984.

*Ruddick JA, Newsome WH. 1979. A teratogenicity and tissue distribution study on dibromochloropropane in the rat. Bull Environ Contam Toxicol 21:483-487.

Rush G, Smith J, Newton J, et al. 1984. Chemically induced nephrotoxicity: Role of metabolic activation. CRC Crit Rev Toxicol 13:99-160.

*Russell LA. 1989. 1,2-dibromo-3-chloropropane (DBCP)-induced nuclear atypia in rat kidney. J Environ Pathol Toxicol Oncol 9:145-157.

8. REFERENCES

*Russell LB, Hunsicker PR, Cacheiro NLA. 1986. Mouse specific-locus test for the induction of heritable gene mutations by dibromochloropropane (DBCP). Mutat Res 170:161-166.

Russell W. 1986. Positive genetic hazard predictions from short-term tests have proved false for results in mammalian spermatogonia with all environmental chemicals so far tested. Prog Clin Biol Res 209B:67-74.

*Ruth JH. 1986. Odor thresholds and irritation levels of several chemical substances: A review. Am Ind Hyg Assoc J 47:A-142-A151.

*Ryu JC, Kim YJ, Chai YG. 2002. Mutation spectrum of 1,2-dibromo-3-chloropropane, an endocrine disruptor, in the *lac*I transgenic Big Blue Rat2 fibroblast cell line. Mutagenesis 17(4):301-307.

*Sabljic A. 1984. Predictions of the nature and strength of soil sorption of organic pollutants by molecular topology. J Agric Food Chem 32:243-246.

*Saegusa J. 1986. Radiomimetic toxicity of 1,2-dibromo-3-chloropropane (DBCP). Ind Health 24:1-14.

Saegusa J. 1987. Age-related susceptibility to dibromochloropropane. Toxicol Lett 36:45-50.

*Saegusa J, Hasegawa H, Kawai K. 1982. Toxicity of 1,2-dibromo-3-chloropropane (DBCP): I. Histopathological examination of male rats exposed to DBCP vapour. Ind Health 20:315-323.

*Saito-Suzuki R, Teramoto S, Shirasu Y. 1982. Dominant lethal study in rats with 1,2-dibromo-3-chloropropane and its structurally related compounds. Mutat Res 101:321-327.

*Sandifer S, Wilkins R, Loadhold C, et al. 1979. Spermatogenesis in agricultural workers exposed to dibromochloropropane (DBCP). Bull Environ Toxicol 23:703-710.

*Sasaki YF, Imanishi H, Watanabe M, et al. 1986. Mutagenicity of 1,2-dibromo-3-chloropropane (DBCP) in the mouse spot test. Mutat Res 174:145-147.

*Sasaki YF, Saga A, Akasaka M, et al. 1998. Detection of *in vivo* genotoxicity of haloalkanes and haloalkenes carcinogenic to rodents by the alkaline single cell gel electrophoresis (comet) assay in multiple mouse organs. Mutat Res 419(1-3):13-20.

*Sax NI, Lewis RJ. 1987. Hawley's condensed chemical dictionary. 10th ed. New York, NY: Van Nostrand Reinhold Co., 367.

*Scharnweber HC. 1979. The Dow Experience. In: Proceedings of the October 19-20, 1977 NIOSH conference on dibromochloropropane, Cincinnati, OH, 30-38.

*Schenker MB, Samuels SJ, Perkins C, et al. 1988. Prospective surveillance of semen quality in the workplace. J Occup Med 30:336-344.

Schneiderman M. 1987. Mortality experience of employees with occupational exposure to DBCP [letter]. Arch Environ Health 42:245-247.

Schrag S, Dixon R. 1985. Occupational exposures associated with male reproductive dysfunction. Ann Rev Pharmacol Toxicol 25:567-592.

Sever L, Hess01 N. 1985. Toxic effects of occupational and environmental chemicals on the testes. In: Thomas J, Korach K, McLachlan J, ed. Endocrine toxicology. New York, NY: Raven Press, 211-248.

*Shaked I, Sod-Moriah UA, Kaplanski J, et al. 1988. Reproductive performance of dibromochloropropane-treated female rats. Int J Fertil 331:129-133.

*Shelby MD, Witt KL. 1995. Comparison of results from mouse bone marrow chromosome aberration and micronucleus tests. Environ Mol Mutagen 25(4):302-313.

*Shelby MD, Erexson GL, Hook GJ, et al. 1993. Evaluation of a three-exposure mouse bone marrow micronucleus protocol: Results with 49 chemicals. Environ Mol Mutagen 21(2):160-179.

*Shemi D, Sod-Moriah UA, Kaplanski J, et al. 1987. Gonadotoxicity and kinetics of dibromochloropropane in male rats. Toxicol Lett 36:209-212.

Shiau S, Huff R, Wells B, et al. 1980. Mutagenicity and DNA-damaging activity for several pesticides tested with bacillus subtilis mutants. Mutat Res 71:169-179.

Shirasu Y, Moriya M, Tezuka H, et al. 1984. Mutagenicity of pesticides. Environ Sci Res 31:617-624.

*Silverstein RM, Bassler GC, Morrill TC. 1974. Spectrometric identification of organic compounds. 3rd ed. New York, NY: John Wiley & Sons, 239.

8. REFERENCES

*Simula TP, Glancey MJ, Soderlund EJ, et al. 1993. Increased mutagenicity of 1,2-dibromo-3-chloropropane and tris(2,3-dibromopropyl)phosphate in Salmonella TA100 expressing human glutathione S-transferases. Carcinogenesis 14(11):2303-2307.

*Slutsky M, Levin JL, Levy BS. 1999. Azoospermia and oligospermia among a large cohort of DBCP applicators in 12 countries. Int J Occup Environ Health 5(2):116-122. 10.1179/oeh.1999.5.2.116.

*Soderlund EJ, Brunborg G, Holme JA, et al. 1991. Co-culture systems for assessing the stability and genotoxicity of reactive 1,2-dibromo-3-chloropropane (DBCP) metabolites. Mutagenesis 6(1):25-30.

*Soderlund EJ, Brunborg G, Omichinski JA, et al. 1988. Testicular necrosis and DNA damage caused by deuterated and methylated analogs of 1;2-dibromo-3-chloropropane in the rat. Toxicol Appl Pharmacol 94:437-447.

*Soderlund EJ, Lag M, Holme JA, et al. 1990. Species differences in kidney necrosis and DNA damage, distribution and glutathione-dependent metabolism of 1,2-dibromo-3-chloropropane (DBCP). Pharmacol Toxicol 66(4):287-293.

