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-dibromoethane. 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.

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-dibromoethane, 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. Dermal data is 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-dibromoethane are indicated in Tables 2-1 and 2-2 and Figures 2-2 and 2-3.

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

The health effects of 1,2-dibromoethane have been evaluated in a few studies in humans and in several studies in laboratory animals. Data in humans consist of few cases reports of toxicity at lethal or near-lethal exposures and a few occupational studies in pesticide workers examining respiratory and male reproductive effects. Of the available studies in workers, only one study included appropriate controls and accounted for potential confounding factors. Thus, interpretation of studies evaluating effects of 1,2-dibromoethane in humans is limited. As illustrated in Figure 2-1, studies in animals have evaluated effects of inhalation, oral, and dermal exposure to 1,2-dibromoethane; the inhalation database is more extensive than the oral database. Most oral exposure studies administered 1,2-dibromoethane by gavage; one study evaluated dietary exposure and two studies evaluated exposure in drinking water.

Of the available chronic-duration studies in animals, the most extensive evaluations were conducted in the NTP (1982) inhalation and the NCI (1978) oral cancer bioassays. However, both studies were terminated early due to extensive mortality. In the NTP (1982) inhalation study, nearly all male mice, including controls, died due to complications from urinary tract infections that were not related to exposure. Therefore, data in male mice are not included in the profile. Also note that extensive treatment-related mortality was observed in male and female rats exposed to the high concentration (40 ppm) and in female mice exposed to the low (10 ppm) and high (40 ppm) concentrations of 1,2-dibromoethane.

The NCI (1978) oral (gavage) of rats and mice also was terminated early due to extensive mortality. In rats, the initial treatment groups were 40 and 80 mg/kg/day. Due to marked treatment-related morality by exposure week 16 in males (18/50) and females (20/50) administered 80 mg/kg/day, treatment of this

group was discontinued for 13 weeks. The study authors stated that mortality in high-dose male rats may have been associated with early tumor incidence. High-dose female rats died either during or soon after intubation, suggesting a problem with the intubation procedure. The study authors speculated that mortality may have been due to "acute toxic reactions" to treatment; however, the study report did not provide any additional information to support this suggestion. At week 30 of the study, treatment was reinitiated, but at the low dose level (40 mg/kg/day; time-weighted average: 38 mg/kg/day). However, due to the interruption in dosing and substantial change in dose, data from this group in rats are not considered reliable for quantitative use; thus, data from the 80 mg/kg/day group for the time period after this dose was discontinued are not included in the profile. Male rats were administered the low dose of 1,2-dibromoethane for 47 weeks and the study was terminated after 49 weeks due to treatment-related mortality; therefore, the exposure duration for male rats is intermediate, not chronic, duration. Female rats had a time-weighted exposure of 38 mg/kg/day for 57 weeks and the study was terminated at 61 weeks due to treatment-related mortality. For the NCI (1978) study in mice, the exposure was terminated at 53 weeks with sacrifice occurring between 77 and 90 weeks due to mortality in both the low (62 mg/kg/day) and high (107 mg/kg/day) dose groups.

Available studies have identified several targets of toxicity for 1,2-dibromoethane, as described below. Unfortunately, it is not possible to identify the most sensitive effects of 1,2-dibromoethane because studies either evaluated only a single exposure level or effects and/or excessive mortalities were observed at the lowest exposures tested. For all portals-of-entry systems (respiratory, gastrointestinal, dermal, and ocular), tissue damage was observed following direct exposure/application.

- ***Body Weight Endpoint.*** Marked body weight loss or reduced weight gain has been consistently observed in laboratory animals following acute-, intermediate- and chronic-duration inhalation and intermediate- and chronic-duration oral exposure.

- ***Respiratory Endpoint.*** Pulmonary edema was observed in one worker who died following acute dermal and inhalation exposure. In some laboratory animals, damage to the nasal cavity (cytomegaly, hyperplasia, metaplasia, and loss of cilia) and lower respiratory tract (leukocytic infiltration of the lungs and hyperplasia of the lung and bronchus) have been observed following inhalation exposure.

- ***Gastrointestinal Endpoint.*** In humans who ingest 1,2-dibromoethane, oral and pharyngeal ulceration, vomiting, and diarrhea have been observed. Gavage exposure of laboratory animals produced damage to the forestomach, including cell proliferation, hyperkeratosis, and acanthosis.

- ***Hematological Endpoint.*** Case studies in acutely exposed humans reported decreased hemoglobin and white blood cell count; however, because pre-exposure values for these parameters were not available, it is not possible to determine if effects were related to exposure.

Histopathological changes in the spleen (hematopoiesis, hemosiderosis, and atrophy) have been observed in laboratory animals following inhalation and oral exposure.

- ***Hepatic Endpoint.*** Case reports of individuals acutely exposed to 1,2-dibromoethane by inhalation or ingestion observed acute, severe liver failure and hepatic necrosis. Hepatic toxicity (cloudy swelling, inflammation, fatty degeneration, necrosis, peliosis hepatis) has also been observed in animals following inhalation and oral exposure to 1,2-dibromoethane.

- ***Renal Endpoint.*** A few studies in laboratory animals following inhalation exposure showed renal damage, including tubular degeneration, interstitial congestion, edema, and nephropathy.

- ***Endocrine Endpoint.*** Degeneration of the adrenal cortex has been observed in rats following intermediate-duration oral exposure and chronic-duration inhalation exposure.

- ***Ocular Endpoint.*** Few studies have investigated ocular effects from 1,2-dibromoethane in air. Eye irritation and retinal degradation occurred in an intermediate and chronic study, respectively, in which laboratory animals were exposed to 1,2-dibromoethane in air. Instillation of 1,2-dibromoethane to the eyes of laboratory animals resulted in conjunctival irritation and corneal damage.

- ***Reproductive Endpoint.*** An occupational study of workers chronically exposed by combined inhalation and dermal exposure reported decreased sperm count, decreased percentages of viable and motile sperm, and increased abnormal sperm. Testicular atrophy and infertility have been observed in laboratory animals exposed to inhaled and oral 1,2-dibromoethane.

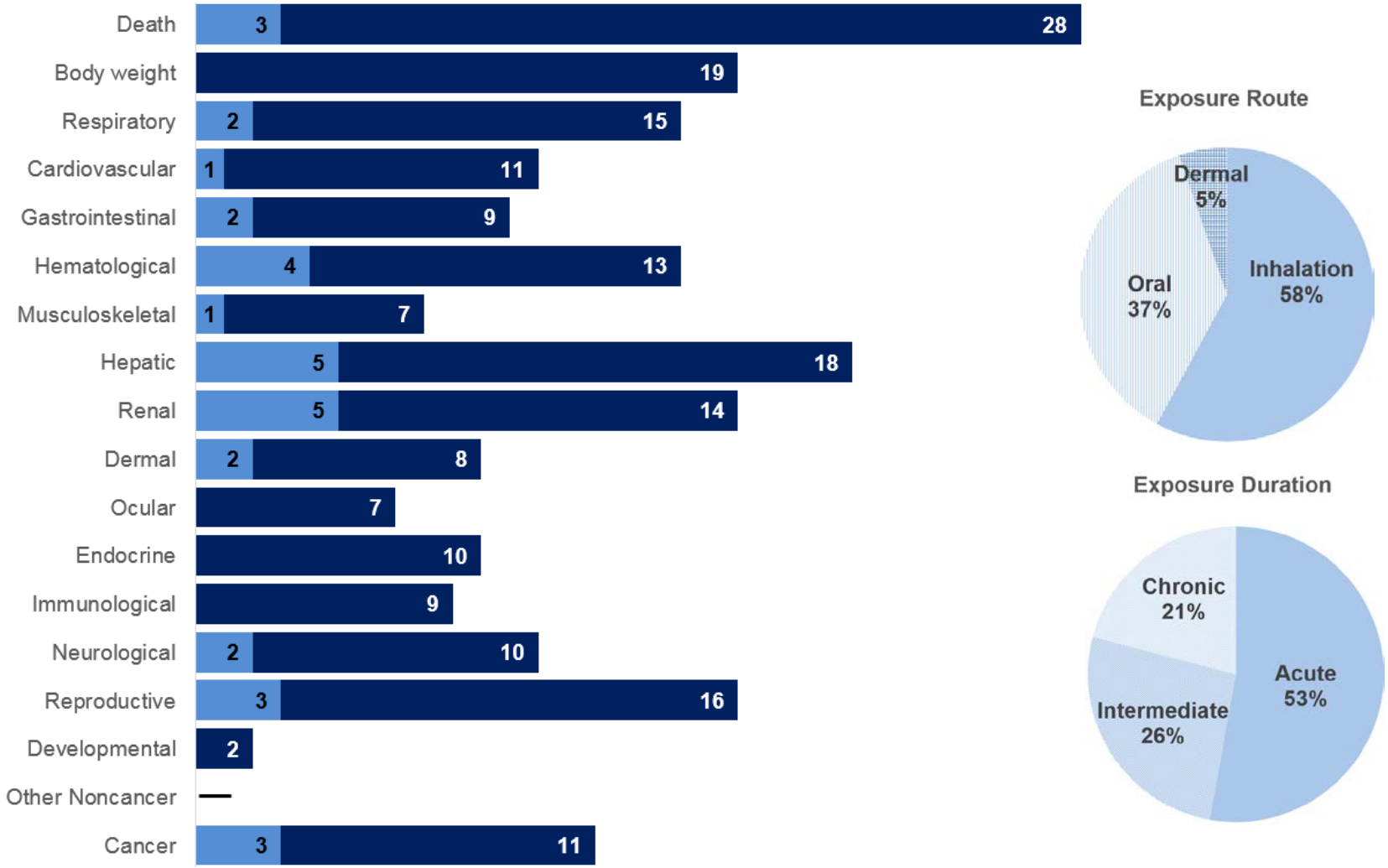
- ***Developmental Endpoint.*** A single inhalation study in rats and mice reported skeletal anomalies at the lowest exposure tested.

- ***Cancer Endpoint.*** In laboratory animals exposed to inhaled and oral 1,2-dibromoethane, cancers have been observed in portal-of-entry tissues (respiratory tract and forestomach) and in several other tissues (spleen, adrenal gland, mesenchymal tissue, subcutaneous tissue, mammary tissue, testes, blood, and cardiovascular tissue). In addition, lung adenomas developed in mice following chronic dermal exposure.

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

Most studies examined the potential body weight, respiratory, hepatic, and reproductive effects of 1,2-dibromoethane

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



*Includes studies discussed in Chapter 2. A total of 55 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to 1,2-Dibromoethane – 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) 4–30 NS	1 day 12 hours	0, 100, 200, 400, 1,600, 5,000, 10,000	OW, GN, CS	Death			200	LC_{50}
Rowe et al. 1952									
2	Rat (NS) 4–30 NS	1 day 2 hours	0, 100, 200, 400, 1,600, 5,000, 10,000	OW, GN, CS	Death			400	16/25 died
Rowe et al. 1952									
3	Rat (NS) 4–30 NS	1 day 0.1 hour	0, 100, 200, 400, 1,600, 5,000, 10,000	OW, GN, CS	Death			5,000	9/10 died
Rowe et al. 1952									
4	Rat (NS) 4–30 NS	1 day 0.5 hour	0, 100, 200, 400, 1,600, 5,000, 10,000	OW, GN, CS	Death			10,000	LC_{50}
Rowe et al. 1952									
5	Rat (NS) 10 F	7 of 9 days 7 hours/day	0, 100	BW, OW, HP, CS	Death			100	3/10 died
					Bd wt		100		13% loss in body weight
					Resp		100		Thickening of alveolar wall and leukocytic infiltration of lungs
					Hemato		100		Spleen hemosiderosis and slight congestion
					Hepatic		100		Cloudy swelling
					Renal	100			
Rowe et al. 1952									

Table 2-1. Levels of Significant Exposure to 1,2-Dibromoethane – 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
6	Rat (NS) 10 F	4–7 hours	50, 100, 200, 800	OW, HP	Hepatic	50	100		Histopathological changes (hepatocellular cloudy swelling, centrilobular fatty change, patchy necrosis)
Rowe et al. 1952									
7	Rat (NS) 15–17 F	10 days 23 hours/day GDs 6–15	0, 20, 38, 80	BW, FI, FX, MX, DX, TG	Death			80	LC_{50}
					Bd wt			38	Body weight gain reduced by 177% with a 68% reduction in food consumption
					Develop			20	Skeletal anomalies
Short et al. 1978									
8	Mouse (NS) 18–22 F	10 days 23 hours/day GDs 6–15	0, 20, 38, 80	BW, OW, GN, FX, MX, DX, TG	Death			38	10/17 died
					Bd wt			20	Body weight gain reduced by 54% with a 38% reduction in food consumption
					Develop			20	Skeletal anomalies
Short et al. 1978									
9	Rabbit (NS) 4 F	4 days 7 hours/day	0, 100	HP	Death			100	3/4 died
					Hepatic		100		Fatty degeneration, necrosis
Rowe et al. 1952									
10	Guinea pig (NS) 15 NS	1 day 7 hours	0, 200, 400	OW, GN, CS, LE	Death			400	No death at 200 ppm; 20/20 died at 400 ppm
Rowe et al. 1952									
11	Guinea pig (NS) 20 NS	1 day 2 hours	0, 400	OW, GN, CS	Death				No death
Rowe et al. 1952									

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Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
INTERMEDIATE EXPOSURE									
12	Rat (F344) 40 M, 20 F	13 weeks 5 days/week 6 hours/day	0, 3, 10, 40	BW, OW, GN, HP, CS, HE	Bd wt	10 M 40 F	40 M		Body weight gain decreased by 8%
					Resp	3	10	40	10 ppm: hyperplasia of nasal turbinates; 40 ppm: squamous metaplasia and necrosis
					Hemato	40			
					Hepatic	40			
					Renal	40			
					Repro	40			
Nitschke et al. 1981									
13	Rat (NS) 5 M, 6 F	13 weeks 5 days/week 6 hours/day	0, 3, 15 75	BW, CS, GN, HP, LE	Death				No death
					Bd wt	3 M		15 M 3 F	(M): Body weight gain decreased by 27%; (F): Body weight gain increased by 30% (3 ppm) and 16% (15 ppm), and decreased by 36% (75 ppm)
					Resp	75			
					Cardio	75			
					Gastro	75			
					Hemato	75			
					Musc/skel	75			
					Hepatic	75			
					Renal	75			
					Dermal	75			
					Endocr	15	75		Slight decrease in thyroid follicular size; swelling and/or vacuolation of adrenal cortical cells of the zona fasciculata

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Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effect
					Immuno	75			
					Neuro	75			
					Repro	75			
NTP 1982									
14	Rat (NS) 5 M, 5 F	13 weeks 5 days/week 6 hours/day	0, 3, 15, 75	HP	Resp	15	75		Cytomegaly, focal hyperplasia, squamous metaplasia, loss of cilia in nasal cavity
Reznik et al. 1980									
15	Rat (NS) 20 M, 20 F	63 7-hour exposures over 91 days	0, 50	OW, HP, BC	Resp	50 F	50 M		Relative lung weight increased by 37%
					Cardio	50			
					Hemato	50			
					Hepatic		50		Relative weight increased by 11% (M) and 25% (F)
					Renal		50		Relative weight increased by 26% (M) and 24% (F)
					Repro		50 M		Relative weight of testes decreased by 9%
Rowe et al. 1952									
16	Rat (NS) 20 F	3 weeks 7 days/week 7 hours/day	0, 20, 39, 80	BW, OF	Death			80	10/50 females died
					Bd wt	39		80	Body weight gain decreased by 169% with a 47% reduction in food consumption
					Repro	39		80	Reduced fertility; vacuolated degeneration of uterine epithelium
Short et al. 1979									
17	Rat (CD) 18–20 M	10 weeks 5 days/week 7 hours/day	0, 19, 39, 89	BW, OW, HP, BI, RX	Death			89	7/33 males died
					Bd wt	19	39		Body weight gain decreased by 18%, with no decrease in food consumption

Table 2-1. Levels of Significant Exposure to 1,2-Dibromoethane – 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
					Repro	39		89	Infertility; 54% decrease in serum testosterone; testicular atrophy
Short et al. 1979									
18	Mouse (A/J) 20–30 F	6 months 5 days/week 6 hours/day	0, 20, 50	GN, HP, CS, LE	Death			20	Death in 9/30
					Cancer			20	CEL: lung tumors
Adkins et al. 1986									
19	Mouse (B6C3F1) 10 M,10 F	13 weeks 5 days/week 6 hours/day	0, 3, 15, 75	BW, GN, CS, HP, LE	Death				4/10 male mice died at 3 ppm; 1/10 female mice died at 75 ppm
					Bd wt	3 M	3 F	15 M	Body weight gain decreased by 21% in males and 15% in females; no data on food consumption
					Resp	15	75		Megalocytic cells in bronchioles
					Cardio	75			
					Gastro	75			
					Hemato	75			
					Musc/skel	75			
					Hepatic	75			
					Renal	75			
					Dermal	75			
					Ocular	15	75		Eye irritation
					Endocr	15	75		Slight decrease in thyroid follicular size
					Immuno	75			
					Neuro	75			
					Repro	75			
NTP 1982									
20	Mouse (B6C3F1) 10 M,10 F	13 weeks 5 days/week 6 hours/day	0, 3, 15, 75	HP	Resp	15	75		Cytomegaly, focal hyperplasia, squamous metaplasia, loss of cilia in nasal cavity
Reznik et al. 1980									

