Toxicological Profile for 1,2-Dibromoethane

September 2018

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

CS274127-A

FOREWORD

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

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

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

Each profile includes the following:

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

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

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

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

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

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*Legislative Background

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

VERSION HISTORY

Date	Description
September 2018	Update of the Relevance to Public Health, Health Effects, and Regulations and Advisories
July 1992	Final toxicological profile released

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CONTENTS

LIST OF FIGURES

LIST OF TABLES

CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

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

1,2-Dibromoethane ($C_2H_4Br_2$; CAS Number 106-93-4) is a colorless liquid with a mild, sweet odor. It is volatile and soluble in water. 1,2-Dibromoethane is used as an intermediate in the production of dyes, resins, gums, and waxes and as a pesticide treatment of felled logs. Previously, 1,2-dibromoethane was used as an additive to leaded gasoline and as a fumigant; however, these uses are historical only. The primary source of 1,2-dibromoethane released to the environment is from emissions into air from industrial processing facilities. 1,2-Dibromoethane is highly mobile in soil and can persist in soils and groundwater. The most likely exposure to 1,2-dibromoethane for the general population is from inhalation of air near processing facilities or ingestion of contaminated drinking water.

1.2 SUMMARY OF HEALTH EFFECTS

Little information on the effects of 1,2-dibromoethane in humans is available. Case reports of individuals exposed acutely to 1,2-dibromoethane by inhalation or ingestion at lethal or near-lethal levels identify the respiratory tract, gastrointestinal tract, liver, and kidney as targets of 1,2-dibromoethane (Letz et al. 1984; Olmstead 1960; Prakash et al. 1999; Singh et al. 2000; Saraswat et al. 1986). Cross-sectional studies of the same occupational cohort showed serious effects to the male reproductive system (Ratcliffe et al. 1987; Schrader et al. 1988).

Studies in laboratory animals have been conducted for acute-, intermediate-, and chronic-duration inhalation and oral exposures. Many studies include assessment of comprehensive toxicological endpoints, including cancer. Studies in animals provide support for the target organs observed in humans and identify additional targets, as discussed below. By all routes, tissue damage is observed at the point of contact (e.g., portal-of-entry). Most animal exposure studies had treatment-related mortality or serious adverse effects at the lowest exposures tested. Therefore, it is not possible to determine the most sensitive

effects of exposure for 1,2-dibromoethane. Effects of inhaled and oral 1,2-dibromoethane are depicted in Figures 1-1 and 1-2, respectively.

Body Weight Effects. Results of most acute-, intermediate-, and chronic-duration inhalation and intermediate- and chronic-duration oral exposure in laboratory animals consistently show marked body weight loss or reduced weight gain.

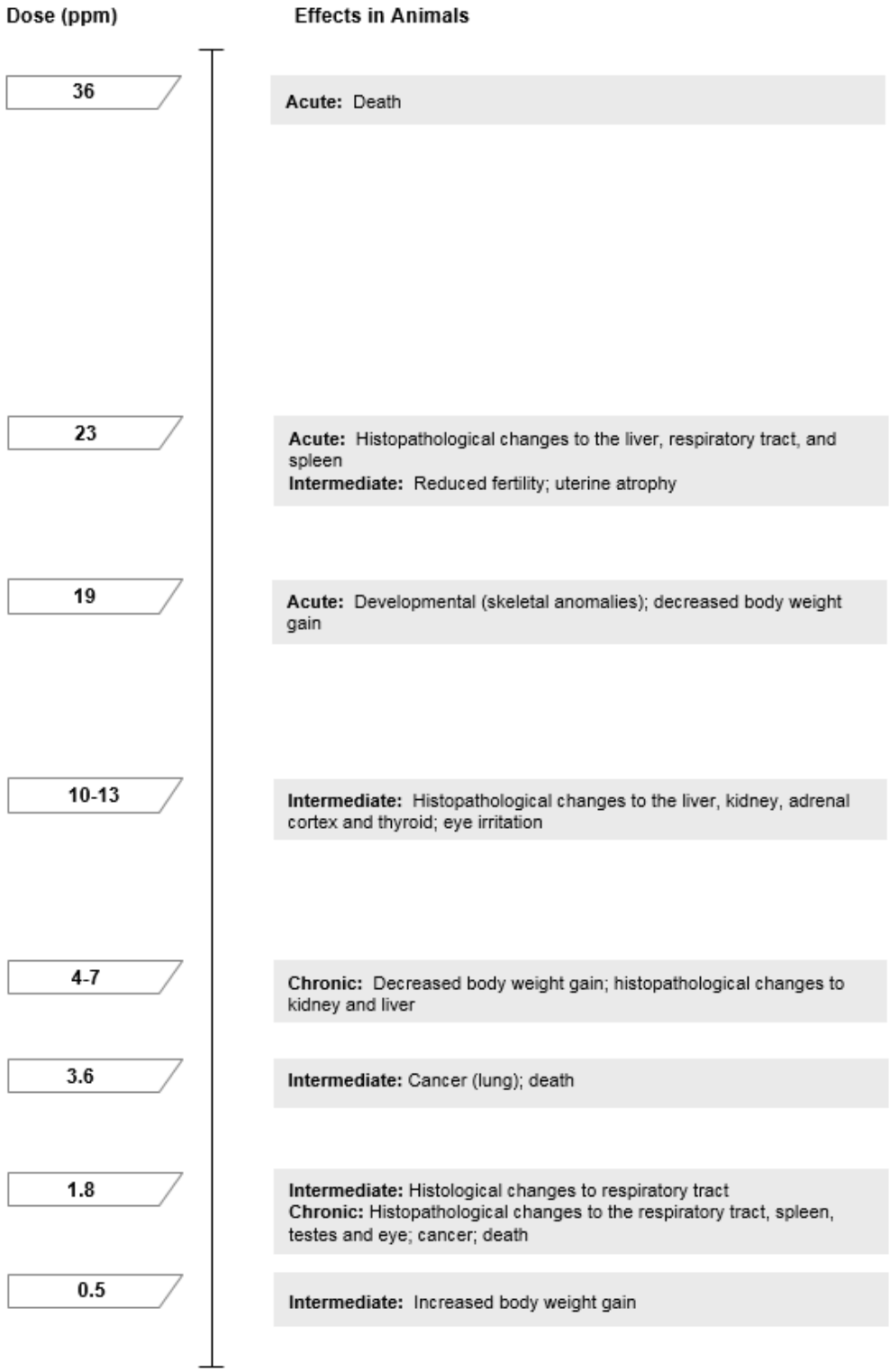
Respiratory Effects. Pulmonary edema was observed in one worker who died following dermal and inhalation exposure (exposure levels not reported). In some laboratory animals, acute-, intermediate- and chronic-duration inhalation exposure to 1,2-dibromoethane caused damage to the upper and/or lower respiratory tract. Effects in the nasal cavity include cytomegaly, hyperplasia, metaplasia and loss of cilia in rats and mice exposed for intermediate and chronic durations. Effects in the lower respiratory tract include leukocytic infiltration of the lungs and hyperplasia of the lung and bronchus in mice exposed for intermediate durations and rats and mice exposed for chronic durations.