Sod-Moriah UA, Sror U, Shemi D, et al. 1988. Long term effects of dibromochloropropane (DBCP) on male rats' reproductive system. Andrologia 20:60-66.

Starr T, Dalcorso R, Levine R. 1986. Fertility of workers. A comparison of logistic regression and indirect standardization. Am J Epidemiol 123:490-498.

*State of Kentucky. 1986. New or modified sources emitting toxic air pollutants. Natural Resources and Environmental Protection, Cabinet, Department for Environmental Protection, Division of Air Pollution (Proposed Regulation).

Steeno O, Pangkahila A. 1984. Occupational influences on male fertility and sexuality. Andrologia 16:5-22.

Stellman J. 1986. Environmental agents and birth outcomes. Ann NY Acad Sci 477:116-122.

*Stenger VA. 1978. Bromine compounds. In: Kirk-Othmer encyclopedia of chemical technology, 3rd. ed. New York, NY: Wiley-Interscience, 243-263.

*Stolzenberg SJ, Hine CH. 1979. Mutagenicity of halogenated and oxygenated three-carbon compounds. J Toxicol Environ Health 5:1149-1158.

STORET. 1989. STORET database. U.S. Environmental Protection Agency, Washington, DC. December 14, 1989.

*Stutz DR, Janusz SJ. 1988. Hazardous materials injuries: A handbook for pre-hospital care. 2nd ed. Beltsville, Maryland: Bradford Communications Corporation, 300-301.

*Suzuki K, Lee I. 1981. Induction of aryl hydrocarbon hydroxylase and epoxide hydrolase in rat liver, kidney, testis, prostate glands, and stomach by a potent nematocide, 1,2-dibromo-3-chloropropane. Toxicol Appl Pharmacol 58:151-155.

*Swann RL, Laskowski DA, McCall PJ, et al. 1983. A rapid method for the estimation of the environmental parameters of octanol/water partition coefficient, soil sorption constant, water to air ratio, and water solubility. Res Rev 85:17-28.

*Takahashi W, Wong L, Rogers B, et al. 1981. Depression of sperm counts among agricultural workers exposed to dibromochloropropane and ethylenedibromide. Bull Environ Contam Toxicol 27:551-558.

Teramoto S, Shirasu Y. 1989. Genetic toxicology of 1,2-dibromo-3-chloropropane(DBCP). Mutat Res 221:1-9.

*Teramoto S, Saito R, Aoyama H, et al. 1980. Dominant lethal mutation induced in male rats by 1,2-dibromo-3-chloropropane (DBCP). Mutat Res 77:71-78.

*Tezuka H, Ando N, Suzuki R, et al. 1980. Sister-chromatid exchanges and chromosomal aberrations in cultured Chinese hamster cells treated with pesticides positive in microbial reversion assays. Mutat Res 78:177-191.

*Thomas RG. 1982. Volatilization from water. In: Lyman WJ, Reehl WF, Rosenblatt DH, eds. Handbook of chemical property estimation methods. New York, NY: McGraw-Hill Book Co., 4-9; 5-5; 15-9 to 15-31.

8. REFERENCES

*Tofilon PJ, Clement RP, Piper WN. 1980. Inhibition of the biosynthesis of rat testicular heme by 1,2-dibromo-3-chloropropane. Biochem Pharmacol 29:2563-2566.

Tofilon P. 1981. Investigations into the regulation of rat testicular heme synthesis. Diss Abstr Int 42/08-B:3223-3304.

*Tonogai Y, Ito Y, Ogawa S, et al. 1986. Determination of dibromochloropropane and related fumigants in citrus fruit. J Food Prot 49:909-913.

Torkelson TR, Rowe VK. 1981. Halogenated aliphatic hydrocarbons: 1,2-dibromo-3-chloropropane. In: Clayton GD, Clayton FE, eds. Patty's industrial hygiene and toxicology, Vol. 2B, 3rd ed. New York, NY: John Wiley& Sons.

*Torkelson TR, Sadek SE, Rowe VK. 1961. Toxicologic investigations of 1,2-dibromo-3-chloropropane. Toxicol Appl Pharmacol 3:545-559.

Traul K, McKee R, Phillips R. 1985. The genetic toxicity of 1,2-dibromo-3-chloropropane, 1,2-dibromo-3-chloro-2-methylpropane, and 1,2,3-tribromo-2-methylpropane (Meeting Abstract). Environ Mutagen 7(Suppl 3):17-18.

*TRI16. 2017. TRI explorer: Providing access to EPA's toxics release inventory data. Washington, DC: Office of Information Analysis and Access. Office of Environmental Information. U.S. Environmental Protection Agency. Toxics Release Inventory. http://www.epa.gov/triexplorer/. November 10, 2017.

Tsongas T, Infante P. 1984. Occupational reproductive hazards: Regulatory concerns. Prog Clin Biol Res 160:533-539.

*Tuazon EC, Atkinson R, Aschmann SM, et al. 1986. Atmospheric loss processes of 1,2-dibromo-3-chloropropane and trimethyl phosphate. Environ Sci Technol 20:1043-1046.

*Van Duuren BI, Goldschmidt BM, Loewengart G, et al. 1979. Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. J Natl Cancer Inst 63:1433-1439.

*Verschueren K, ed. 1983. Handbook of environmental data on organic chemicals. New York, NY: Van Nostrand Reinhold Co., 464-465.

*View. 1990. On-line database. Atlanta, GA: Agency for Toxic Substances and Disease Registry (ATSDR), Office of External Affairs, Exposure and Disease Registry Branch. November 8, 1989.

*Wallace LA, Pellizzari ED, Hartwell TD, et al. 1986. Total Exposure Assessment Methodology (TEAM) study: Personal exposures. Indoor-outdoor relationships, and breath levels of volatile organic compounds in New Jersey. Environ Int 12:369-387.

*Warren DW, Wisner JR, Ahmad N. 1984. Effects of 1,2-dibromo-3-chloropropane on male reproductive function in the rat. Biol Reprod 31:454-463.

Warren DW, Ahmad N. 1986. Effect of maternal administration of 1,2-dibromo-3-chloropropane on fetal testosterone production and adult sexual behavior of male offspring. J Androl 7:20.

*Warren DW, Ahmad N, Rudeen P. 1988. The effects of fetal exposure to 1,2-dibromo-3-chloropropane on adult male reproductive function. Biol Reprod 39:707-716.

Weisburger E. 1977. Carcinogenicity studies on halogenated hydrocarbons. Environ Health Perspect 21:7-16.