Table 2-1. Levels of Significant Exposure to 1,2-Dibromoethane – 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
21	Rabbit (NS) 3 M, 1 F	59 7-hour exposures over 84 days	0, 50	BW, OW, OF, CS, BI, HP	Bd wt	50			
					Hepatic	50			
					Renal	50			
Rowe et al. 1952									
22	Guinea pig (NS) 8 M, 8 F	57 7-hour exposures over 80 days	0, 25, 50	BW, OW, HP, GN	Death				No death
					Bd wt	25		50	Terminal BW decreased by 26% in males and 24% in females; no data on food consumption
					Resp	50			
					Cardio	50			
					Hemato	50			
					Hepatic	25	50 M		Fatty degeneration
					Renal	25	50		Tubular degeneration, interstitial congestion and edema
					Endo	50			
					Immuno	50			
					Repro	50 M			
Rowe et al. 1952									
CHRONIC EXPOSURE									
23	Human 46 M	5 years	0.088	OF	Repro			0.088	Decreased sperm count (42%), decreased percentages of viable (11%) and motile (24%) sperm; increased abnormal sperm (tapered heads [69%], absent heads [45%], abnormal tails [14%])
Ratcliffe et al. 1987; Schrader et al. 1988									

Table 2-1. Levels of Significant Exposure to 1,2-Dibromoethane – 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
24	Rat (F344) 50 M, 50 F	89–104-106 weeks 5 days/week 6 hours/day	0, 10, 40	BW, GN, HP, CS	Death			40	45/50 males by week 89 and 42/50 females died by week 91
					Bd wt	10		40	Terminal body weight decreased by 33% (M) and 23% (F); no data on food consumption
					Resp		10		Nasal cavity inflammation (M) and hyperplasia (M, F), lung/bronchus hyperplasia (M)
					Cardio	40			
					Gastro	40			
					Hematol	40			
					Musc/skel	40			
					Hepatic	10	40		Liver congestion (M), hepatocellular necrosis (F)
					Renal	10	40 M		Nephropathy (M)
					Dermal	40			
					Ocular	10 M	10 F		Retinal degeneration
					Endocr	10 M	10 F		Degeneration of the adrenal cortex
					Immuno	40			
					Neuro	40			
					Repro	10 F		10 M	Testicular degeneration

Table 2-1. Levels of Significant Exposure to 1,2-Dibromoethane – 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
					Cancer			10	CEL 10 ppm: nasal cavity adenomas and carcinomas (M, F), mesothelioma of the tunica vaginalis (M), pituitary adenoma (F), mammary fibroadenoma (F); 40 ppm: nasal cavity adenomas and carcinomas (M, F), mesothelioma of the tunica vaginalis (M), spleen hemangiosarcoma (M, F), alveolar/bronchiolar carcinoma or adenoma (F), mammary fibroadenoma (F)
NTP 1982									
25	Rat (NS) 48 M, 48 F	18 months 5 days/week 7 hours/day	0, 20	BW, HP, LE, HE	Death			20	30/48 males and 19/48 females within 15 months of treatment; 43/48 males and 37/48 females died within 18 months of treatment
					Bd wt		20		Body weight gain decreased by 19% (M) and 17% (F); no data on food consumption
					Resp	20			
					Cardio	20			
					Gastro	20			
					Hemato	20 F	20 M		Splenic atrophy, hemosiderosis
					Hepatic	20			
					Renal	20			
					Endocr	20			
					Immuno	20			
					Neuro	20			
					Repro	20			

Table 2-1. Levels of Significant Exposure to 1,2-Dibromoethane – 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
					Cancer			20	CEL: spleen hemangiosacroma (M, F), adrenal adenoma or carcinoma (M, F), mesenchymal tumor (M), mammary adenocarcinoma or carcinoma (F)
Wong et al. 1982									
26	Mouse (B6C3F1) 50 F	91–104-106 weeks 5 days/week 6 hours/day	0, 10, 40	BW, GN, CS	Death			10	10 ppm: 31/50 died by 104 weeks; 40 ppm: 42/50 died by week 71
					Bd wt	10	40		Terminal body weight decreased by 15%; no data on food consumption
					Resp		10		Nasal cavity inflammation and hyperplasia, lung/bronchiole hyperplasia
					Cardio	40			
					Gastro	40			
					Hematol		10		Spleen hemosiderosis
					Musc/skel	40			
					Hepatic	40			
					Renal	40			
					Dermal	40			
					Ocular	40			
					Endocr	40			
					Immuno	40			
					Neuro	40			
					Repro	40			

Table 2-1. Levels of Significant Exposure to 1,2-Dibromoethane – 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
					Cancer			10	CEL 10 ppm alveolar/bronchiolar carcinoma or adenoma (M, F), subcutaneous fibrosarcoma (M, F), spleen hemangiosarcoma (M, F), mammary adenocarcinoma (F); 40 ppm: alveolar/bronchiolar carcinoma or adenoma (M, F), nasal cavity adenomas and carcinomas (F), subcutaneous fibrosarcoma (F), mammary adenocarcinoma (F) lymphomas (F)
NTP 1982									

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the lowest levels of effect, regardless of gender, are presented.

BC = serum (blood) chemistry); Bd wt or BW = body weight; BI = biochemical changes; Cardio = cardiovascular; CEL = cancer effect level; a CEL can represent levels for neoplasms (including benign or malignant lesions/tumors); CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; F = female(s); FI = food intake; FX = fetal toxicity; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LC_{50} = lethal concentration with 50% mortality; LE = lethal dose; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = musculoskeletal; MX = maternal toxicity; Neuro = neurological; NOAEL = no-observed-effect-level; NS = not specified; OF = organ function; OW = organ weight; Repro = reproductive; Resp = respiratory; RX = reproductive effects; TG = teratogenicity

Figure 2-2. Levels of Significant Exposure to 1,2-Dibromoethane – Inhalation

Acute (≤14 days)

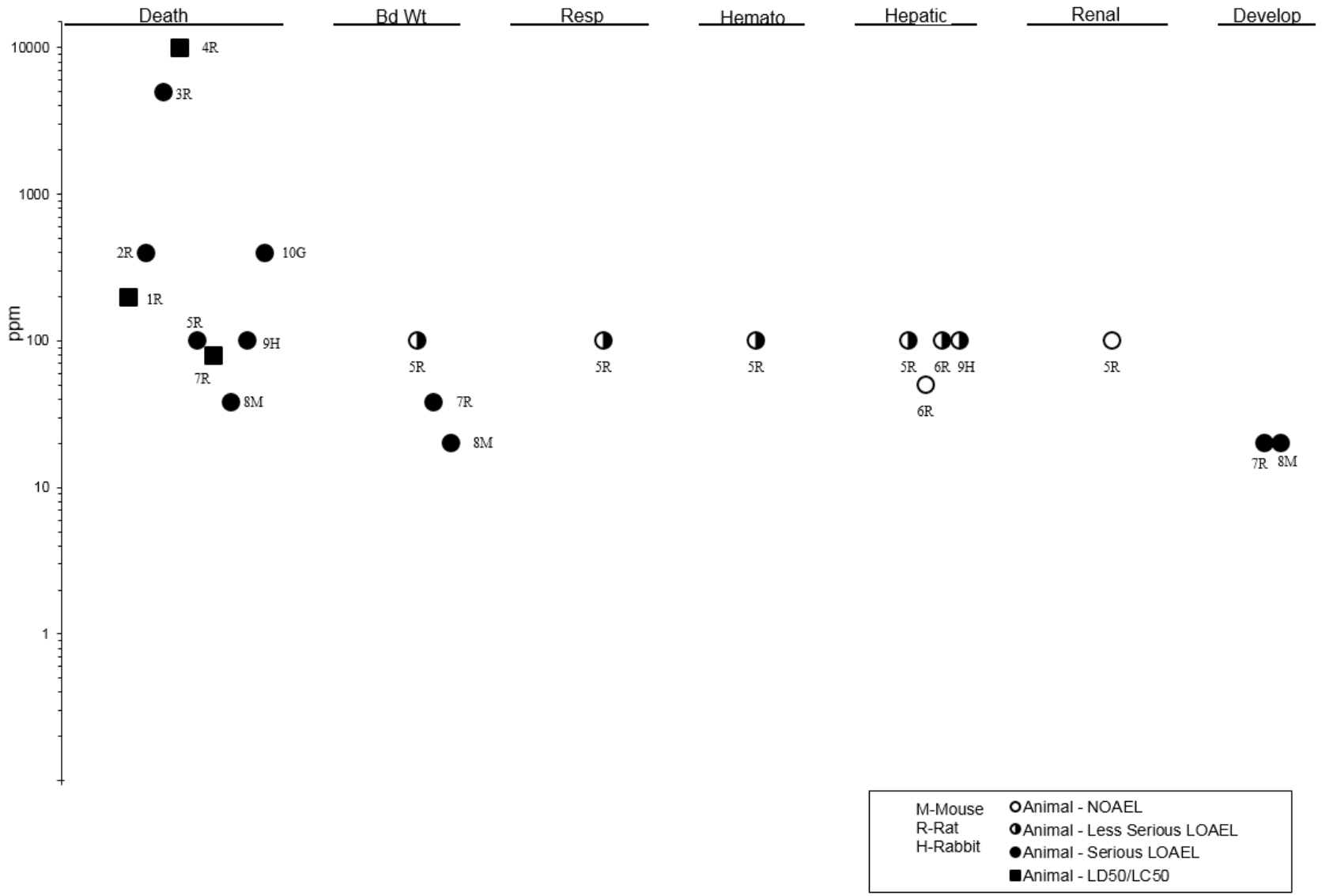

Figure 2-2. Levels of Significant Exposure to 1,2-Dibromoethane – Inhalation
Intermediate (15-364 days)

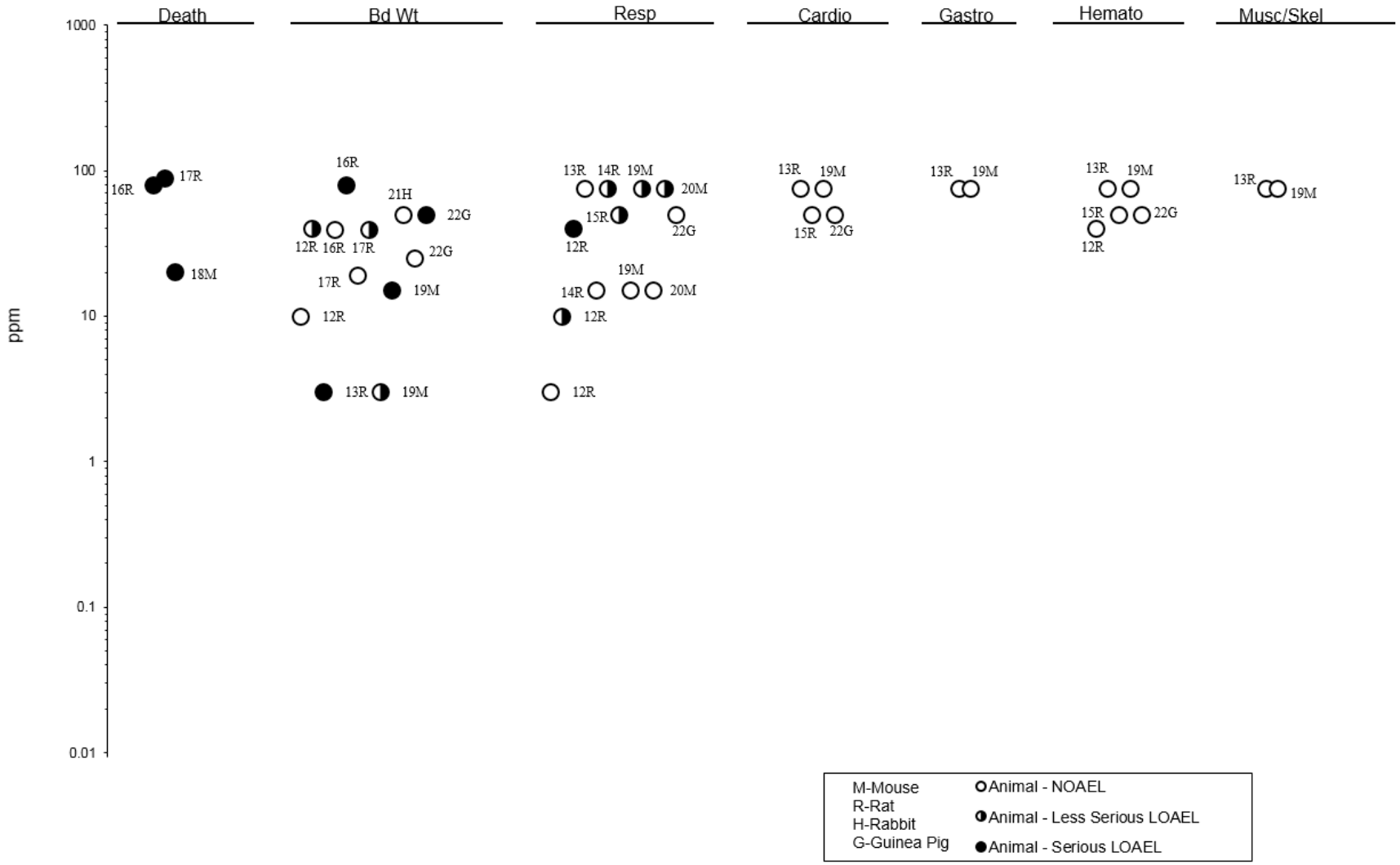

Figure 2-2. Levels of Significant Exposure to 1,2-Dibromoethane – Inhalation
Intermediate (15-364)

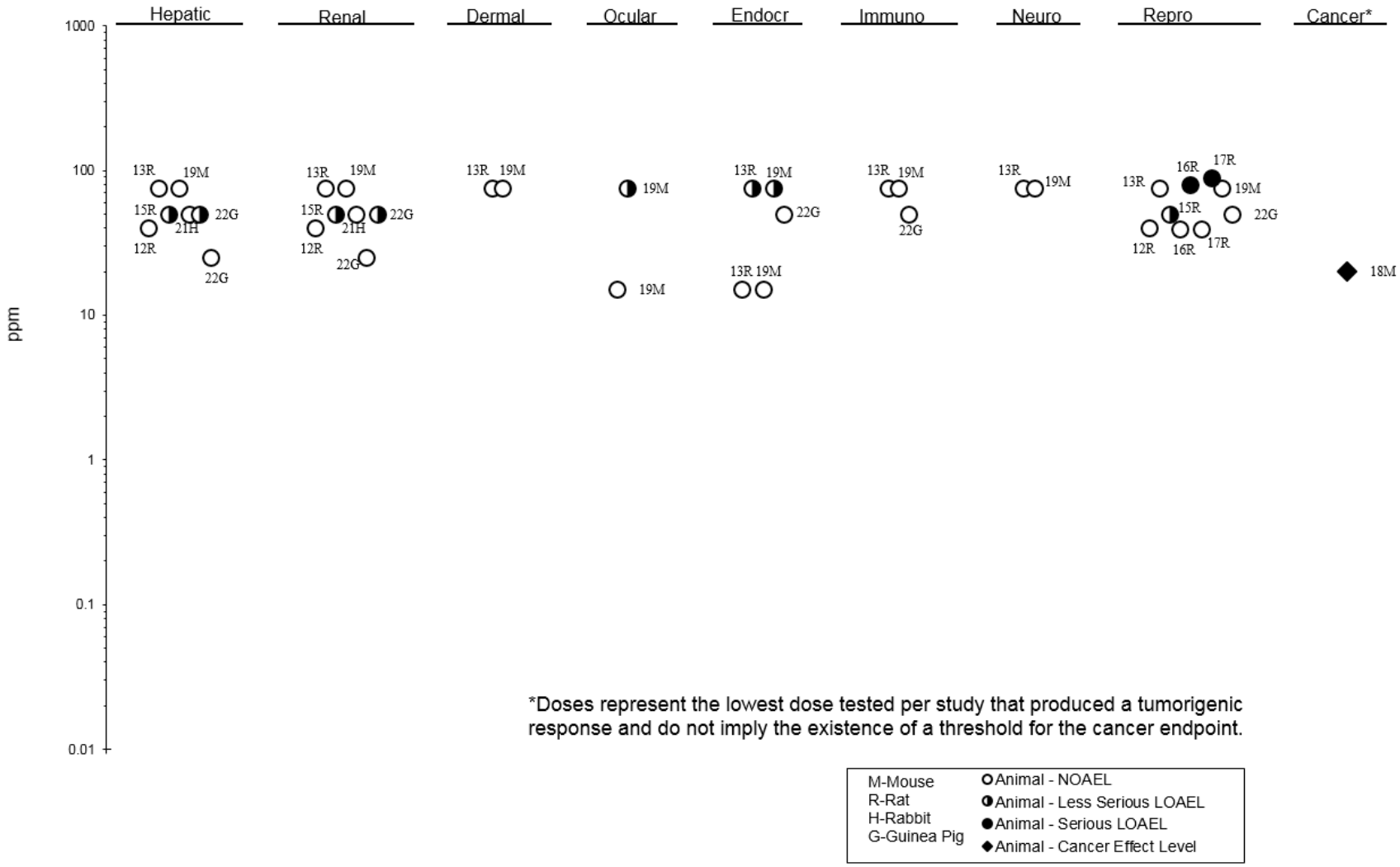

Figure 2-2. Levels of Significant Exposure to 1,2-Dibromoethane – Inhalation
Chronic (≥365 days)