Gastrointestinal Effects. In humans ingesting 1,2-dibromoethane, oral and pharyngeal ulceration, vomiting, and diarrhea have been observed. Acute-duration gavage exposure of rats and chronic-duration gavage exposure of mice to 1,2-dibromoethane produced damage to the forestomach, including cell proliferation, hyperkeratosis, and acanthosis.

Hematological Effects. 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 acute- and chronic-duration inhalation exposure and chronic-duration oral exposure. Effects on hematological parameters in blood have not been observed, although few studies evaluated these parameters.

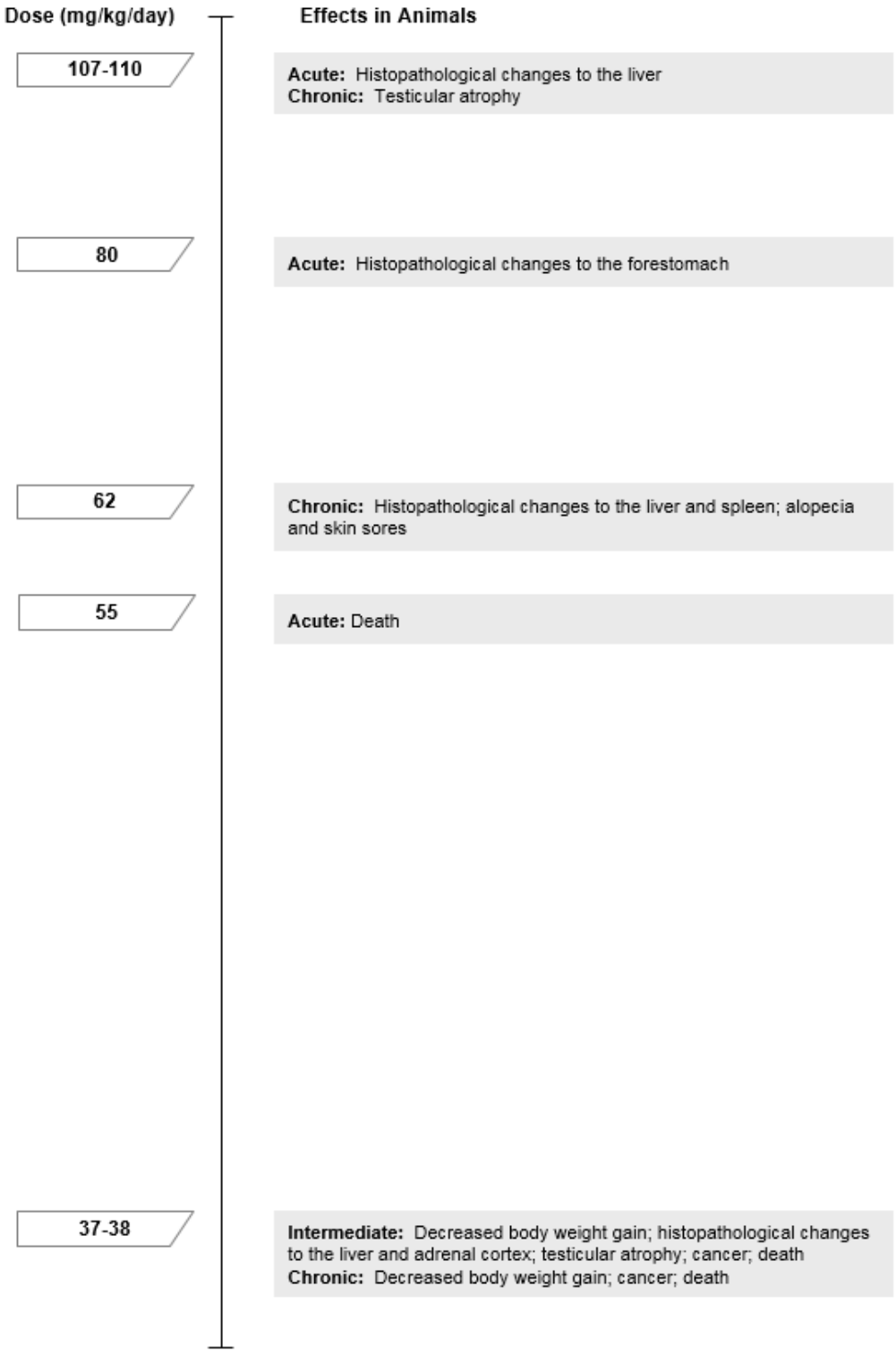
Hepatic Effects. Case reports of individuals acutely exposed to 1,2-dibromoethane at lethal or near-lethal levels by inhalation or ingestion observed acute, severe liver failure and hepatic necrosis. Oral and inhalation exposure studies in laboratory animals also show that the liver is a target organ for 1,2-dibromoethane, with studies reporting histopathological lesions (cloudy swelling, inflammation, fatty degeneration, necrosis, peliosis hepatis).

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to 1,2-Dibromoethane*



*Doses adjusted for continuous exposure and are the lowest level found for each effect

Figure 1-2. Health Effects Found in Animals Following Oral Exposure to 1,2-Dibromoethane*



*Doses are the lowest dose found for each effect

Ocular Effects. 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.

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

Reproductive Effects. Exposure of humans and laboratory animals to 1,2-dibromoethane produces adverse effects to the male reproductive system. A cross-sectional study in fumigant workers with combined inhalation and dermal exposure reported decreased sperm count, decreased percentages of viable and motile sperm, and increased abnormal sperm. The time-weighted (5-year) exposure concentration was 0.088 ppm. Testicular atrophy or infertility have been observed in laboratory animals exposed to inhaled and oral 1,2-dibromoethane. In female rats, reduced fertility and degeneration of the uterine epithelium were observed following intermediate-duration inhalation exposure; however, this finding has not been corroborated in other inhalation or oral exposure studies.

Developmental Effects. Developmental effects have only been evaluated in a single inhalation study in rats and mice. In both species, skeletal anomalies (incomplete ossification) were observed at the lowest exposure tested.

Cancer Effects. In laboratory animals exposed to inhaled and oral 1,2-dibromoethane for intermediate and/or chronic durations, cancers have been observed in portal-of-entry tissues (respiratory tract and forestomach). Cancers also developed in several other tissues, including spleen, adrenal gland, mesenchymal tissue, subcutaneous tissue, mammary tissue, testes, blood, and cardiovascular tissue. In addition, lung adenomas were observed in mice following chronic-duration dermal exposure. Cancer was observed at the lowest exposures tested in all studies evaluating this endpoint.