*Westrick JJ, Mello JW, Thomas RF. 1984. The groundwater supply survey. J Am Water Works Assoc 76:52-59.

*WHO. 2010. Guidelines for indoor air quality: Selected pollutants. Geneva, Switzerland: World Health Organization. http://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf. January 08, 2014.

*WHO. 2017. Guidelines for drinking-water quality. Fourth edition incorporating the first addendum. Geneva, Switzerland: World Health Organization. http://apps.who.int/iris/bitstream/10665/254637/1/9789241549950-eng.pdf?ua=1. February 28, 2017.

*Whorton M, Foliart D. 1983. Mutagenicity, carcinogenicity and reproductive effects of dibromochloropropane (DBCP). Mutat Res 123:13-30.

8. REFERENCES

*Whorton D, Krauss RM. Marshall S, et al. 1977. Infertility in male pesticide workers. Lancet 2:1259-1261.

*Whorton MD, Milby TH, Krauss RM, et al. 1979. Testicular function in DBCP exposed pesticide workers. J Occup Med 21:161-166.

Whorton M, Morgan R, Wong O, et al. 1988. Problems associated with collecting drinking water quality data for community studies: A case example, Fresno County, California. Am J Public Health 78:46-51.

*Whorton MD, Wong O, Morgan RW, et al. 1989. An epidemiologic investigation of birth outcomes in relation to dibromochloropropane contamination in drinking water in Fresno County, California, USA. Int Arch Occup Environ Health 61:403-407.

*Wiger R, Holme JA, Hongslo JK, et al. 1998. Single-strand breaks, cell cycle arrest and apoptosis in HL-60 and $LLCPK_1$ cells exposed to 1,2-dibromo-3-chloropropane. Cell Biol Toxicol 14(4):267-282.

Wilbur S, Gray DA, Durkin P. 1984. Preliminary draft: External review draft of drinking water criteria documents on 1,2-dibromo-3-chloropropane. Prepared by Syracuse Research Corporation, Syracuse, NY for Environmental Criteria and Assessment Office, U.S. EPA, Cincinnati, OH.

Wills J. 1983. Dibromochloropropane. Encyclopedia of occupational health and safety, Vol. 1, 621-623.

*Wilson JT, Enfield CG, Dunlap WJ, et al. 1981. Transport and fate of selected organic pollutants in a sandy soil. J Environ Qual 10:501-506.

*Windholz M, ed. 1983. The Merck index. 10th ed. Rahway, NJ: Merck and Co., Inc., 438.

*Wong O, Brocker W, Davis HV, et al. 1984. Mortality of workers potentially exposed to organic and inorganic brominated chemicals, DBCP, TRIS, PBB, and DDT. Br J Ind Med 41:15-24.

*Wong O, Whorton MD, Gordon N, et al. 1988. An epidemiologic investigation of the relationship between DBCP contamination in drinking water and birthrates in Fresno County, California. Am J Public Health 78:43-46.

*Wong O, Morgan RW, Whorton MD, et al. 1989. Ecological analyses and case control studies of gastric cancer and leukemia in relation to DBCP in drinking water in Fresno County, California. Br J Ind Med 46:521-528.

*Yoon J, Mason J, Valencia R, et al. 1985. Chemical mutagenesis testing in drosophila. IV. Results of 45 coded compounds tested for the National Toxicology Program. Environ Mutagen 7:349-367.

*Zimmering S. 1983. 1,2-dibromo-3-chloropropane (DBCP) is positive for sex linked recessive lethals, heritable translocations and chromosome loss in drosophila. Mutat Res 119:287-288.

APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

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Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dibromo-3-chloropropane
CAS Numbers: 96-12-8
Date: September 1992
March 2017—Updated literature search
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL.

Rationale for Not Deriving an MRL: Sufficient information was not available on the health effects of 1,2-dibromo-3-chloropropane to derive an MRL for acute-duration inhalation exposure. In one study, reproductive effects were noted in rats following acute inhalation exposure to 1,2-dibromo-3-chloropropane (Saegusa et al. 1982). The male reproductive system is a particularly sensitive endpoint for 1,2-dibromo-3-chloropropane toxicity. Available human and animal data indicate that humans and rabbits are more sensitive than rats and mice to 1,2-dibromo-3-chloropropane effects on the male reproductive system. Acute-duration inhalation data for rabbits are lacking; therefore, an acute-duration inhalation MRL was not derived for 1,2-dibromo-3-chloropropane.

Agency Contact (Chemical Manager): Rae T. Benedict, Ph.D.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	1,2-Dibromo-3-chloropropane
CAS Numbers:	96-12-8
Date:	September 1992 March 2017—Updated literature search
Profile Status:	Final
Route:	Inhalation
Duration:	Intermediate
MRL	0.0002 ppm
Critical Effect:	Changes in spermatogenesis and testicular atrophy
Reference:	Rao et al. 1982
Point of Departure:	NOAEL of 0.1 ppm
Uncertainty Factor:	100
LSE Graph Key:	9
Species:	Rabbit

MRL Summary: An intermediate-duration inhalation MRL of 0.0002 ppm was derived for 1,2-dibromo-3-chloropropane. The MRL is based on a NOAEL of 0.1 ppm and a LOAEL of 1 ppm for changes in spermatogenesis and testicular atrophy in rabbits exposed to 1,2-dibromo-3-chloropropane for 6 hours/day, 5 days/week for up to 14 weeks (Rao et al. 1982). The NOAEL was adjusted for intermittent exposure, converted to a human equivalent concentration (assuming a value of 1 for ratio of blood/gas partition coefficients), and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: No human data are available. Intermediate-duration inhalation data for animals include a series of studies in rats, rabbits, guinea pigs, and monkeys (Torkelson et al. 1961); 13-week studies in rats and mice (NTP 1982); a 14-week study in rats (Rao et al. 1983); and an 8–14-week study in rabbits (Rao et al. 1983). Table A-1 summarizes available NOAEL and LOAEL values for noncancer health effects in animals following intermediate-duration inhalation exposure to 1,2-dibromo-3-chloropropane. The lowest LOAEL value of 1 ppm is associated with testicular effects in rabbits (Rao et al. 1982); respiratory, hepatic, and renal effects in rats (NTP 1982; Reznik et al. 1980a); and endocrine effects in rats (Rao et al. 1983). Among available intermediate-duration inhalation studies, reproductive toxicity was selected as the critical effect because male reproductive effects have been reported in multiple animal species and in humans.