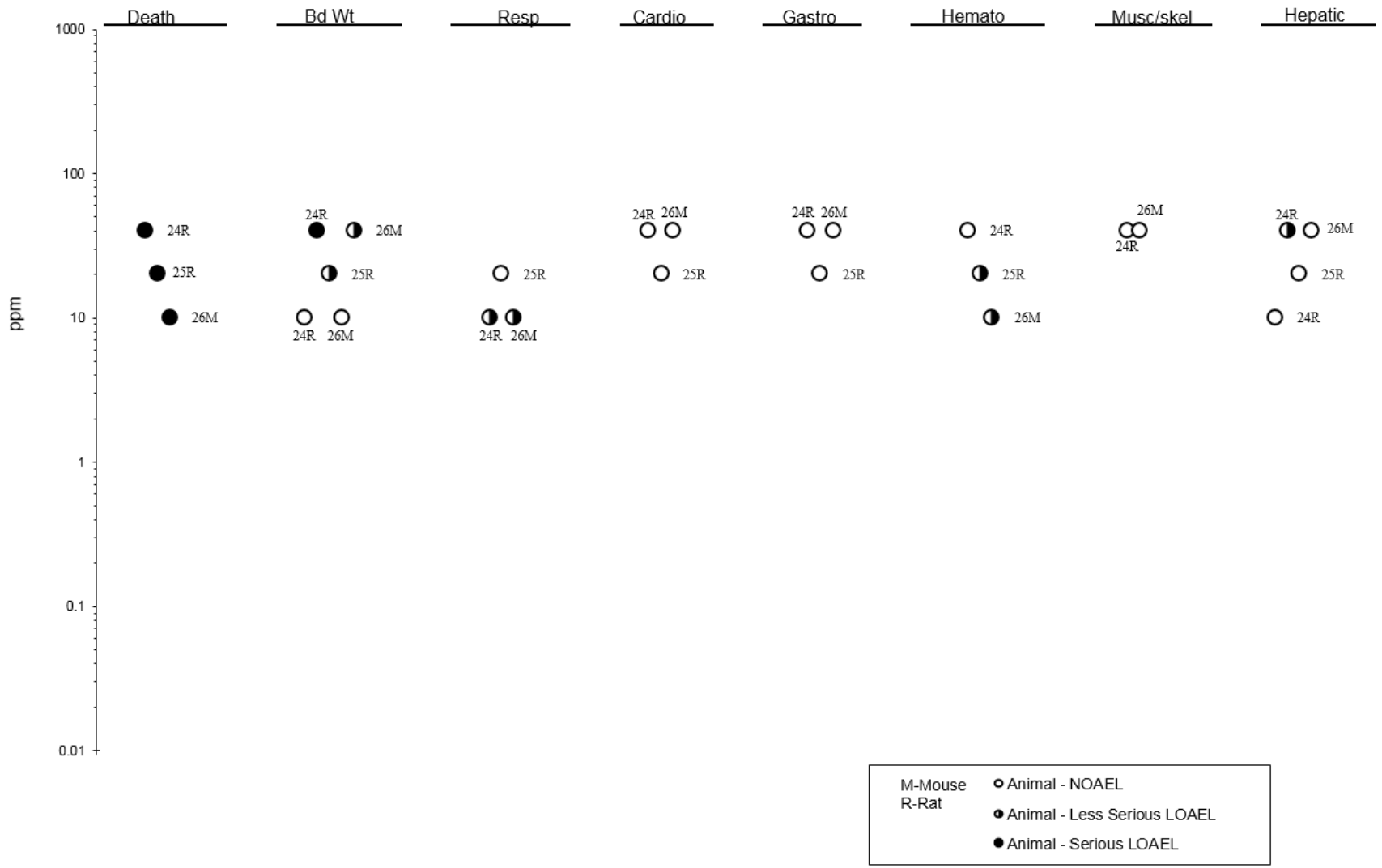

Figure 2-2. Levels of Significant Exposure to 1,2-Dibromoethane – Inhalation

Chronic (≥365 days)

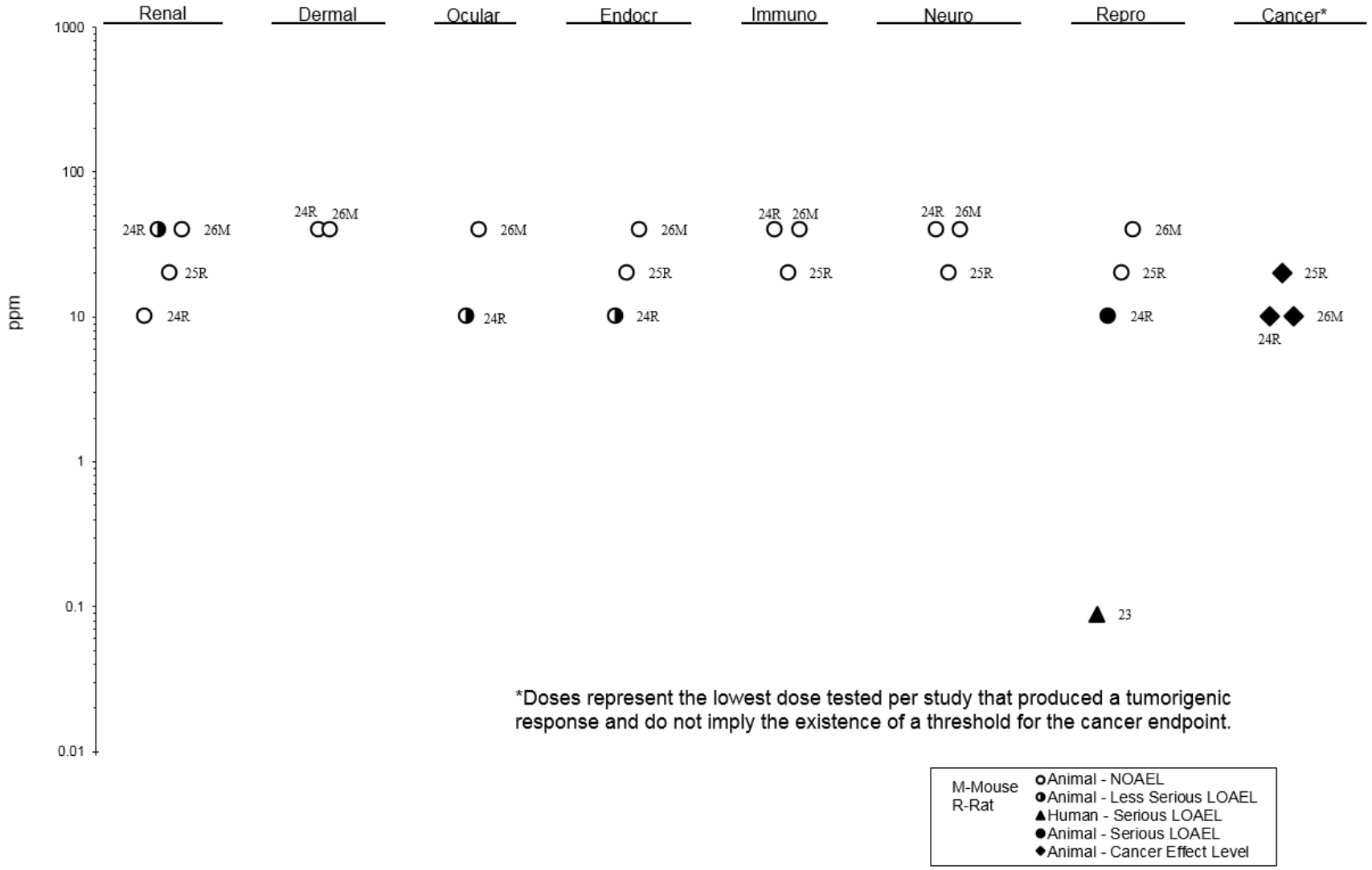

Table 2-2. Levels of Significant Exposure to 1,2-Dibromoethane – Oral

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 (NS) 8 M	1 day once (GO)	0, 107	BI, HP	Hepatic		107		Fatty degeneration
Botti et al. 1986									
2	Rat (albino) 36–48 M	1 day once (GO)	0, 110	HP	Hepatic			110	Necrosis
Broda et al. 1979									
3	Rat (white) 8 M	2 weeks 5 days/week (G)	0, 40, 80	HP	Gastro	40	80		Forestomach cell proliferation and hyperkeratosis
Ghanayem et al. 1986									
4	Rat (NS) 60 M/40 F	1 day once (GO)	NS	LE	Death			117 F 146 M	LD_{50}
Rowe et al. 1952									
5	Rat (Sprague-Dawley) 15 M	5 days 1 time/day (GO)	0, 10, 30	OF	Repro	30			Dominant lethal mutagenicity test
Teramoto et al. 1980									
6	Mouse (NS) 20 F	1 day once (GO)	NS	LE	Death			420 F	LD_{50}
Rowe et al. 1952									
7	Mouse (BDF1) 7–9 M	5 days 1 time/day (GO)	0, 100, 150	OF	Repro	150			Dominant lethal mutagenicity test
Teramoto et al. 1980									

Table 2-2. Levels of Significant Exposure to 1,2-Dibromoethane – 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
8	Rabbit (NS) 55 F	1 day once (GO)	110	LE	Death			55 F	LD_{50}
Rowe et al. 1952									
9	Guinea pig (NS) 40	1 day once (GO)	NS	LE	Death			110	LD_{50}
Rowe et al. 1952									
INTERMEDIATE EXPOSURE									
10	Rat (Osborne-Mendel) 50 M, 50 F	16 weeks 5 days/week	0, 80	LE	Death			80	18/50 males and 20/50 females died
NCI 1978									
11	Rat (Osborne-Mendel) 50 M	47 weeks 5 days/week 1 time/day (GO)	M: 0, 38	BW, FI, GN, HP, CS	Death			38	31/50 died before week 47 of treatment
					Bd wt			38	Decreased body weight gain (terminal body weight decreased by 23%); no data on food consumption
					Resp	38			
					Cardio	38			
					Gastro	38			
					Hemato	38			
					Musc/skel	38			
					Hepatic		38		Peliosis hepatis
					Renal	38			
					Dermal	38			
					Ocular	38			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
					Endocr		38		Adrenal cortical cell degeneration
					Immuno	38			
					Neuro		38		Hunched appearance
					Repro			38	testicular atrophy
					Cancer			38	CEL: stomach squamous cell carcinoma, hemangiosarcoma
NCI 1978									
12	Rat (NS) 5 M	90 days (F)	0, 5, 10, 25, 50	BW, FI, OW, HP, OF	Bd wt	50			
					Resp	50			
					Cardio	50			
					Hemato	50			
					Hepatic	50			
					Renal	50			
					Endocr	50			
					Neuro	50			
					Repro	50			
Shivanandappa et al. 1987									
CHRONIC EXPOSURE									
13	Rat (Osborne-Mendel) 50 F	57 weeks 5 days/week 1 time/day (GO)	0, 37	BW, FI, GN, HP, CS	Death			37	48/50 females died before week 57 of treatment
					Bd wt		37		Terminal BW decreased by 16%; no data on food consumption
					Resp	37			
					Cardio	37			
					Gastro	37			
					Hemato	37			

Table 2-2. Levels of Significant Exposure to 1,2-Dibromoethane – 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
					Musc/Skel	37			
					Hepatic	37			
					Renal	37			
					Dermal	37			
					Ocular	37			
					Endocr	37			
					Immuno	37			
					Neuro	37			
					Repro	37			
					Cancer			37	CEL: stomach squamous cell carcinoma
NCI 1978									
14	Mouse (B6C3F1) 50 M, 50 F	53 weeks 5 days/week 1 time/day (GO)	0, 62, 107	BW, FI, GN, HP, CS	Death			62	30/50 males died by week 58; 22/50 females died by week 70
					Bd wt	62		107	Body weight gain decreased by approximately 57% (M) and 50% (F)
					Resp	107			
					Cardio	107			
					Gastro	107 M 62 F	 107 F		Forestomach hyperkeratosis and acanthosis
					Hemato	107 M	62 F		Splenic hematopoiesis (F)
					Musc/skel	107			
					Hepatic	107 F	62 M		Liver inflammation
					Renal	107			
					Dermal		62		Alopecia, skin sores
					Ocular	107			
					Endocr	107			

Table 2-2. Levels of Significant Exposure to 1,2-Dibromoethane – 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
					Immuno	107			
					Neuro	107			
					Repro	62 M 107 F		107 M	Testicular atrophy
					Cancer			62	CEL: stomach squamous cell carcinoma or papilloma (M, F), alveolar or bronchiolar adenoma or carcinoma (F), lymphoma (F)
NCI 1978									
15	Mouse (B6C3F1) 30 M, 30 F	15–18 months 7 days/week 1 times/day (W)	0, 103 (F), 116 (M)	BW, WI, GN, HP	Bd wt		116 M 103 F		Body weights in males and females decreased by 10–20%
					Cancer			103 F 116 M	CEL: esophageal squamous papillomas (F), forestomach squamous carcinomas (M, F), glandular stomach carcinoma (M), liver carcinoma (M, F)
Van Duuren et al. 1985									

Table 2-2. Levels of Significant Exposure to 1,2-Dibromoethane – 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
16	Mouse (B6C3F1) 50 M, 50 F	18 months 7 days/week 24 hours/day (W)	0, 43 (M), 52 (F)	BW, WI, HP	Bd wt		52 F	43 M	Average body weights decreased by 20% in males and 15% in females
					Cancer			43 M 52 F	CEL: forestomach papilloma and carcinoma, esophageal papilloma and/or carcinoma

Van Duuren et al. 1986

[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 lowest levels of effect, regardless of gender, are presented.

BI = biochemical changes; Bd wt or BW = body weight; CEL = cancer effect level; CS = clinical signs; Endocr = endocrine; (F) = feed; F = female(s); FI = food intake; Gastro = gastrointestinal; GN = gross necropsy; GO = gavage in oil vehicle; Hemato = hematological; HP = histopathology; Immuno = immunological; LE = lethality; LOAEL = lowest-observed-adverse-effect level; LD_{50} = lethal dose with 50% mortality; M = male(s); Musc/skel = musculoskeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OF = organ function; OW = organ weight; Repro = reproductive; Resp = respiratory; W = water; WI = water intake

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

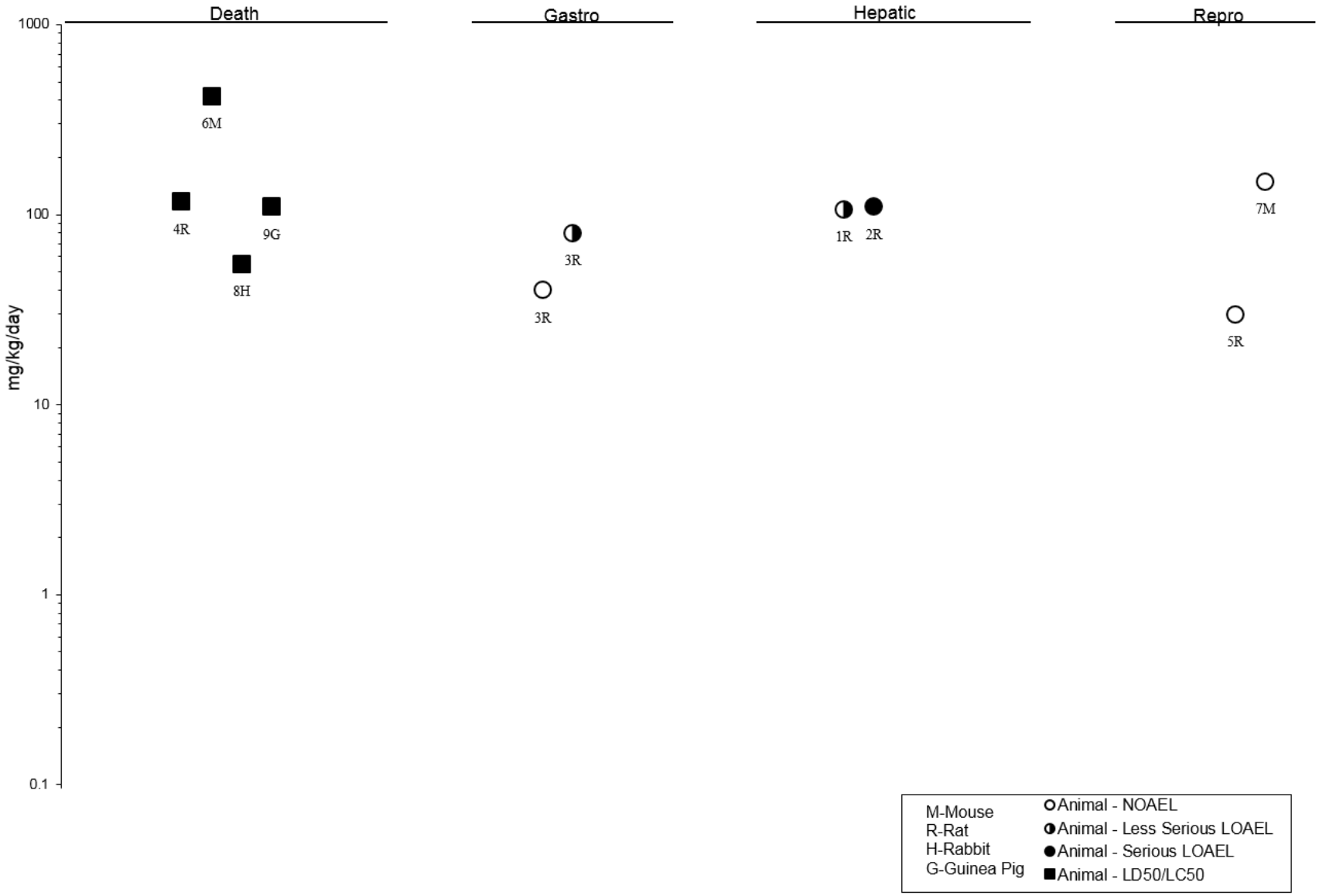

Figure 2-3. Levels of Significant Exposure to 1,2-Dibromoethane – Oral
Intermediate (14-364 days)