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. The International Agency for Research on Cancer (IARC) has classified 1,2-dibromoethane as a group 2A

chemical, “probably carcinogenic to humans” based on sufficient evidence in animals and inadequate evidence in humans (IARC 1999).

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was not considered adequate for deriving inhalation MRLs. As presented in Figure 1-3, the limited available data do not provide adequate information to identify the most sensitive effects of 1,2-dibromoethane, with adverse effects occurring at the lowest concentrations tested. Because mortality or serious adverse health effects were observed at the lowest concentrations tested, this precludes identification derivation of MRLs.

The oral database was not considered adequate for deriving oral MRLs; data are presented in Figure 1-4. At the lowest exposure levels evaluated in acute-, intermediate- and chronic-duration oral studies, excessive treatment-related mortality was observed (NCI 1978; NTP 1982; Rowe et al. 1952; Short et al. 1978). Therefore, MRLs could not be derived.

Inhalation and oral MRL values are summarized in Table 1-1.

Figure 1-3. Summary of Sensitive Targets of 1,2-Dibromoethane – Inhalation

Numbers in triangles and circles are the lowest LOAELs (ppm) among health effects in humans and animals, respectively.

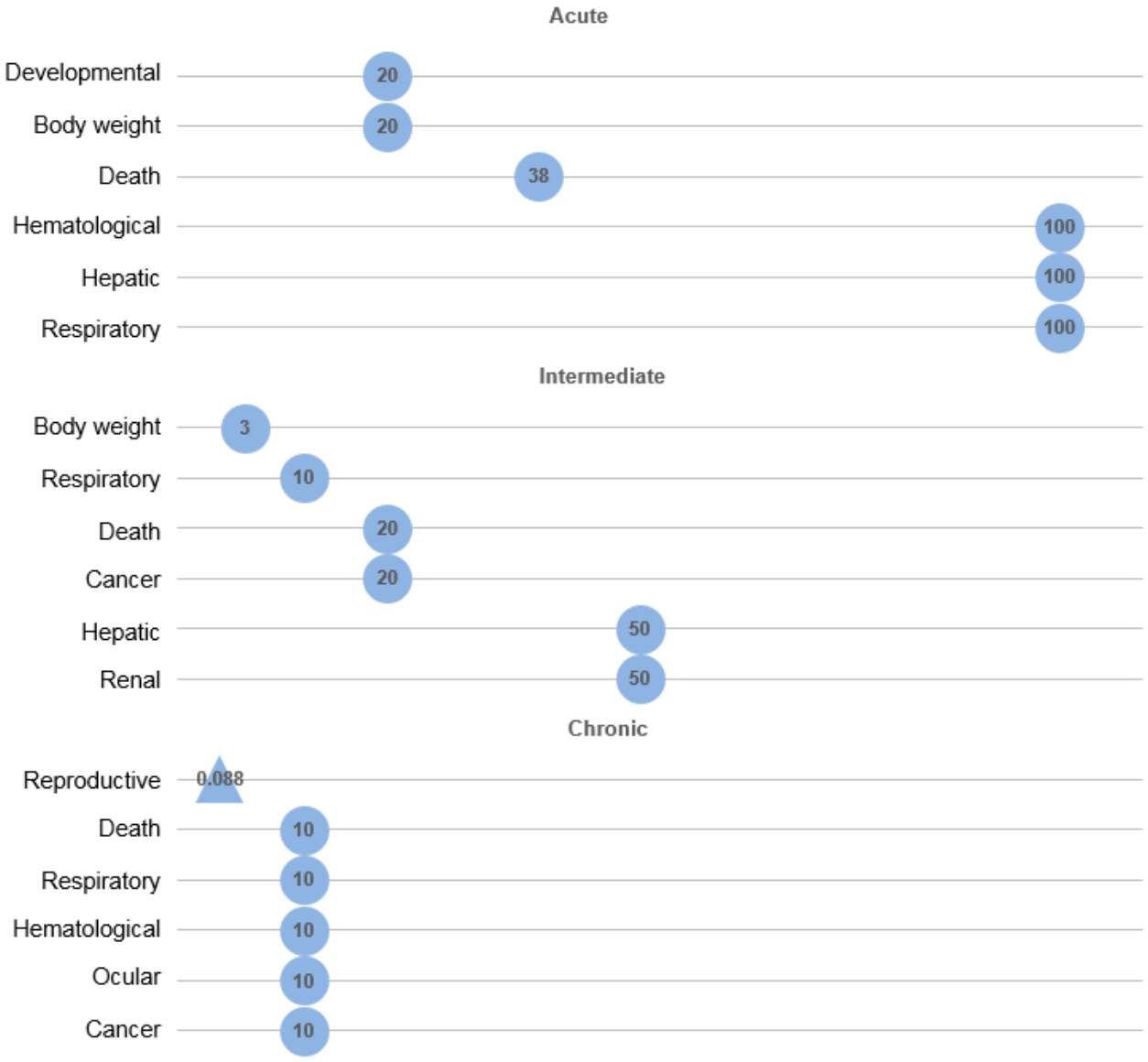


Figure 1-4. Summary of Sensitive Targets of 1,2-Dibromoethane – Oral

Numbers in circles are the lowest LOAELs (mg/kg/day) for all health effects in animals; except for case reports, no human data were identified.