Selection of the Principal Study: Male reproductive effects have been reported in studies of rats and rabbits following intermediate-duration inhalation exposure to 1,2-dibromo-3-chloropropane (NTP 1982; Rao et al. 1982; Torkelson et al. 1961). The study in rabbits (Rao et al. 1982) identified the lowest LOAEL and corresponding NOAEL for reproductive effects, indicating that rabbits may be more sensitive than rats to 1,2-dibromo-3-chloropropane-induced male reproductive effects. Therefore, the rabbit study (Rao et al. 1982) was selected as the principal study for deriving an intermediate-duration inhalation MRL for 1,2-dibromo-3-chloropropane.

Table A-1. Summary of Relevant NOAEL and LOAEL Values from Studies Considered for Derivation of an Intermediate-Duration Inhalation MRL for 1,2-Dibromo-3-Chloropropane

Species	Duration/ route	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Reproductive effects					
Unspecified rat strain	≤10 weeks 5 days/week 7 hours/day		5	Testicular atrophy	Torkelson et al. 1961
New Zealand White rabbit	14 weeks 5 days/week 6 hours/day	0.1	1.0	Testicular atrophy, sperm abnormalities, decreased serum FSH	Rao et al. 1982
Respiratory effects					
F344 rat	13 weeks 5 days/week 6 hours/day		1	Respiratory tract lesions (necrotic and proliferative)	NTP 1982; Reznik et al. 1980a
B6C3F1 mouse	13 weeks 5 days/week 6 hours/day	1	5	Respiratory tract lesions (necrotic and proliferative)	NTP 1982; Reznik et al. 1980a
Body weight effects					
Unspecified rat strain	≤10 weeks 5 days/week 7 hours/day	Not determined	5	Depressed body weight gain	Torkelson et al. 1961
Hepatic effects					
F344 rat	13 weeks 5 days/week 6 hours/day	Not determined	1	Hydropic changes of hepatocytes	NTP 1982; Reznik et al. 1980a
Renal effects					
F344 rat	13 weeks 5 days/week 6 hours/day		1	Nephrosis	NTP 1982; Reznik et al. 1980a
Unspecified rat strain	≤10 weeks 5 days/week 7 hours/day		5	Unspecified epithelial changes in renal collecting tubules	Torkelson et al. 1961

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Table A-1. Summary of Relevant NOAEL and LOAEL Values from Studies Considered for Derivation of an Intermediate-Duration Inhalation MRL for 1,2-Dibromo-3-Chloropropane

Species	Duration/ route	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Endocrine effects					
Sprague-Dawley rat	4 or 14 weeks 5 days/week 6 hours/day	0.1	1	Hyperplastic nodules in adrenal gland	Rao et al. 1983
Ocular effects					
Unspecified rat strain	≤10 weeks 5 days/week 7 hours/day		5	Ocular irritation	Torkelson et al. 1961

FSH = follicle stimulating hormone; LOAEL = lowest observed adverse effect level; NOAEL = no-observed-adverse-effect level; WBCs = white blood cells

Summary of the Principal Study:

Rao KS, Burek JD, Murray FJ, et al. 1982. Toxicologic and reproductive effects of inhaled 1,2-dibromo-3-chloropropane in male rabbits. Fundam Appl Toxicol 2:241-251.

Groups of male New Zealand White rabbits were exposed by inhalation to 0, 0.1, 1.0, or 10 ppm of 1,2-dibromo-3-chloropropane for 6 hours/day, 5 days/week for up to 14 weeks. Semen was evaluated weekly during the exposure period and periodically during a 32- or 38-week recovery period. Fertility was assessed by mating males with unexposed females at study weeks 14 and 41. At sacrifice, male reproductive organs and tissues were processed for gross and histopathologic evaluations. Exposure at 10 ppm was terminated at week 8 due to two mortalities. Exposure concentration-related increasing severity of gross and histopathologic testicular effects were noted at 1.0 and 10 ppm exposure levels. Surviving 10 ppm rabbits were infertile. Evidence of recovery was noted during the recovery period. An equivocal increase in abnormal sperm was reported among the 0.1 ppm males at week 14, which was not evident at the end of the recovery period; therefore, the 0.1 ppm exposure level was considered a NOAEL for testicular effects.

Selection of the Point of Departure for the MRL: The NOAEL of 0.1 ppm was selected as the basis for the MRL.

Intermittent Exposure: The NOAEL was adjusted from intermittent exposure (6 hours/day, 5 days/week) to account for continuous exposure:

NOAEL of 0.1 ppm x 6 hours/24 hours x 5 days/7 days = 0.0179 ppm ($NOAEL_{ADJ}$)

Human Equivalent Concentration: The duration-adjusted NOAEL was converted to a human equivalent concentration (assuming a value of 1 for ratio of blood/gas partition coefficients):

$NOAEL_{ADJ} = NOAEL_{HEC} = 0.0179$ ppm

Uncertainty Factor: The human equivalent NOAEL was divided by a total uncertainty factor of 100:

- 10 for extrapolation from animals to humans
- 10 for human variability

$MRL = NOAEL_{HEC} \div$ uncertainty factors
$0.0179 \text{ ppm} \div (10 \times 10) \approx 0.0002$ ppm

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Testicular effects were also observed in rats repeatedly exposed to 1,2-dibromo-3-chloropropane vapor for 2–13 weeks (NTP 1982; Saegusa et al. 1982; Torkelson et al. 1961).

Agency Contact (Chemical Manager): Rae T. Benedict, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dibromo-3-chloropropane
CAS Numbers: 96-12-8
Date: September 1992
March 2017—Updated literature search
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL.

Rationale for Not Deriving an MRL: Information regarding effects following chronic-duration inhalation exposure to 1,2-dibromo-3-chloropropane was available for rats and mice (NTP 1982). The lowest LOAEL for nonneoplastic effects was 0.6 ppm (the lowest exposure level tested in rats and mice of NTP 1982); effects included inflammation and hyperplasia in nasal cavity and hyperplasia in lungs; hyperkeratosis and acanthosis in forestomach; and hyperplasia in the urinary bladder and inflammation in the kidney. These nonneoplastic lesions may represent precancerous lesions as a variety of nasal cavity tumors were also observed at this exposure level. In the absence of adequate data regarding nonneoplastic effects in laboratory animals exposed to 1,2-dibromo-3-chloropropane that would not be considered potential precancerous lesions, the database of information is considered inadequate to derive a chronic-duration inhalation MRL for 1,2-dibromo-3-chloropropane.