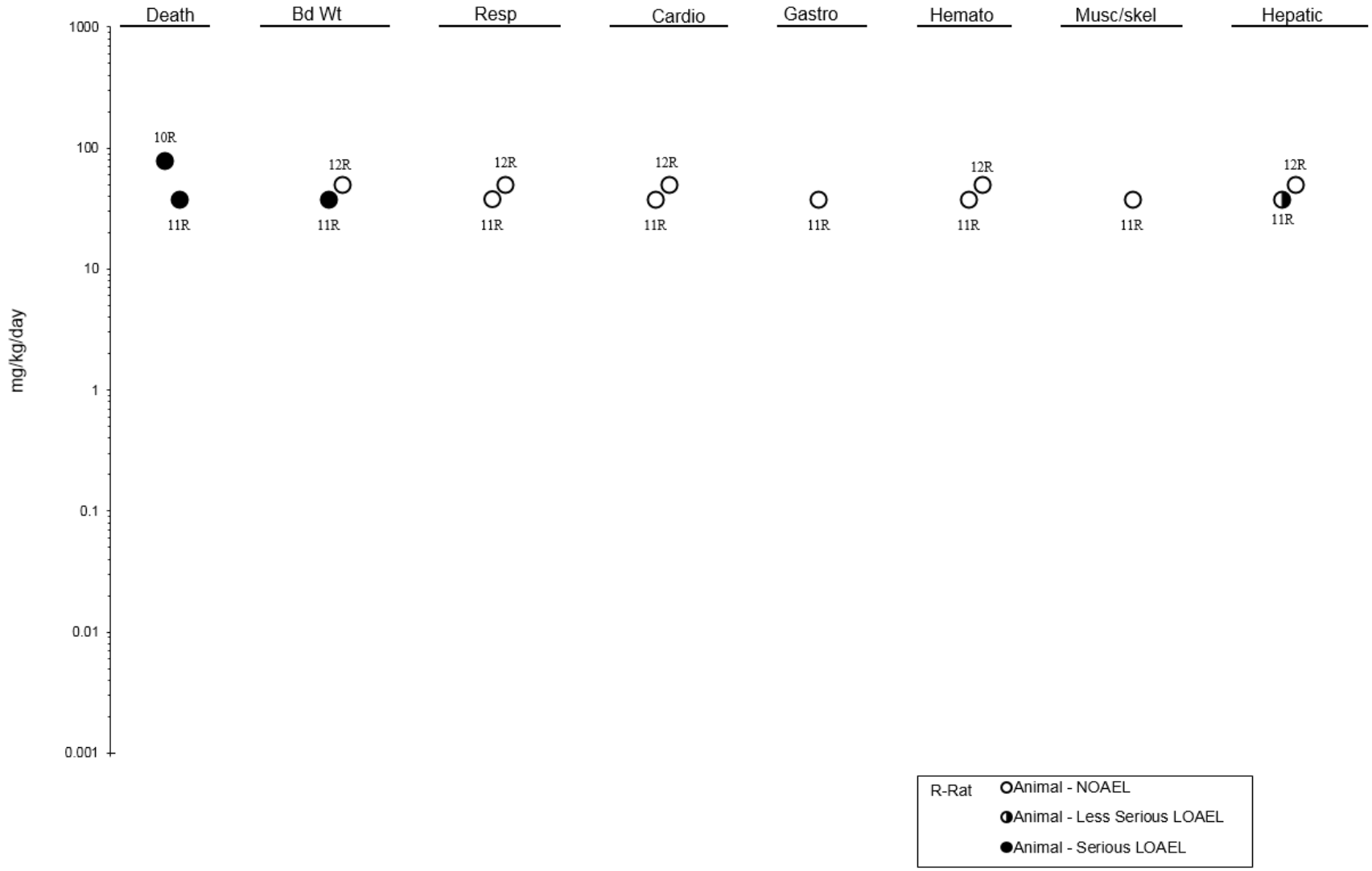

Figure 2-3. Levels of Significant Exposure to 1,2-Dibromoethane – Oral

Intermediate (14-364 days)

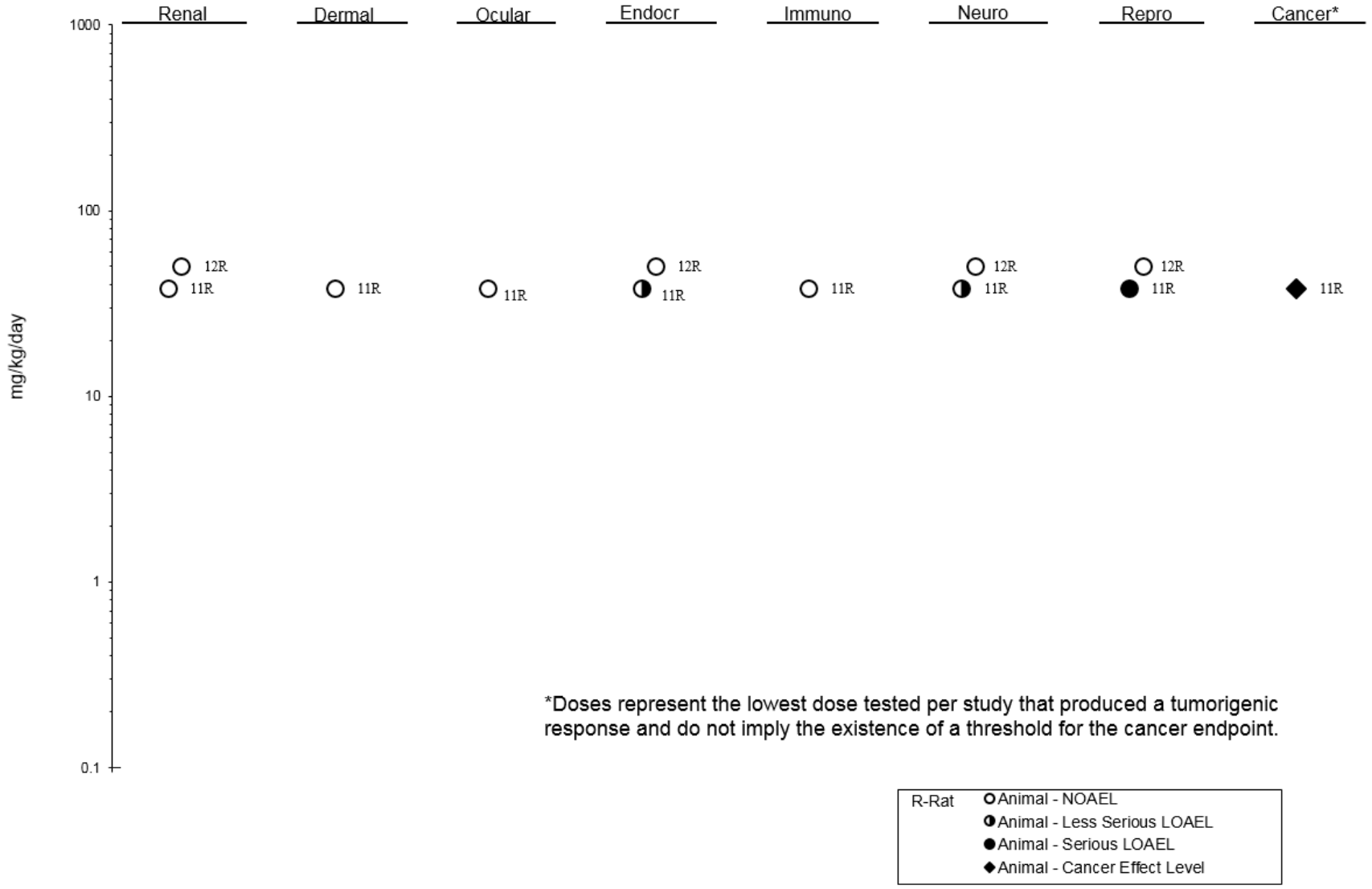

Figure 2-3. Levels of Significant Exposure to 1,2-Dibromoethane – Oral
Chronic (≥365 days)

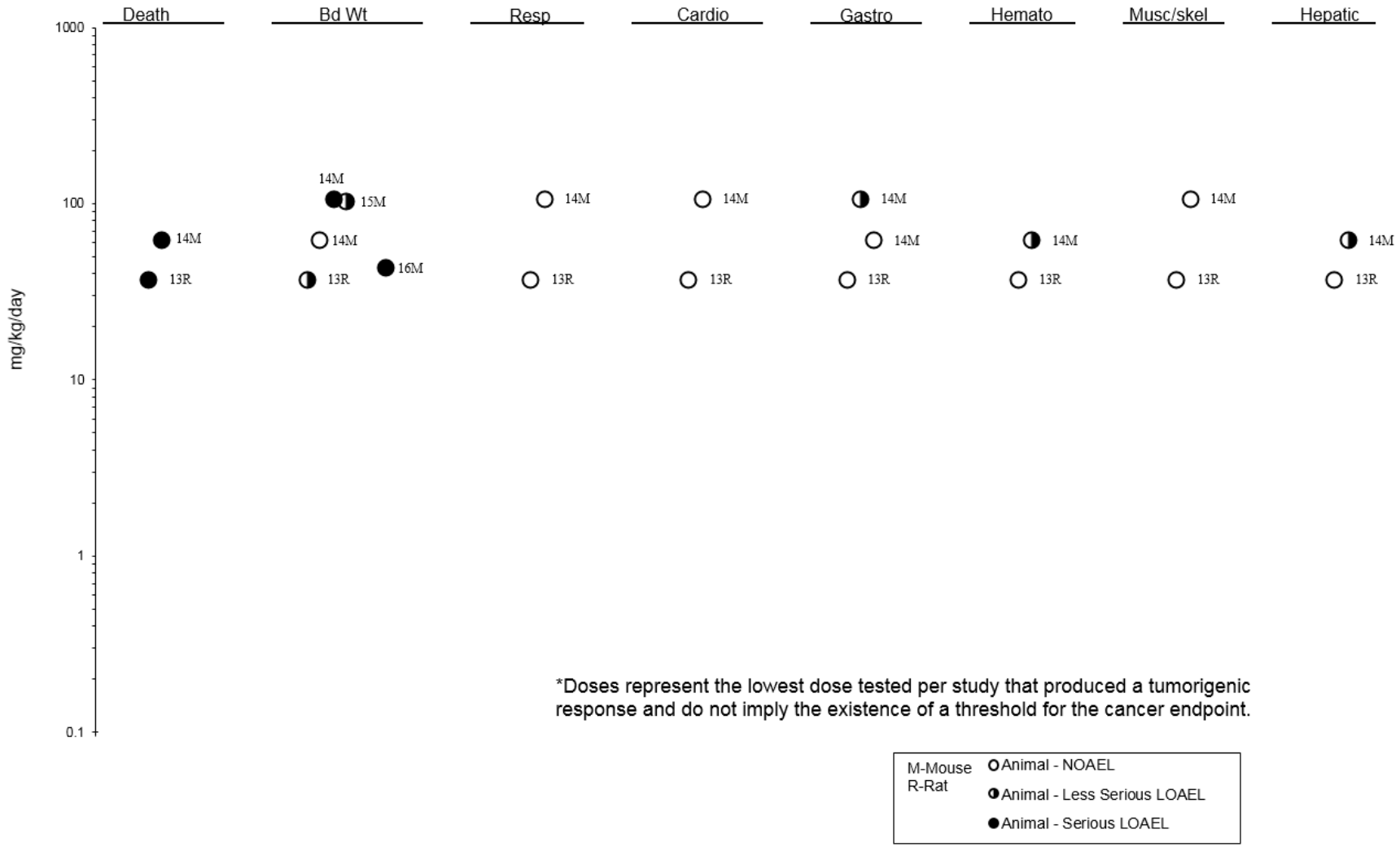

Figure 2-3. Levels of Significant Exposure to 1,2-Dibromoethane – Oral
Chronic (≥365 days)

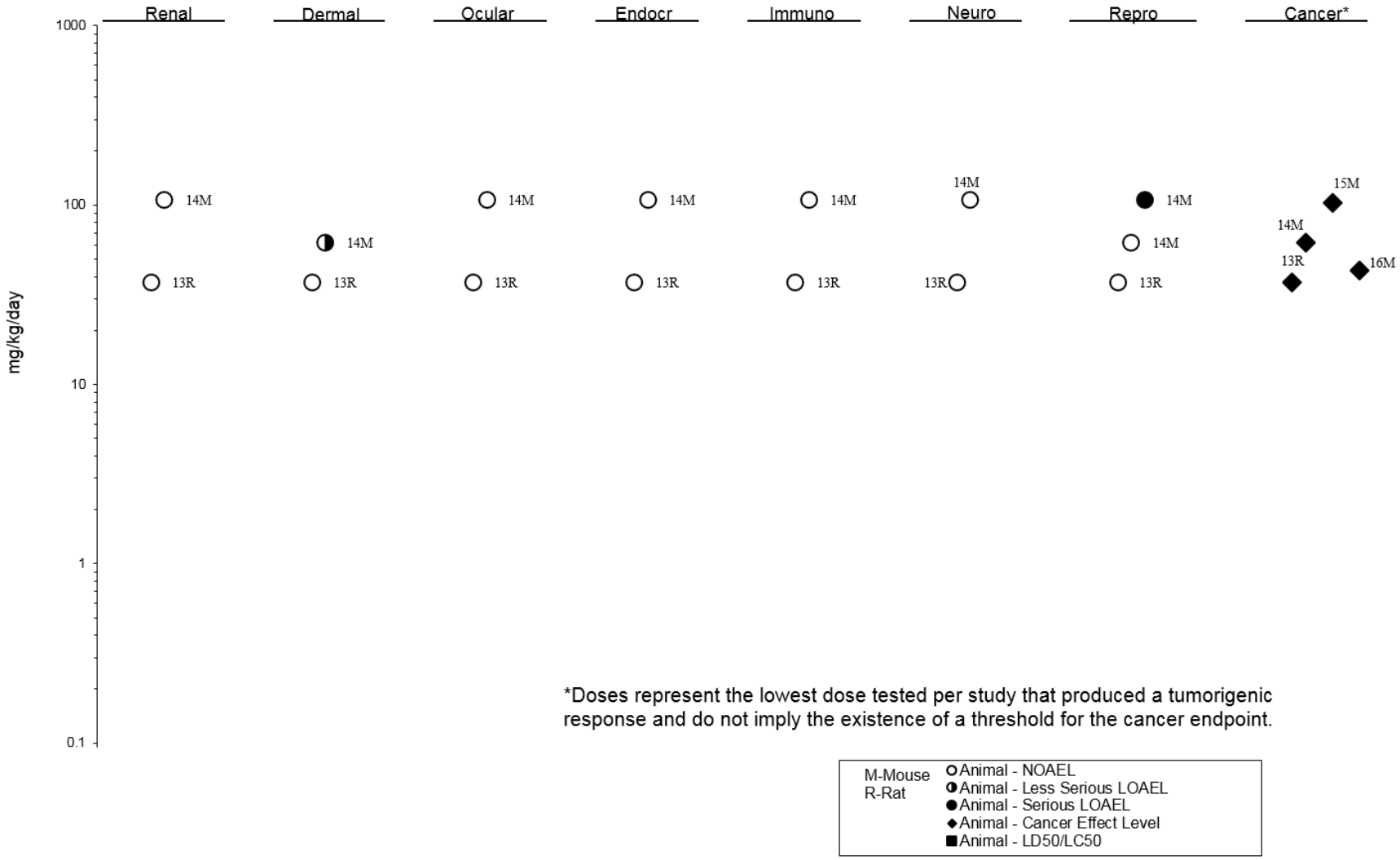

Table 2-3. Levels of Significant Exposure to 1,2-Dibromoethane – Dermal

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) 5–15 NS	24 hours	210, 300, 650, 1,100	GN, CS	Death			300	Approximate LD_{50}
				Dermal		210		Erythema, necrosis
				Neuro		210		Central nervous system depression
Rowe et al. 1952								
CHRONIC EXPOSURE								
Mouse (Ha:ICR Swiss) 30 F	428–576 days 3 days/week 1 time/day	0, 71, 143, 214	HP	Cancer			71	CEL: 71 mg/kg/day: lung adenomas; 143 mg/kg/day: lung adenoma, skin papillomas; 214 mg/kg/day: lung adenomas
Van Duuren et al. 1979								

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

2.2 DEATH

Information on the lethality of 1,2-dibromoethane in humans is available from a few case reports (Letz et al. 1984; Olmstead 1960; Saraswat et al. 1986). In all cases, death was due to severe damage to multiple organ systems. Two male workers died within 3 days following combined inhalation and dermal exposure to 1,2-dibromoethane (Letz et al. 1984). Measurements of air concentrations in these case reports were not obtained at the time of exposure; thus, 1,2-dibromoethane levels are most likely higher than those reported. The mean concentration of 1,2-dibromoethane measured 20 hours after exposure was 28 ppm. Clinical findings included pulmonary edema, metabolic acidosis, acute renal and hepatic failure, skeletal muscle necrosis, and cardiac inflammation and edema. One female died 54 hours after ingesting 4.5 mL of 1,2-dibromoethane (approximately 140 mg/kg) (Olmstead 1960), and two females died within 36 hours of ingesting 1,2-dibromoethane (dose not reported) (Saraswat et al. 1986). Clinical signs prior to death included emesis, diarrhea, anuria, tachypnea, and agitation; pathological findings included oropharyngeal ulceration, gastric mucosal erosions, centrilobular hepatocellular necrosis, and renal tubular necrosis.