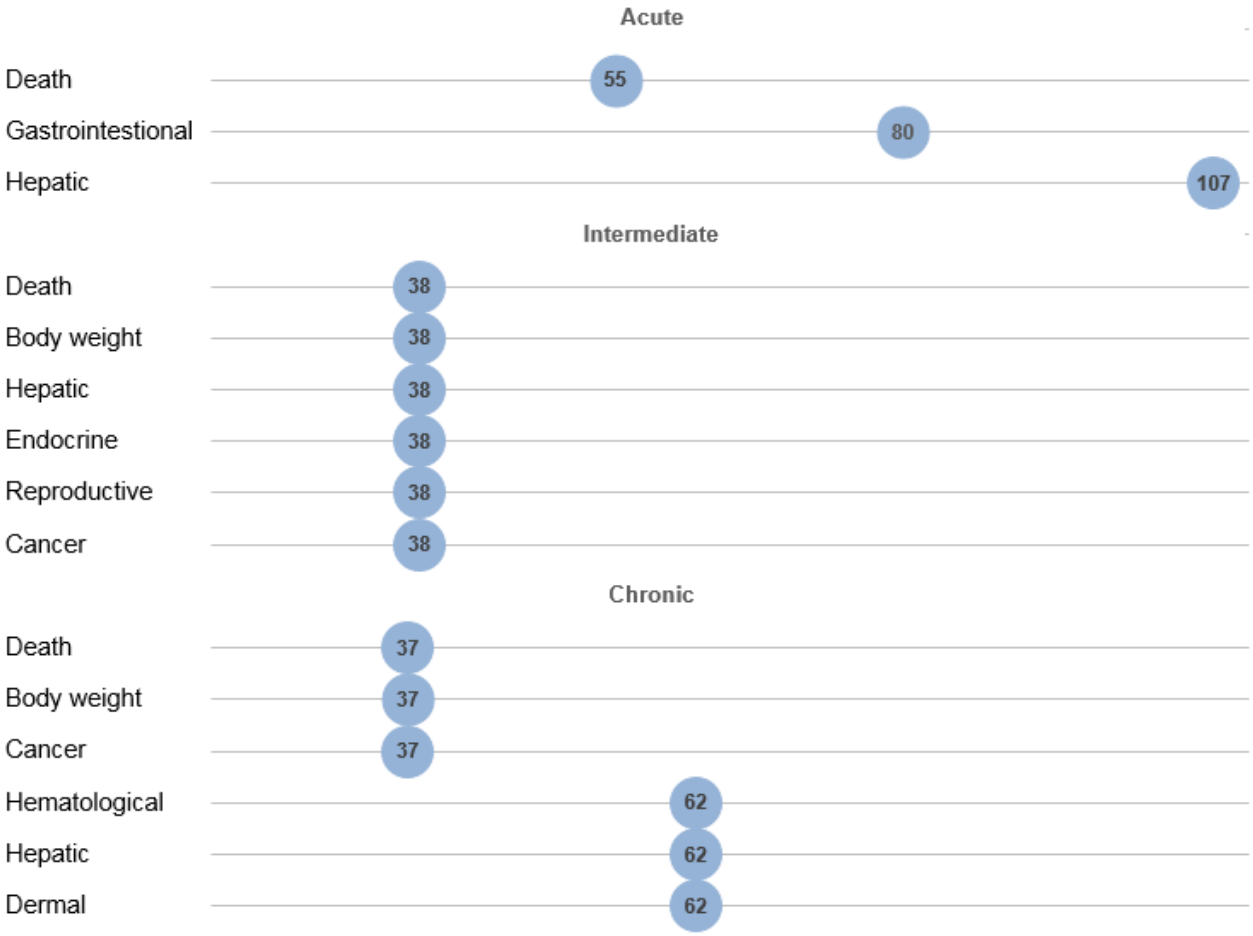


Table 1-1. Minimal Risk Levels (MRLs) for 1,2-Dibromoethane[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				

[a]See Appendix A for additional information.

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.

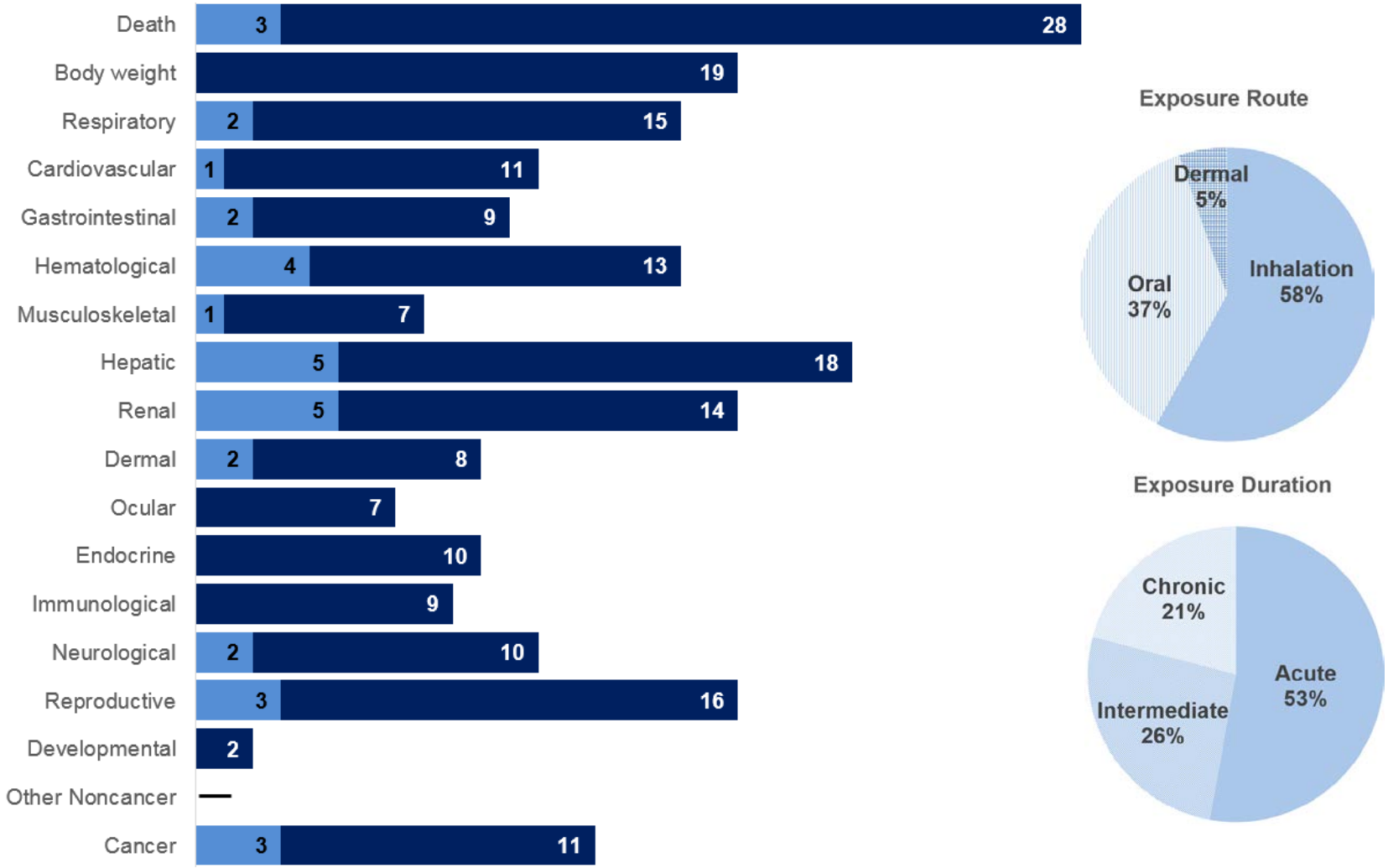
- ***Developmental Endpoint.*** A single inhalation study in rats and mice reported skeletal anomalies at the lowest exposure tested.