Agency Contact (Chemical Manager): Rae T. Benedict, Ph.D.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dibromo-3-chloropropane
CAS Numbers: 96-12-8
Date: September 1992
March 2017—Updated literature search
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL.

Rationale for Not Deriving an MRL: Several studies provided information on LD_{50} values and selected nonneoplastic effects following acute oral exposure to 1,2-dibromo-3-chloropropane. However, among the available acute-duration oral studies, no acute-duration oral MRL was derived for 1,2-dibromo-3-chloropropane because dominant lethality (which represents a serious LOAEL) was observed at the lowest dose tested (10 mg/kg/day) (Teramoto et al. 1980).

Agency Contact (Chemical Manager): Rae T. Benedict, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	1,2-Dibromo-3-chloropropane
CAS Numbers:	96-12-8
Date:	September 1992 March 2017—Updated literature search
Profile Status:	Final
Route:	Oral
Duration:	Intermediate
MRL	0.002 mg/kg/day
Critical Effect:	Decreased spermatogenesis and increased abnormal sperm morphology
Reference:	Foote 1986a, 1986b
Point of Departure:	LOAEL of 1.88 mg/kg/day
Uncertainty Factor:	1,000
LSE Graph Key:	22
Species:	Rabbit

MRL Summary: An intermediate-duration oral MRL of 0.002 mg/kg/day was derived for 1,2-dibromo-3-chloropropane. The MRL is based on a LOAEL of 1.88 mg/kg/day for effects on spermatogenesis and sperm morphology in rabbits administered 1,2-dibromo-3-chloropropane in the drinking water for 10 weeks (Foote et al. 1986a, 1986b). The LOAEL was divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Selection of the Critical Effect: No human data are available. Intermediate-duration oral data for animals include a 77-day gavage study in rats (Amann and Berndtson 1986); 60- and 64-day drinking water studies in rats (Heindel et al. 1989; Johnston et al. 1986); a 90-day feeding study in rats (Torkelson et al. 1961); 6-week gavage studies in rats and mice (NCI 1978); 128- and 140-day gavage studies in mice (Reel et al. 1984); and a 10-week drinking water study in rabbits (Foote et al. 1986b). Table A-2 summarizes relevant NOAEL and LOAEL values for noncancer health effects in animals following intermediate-duration oral exposure to 1,2-dibromo-3-chloropropane from studies that serve as candidate principal studies for deriving an intermediate-duration oral MRL. Among available intermediate-duration oral studies, male reproductive toxicity was selected as the critical effect because it represents the lowest LOAEL, which is lower than the lowest NOAEL for other effects.

Selection of the Principal Study: Male reproductive effects have been reported in studies of rats and rabbits following intermediate-duration oral exposure to 1,2-dibromo-3-chloropropane (Amann and Berndtson 1986; Foote et al. 1986a, 1986b; Heindel et al. 1989; Johnston et al. 1986). The study in rabbits (Foote et al. 1986a, 1986b) identified the lowest LOAEL for male reproductive effects, indicating that rabbits may be more sensitive than rats to 1,2-dibromo-3-chloropropane-induced male reproductive effects. Therefore, the rabbit study (Foote et al. 1986a, 1986b) was selected as the principal study for deriving an intermediate-duration oral MRL for 1,2-dibromo-3-chloropropane.

Table A-2. Summary of Relevant NOAEL and LOAEL Values from Studies Considered for Derivation of an Intermediate-Duration Oral MRL for 1,2-Dibromo-3-Chloropropane

Species	Duration/route	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Reproductive effects					
Dutch rabbit	10 weeks 5 days/week in drinking water	0.94[a]	1.88	Abnormal sperm morphology, decreased spermatogenesis	Foote et al. 1986b
Body weight effects					
Sprague-Dawley rat	64 days in drinking water	5.4	9.7	Depressed body weight gain	Heindel et al. 1989
Unspecified rat strain	90 days in food	2.5	7.5	Depressed body weight gain	Torkelson et al. 1961
Renal effects					
Sprague-Dawley rat	64 days in drinking water	3.3	5.4	Increased turnover of proximal tubular cells	Heindel et al. 1989

[a]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 basis for deriving an intermediate-duration oral MRL for 1,2-dibromo-3-chloropropane.

DBCP = 1,2-dibromo-3-chloropropane; GD = gestation day; LOAEL = lowest observed adverse effect level; NOAEL = no-observed-adverse-effect level; PPD = postpartum day

Summary of the Principal Study:

Foote RH, Berndtson WE, Rounsaville TR. 1986a. Use of quantitative testicular histology to assess the effect of dibromochloropropane (DBCP) on reproduction in rabbits. Fundam Appl Toxicol 6:638-647.

Foote RH, Schermerhorn EC, Simkin ME. 1986b. Measurement of semen quality, fertility, and reproductive hormones to assess dibromochloropropane (DBCP) effects in live rabbits. Fundam Appl Toxicol 6:628-637.

Groups of male Dutch belted rabbits (6/group) were administered 1,2-dibromo-3-chloropropane in the drinking water 5 days/week for 10 weeks at concentrations resulting in 1,2-dibromo-3-chloropropane intakes of 0, 0.94, 1.88, 3.75, 7.5, or 15 mg/kg/day during each 5-day period. Ejaculate was evaluated periodically during the exposure period for volume, percent motile sperm, and sperm concentration. Fertility was assessed by mating males with unexposed females during the last week of the study or collecting ejaculate and artificially inseminating unexposed females. Blood levels of FSH, LH, and testosterone were determined during the last week of the study as well. At sacrifice, epididymal sperm was collected for analysis and reproductive organs and tissues were processed for gross and histopathologic evaluations. There were no treatment-related effects on blood LH or testosterone levels. High-dose rabbits exhibited significantly elevated blood FSH (consistent with impaired spermatogenesis). Percent normal sperm was significantly decreased at the two highest dose levels; mean seminiferous tubule diameter was significantly reduced at these dose levels as well. Testicular weight was significantly decreased in high-dose rabbits (55% less than controls). Mean numbers of spermatogonia per stage I seminiferous tubular cross section were significantly decreased at doses ≥1.88 mg/kg/day (mean numbers for controls, 0.94, 1.88, 3.75, 7.5, and 15 mg/kg/day dose groups were 2.3±0.13 [SE], 2.0±0.13, 1.8±0.12, 1.6±0.12, 1.5±0.12, and 1.0±0.15, respectively). Mean numbers of preleptotene primary spermatocytes per stage I seminiferous tubular cross-section were significantly decreased at doses ≥1.88 mg/kg/day as well (mean numbers for controls, 0.94, 1.88, 3.75, 7.5, and 15 mg/kg/day dose groups were 42.5±0.2.4, 41.9±2.4, 35.0±2.2, 29.3±2.2, 26.0±2.2, and 13.6±2.6, respectively). Dose-related increases in percent abnormal sperm were noted starting with the 1.88 mg/kg/day dose level. At the highest dose, mean testes weight was 55% less than that of controls. Dose-related decreased mean seminiferous tubular diameter was noted at the two highest dose levels. There was no apparent treatment-related effect on fertility. The 1.88 mg/kg/day dose level is considered a LOAEL for effects on sperm morphology.