Acute lethality in laboratory animals has been investigated for inhalation, oral, and dermal exposure; lethality values are presented in Tables 2-1, 2-2, and 2-3, respectively. Death associated with acute inhalation exposure has been investigated in rats, mice, and guinea pigs (EPA 1976; Rowe et al. 1952). In rats, LC_{50} values for single inhalation exposures of 1,2-dibromoethane were inversely related to exposure duration, with values ranging from 200 ppm for a 12-hour exposure to 10,000 ppm for a 30-minute exposure (Rowe et al. 1952). Deaths were attributed to cardiac or respiratory failure. Lethality values for single exposures of guinea pigs were not identified, although no deaths occurred following exposure to 200 ppm for 7 hours or 400 ppm for 2 hours (Rowe et al. 1952). Maternal lethality values (LC_{50}) in rats and mice exposed during gestation (23 hours/day) were 80 and 38 ppm, respectively (Short et al. 1978). Mortality following single oral doses of 1,2-dibromoethane has been evaluated in rats, mice, rabbits, and guinea pigs, with LD_{50} values ranging from 55 mg/kg in rabbits to 420 mg/kg in mice (Rowe et al. 1952). The LD_{50} for a single dermal application (occluded) of 1,2-dibromoethane to rabbits was 300 mg/kg (Rowe et al. 1952).

An intermediate-duration inhalation exposure study reported 21% mortality in male rats exposed to 89 ppm for 10 weeks and 20% mortality in female rats exposed to 80 ppm for 3 weeks; no morality was observed at concentrations ≤39 ppm (Short et al. 1979). The cause of death was not identified. No increase in mortality was observed in rats exposed to up to 75 ppm for 13 weeks (NTP 1982).

As noted in the introduction to Chapter 2 regarding the NCI (1978) oral (gavage) study in rats, administration of high-dose (80 mg/kg/day) 1,2-dibromoethane was stopped after 16 weeks of treatment due to high mortality (males 36%; females 40%) associated with early developing carcinomas of the stomach. No increased mortality was observed in male rats exposed to 1,2-dibromoethane in the diet at doses up to 50 mg/kg/day for 90 days (Shivanandappa et al. 1987).

Chronic inhalation and oral exposure studies in rats and mice reported increased mortality primarily associated with cancer (NCI 1978; NTP 1982; Wong et al. 1982). Information regarding cancer endpoints is discussed in Section 2.19. The NTP (1982) inhalation cancer bioassay reported accelerated mortality in male and female rats and female mice exposed to 1,2-dibromoethane. In male and female rats exposed to 40 ppm, 90% mortality was observed at 89 weeks and 84% mortality was observed at 91 weeks of exposure, respectively. Decreased survival was observed in female mice exposed to 10 and 40 ppm. In the 10 ppm group, 62% mortality was observed at the end of the 104-week treatment period, compared to 20% in controls (at 106 weeks). In the 40 ppm group, 86% mortality was observed after 90 weeks of treatment. Decreased survival also was observed in rats exposed to 20 ppm for 15–18 months (Wong et al. 1982). Within 15 and 18 months of exposure, mortality was 63 and 90%, respectively, in male rats and 40 and 77%, respectively, in female rats; mortality in controls at 18 months was 10 and 13% in males and females, respectively.

Marked decreases in survival were observed in rats and mice administered 1,2-dibromoethane by gavage in the NCI (1978) cancer bioassay. For female rats exposed to 36 mg/kg/day, 96% died by week 57 of treatment, with only 4% (i.e., 2 rats) alive for monitoring through study week 61. Increased mortality also was observed in male and female mice administered 1,2-dibromoethane doses of 62 and 107 mg/kg/day. For all mice, treatment ended after 53 weeks; however, all males and high-dose females were observed through study week 78, and low-dose females were observed through study week 90. In male mice, 60 and 80% of animals in the low- and high-dose groups, respectively, died by week 58. In female mice, 44 and 84% of animals in the low- and high-dose groups, respectively, died by study week 70.

2.3 BODY WEIGHT

Numerous inhalation and oral studies in laboratory animals exposed to 1,2-dibromoethane for acute, intermediate, and chronic durations provide evidence of decreased body weight gain or body weight loss. Acute inhalation exposure of rats to 100 ppm for 9 days produced a loss in body weight of 11%; 30%

mortality was also observed at this exposure (Rowe et al. 1952). Marked decreases in maternal body weight gain were observed in rats and mice exposed to 1,2-dibromoethane during gestation (Short et al. 1978). Pregnant rats exposed to 38 ppm 1,2-dibromoethane for 23 hours/day for 10 days resulted in significant reductions in body weight gain (177% compared to controls) and food consumption (68% compared to controls); no significant change in mortality occurred in this group compared to control (Short et al. 1978). Using the same protocol, the authors reported similar observations in mice (Short et al. 1978). Body weight gain and food consumption were decreased by 54 and 38%, respectively, compared to controls, in mice exposed to 20 ppm 1,2-dibromoethane; no significant change in mortality was observed in this group compared to control.

Decreased body weight gain has been observed in rats and mice in intermediate-duration inhalation studies (NTP 1982; Short et al. 1979) and an oral exposure study (NCI 1978). In female rats exposed to 80 ppm for 3 weeks, body weight gain and food consumption were decreased by 169 and 47%, respectively, compared to control; mortality was 20% (Short et al. 1979). Body weight gain was significantly reduced by 18 and 77% in male rats exposed to 39 and 89 ppm 1,2-dibromoethane, respectively, for 10 weeks, compared to controls (Short et al. 1979). No decrease in food consumption was observed in the 39 ppm group, but was reduced by 45% in the 89 ppm group. Mortality was observed in 21% males exposed to 89 ppm.

Dose-related decreases on body weight gain were observed in rats and mice exposed to inhaled 1,2-dibromoethane at nonlethal concentrations for 90 days (NTP 1982). In male rats, decreases in body weight gain, relative to control, ranged from 8% in the 3 ppm group to 42% in the 75 ppm group. In female rats, body weight gain increased by 30% (at 3 ppm) and 16% (at 15 ppm) with a reduction of 36%, compared to controls, in the 75 ppm group. Dose-related decreases in body weight gain were observed in male and female mice at exposure concentrations ≥3 and ≥15 ppm in males and females, respectively (NTP 1982). NTP (1982) did not report data on food consumption in the 90-day exposure study. Decreases in weight gain (20% compared to controls) was observed following oral (gavage) exposure of male rats to 38 mg/kg/day for 47 weeks (NCI 1978); no information on food consumption was reported.

Chronic-duration inhalation and oral exposure of laboratory animals to 1,2-dibromoethane resulted in decreased body weight gain (NCI 1978; NTP 1982; Wong et al. 1982). At 40 ppm, decreased terminal body weights were observed in male rats (33%), female rats (23%) and female mice (15%); lethality was also observed; however, no information on food consumption was reported (NTP 1982). Wong et al. (1982) reported decreased terminal body weights of 19 and 17% in male and female rats, respectively,

exposed to inhaled 1,2-dibromoethane at 20 ppm for 18 months. Male and female mice exposed to 107 mg/kg/day for 53 weeks experienced decreased body weight gain of 57 and 50%, respectively (NCI 1978). Other chronic-duration oral studies reported decreases in body weights of 10–20% in male and female mice exposed to 1,2-dibromoethane in drinking water at doses of 50–116 mg/kg/day (Van Duuren et al. 1985, 1986).

2.4 RESPIRATORY

Little information is available on respiratory toxicity of 1,2-dichloroethane in humans. Pulmonary edema were observed in two workers who died following combined acute inhalation and dermal exposure (Letz et al. 1984). A cross-sectional study in 19,704 pesticide workers reported an odds ratio of 2.07 (95% confidence interval [CI]: 1.02, 4.20) in workers exposed to 1,2-dibromoethane; however, exposure estimates were not reported (Hoppin et al. 2009).

Studies in laboratory animals have identified toxicity to the respiratory tract as a portal-of-entry effect of acute, intermediate and chronic exposure to inhaled 1,2-dibromoethane (Nitchke et al. 1981; NTP 1982; Reznik et al. 1980; Rowe et al. 1952). Following repeated acute-duration exposure of female rats to 100 ppm 1,2-dibromoethane for 9 days (7 hours/day), leukocyte infiltration was observed in the pulmonary septa; no information regarding examination of the nasal cavity was reported (Rowe et al. 1952).

Adverse respiratory effects have been reported following intermediate-duration inhalation exposure to 1,2-dibromoethane (Nitchke et al. 1981; NTP 1982; Reznik et al. 1980; Rowe et al. 1952). Although some studies did not observe respiratory tract toxicity (NTP 1982; Rowe et al. 1952), this could be due to testing in smaller numbers of animals and species differences. Hyperplasia of nasal turbinates in male and female rats exposed to 10 ppm for 13 weeks, with hyperplasia, squamous metaplasia, and necrosis, was observed at 40 ppm (Nitchke et al. 1981). Nasal cavity epithelial hyperplasia, squamous metaplasia, cytomegaly, and loss of cilia were observed in male and female rats and mice exposed to 75 ppm 1,2-dibromoethane for 13 weeks, with no significant increase in nasal lesions at 3 or 15 ppm (Reznik et al. 1980).

In deeper respiratory tissues, megalocytic cells were observed in bronchioles of male and female mice exposed to 75 ppm, but not ≤15 ppm, for 13 weeks (NTP 1982). Relative lung weight was increased by 37% in male rats, but not female rats, exposed to 50 ppm for 91 days, although no information on

histopathological findings was reported (Rowe et al. 1952). In contrast, no histopathological lesions of the respiratory tract were observed in male or female rats exposed to 75 ppm for 13 weeks (NTP 1982) or in guinea pigs exposed to 50 ppm for 80 days (Rowe et al. 1952). Based on findings of the NTP (1982) study in rats and mice, the respiratory tract of mice may be more sensitive than rats to intermediate-duration inhalation exposure to 1,2-dibromoethane.

Several respiratory tract lesions were observed in male and female rats and female mice exposed to inhaled 1,2-dibromoethane at concentrations of 10 and 40 ppm (NTP 1982), with concentration-dependent increases in lesion incidence. Lesions included nasal cavity inflammation (male rats and female mice) and epithelial hyperplasia (male and female rats), lung/bronchus or bronchiole epithelial hyperplasia (male rats and female mice), and alveolar hyperplasia (male rats and female mice). In addition, lung congestion was observed in male rats exposed to 40 ppm (NTP 1982). No lung lesions were observed in rats exposed to 20 ppm for up to 18 months; the nasal cavity was not examined. Chronic inhalation exposure of rats and mice resulted in carcinogenic nasal (rats and mice) and pulmonary (mice) tumors (NTP 1982). Additional information on these cancer findings are provided in Section 2.19.

No acute oral studies examining the respiratory endpoint were located in literature. Intermediate-duration oral studies did not find histopathological changes to respiratory tissues in male rats administered 38 mg/kg/day by gavage for 47 weeks (NCI 1978) or up to 50 mg/kg/day in the diet for 90 days (Shivananvappa et al. 1987).

No respiratory effects were reported for rats exposed gavage to 37 mg/kg/day nor mice exposed to 107 mg/kg/day (NCI 1978). However, it should be noted that alveolar or bronchial adenomas and carcinomas were observed in female mice following oral exposure to 62 mg/kg/day for up to 53 weeks, although not in female mice administered 107 mg/kg/day (NCI 1978).

2.5 CARDIOVASCULAR

A case report of two workers who died following acute combined inhalation and dermal exposure to 1,2-dibromoethane noted cardiovascular effects (Letz et al. 1984). One worker had acute myocardial interstitial edema and inflammation and terminal cardiopulmonary arrest. The second worker developed supraventricular tachycardia and asystole. No additional information on cardiovascular toxicity in humans exposed to 1,2-dibromoethane was identified.

Cardiovascular endpoints for any exposure type were not examined in acute-duration animal studies. Intermediate- and chronic-duration inhalation and oral studies in laboratory animals did not find evidence of cardiovascular effects of 1,2-dibromoethane based on histopathological examination of heart tissue and/or changes in organ weight (NCI 1978; NTP 1982; Rowe et al. 1952; Shivanandappa et al. 1987 Wong et al. 1982). For inhalation studies, the highest intermediate-duration exposures evaluated were 75 ppm for 13 weeks in rats and mice (NTP 1982) and 50 ppm for 80 days in guinea pigs (Rowe et al. 1952); the highest exposure tested in chronic-duration studies was 40 ppm in rats and mice (NTP 1982). The highest intermediate-duration oral exposure (diet) evaluated was 50 mg/kg/day in rats (Shivanandappa et al. 1987) and the highest chronic-duration oral exposures (gavage) evaluated were 37 mg/kg/day in female rats and 107 mg/kg/day in mice (NCI 1978).

2.6 GASTROINTESTINAL

Case reports of humans and studies in laboratory animals have identified damage to the gastrointestinal system as a portal-of-entry effect of oral exposure to 1,2-dibromoethane; however, little information is available. Oral and/or pharyngeal ulceration occurred in five of six humans who ingested commercial 1,2-dibromoethane ampules (Saraswat et al. 1986). Following combined dermal and inhalation exposure of two workers, vomiting and diarrhea were observed (Letz et al. 1984). No additional information was identified regarding gastrointestinal toxicity of humans following exposure to 1,2-dibromoethane.

No acute-duration inhalation studies examining gastrointestinal endpoints in animals were identified. In laboratory animals, oral exposure, but not inhalation exposure (≤75 ppm), to 1,2-dibromoethane produced histopathological lesions of the gastrointestinal tract. Gavage exposure of rats to 80 mg/kg/day 1,2-dibromoethane for 2 weeks produced forestomach mucosal cell proliferation and hyperkeratosis; no gastrointestinal effects were observed at 40 mg/kg/day (Ghanayem et al. 1986). Hyperplasia and acanthosis of the forestomach were observed in female mice administered 107 mg/kg/day for 53 weeks, although no lesions were observed following exposure to 62 mg/kg/day (NCI 1978). In contrast, no noncancer gastrointestinal lesions were found in male rats administered 38 mg/kg/day for 49 weeks or in female rats administered 37 mg/kg/day for 61 weeks (NCI 1978). At the lowest doses tested in the NCI (1978) cancer bioassay, forestomach cancer (squamous cell carcinoma or papilloma) was observed in male rats (38 mg/kg/day for 49 weeks), female rats (37 mg/kg/day for 61 weeks), and male and female mice (62 mg/kg/day for 78 and 53 weeks, respectively); these findings are discussed in Section 2.19 (Cancer).

No non-neoplastic or neoplastic lesions of gastrointestinal tissues were observed in laboratory animals following intermediate- or chronic-duration inhalation exposure of rats or mice to 1,2-dibromoethane (NTP 1982; Wong et al. 1982); see Table 2-1 for details.

2.7 HEMATOLOGICAL

Human case studies by Letz et al. (1984), Singh et al. (2000), and Olmstead (1960) observed changes to blood parameters. Specifically, hemoglobin was depressed and white blood cell count was markedly increased. However, due to lack of pre-exposure values for these parameters, it is not possible to determine if effects are related to 1,2-dibromoethane exposure. Also, note that exposure in the Letz et al. (1984) study was to a mixture of chemicals. Prakash et al. (1999) did not observe these hematological changes. Most studies evaluating the potential hematological effects of 1,2-dibromoethane were based on assessments of histopathological examination of the spleen and/or bone marrow (NCI 1978; NTP 1982; Rowe et al. 1952; Wong et al. 1982), with few studies evaluating hematological parameters in blood (Nitschke et al. 1981; Rowe et al. 1952; Wong et al. 1982). No effects on hematological parameters in blood were observed in rats exposed to up to 40 ppm 1,2-dibromoethane for 13 weeks (Nitschke et al. 1981), 50 ppm for 91 days (Rowe et al. 1952), or 20 ppm for up to 18 months.

Results of histopathological assessments of hematological tissues are mixed. Hemosiderosis and slight congestion of the spleen were observed following acute-duration inhalation exposure to 100 ppm for 7 days (Rowe et al. 1952). Wong et al. (1982) reported splenic atrophy and hemosiderosis in rats chronically exposed to 20 ppm 1,2-dibromoethane.