- ***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									

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
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

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
					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)

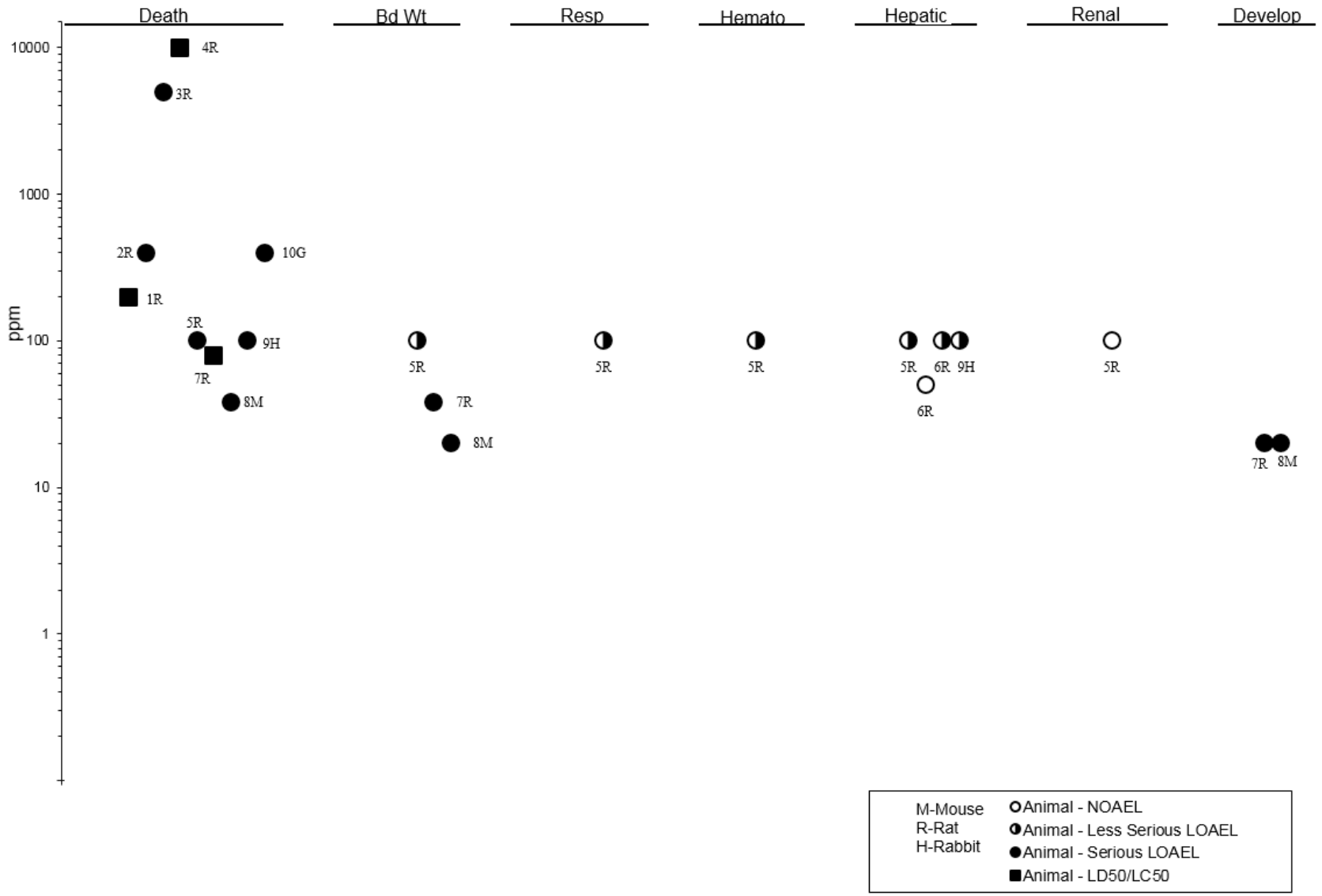


Figure 2-2. Levels of Significant Exposure to 1,2-Dibromoethane – Inhalation
Intermediate (15-364 days)

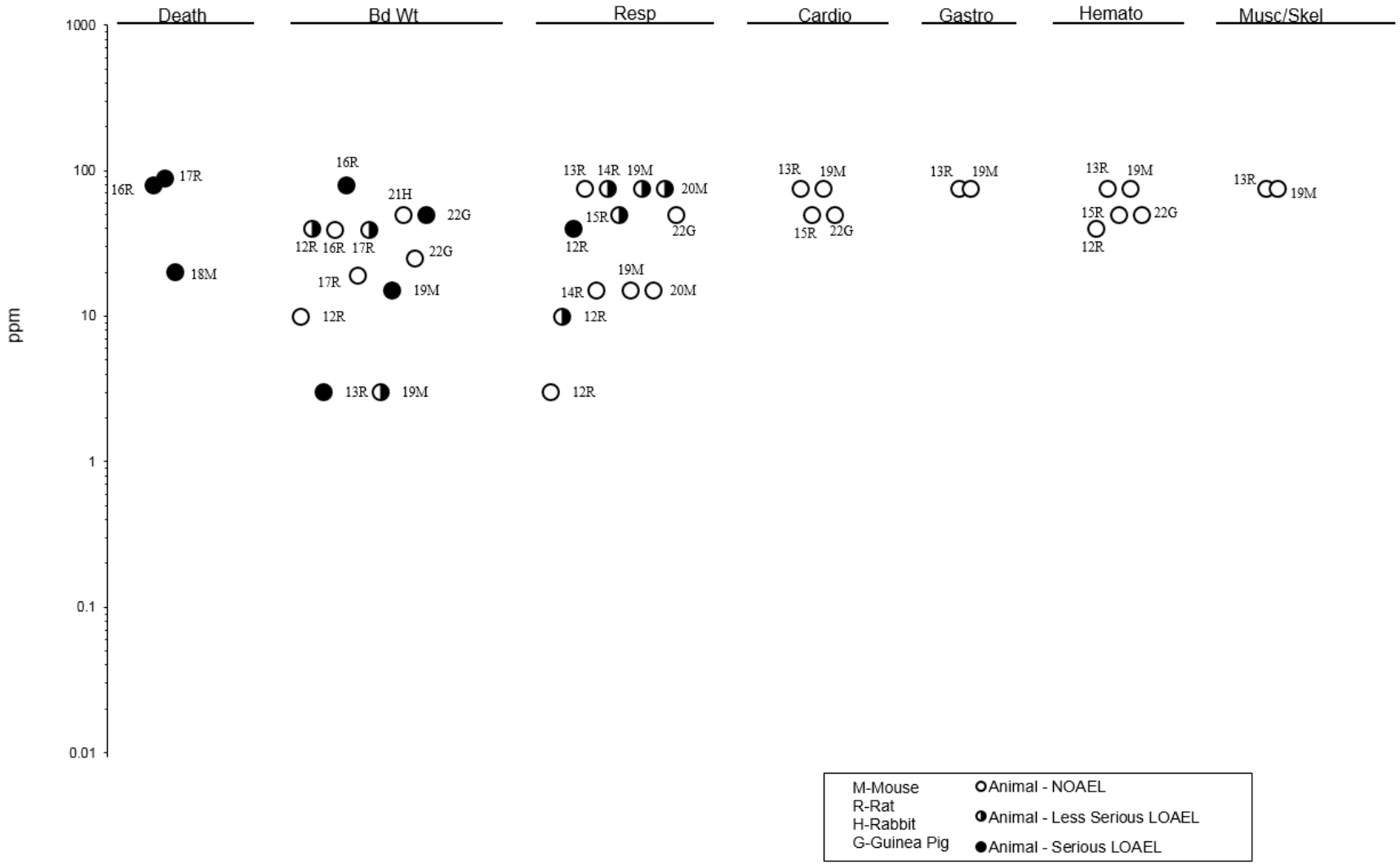


Figure 2-2. Levels of Significant Exposure to 1,2-Dibromoethane – Inhalation
Intermediate (15-364)