Selection of the Point of Departure for the MRL: The LOAEL of 1.88 mg/kg/day was selected as the basis for the MRL.

Intermittent Exposure: No adjustment was made for treatment in the drinking water for only 5 days/week.

Uncertainty Factor: The LOAEL was divided by a total uncertainty factor of 1,000:

- 10 for use of a LOAEL
- 10 for extrapolation from animals to humans
- 10 for human variability

MRL = LOAEL ÷ uncertainty factors

1.88 mg/kg/day ÷ (10 x 10 x 10) ≈ 0.002 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Testicular effects were also observed in rats orally exposed to 1,2-dibromo-3-chloropropane for 60–77 days (Amann and Berndtson 1986; Heindel et al. 1989; Johnston et al. 1986).

Agency Contact (Chemical Manager): Rae T. Benedict, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dibromo-3-chloropropane
CAS Numbers: 96-12-8
Date: September 1992
March 2017—Updated literature search
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL.

Rationale for Not Deriving an MRL: Available chronic-duration oral data are not suitable for MRL development. The lowest LOAEL is 1 mg/kg/day for hyperkeratosis and acanthosis in the gastrointestinal tract of rats (Hazleton 1977, 1978a, 1978b). The same study reported liver, kidney, and stomach tumors at the next higher dose level (3 mg/kg/day). The nonneoplastic stomach lesions may be representative of precancerous lesions. NOAELs and LOAELs for other endpoints are higher than the lowest LOAEL and corresponding NOAEL for intermediate-duration oral exposure. Therefore, a chronic-duration oral MRL was not derived for 1,2-dibromo-3-chloropropane.

Agency Contact (Chemical Manager): Rae T. Benedict, Ph.D.

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR 1,2-DIBROMO-3-CHLOROPROPANE

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to 1,2-dibromo-3-chloro-propane.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, and chemical interactions data for 1,2-dibromo-3-chloropropane. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of 1,2-dibromo-3-chloropropane have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of 1,2-dibromo-3-chloropropane are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

- Health Effects
  - Species
    - Human
    - Laboratory mammals
  - Route of exposure
    - Inhalation
    - Oral
    - Dermal (or ocular)
    - Parenteral (these studies will be considered supporting data)
  - Health outcome
    - Death
    - Systemic effects
    - Body weight effects
    - Respiratory effects
    - Cardiovascular effects
    - Gastrointestinal effects
    - Hematological effects
    - Musculoskeletal effects
    - Hepatic effects
    - Renal effects
    - Dermal effects
    - Ocular effects
    - Endocrine effects
    - Immunological effects
    - Neurological effects
    - Reproductive effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

Developmental effects
Other noncancer effects
Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals

B.1.1 Literature Search

The current literature search was intended to update the health effects sections of the existing toxicological profile for 1,2-dibromo-3-chloropropane (ATSDR 1992), thus, the literature search was restricted to studies published between January 1990 to March 2017. The following main databases were searched in March 2017:

- PubMed
- National Library of Medicine's TOXLINE
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, and Medical Subject Headings (MeSH) terms for 1,2-dibromo-3-chloropropane. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance priority list (SPL) resource page, and other items as needed. Regulations applicable to 1,2-dibromo-3-chloropropane were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
03/2017	((96-12-8[rn] OR 67708-83-2[rn] OR 96K0FD4803[rn] OR "1,2-dibromo-3-chloropropane"[supplementary concept] OR "1,2-dibromo-3-chloropropane"[nm]) AND (1990/01/01 : 3000[dp] OR 1990/01/01 : 3000[mhda])) OR (("1,2-Dibrom-3-chlor-propan"[tw] OR "1,2-Dibromo-3-chloropropane"[tw] OR "1,2-Dibromo-3-cloro-propano"[tw] OR "1,2-Dibromochloropropane"[tw] OR "1,2-Dibroom-3-chloorpropaan"[tw] OR "1-Chloro-2,3-dibromopropane"[tw] OR "2,3-Dibromo-1-chloropropane"[tw] OR "3-Chloro-1,2-dibromopropane"[tw] OR "BBC 12"[tw] OR "Dibromchlorpropan"[tw] OR "Dibromochloropropane"[tw] OR "Durham Nematicode EM 17.1"[tw] OR "Fumagon"[tw] OR "Fumazon 86"[tw] OR "Fumazone"[tw] OR "Fumazone 86"[tw] OR "Fumazone 86E"[tw] OR "Gro-Tone Nematode Granular"[tw] OR "Nemabrom"[tw] OR "Nemafume"[tw] OR "Nemagon"[tw] OR "Nemagone"[tw] OR "Nemanax"[tw] OR "Nemanex"[tw] OR "Nemapaz"[tw] OR "Nemaset"[tw] OR "Nematocide EM 12.1"[tw] OR "Nematocide EM 15.1"[tw] OR "Nematocide Solution EM 17.1"[tw] OR "Nematox"[tw] OR "Nemazon"[tw] OR "Oxy DBCP"[tw]) NOT medline[sb]) AND (1990/01/01 : 3000[dp] OR 1990/01/01 : 3000[crdat] OR 1990/01/01 : 3000[edat]))
Toxline	
03/2017	("1 2-dibrom-3-chlor-propan" OR "1 2-dibromo-3-chloropropane" OR "1 2-dibromo-3-cloro-propano" OR "1 2-dibromochloropropane" OR "1 2-dibroom-3-chloorpropaan" OR "1-chloro-2 3-dibromopropane" OR "2 3-dibromo-1-chloropropane" OR "3-chloro-1 2-dibromopropane" OR "bbc 12" OR "dibromchlorpropan" OR "dibromochloropropane" OR "durham nematicode em 17 1" OR "fumagon" OR "fumazon 86" OR "fumazone" OR "fumazone 86" OR "fumazone 86e" OR "gro-tone nematode granular" OR "nemabrom" OR "nemafume" OR "nemagon" OR "nemagone" OR "nemanax" OR "nemanex" OR "nemapaz" OR "nemaset" OR "nematocide em 12 1" OR "nematocide em 15 1" OR "nematocide solution em 17 1" OR "nematox" OR "nemazon" OR "oxy dbcp" OR 96-12-8 [rn] OR 67708-83-2 [rn]) AND 1990:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
Toxcenter	
03/2017	FILE 'TOXCENTER' ENTERED AT 09:06:42 ON 23 MAR 2017 L1 2132 SEA 96-12-8 L2 11 SEA 67708-83-2 L3 2141 SEA L1 OR L2 L4 2113 SEA L3 NOT TSCATS/FS L5 2029 SEA L4 NOT PATENT/DT L6 781 SEA L5 AND PY>=1990 ACTIVATE TOXQUERY/Q --------- L7 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L8 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L9 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L10 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L11 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)