Other chronic- and intermediate-duration inhalation studies conducted at higher exposures than in the Wong et al. (1982) study did not observe histopathological changes to the spleen. In the NTP (1982) chronic-duration inhalation study, the highest exposure tested was 40 ppm in rats and mice. The NTP study was of longer duration and a higher exposure concentration, yet did not result in spleen changes. See Table 2-1 for additional study details. The highest exposures evaluated in intermediate-duration studies were 75 ppm in rats and mice (NTP 1982) and 50 ppm in guinea pigs (Rowe et al. 1952).

No histopathological changes were observed after oral intermediate- or chronic-duration exposure of rats and mice to 1,2-dibromoethane (NCI 1978; Shivanandappa et al. 1987). The highest intermediate-duration oral exposure evaluated was 50 mg/kg/day in rats (Shivanandappa et al. 1987) and the highest

chronic-duration oral exposures (gavage) evaluated were 37 mg/kg/day in female rats and 107 mg/kg/day in male mice (NCI 1978). However, splenic hemosiderosis was observed in female mice exposed to 63 mg/kg/day (NCI 1978). See Table 2-2 for study details.

2.8 MUSCULOSKELETAL

Elevated serum levels of creatine phosphokinase, indicative of skeletal muscle necrosis, was observed in two workers who died following combined inhalation and dermal exposure to 1,2-dibromoethane (Letz et al. 1984). No additional information regarding musculoskeletal effects in humans was identified.

In rats and mice exposed up to 75 ppm, no histopathological lesions in musculoskeletal tissues were observed following intermediate- or chronic-duration inhalation exposure (NTP 1982) or chronic-duration oral exposure of rats and mice exposed up to 107 mg/kg/day (NCI 1978). Exposure details are provided in Tables 2-1 and 2-2.

2.9 HEPATIC

Information regarding hepatic toxicity of 1,2-dibromoethane in humans is obtained from case reports (Letz et al. 1984; Olmstead 1960; Prakash et al. 1999; Saraswat et al. 1986; Singh et al. 2000). In two workers exposed acutely by combined inhalation and dermal exposure, clinical chemistry revealed acute hepatic failure (Letz et al. 1984). Severe liver necrosis was observed in three people who died following ingestion of commercial 1,2-dibromoethane, with extensive necrosis in one individual and centrilobular hepatocellular necrosis in two individuals (Olmstead 1960; Saraswat et al. 1986). Reliable exposure estimates were not available for these reports. Acute hepatic failure was reported in a 16-year-old male who ingested approximately 6,000 mg and a 20-year-old male ingesting 6,480 mg of 1,2-dibromoethane in suicide attempts; both individuals survived (Prakash et al. 1999; Singh et al. 2000).

The liver is a target organ for toxic effects of 1,2-dibromoethane in experimental animals following inhalation and oral exposure. Acute inhalation exposure to 1,2-dibromoethane produced hepatotoxicity in rats and rabbits (Rowe et al. 1952). Exposure of rats to 100 ppm for 4 hours resulted in hepatocellular cloudy swelling, centrilobular fatty change, and patchy necrosis. Repeated inhalation exposures of rats and rabbits (7 hours/day; 9 days in rats; 4 days in rabbits) to 100 ppm 1,2-dibromoethane induced diffuse hepatocellular cloudy swelling in rats and centrilobular hepatocellular fatty change and necrosis in rabbits (Rowe et al. 1952). In rats, a single oral exposure to 107 mg/kg 1,2-dibromoethane produced hepatocellular degeneration (Botti et al. 1986). A single gavage dose of 110 mg/kg 1,2-dibromoethane to

rats caused centrilobular dilatation within 8 hours after exposure, hepatocellular degeneration within 17 hours after exposure, and frank centrilobular necrosis 22 hours after 1,2-dibromoethane exposure, although hepatocellular fatty changes in livers were not observed (Broda et al. 1976).

Results of studies investigating hepatic effects following intermediate-duration exposure to 1,2-dibromoethane are conflicting. Minimal centrilobular hepatocellular fatty degeneration was observed in guinea pigs exposed to 50 ppm for 90 days (Rowe et al. 1952). However, no histopathological lesions of the liver were observed in rats or mice exposed to 75 ppm for 13 weeks (NTP 1982) or in rabbits exposed to 50 ppm for 80 days (Rowe et al. 1952). Although Rowe et al. (1952) reported increased relative liver weights in male (11%) and female (25%) rats exposed to 50 ppm for 91 day, no liver lesions were observed; thus, the toxicological significance of the change in relative liver weight is uncertain. Peliosis hepatis (blood-filled cavities) was observed in 20% of male rats (versus 0% in control) administered 38 mg/kg/day by gavage for 49 weeks. In contrast, no liver lesions or changes to serum liver enzymes were observed following dietary exposure of rats to 50 mg/kg/day 1,2-dibromoethane for 90 days (Shivanandappa et al. 1987).

Chronic-duration inhalation and oral studies provide evidence of 1,2-dibromoethane-induced hepatotoxicity in rats (NCI 1978; NTP 1982). Increased incidences of focal and centrilobular hepatocellular necrosis were observed in male and female rats exposed to 40 ppm of 1,2-dibromoethane for 89–104 weeks (NTP 1982). Under these same exposure conditions, no hepatic toxicity was observed in male or female mice (NTP 1982), and no hepatic lesions occurred in rats exposed to 20 ppm for up to 18 months (Wong et al. 1982). The incidence of liver inflammation was increased in male mice administered oral 1,2-dibromoethane at a dose of 62 mg/kg/day for 53 weeks, compared to controls, although female rats had no inflammation following exposure to 37 mg/kg/day for 61 weeks (NCI 1978).

2.10 RENAL

Although there are epidemiological studies with inhalation as the primary exposure route (Ratcliffe et al. 1987; Schrader et al. 1988; Wong et al. 1979), none of the studies were for acute exposure and they did not assess renal endpoints. Renal effects were apparent in two workers (Letz et al. 1984); however, 1,2-dibromoethane was not the only chemical exposure for these individuals. For these reasons, we cannot be certain that inhaled 1,2-dibromoethane, alone, causes renal effects. However, information from case reports indicates that acute oral exposure of humans to 1,2-dibromoethane produces renal toxicity. Examination of kidneys of individuals who died following ingestion of 1,2-dibromoethane showed severe

renal damage, including proximal convoluted tubular cytoplasmic vacuolization and proteinaceous casts in tubules near the corticomedullary junction (Olmstead 1960; Prakash et al. 1999; Saraswat et al. 1986).

In a case of nonfatal ingestion of 6,450 mg 1,2-dibromoethane by a 20-year-old male in a suicide attempt, urinalysis showed albuminuria and urinary erythrocytes, and the patient developed anuria. Renal function returned to normal within 4 weeks (Prakash et al. 1999). Acute renal failure was reported in a 16-year-old male who ingested approximately 6,000 mg in a suicide attempt; the individual survived (Singh et al. 2000).

Renal effects have been reported in laboratory animals. Slight renal congestion, edema, and cloudy swelling of tubular epithelium (mild and nonspecific lesions) occurred in rats and rabbits following a single inhalation exposure; however, specific information regarding exposure concentrations and durations associated with renal effects was not reported (Rowe et al. 1952). No increase in blood urea nitrogen (BUN) levels was observed in either species, suggesting that renal function was not compromised, though no information on other renal markers was reported. Cell proliferation, predominantly in the proximal tubules, occurred in rats following a single oral dose of 100 mg/kg 1,2-dibromoethane in corn oil. Mitotic activity peaked at 30 hours. Lack of any histologic evidence of tubular necrosis between 8 and 48 hours after treatment indicates that such proliferation was not a regenerative response (Ledda-Columbano et al. 1987b).

For intermediate-duration exposure of laboratory animals, inconsistent results have been reported regarding renal toxicity. Renal congestion, edema, and tubular epithelial degeneration were observed in guinea pigs repeatedly exposed to 50 ppm 1,2-dibromoethane over 80 days; however, no renal damage was observed in rats exposed to 100 ppm 1,2-dibromoethane under similar conditions for 91 days (Rowe et al. 1952). No alterations in urinalysis parameters or histopathological changes to the kidney were observed in rats exposed to 40 ppm for 13 weeks (Nitschke et al. 1981), or rats or mice exposed by inhalation to up to 75 ppm of 1,2-dibromoethane for 13 weeks (NTP 1982). Although relative kidney weight was increased in male (26%) and female (24%) rats exposed to 50 ppm 1,2-dibromoethane for 91 days, the toxicological significance of this finding is uncertain due to lack of abnormal renal histopathology (Rowe et al. 1952). No histopathological lesions of the kidney were observed in rats exposed to up to 50 mg/kg/day of 1,2-dibromoethane in feed for 90 days (Shivanandappa et al. 1987) or in male rats exposed to 38 mg/kg/day by gavage for 47 weeks (NCI 1978).

The NTP (1982) chronic-duration inhalation study observed renal damage (toxic nephropathy; not otherwise characterized) in male rats following exposure to 40 ppm 1,2-dibromoethane. No exposure-related renal lesions were observed in mice at concentrations up to 40 ppm, although ascending suppurative urinary tract infections in control and exposed mice may have masked renal lesions due to early mortality and/or pyelonephritis (NTP 1982). No renal toxicity was observed in rats exposed to 20 ppm for up to 18 months (Wong et al. 1982). Chronic-duration oral (gavage) exposure to 1,2-dibromoethane did not produce renal lesions in female rats (37 mg/kg/day for 61 weeks), or mice (107 mg/kg/day for 78 weeks) (NCI 1978).

2.11 DERMAL

1,2-Dibromoethane produces damage to the skin following dermal exposure, although little information is available. Erythema and blisters developed on the trunk and legs of a worker within 24 hours of exposure to residues of 1,2-dibromoethane in a pesticide tank; the study authors considered effects to be due to dermal, rather than inhalation, exposure (Letz et al. 1984). Skin damage occurred in volunteers dermally exposed to 0.5 mL 1,2-dibromoethane (purity not specified) under various conditions (Pflesser 1938). A 1-minute exposure, followed by washing, produced edema, erythema, and itchiness, which resolved after 2–3 days. A 10-minute occluded exposure, followed by washing, produced a burning sensation, painful erythema, and swelling; effects resolved within 3–5 days, in some cases following treatment with zinc-sulfate. A 30-minute occluded exposure, following by washing, caused painful inflammation, edema, and blistering 15–20 hours after exposure.

No dermal effects were observed in rats or mice expose to 75 ppm for 13 weeks or 40 ppm for ≥89 weeks (NTP 1982). Intermediate- and chronic-duration inhalation exposure of rats and mice did not produce adverse dermal effects based on histopathological examination of skin (NTP 1982); study details are provided in Table 2-1.

Studies in laboratory animals show that oral and dermal exposure can produce damage to the skin. Gavage exposure of male and female mice to 62 mg/kg/day for 53 weeks resulted in alopecia and skin sores (NCI 1978). No dermal effects were observed in male rats administered 38 mg/kg/day for 47 weeks or in female rats administered 37 mg/kg/day for 61 weeks (NCI 1978). A single 24-hour dermal exposure of rabbits to 210 mg/kg produced erythema and necrosis of the skin (Rowe et al. 1952). Rowe et al. (1952) also reported that dermal exposure of rabbits to a 10% solution of 1,2-dibromoethane in butyl carbitol acetate (amount applied was not reported) under occlusive conditions produced moderate to

severe cutaneous erythema, edema, and necrosis with sloughing (Rowe et al. 1952). When exposure was uncovered, slight erythema, but no additional damage, occurred.

2.12 OCULAR

No literature was located regarding ocular effects in humans as a result of 1,2-dibromoethane exposure. In mice exposed to airborne 1,2-dibromoethane for 13 weeks, eye irritation was observed at an exposure concentration of 75 ppm (NTP 1982). The study report did not note the presence or absence of eye irritation in rats exposed under the same conditions (NTP 1982). In the chronic-duration exposure portion of the NTP (1982) inhalation study, the incidence of retinal atrophy in female rats exposed to 10 ppm was increased compared to control (control: 0/50; 10 ppm: 10/50); however, the incidence was not increased in the 40 ppm group (5/50), compared to control. No ocular effects were observed in male rats or male or female mice exposed to 10 and 40 ppm 1,2-dibromoethane (NTP 1982). Chronic-duration oral exposure of rats and mice to 1,2-dibromoethane did not produce histopathological lesions of ocular tissues (NCI 1978). Additional details for these studies are provided in Tables 2-1 and 2-2.

Undiluted 1,2-dibromoethane applied topically to rabbit eyes caused pain, conjunctival irritation, and superficial corneal necrosis. A 10% solution of 1,2-dibromoethane in propylene glycol applied topically produced more ocular damage to rabbit eyes than undiluted 1,2-dibromoethane. Conjunctival irritation and corneal damage were more pronounced and persistent. Healing was complete 2 and 12 days after exposure to the undiluted 1,2-dibromoethane and the 10% solution, respectively (Rowe et al. 1952).

2.13 ENDOCRINE

No literature was found that indicates endocrine effects in humans exposed to 1,2-dibromoethane. Exposure of laboratory animals to 1,2-dibromoethane has been shown to produce adverse effects to the thyroid and adrenal gland; however, mixed results have been observed.

Decreased thyroid follicular size was observed in rats and mice exposed to 75 ppm 1,2-dibromoethane for 13 weeks; however, chronic-duration inhalation exposure of rats and mice to a lower exposure level (40 ppm) did not produce thyroid toxicity based on histopathological examinations (NTP 1982). No thyroid lesions were observed in mice exposed to 20 ppm for up to 18 months (Wong et al. 1982).

Toxicity to the adrenal gland has been observed following intermediate- and chronic-duration inhalation exposure and chronic-duration oral exposure. Adrenal lesions, consisting of swelling and/or cytoplasmic

vacuolization of cells in the zona fasciculata of the cortex, occurred in rats exposed by inhalation to 75 ppm 1,2-dibromoethane for 13 weeks (NTP 1982). No adrenal toxicity was observed in mice under the same exposure conditions (NTP 1982). Similarly, chronic-duration inhalation exposure of rats, but not mice, to 40 ppm 1,2-dibromoethane produced degeneration of the adrenal cortex (NTP 1982). However, rats exposed to 20 ppm for up to 18 months showed no histopathological effects (Wong et al. 1982).

Degeneration of the adrenal cortex occurred in male rats following oral (gavage) exposure to 38 mg/kg/day for 47 weeks (NCI 1978), although no lesions of the adrenal cortex were observed following oral (diet) exposure rats at doses up to 50 mg/kg/day for 90 days (Shivanandappa et al. 1987). Degeneration of the adrenal cortex was also observed following chronic-duration oral exposure of female rats (37 mg/kg/day for 61 weeks) and male and female mice (107 mg/kg/day for 53 weeks) (NCI 1978).

2.14 IMMUNOLOGICAL

No studies were located concerning human immunological effects from 1,2-dibromoethane exposure. The immune system does not appear to be a target for toxicity of 1,2-dibromoethane, based on histopathological assessments of immune tissues (primarily lymph nodes) in laboratory animals. However, no studies evaluating the potential effects of 1,2-dibromoethane exposure on immune function were identified. No lesions of immune tissues were observed following intermediate-duration inhalation exposure of rats, mice, and guinea pigs (NTP 1982; Rowe et al. 1952), chronic-duration inhalation exposure of rats and mice (NTP 1982), intermediate-duration oral exposure of rats (NCI 1978), or chronic-duration oral exposure of rats and mice (NCI 1978). Study details are provided in Tables 2-1 and 2-2.

2.15 NEUROLOGICAL

Little information is available regarding neurological effects of 1,2-dibromoethane in humans or laboratory animals. A case report of accidental combined inhalation and dermal exposure of workers noted signs of neurotoxicity, including depression, lethargy, and confused, combative, and incoherent behavior; workers became semicomatose (Letz et al. 1984). Neurotoxicity was also observed in humans following ingestion of 1,2-dibromoethane (Saraswat et al. 1986). Of the surviving four patients, three had symptoms of confusion upon admission, although they were conscious. One of the patients who became comatose and died after ingestion of 1,2-dibromoethane had nonspecific brain lesions (meningeal congestion and interstitial cortical edema). No exposure estimates are available from these studies.

In laboratory animals, Rowe et al. (1952) reported "depression of the central nervous system" following acute inhalation exposure, although a description of the signs of depression, incidence, species, and exposure concentrations were not specified. Studies conducting histopathological assessments of brain tissues did not reveal lesions following intermediate-duration inhalation exposure of rats and mice to 75 ppm (NTP 1982); chronic-duration inhalation exposure of rats and mice to 40 ppm (NTP 1982); intermediate-duration oral (diet) exposure of rats to 50 mg/kg/day for 90 days (Shivanandappa et al. 1987) or male rats to 38 mg/kg/day for 47 weeks (NCI 1978); or chronic-duration oral (gavage) exposure of female rats to 37 mg/kg/day (61 weeks) or mice to 107 mg/kg/day (53 weeks) (NCI 1978).

2.16 REPRODUCTIVE

Male Reproductive System. Studies of 1,2-dibromoethane in workers and animals provide evidence of effects on the male reproductive system, including damage to sperm and male reproductive organs and infertility, following inhalation and oral exposure.