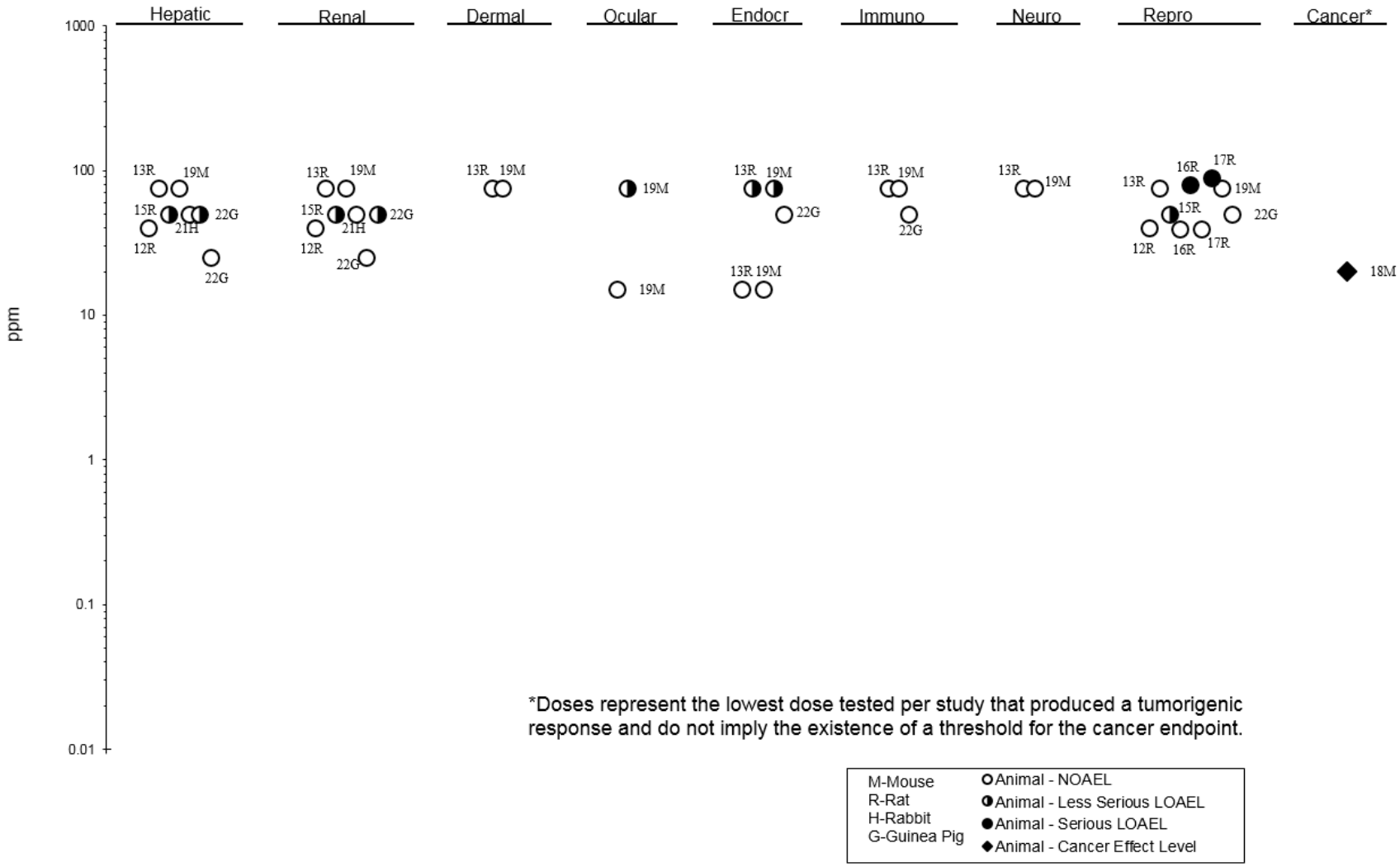


Figure 2-2. Levels of Significant Exposure to 1,2-Dibromoethane – Inhalation
Chronic (≥365 days)