Table B-2. Database Query Strings

Database search date	Query string
	L12 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L13 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L14 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L15 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L16 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L17 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L18 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L19 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L20 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L21 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L22 QUE (ENDOCRIN? AND DISRUPT?)
	L23 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L24 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L25 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L26 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L27 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L28 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L29 QUE (NEPHROTOX? OR HEPATOTOX?)
	L30 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L31 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L32 QUE L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31
	L33 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L34 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L35 QUE L32 OR L33 OR L34
	L36 QUE (NONHUMAN MAMMALS)/ORGN

Table B-2. Database Query Strings

Database search date	Query string
	L37 QUE L35 OR L36 L38 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L39 QUE L37 OR L38 --------- L40 595 SEA L6 AND L39 L41 83 SEA L40 AND MEDLINE/FS L42 97 SEA L40 AND BIOSIS/FS L43 332 SEA L40 AND CAPLUS/FS L44 83 SEA L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L45 469 DUP REM L41 L42 L44 L43 (126 DUPLICATES REMOVED) L*** DEL 83 S L40 AND MEDLINE/FS L*** DEL 83 S L40 AND MEDLINE/FS L46 83 SEA L45 L*** DEL 97 S L40 AND BIOSIS/FS L*** DEL 97 S L40 AND BIOSIS/FS L47 53 SEA L45 L*** DEL 332 S L40 AND CAPLUS/FS L*** DEL 332 S L40 AND CAPLUS/FS L48 267 SEA L45 L*** DEL 83 S L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L*** DEL 83 S L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L49 66 SEA L45 L50 386 SEA (L46 OR L47 OR L48 OR L49) NOT MEDLINE/FS D SCAN L50

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS[a]	
03/2017	Compounds searched: 96-12-8, 67708-83-2
NTP	
03/2017	96-12-8 67708-83-2 1,2-Dibromo-3-chloropropane 1,2-Dibromochloropropane 1-Chloro-2,3-dibromopropane 2,3-Dibromo-1-chloropropane 3-Chloro-1,2-dibromopropane Dibromochloropropane
NIH RePORTER	
06/2017	Text Search: "1,2-Dibrom-3-chlor-propan" OR "1,2-Dibromo-3-chloropropane" OR "1,2-Dibromo-3-cloro-propano" OR "1,2-Dibromochloropropane" OR "1,2-Dibroom-3-chloorpropaan" OR "1-Chloro-2,3-dibromopropane" OR "2,3-Dibromo-1-chloropropane" OR "3-Chloro-1,2-dibromopropane" OR "BBC 12" OR "Dibromchlorpropan" OR "Dibromochloropropane" OR "Durham Nematicode EM 17.1" OR "Fumagon" OR

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	"Fumazon 86" OR "Fumazone" OR "Fumazone 86" OR "Fumazone 86E" OR "Gro-Tone Nematode Granular" OR "Nemabrom" OR "Nemafume" OR "Nemagon" OR "Nemagon 20" OR "Nemagon 206" OR "Nemagon 20G" OR "Nemagon 90" OR "Nemagon soil fumigant" OR "Nemagone" OR "Nemanax" OR "Nemanex" OR "Nemapaz" OR "Nemaset" OR "Nematocide EM 12.1" OR "Nematocide EM 15.1" OR "Nematocide Solution EM 17.1" OR "Nematox" (Advanced), Search in: Projects Admin IC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

[a]Several versions of the TSCATS database were searched, as needed, by CASRN including TSCATS1 via Toxline (no date limit), TSCATS2 via https://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearch?OpenForm (date restricted by EPA receipt date), and TSCATS via CDAT (date restricted by 'Mail Received Date Range'), as well as google for recent TSCA submissions.

The 2017 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 813
- Number of records identified from other strategies: 35
- Total number of records to undergo literature screening: 848

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on 1,2-dibromo-3-chloropropane:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