Studies in workers have examined effects of inhalation exposure to 1,2-dibromoethane on sperm and fertility (Ratcliffe et al. 1987; Schrader et al. 1988; Ter Haar 1980; Wong et al. 1979). A cross-sectional study in fruit fumigation workers (n=46) in Hawaii examined the effects of inhalation exposure to 0.088 ppm (time-weighted average) 1,2-dibromoethane for an average exposure duration of 5 years (Ratcliffe et al. 1987; Schrader et al. 1988). Schrader et al. (1988) noted that "moderate" dermal exposure also occurred in workers, although this was not quantified. It appears that the only chemical exposure was to 1,2-dibromoethane, however, the study report did not specifically state this. Compared to controls (n=43), significant ($p<0.01$) decreases in sperm count (42% decrease) and the percentages of viable (11% decrease) and motile (24% decrease) sperm, and increases in abnormal sperm (tapered heads [69% increase], absent heads [45% increase], abnormal tails [14% increase]) were observed.

Ter Haar (1980) examined the relationship between sperm count and 1,2-dibromoethane exposure of 59 men employed at a production plant for antiknock compounds in Arkansas. The group was divided into two 1,2-dibromoethane exposure groups: low exposure (<0.5 ppm; n=40) and high exposure (0.5–5 ppm; n=19). In the high exposure group, 42% of workers had sperm counts below 40 million, compared to 20% of workers in the low exposure group. However, no control group was included and no information regarding adjustment for potential confounding factors was reported. No reduction in fertility was found in a retrospective study of 1,2-dibromoethane male manufacturing workers (n=297 couples); exposures

ranged from <0.5 to 5.0 ppm (Wong et al. 1979). The study did not account for potential confounding factors or include a matched control group. No studies on reproductive effects following oral exposure of humans were located.

Studies examining the effects of 1,2-dibromoethane exposure on the male reproductive system in laboratory animals provide mixed results. Adverse male reproductive effects have been reported in laboratory animals following intermediate- and chronic-duration inhalation and oral exposure to 1,2-dibromoethane (NCI 1978; NTP 1982; Short et al. 1979). However, other studies found no adverse effects in male reproductive tissues (Nitschke et al. 1981; NTP 1982; Rowe et al. 1952; Shivanandappa et al. 1987; Wong et al. 1982).

Atrophy of the testis, epididymis, prostate, and seminal vesicles; complete infertility; and decreased serum testosterone (54% lower than control) were observed following inhalation exposure of rats exposed to 89 ppm for 10 weeks (Short et al. 1979). Testicular degeneration and testicular atrophy occurred in rats exposed to 10 ppm 1,2-dibromoethane for up to 104 or 106 weeks; these effects were observed in conjunction with spontaneous interstitial cell tumors and mesotheliomas of the epididymis and tunica vaginalis (NTP 1982). Note that in both studies, high morbidity and mortality also were observed at these exposure concentrations. Testicular atrophy was observed in the NCI (1978) cancer bioassay in rats and mice administered 38 mg/kg/day for 47 weeks and 107 mg/kg/day for 53 weeks, respectively.

In contrast, no effects on fertility, spermatogenesis, healthy sperm, or lesions of male reproductive tissues were observed in rats exposed to oral (diet) 1,2-dibromoethane at doses up to 50 mg/kg/day for 90 days (Shivanandappa et al. 1987). No lesions of male reproductive tissues were observed in rats exposed to inhaled 1,2-dibromoethane at 40 ppm for 13 weeks (Nitschke et al. 1981), rats or mice exposed to 75 ppm for 13 weeks (NTP 1982), guinea pigs exposed to 50 ppm for 80 days (Rowe et al. 1952), or rats exposed to 20 ppm for up to 18 months (Wong et al. 1982).

The mechanism of action for the antispermatogenic effects of 1,2-dibromoethane may be related to covalent binding of metabolites of 1,2-dibromoethane with thiol groups of nucleoproteins in nuclei of spermatozoa. Such adduct formation interferes with DNA, causing improper packing of the chromatin (Amir and Lavon 1976; Amir et al. 1977).

Female Reproductive System. Little information on the potential for 1,2-dibromoethane to produce adverse effects on the female reproductive system is available. Diestrus occurred during exposure of

female rats exposed to 80 ppm for 3 weeks; the normal estrus cycle resumed 3–4 days following cessation of exposure (Short et al. 1979). No effects on total implants, viable implants, or resorptions per dam were observed when female rats in this exposure group were mated with unexposed males. Histopathological examination of female reproductive organs revealed mild vacuolated degeneration of the uterine epithelium with and without necrosis in the 80 ppm group, with no effects at ≤39 ppm. No lesions of female reproductive tissues (i.e., uterus, ovaries, cervix) were observed in rats or mice exposed in intermediate- and chronic-duration inhalation studies (NTP 1982; Wong et al. 1982) or chronic-duration oral exposure studies (NCI 1978). See Tables 2-1 and 2-2 for study details.

2.17 DEVELOPMENTAL

The only information on developmental effects of 1,2-dibromoethane is from a single study in rats and mice exposed by inhalation during gestation (Short et al. 1978). Exposures were for 23 hours/day on gestational days 6–15. In rats and mice, incomplete ossification of the skeleton was observed in fetuses of dams exposed to ≥20 ppm. No soft tissue anomalies were observed. Fetal weight was decreased in dams exposed to 38 ppm for rats and 20 ppm for mice. In both species, maternal toxicity, as indicated by weight loss and reduction in food intake, was observed at concentrations ≥20 ppm.

2.18 OTHER NONCANCER

No other noncancer effects of 1,2-dibromoethane were identified.

2.19 CANCER

Studies examining cancer mortality of 1,2-dibromoethane manufacturing workers are limited by lack of exposure estimates, adjustments for confounding factors (e.g., smoking, co-exposure to other chemicals), lack of matched control groups, and incomplete data reporting (Ott et al. 1980; Turner and Barry 1979). Ott et al. (1980) studied cancer mortality in 161 male employees in two manufacturing plants located in Texas and Michigan. Because the Texas and Michigan plants ceased operations in 1969 and 1976, respectively, assessments were based on existing records and discussions with workers formerly associated with the plants. Exposure estimates were not available for the facility in Texas. For the Michigan facility, exposures ranged from 0 to 100 ppm, based on personal air monitors. There was an increase in mortality due to cancer among employees with >6 years of exposure to 1,2-dibromoethane in both plants (observed: 5 deaths; expected: 2.2 deaths; $p<0.072$; 95% CI not reported). Turner and Barry (1979) conducted a survey study examining cancer mortality in 351 workers in two 1,2-dibromoethane

manufacturing plants in Great Britain. No increase in mortality from any cause, including cancer, was observed. However, the study did not include a matched-control group or account for confounding factors.

A study of 2,510 male workers at a tetraethyl lead manufacturing plant investigated cause of death, including cancer (Sweeney et al. 1986). Workers were employed for at least 1 day during the time period 1952–1977 (mean employment duration not reported), and were exposed to several chemicals, including ethylene dibromide, ethylene dichloride, chloroethane, ethylene, and inorganic lead. However, no exposure estimates for any one chemical, including 1,2-dibromoethane, were reported. Standard mortality ratios were calculated based on exposure to all substances. This study has several limitations, including small sample size, no control group, exposure to other carcinogens, no exposure levels, and lack of consideration of confounders, including smoking and alcohol use; thus, results of this study are inconclusive.

Several studies have investigated the potential for 1,2-dibromoethane to induce cancer in laboratory animals (Adkins et al. 1986; NCI 1978; NTP 1982; van Duuren et al. 1979, 1985, 1986; Wong et al. 1982). In addition to cancers occurring in portal-of-entry tissues (e.g., respiratory and gastrointestinal), neoplasms have been observed in several tissue types. Results of these studies are summarized in Table 2-4.

Table 2-4. Summary of Neoplasms in Rats and Mice Exposed to 1,2-Dibromoethane by Inhalation or Oral Exposure[a]

Reference	Species/sex	Exposure[b]	Effect
Inhalation exposure			
Adkins et al. 1986	Mouse/M+F	20 ppm (6 months)	Pulmonary adenoma[c]
		50 ppm (6 months)	Pulmonary adenoma[c]
NTP 1982	Rat/M	10 ppm	Nasal cavity: adenomas and carcinomas
			Reproductive system: mesothelioma of the tunica vaginalis
		40 ppm	Nasal cavity: adenomas and carcinomas
			Reproductive system: mesothelioma of the tunica vaginalis
			Spleen: hemangiosarcoma
	Rat/F	10 ppm	Nasal cavity: adenomas and carcinomas
			Pituitary: adenoma
			Mammary gland: fibroadenoma
		40 ppm	Nasal cavity: adenomas and carcinomas

Table 2-4. Summary of Neoplasms in Rats and Mice Exposed to 1,2-Dibromoethane by Inhalation or Oral Exposure[a]

Reference	Species/sex	Exposure[b]	Effect
			Lung: alveolar/bronchiolar carcinoma or adenoma
			Mammary gland: fibroadenoma
			Circulatory system (spleen): hemangiosarcoma
	Mouse/M	40 ppm	Lung: alveolar/bronchiolar carcinoma or adenoma
	Mouse/F	10 ppm	Subcutaneous tissue: fibrosarcoma
			Lung: alveolar/bronchiolar carcinoma or adenoma
			Spleen: hemangioma or hemangiosarcoma
			Mammary gland: adenocarcinoma
		40 ppm	Subcutaneous tissue: fibrosarcoma
			Nasal cavity: adenomas and carcinomas
			Lung: alveolar/bronchiolar carcinoma or adenoma
			Hematopoietic system: lymphomas
			Mammary gland: adenocarcinoma
Wong et al. 1982	Rats/M	20 ppm[d]	Spleen: hemangiosarcoma
			Adrenal gland: adenoma or carcinoma
			Subcutaneous tissue: mesenchymal tumor
	Rat/F	20 ppm[d]	Spleen: hemangiosarcoma
			Adrenal gland: adenoma or carcinoma
			Mammary gland: adenocarcinoma or carcinoma
Oral exposure			
NCI 1978	Rats/M	38 mg/kg/day (G) (49 weeks)	Stomach (not specified): squamous cell carcinoma
			Cardiovascular system: Hemangiosarcoma
	Rats/F	37 mg/kg/day (G)	Stomach: squamous cell carcinoma
	Mouse/M	62 mg/kg/day (G)	Stomach: squamous cell carcinoma or papilloma
		107 mg/kg/day (G)	Stomach: squamous cell carcinoma or papilloma
			Lung: alveolar or bronchiolar adenoma
	Mouse/F	62 mg/kg/day (G)	Stomach: squamous cell carcinoma
			Lung: alveolar or bronchiolar adenoma or carcinoma
			Hematopoietic system: lymphoma
		107 mg/kg/day (G)	Stomach: squamous cell carcinoma
			Lung: alveolar or bronchiolar adenoma or carcinoma
Van Duuren et al. 1985	Mouse/M	116 mg/kg/day[d] (DW)	Forestomach: squamous cell carcinoma or papilloma
			Glandular stomach: squamous cell carcinoma
			Liver: squamous cell carcinoma
	Mouse/F	103 mg/kg/day[d] (DW)	Forestomach: squamous cell carcinoma or papilloma
			Esophagus: squamous papilloma
			Liver: squamous cell carcinoma

Table 2-4. Summary of Neoplasms in Rats and Mice Exposed to 1,2-Dibromoethane by Inhalation or Oral Exposure[a]

Reference	Species/sex	Exposure[b]	Effect
Van Duuren et al. 1986	Mouse/M	43 mg/kg/day[d] (DW)	Forestomach: squamous cell carcinoma
			Esophagus: papilloma or carcinoma
	Mouse/F	52 mg/kg/day[d] (DW)	Forestomach: squamous cell carcinoma or papilloma
			Esophagus: papilloma or carcinoma
Stoner et al. 1986	Mouse/M, F	840 mg/kg/day (G) (24 weeks)	No increase in lung tumors
Dermal exposure			
Van Duuren et al. 1979	Mouse/F	71 mg/kg/day[e]	Lung: papillary adenoma
		143 mg/kg/day[e]	Skin: papilloma
			Lung: papillary adenoma
		214 mg/kg/day[e]	Lung: papillary adenoma

[a]Tumor incidence significantly increased compared to matched control groups.
[b]Unless otherwise indicated, all exposures were >1 year.
[c]Animals were not examined for tumors other than of the pulmonary system.
[d]Only one concentration or dose tested.
[e]Applied to shaved skin 3 times/week for 14–15 months. Doses applied were 25, 50, and 75 mg/animal. Doses in terms of mg/kg/day were calculated for this report using a default chronic body weight of 0.35 kg for female B6C3F1 mice (EPA 1988).

DW = administered in drinking water; F = female(s); G = administered by gavage; M = male(s)

Studies examining effects of inhalation exposure show the development of tumors in the nasal cavity of rats and pulmonary tissues in rats and mice (Adkins et al. 1986; NTP 1982). In addition, inhalation of 1,2-dibromoethane produced tumors of the spleen, hematopoietic system, pituitary, adrenal gland, subcutaneous tissues, male reproductive system, and mammary gland (NTP 1982; Wong et al. 1982). The lowest exposure level tested (10 ppm, 6 hours/day, 5 days/week) produced neoplasms of the nasal cavity (male and female rats), lung (female mice), pituitary (female rats), subcutaneous tissue (female mice), spleen (female mice), male reproductive system (rats), and mammary gland (female rats) (NTP 1982). In male and female mice exposed to inhaled 1,2-dibromoethane at an exposure of 20 ppm (6 hours/day, 5 days/week for 6 months), pulmonary adenomas were observed; however, other tissues were not examined (Adkins et al. 1986).

Chronic oral exposure to 1,2-dibromoethane by gavage or drinking water show the development of tumors of the stomach, esophagus, liver, lung, cardiovascular system, and hematopoietic system (NCI 1978; van Durren 1985, 1986). The lowest doses tested (38 mg/kg/day in male rats and 37 mg/kg/day in female rats) produced tumors of the forestomach (squamous cell carcinoma) in male and female rats and hemangiosarcomas of the circulatory system in male rats (NCI 1978). Studies also have examined the

carcinogenic potential of 1,2-dibromoethane using the rat liver foci assay (Ledda-Colwnbano et al. 1987a; Milks et al. 1982; Moslen 1984). These oral exposure (drinking water and gavage) studies show that 1,2-dibromoethane has both initiating and promoting activity, which correlates with carcinogenic effects observed in laboratory animals.

Stoner et al. (1986) did not find an increase in the incidence of lung cancer following oral administration of 840 mg/kg/day to male and female mice for 24 weeks. In this study, the percentage mice in the untreated control and vehicle (tricaprylin) control groups with lung cancer was high: untreated control males, 38%; untreated control females, 25%; vehicle control males, 20%; and vehicle control females, 14%. In male and female mice treated with 1,2-dibromoethane, the percentage of mice with lung tumors was 44 and 31%, respectively; these increases were not statistically significant compared to control. In female mice administered 840 mg/kg/day by intraperitoneal (i.p.) injection, a statistically significant ($p<0.001$) increase in the percentage of mice with lung tumors was observed, relative to the i.p. control group (control i.p., 15%; 1,2-dibromoethane i.p., 88%). However, no statistically significant difference was observed for male mice (control i.p., 25%; 1,2-dibromoethane i.p., 44%). The power to detect differences between treatment and control groups in this study is limited due to the small numbers of mice tested in each group (16 males, 16 females).

Dermal exposure of female mice to 1,2-dibromoethane (three applications per week for 14–15 months) induced skin papillomas (143 mg/kg/day) and papillary adenomas of the lung (71 and 143 mg/kg/day) (Van Durren et al. 1979).

The Department of Health and Human Services classified 1,2-dibromoethane as “reasonably anticipated to be a human carcinogen” based on sufficient evidence of carcinogenicity from studies in laboratory animals (NTP 2016). EPA (2004) concluded that 1,2-dibromoethane is “likely to be carcinogenic to humans” based on strong evidence of carcinogenicity in animals and inconclusive evidence in humans. IARC has classified 1,2-dibromoethane as “probably carcinogenic to humans” based on sufficient evidence in animals and inadequate evidence in humans (2A) (IARC 1999).

2.20 GENOTOXICITY

1,2-Dibromoethane has been tested extensively to assess its genotoxic potential in prokaryotic, eukaryotic, and mammalian systems. Tables 2-5 and 2-6 present the results of *in vivo* and *in vitro* genotoxicity studies, respectively. The results of these studies indicate that 1,2-dibromoethane is genotoxic, producing a broad spectrum effects in various test systems.