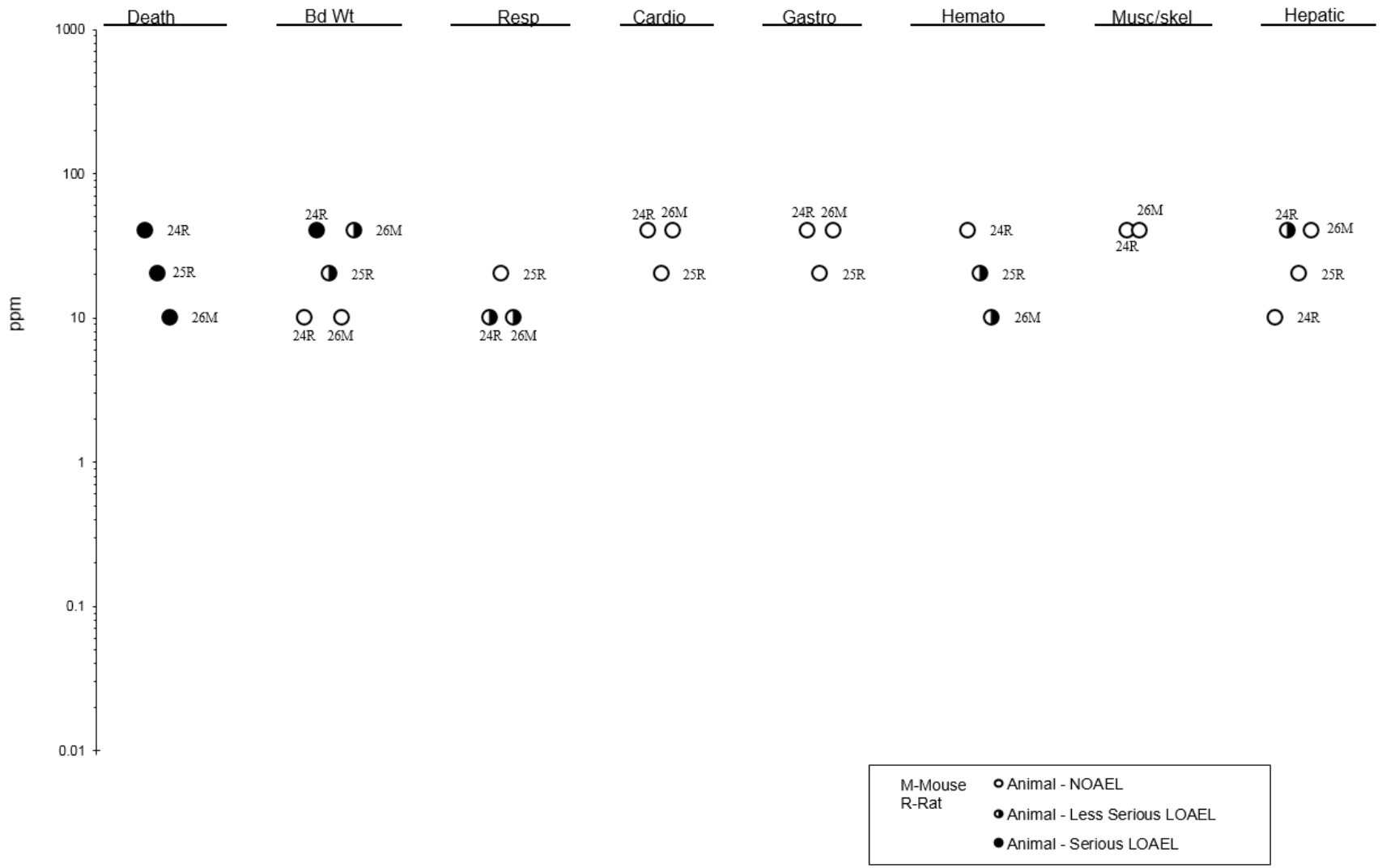


Figure 2-2. Levels of Significant Exposure to 1,2-Dibromoethane – Inhalation

Chronic (≥365 days)

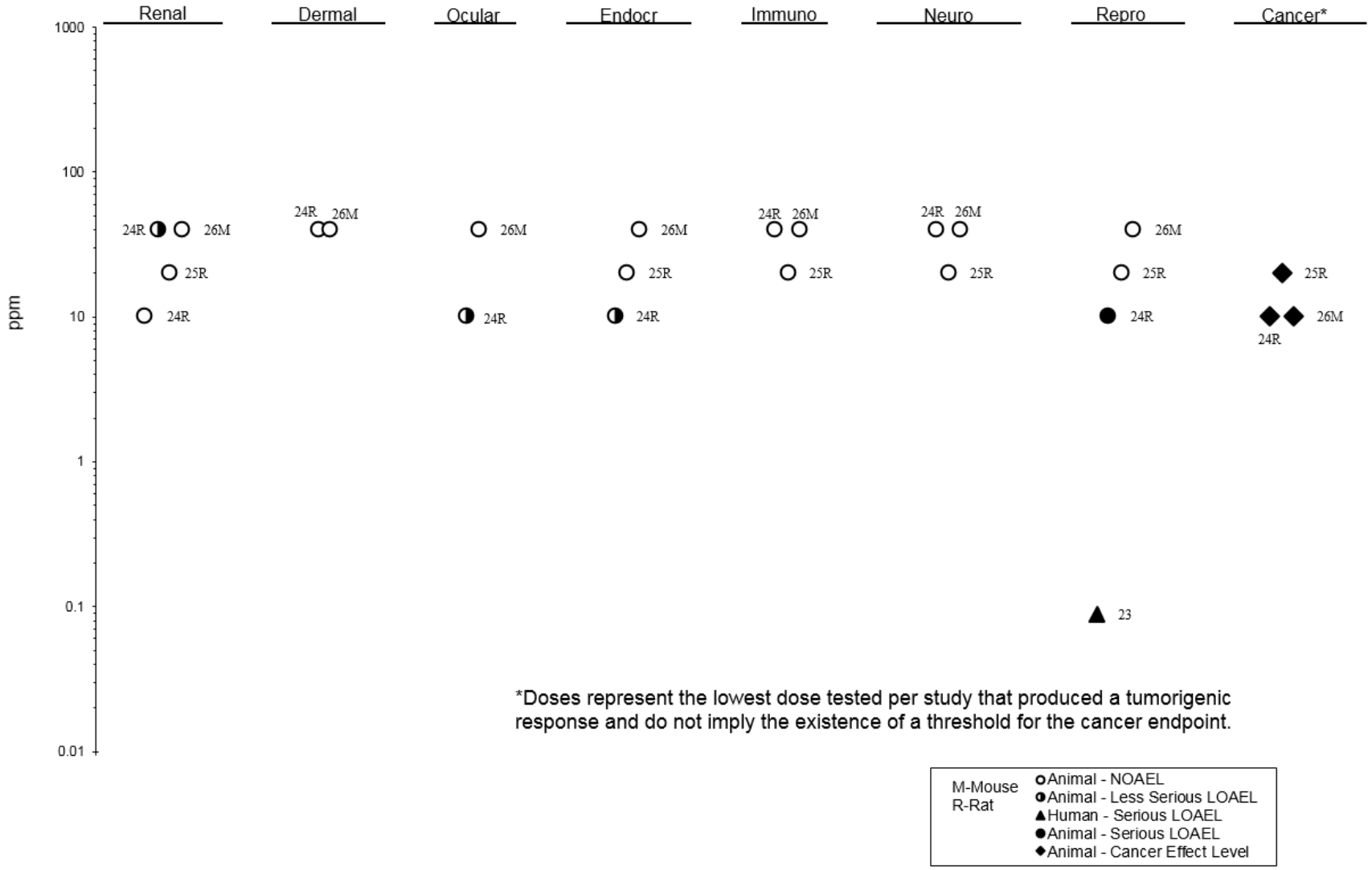


Table 2-2. Levels of Significant Exposure to 1,2-Dibromoethane – Oral

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)