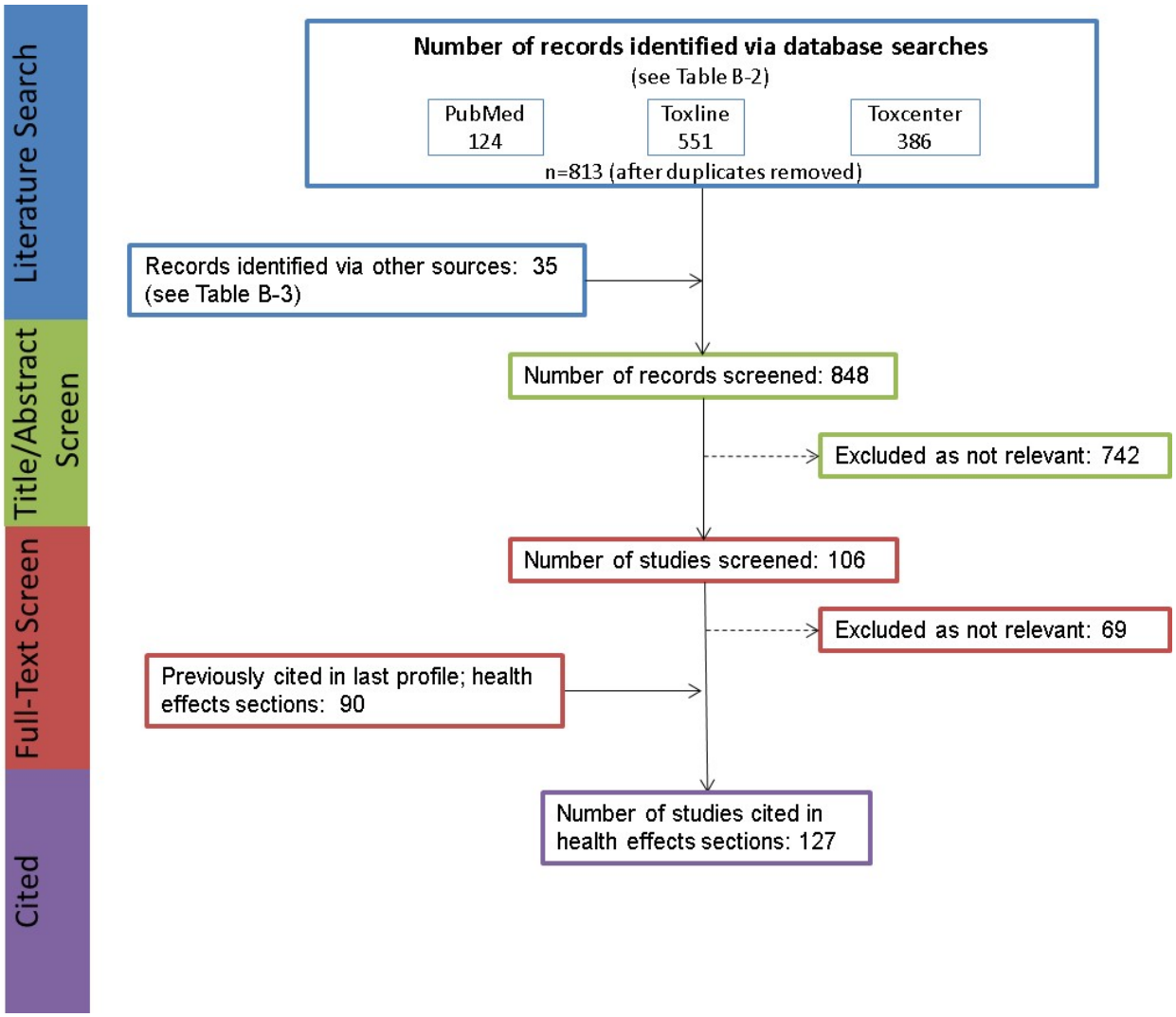
- Number of titles and abstracts screened: 848
- Number of studies considered relevant and moved to the next step: 106

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 106
- Number of studies cited in the health effects sections of the existing toxicological profile (September, 1992): 90
- Total number of studies cited in the health effects sections of the updated profile: 127

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. March 2017 Literature Search Results and Screen for 1,2-Dibromo-3-chloropropane



APPENDIX C. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page C-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page C-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(14) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(15) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(17) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(18) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

APPENDIX C

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

Figure key[a] (3)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

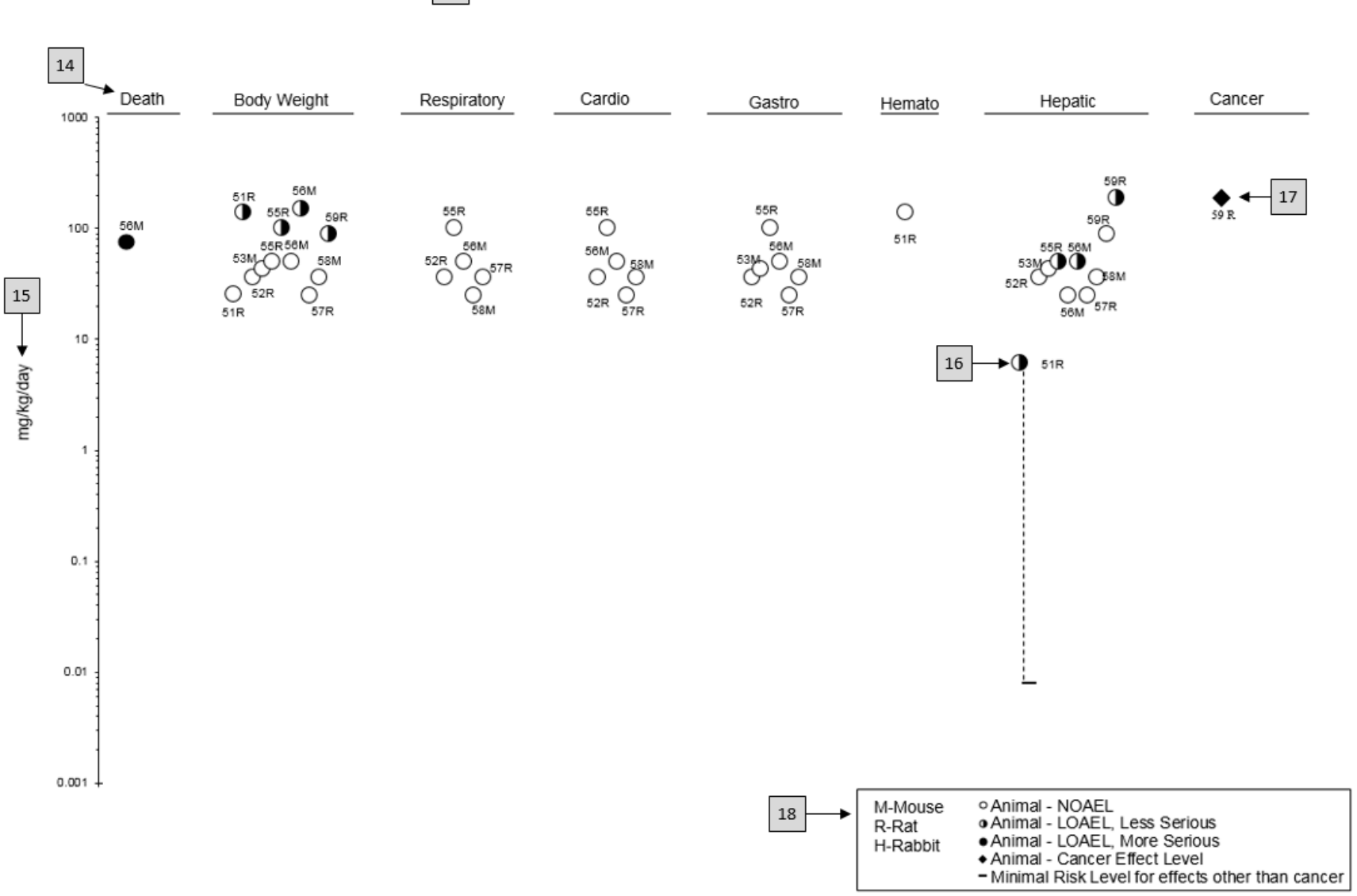
[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

APPENDIX C

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.asp). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX E. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) $\geq$1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act

FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey

NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey

USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result