Table 2-5. Genotoxicity of 1,2-Dibromoethane *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Mammalian systems			
Human (occupational)	Sister chromatid exchange	–	Steenland et al. 1985, 1986
Rat (oral)	Gene mutation (dominant lethal)	–	Teramoto et al. 1980
Rat (intraperitoneal)	Gene mutation (urine extracts)	–	Novotná and Duverger-van Bogaert 1994
Rat (intraperitoneal)	DNA adducts	+	Kim and Guengerich 1990
Rat (intraperitoneal)	DNA adducts	+	Watanabe et al. 2007
Rat (gavage)	Unscheduled DNA synthesis	+	Coni et al. 1992
Rat (intraperitoneal)	Unscheduled DNA synthesis	–	Bentley and Working 1988
Rat (inhalation)	Dominant lethal effect	–	Short et al. 1979
Mouse (inhalation)	Gene mutation	–	Schmezer et al. 1998
Mouse (oral)	Gene mutation (dominant lethal)	–	Epstein et al. 1972
Mouse (oral)	Gene mutation (dominant lethal)	–	Teramoto et al. 1980
Mouse (intraperitoneal)	Gene mutation (dominant lethal)	–	Barnett et al. 1992
Mouse (intraperitoneal)	Gene mutation	+	Cho and Guengerich 2013
Mouse (intraperitoneal)	Gene mutation (dominant lethal)	–	Epstein et al. 1972
Mouse (intraperitoneal)	DNA adducts	+	Cho and Guengerich 2013
Mouse (intraperitoneal)	DNA adducts	+	Kim and Guengerich 1990
Mouse (intraperitoneal)	DNA adducts	+	Watanabe et al. 2007
Mouse (intraperitoneal)	DNA damage	+	Sasaki et al. 1998
Mouse (intraperitoneal)	Chromosome aberrations	–	Krishna et al. 1985
Mouse (intraperitoneal)	Sister chromatid exchange	–	Krishna et al. 1985; Tucker et al. 1993
Mouse (intraperitoneal)	Micronucleus assay	–	Krishna et al. 1985; Tucker et al. 1993
Mouse (intraperitoneal)	Micronucleus assay	–	Sasaki et al. 1998
Invertebrate systems			
Drosophila melanogaster (inhalation)	Sex-linked recessive lethal mutation	+	Ballering et al. 1993
D. melanogaster (dietary)	Sex-linked recessive lethal mutation	+	Foureman et al. 1994
D. melanogaster (inhalation)	Sex-linked recessive lethal mutation	+	Kale and Baum 1979, 1981, 1982, 1983

Table 2-5. Genotoxicity of 1,2-Dibromoethane *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
D. melanogaster (inhalation)	Sex-linked recessive lethal mutation	+	Kale and Kale 1995
D. melanogaster (inhalation)	Sex-linked recessive lethal mutation	+	Kramers et al. 1991
D. melanogaster (dietary)	Sex-linked recessive lethal mutation	+	Vogel and Chandler 1974; Vogel and Nivard 1993; NTP 1989
D. melanogaster (inhalation)	Somatic mutation and recombination (wing spot test)	+	Ballering et al. 1993
D. melanogaster (inhalation)	Somatic mutation and recombination (wing spot test)	+	Kramers et al. 1991
D. melanogaster (inhalation)	Somatic mutation and recombination (wing spot test)	+	Vogel and Nivard 1993; Vogel et al. 1996
D. melanogaster (inhalation)	Chromosome aberrations	+	Ballering et al. 1993

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

Table 2-6. Genotoxicity of 1,2-Dibromoethane *In Vitro*

		Results		
		Activation		
Species (test system)	Endpoint	With	Without	Reference
Mammalian cells				
Human (epithelial cells)	Gene mutation (forward mutation)	ND	+	Ferreri et al. 1983
Human (lymphoblasts; Tk6)	Gene mutation (forward mutation)	ND	+	Crespi et al. 1985
Human (lymphoblasts; AAH-1)	Gene mutation (forward mutation)	ND	+	Crespi et al. 1985
Human (testicular germ cells)	DNA damage (single strand breaks)	ND	+	Bjørge et al. 1996
Human (hepatocytes)	DNA adducts (DNA binding)	ND	+	Cmarik et al. 1990
Human (lymphocytes)	DNA repair	+	–	Perocco and Prodi 1981
Human (hepatocytes)	Unscheduled DNA synthesis	ND	+	Cmarik et al. 1990
Human (skin fibroblasts)	Sister chromatid exchange	ND	+	DeLeve 1997
Human (peripheral lymphocytes)	Sister chromatid exchange	+	ND	Tucker et al. 1984; Tucker et al. 1993
Human (peripheral lymphocytes)	Micronucleus assay	ND	+	Channarayappa et al. 1992
Rat (testicular germ cells)	DNA damage (single strand breaks)	ND	+	Bjørge et al. 1996

Table 2-6. Genotoxicity of 1,2-Dibromoethane *In Vitro*

Species (test system)	Endpoint	Results		Reference
		Activation		
		With	Without	
Rat (hepatocytes)	DNA damage (double strand breaks)	ND	–	Storer et al. 1996
Rat (hepatocytes)	DNA adducts (DNA binding)	ND	+	Cmarik et al. 1990
Rat (primary hepatocytes)	DNA repair	ND	+	Williams et al. 1982; Working et al. 1986
Rat (hepatocytes)	Unscheduled DNA synthesis	ND	+	Cmarik et al. 1990
Mouse (L5178Y lymphoma cells)	Gene mutation (forward mutation)	+	+	Clive et al. 1979; NTP 1989
Chinese hamster ovary (CHO) cells	Gene mutation	ND	+	Ballering et al. 1998
CHO cells	Gene mutation	ND	+	Graves et al. 1996
CHO cells	Gene mutation (forward mutation)	+	+	Tan and Hsie 1981; Brimer et al. 1982
Chinese hamster (V79 cells)	Chromosome aberrations	+	+	NTP 1989
Chinese hamster (V79 cells)	Sister chromatid exchange	+	+	Tezuka et al. 1980; Tucker et al. 1993; NTP 1989
Opossum (lymphocytes)	Unscheduled DNA synthesis	ND	+	Meneghini 1974
Prokaryotic organisms				
Salmonella typhimurium	Gene mutation	+	+	Novotná and Duverger-van Bogaert 1994
S. typhimurium	Gene mutation	+	+	Bakale and McCreary 1992
S. typhimurium	Gene mutation	ND	+	Mersch-Sundermann et al. 1994
S. typhimurium	Gene mutation	+	+	Simula et al. 1993
S. typhimurium	Gene mutation	ND	+	Thier et al. 1993
S. typhimurium	Gene mutation	ND	+	Thier et al. 1996
S. typhimurium	Gene mutation	ND	+	Watanabe et al. 1998
S. typhimurium	Gene mutation	+	+	Zeiger et al. 1992
S. typhimurium	Gene mutation	+	+	Bogen 1994
S. typhimurium	Gene mutation (vapor phase)	+	+	Kado et al. 1992
S. typhimurium	Gene mutation (reverse mutation)	ND	+	Ames and Yanofsky 1971
S. typhimurium	Gene mutation (reverse mutation)	+	+	Barber et al. 1981
S. typhimurium	Gene mutation (reverse mutation)	+	ND	Hughes et al. 1987
S. typhimurium	Gene mutation (reverse mutation)	+	ND	Kerklaan et al. 1985
S. typhimurium	Gene mutation (reverse mutation)	+	ND	McCann et al. 1975; Zoetemelk et al. 1987

Table 2-6. Genotoxicity of 1,2-Dibromoethane *In Vitro*

Species (test system)	Endpoint	Results		Reference
		Activation		
		With	Without	
S. typhimurium	Gene mutation (reverse mutation)	+	+	Stolzenberg and Hine 1980; Principe et al. 1981; NTP 1989; Moriya et al. 1983
S. typhimurium	Gene mutation (reverse mutation)	–	ND	Shiau et al. 1980
S. typhimurium	Gene mutation (reverse mutation; spot test)	+	–	Shiau et al. 1980
S. typhimurium	Gene mutation (Ara test)	+	+	Roldán-Arjona et al. 1991
S. typhimurium	DNA damage (SOS uma test)	+	+	Oda et al. 1996
Escherichia coli	Gene mutation	ND	+	Watanabe et al. 1998
E. coli	Gene mutation (reverse mutation)	ND	+	Hemminki et al. 1980
E. coli	Gene mutation (reverse mutation)	+	ND	Moriya et al. 1983
E. coli	Gene mutation (forward mutation; spot test)	ND	+	Izutani et al. 1980
E. coli	DNA damage (SOS chromotest)	ND	–	Mersch-Sundermann et al. 1994
E. coli	DNA damage (SOS chromotest)	ND	+	Venkat et al. 1995
E. coli	DNA damage (spot test)	ND	+	Rosenkranz 1977; Brem et al. 1974a
Bacillus subtilis	Gene mutation (forward mutation; spot test)	+	–	Shiau et al. 1980
B. subtilis	DNA damage (spot test)	ND	–	Shiau et al. 1980
Aspergillus nidulans	Gene mutation (forward mutation)	ND	+	Principe et al. 1981
A. nidulans	Gene mutation (forward mutation, spot test)	ND	+	Principe et al. 1981
Serratia marcescens (strain a21)	Gene mutation (reverse mutation; host mediated)	–	ND	Buselmaier et al. 1972, 1976
Streptomyces coelicolor	Gene mutation (forward mutation)	ND	–	Principe et al. 1981
S. coelicolor	Gene mutation (forward mutation, spot test)	ND	+	Principe et al. 1981
Neurospora crassa	Gene mutation (recessive lethal)	ND	+	Malling 1969

– = negative result; + = positive result; Ara^r = L-arabinose resistance; DNA = deoxyribonucleic acid; ND = not determined

Occupational Exposure of Humans. The incidence of sister chromatid exchange and chromosomal aberrations in lymphocytes from workers occupationally exposed to 1,2-dibromoethane was investigated by Steenland et al. (1985, 1986). In a study conducted on workers involved in spraying 1,2-dibromo-ethane on fallen pine trees, the estimated average exposure level of 1,2-dibromoethane was 0.06 ppm

(Steenland et al. 1985). The rates of sister chromatid exchange measured *in vitro* in lymphocytes obtained from these workers soon after 1,2-dibromoethane exposure were not higher than those observed in lymphocytes taken from the same individuals before the exposures. In a subsequent study by Steenland et al. (1986), lymphocytes were taken from 60 workers in a papaya processing plant where 1,2-dibromoethane was used to fumigate fruit. The estimated average exposure level was 0.088 ppm 1,2-dibromoethane for an average of 5 years. This study did not detect an increase in the rate of sister chromatid exchange or the frequency of chromosomal aberrations in lymphocytes obtained from these workers.

In Vivo Exposure of Laboratory Animals. Results of *in vivo* studies in rats and mice show that 1,2-dibromoethane induces DNA adduct formation (Cho and Guengerich 2013; Kim and Guengerich 1990; Watanabe et al. 2007) and DNA damage (Sasaki et al. 1998). However, as shown in Table 2-5, results of studies on gene mutation are predominantly negative. Although Cho and Guengerich (2013) reported gene mutation in mice following intraperitoneal exposure to 1,2-dibromoethane, several other studies did not observe gene mutations (Epstein et al. 1972; Novotná and Duverger-van Bogaert 1994; Schmezer et al. 1998; Teramoto et al. 1980). Results of studies on unscheduled DNA synthesis are mixed; unscheduled DNA synthesis was observed in rats following gavage exposure (Coni et al. 1992), but not following intraperitoneal exposure (Bentley and Working 1988). *In vivo* exposure did not produce sister chromatid exchange in mice (Krishna et al. 1985; Tucker et al. 1993) or micronucleus formation in mice (Krishna et al. 1985; Sasaki et al. 1998; Tucker et al. 1993). In *Drosophila melanogaster*, sex-linked recessive lethal mutation (Kale and Baum 1979, 1981, 1982, 1983; Kale and Kale 1995; Kramers et al. 1991; NTP 1989; Vogel and Chandler 1974; 1993), somatic mutation and recombination (Ballering et al. 1993; Kramers et al. 1991; Vogel and Nivard 1993; Vogel et al. 1996) and chromosome aberrations (Ballering et al. 1993) have been observed. 1,2-Dibromoethane did not induce dominant-lethal mutations in rats exposed by inhalation to 1,2-dibromoethane vapor at exposure levels as high as 39 ppm (Short et al. 1979).

In Vitro Exposure. Numerous studies have investigated the genotoxic effects of *in vitro* exposure to 1,2-dibromoethane. Results provide substantial evidence demonstrating that 1,2-dibromoethane is genotoxic. As shown in Table 2-6, in mammalian systems, 1,2-dibromoethane induced gene mutation (Ballering et al. 1998; Brimer et al. 1982; Clive et al. 1979; Crespi et al. 1985; Ferreri et al. 1983; Graves et al. 1996; NTP 1989; Tan and Hsie 1981), DNA damage (Bjørge et al. 1996), DNA adduct formation (Cmarik et al. 1990), DNA repair (Perocco and Prodi 1981; Williams et al. 1982; Working et al. 1986), unscheduled DNA synthesis (Cmarik et al. 1990; Meneghini 1974), chromosome aberrations (NTP 1989),

sister chromatid exchange (DeLeve 1997; Tucker et al. 1984, 1993), and micronucleus formation (Channarayappa et al. 1992). Only one study (Storer et al. 1996) reported negative results for DNA damage. In bacterial and fungal systems, study results are overwhelmingly positive for gene mutation, DNA damage, DNA adducts, unscheduled DNA synthesis, chromosome aberrations, sister chromatid exchange, and micronucleus formation; see Table 2-6 for additional details.

Mechanisms of Genotoxicity. Several researchers have conducted studies on or reviewed the mechanism of genotoxicity of 1,2-dibromoethane (Cho and Guengerich 2013; Cmarik et al. 1990; DeLeve 1997; Guengerich 1994, 2005; Hissink et al. 2000; Humphreys et al. 1990; Liu et al. 2000, 2002, 2004, 2007; Ross and Pegram et al. 2003; Thier et al. 1996; Van Welie et al. 1992). Information reviewed in the following discussion is taken from these publications.

1,2-Dibromoethane is activated to a genotoxic compound through combination with glutathione (GSH) or O6-alkylguanine-DNA alkyltransferase (AGT). The major mechanistic pathway for the genotoxicity of 1,2-dibromoethane is through glutathione *S*-transferase (GST) mediated metabolism. Conjugation of 1,2-dibromoethane GSH forms *S*-(2-bromoethyl)GSH, which reacts intramolecularly to form an episulfonium ion. The episulfonium ion is a strong electrophile that covalently binds strong nucleophiles, such as the nucleoside bases of DNA, to form guanyl adducts. Although several DNA adducts have been identified, *S*-(2-bromoethyl)GSH is the major DNA adduct detected in *in vivo* and *in vitro* studies. The *S*-(2-bromoethyl)GSH adduct blocks DNA polymerase activity, leading to guanine:cytosine to adenine:thymine transition mutations.

Evidence that the GST pathways can contribute to genotoxicity in human tissues comes from studies conducted in human tissues. Genotoxicity in cultured human fibroblasts (sister chromatid exchanges) was lower in fibroblasts cultured from individuals who had a hereditary deficiency in GST, suggesting that lower intracellular GSH levels protected the cells from genotoxic effects of 1,2-dibromoethane (DeLeve 1997). Depletion of GSH in isolated human hepatocytes with diethylmaleate decreased the formation of 1,2-dibromoethane DNA adducts and rate of unscheduled DNA synthesis cells exposed to 1,2-dibromo-ethane (Cmarike et al. 1990). Evidence from animal bioassays supports the hypothesis that the GST pathway is responsible for the mutagenicity and carcinogenicity of 1,2-dibromoethane. Cho and Guengerich (2013) found that depletion of GSH by treatment with butathione sulfoxamine (BSO) decreased the formation of 1,2-dibromoethane-GSH N7guanyl DNA adducts and cII gene mutation frequency in Big Blue mice that received an intraperitoneal dose of 1,2-dibromoethane (30 mg/kg).

In the long-term drinking water study of Van Duuren et al. (1985), mice were administered equimolar concentrations of 1,2-dibromoethane, bromoethanol, and bromoacetaldehyde. Bromoethanol and bromoacetaldehyde, which are cytochrome P450 (CYP450) metabolites of 1,2-dibromoethane, were far less potent carcinogens than 1,2-dibromoethane. The cytosol-induced binding to isolated DNA was 5–10 times greater than that found in microsomal oxidation in isolated rat hepatocytes. The preferential binding of 1,2-dibromoethane metabolites to DNA in tissues of the forestomach, nasal mucosa, oral epithelium, and testis of mice and rats demonstrates the ability of these tissues to metabolize 1,2-dibromoethane by conjugation with glutathione (Brittebo 1997; Kowalski et al. 1985a; Sipes et al. 1986a; Wiersma and Sipes 1983).

A second, more minor conjugation mechanism contributing to the genotoxicity of 1,2-dibromoethane involves the DNA repair protein, AGT. AGT repairs DNA adducts by binding to DNA, causing the transfer of the alkyl group from the O6 position of guanine adducts to a cysteine residue on the protein. 1,2-Dibromoethane binds to an active site on AGT to form the intermediate, *S*-(2-bromoethyl), which then forms a highly reactive half-mustard. The half-mustard reacts with DNA, forming adducts at guanine at various sites on adenine. Thus, conjugation of 1,2-dibromoethane to the AGT repair protein paradoxically enhances the mutagenic activity of 1,2-dibromoethane.

2.21 GENERAL MECHANISMS OF ACTION

The mechanisms of toxicity of 1,2-dibromoethane have not been established. However, it has been proposed that toxicity results from metabolism of 1,2-dibromoethane to more reactive compounds through oxidation reactions or conjugation with GSH or other compounds. These compounds are likely involved in producing general mechanisms of cellular damage, including lipid peroxidation and binding to cellular macromolecules (Albano et al. 1984; DeLeve 1997; EPA 2004; Mann and Darby 1985; Novotna et al. 1994). Additional information on genotoxic mechanisms is reviewed in Section 2.20.