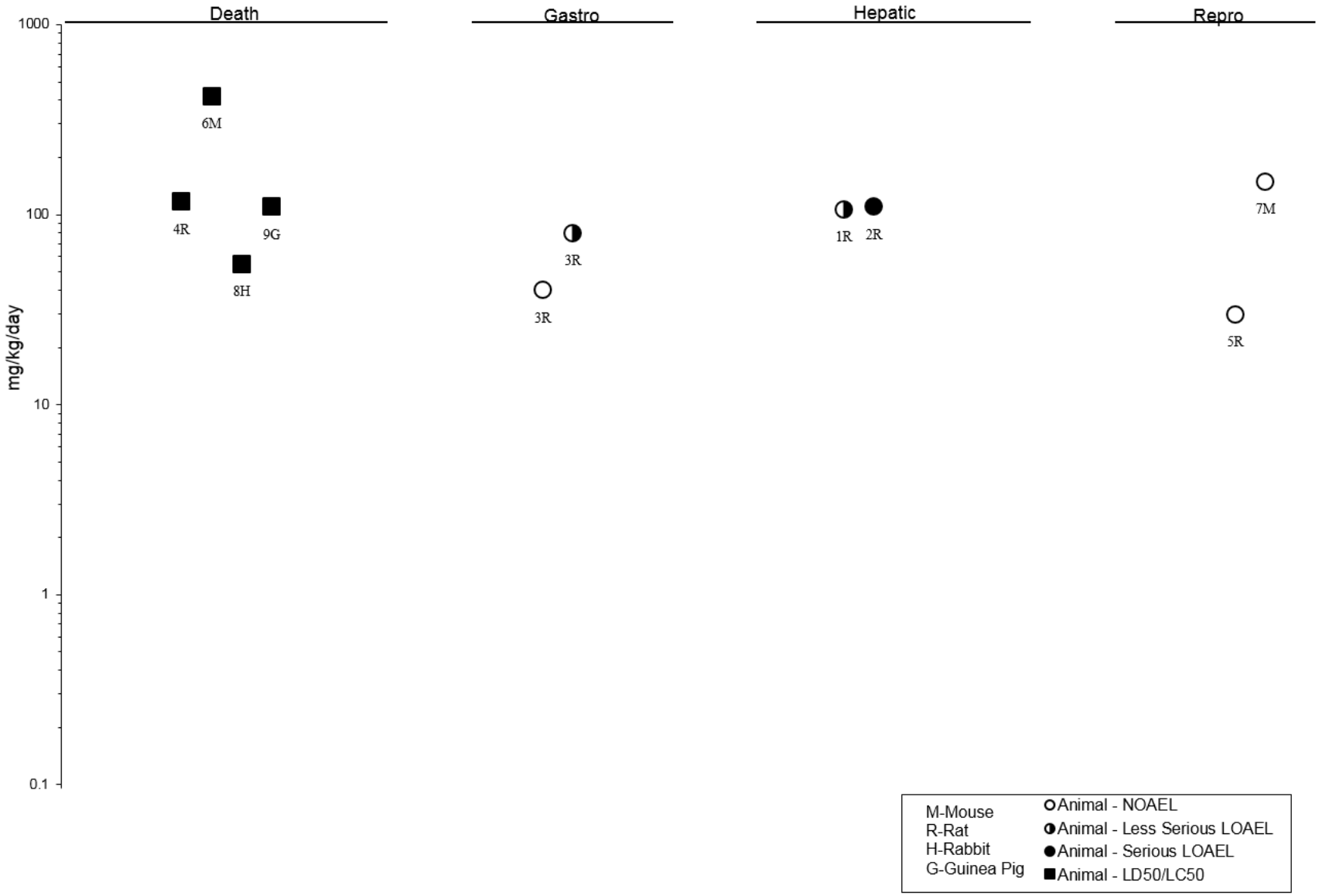


Figure 2-3. Levels of Significant Exposure to 1,2-Dibromoethane – Oral
Intermediate (14-364 days)

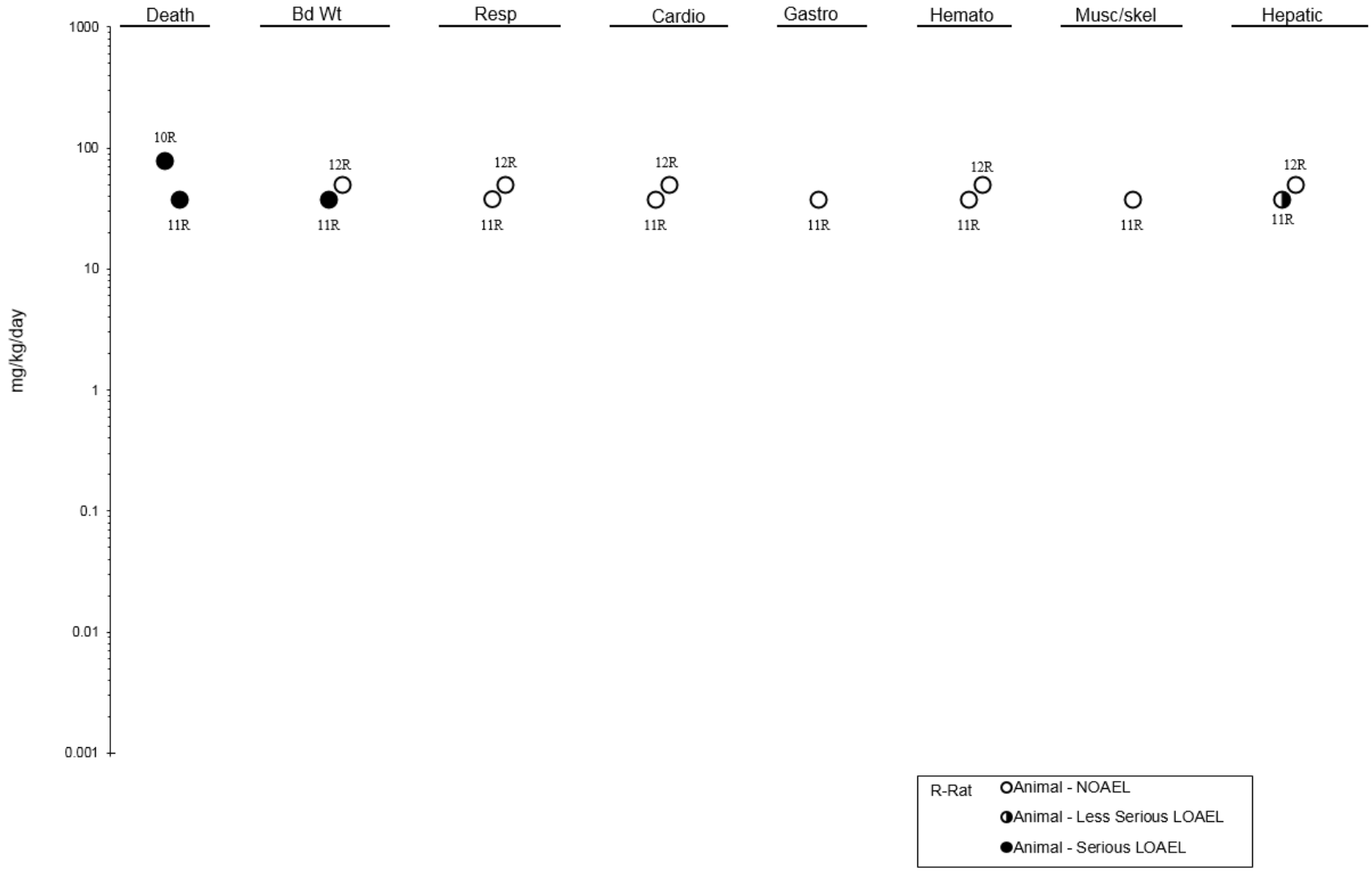


Figure 2-3. Levels of Significant Exposure to 1,2-Dibromoethane – Oral

Intermediate (14-364 days)

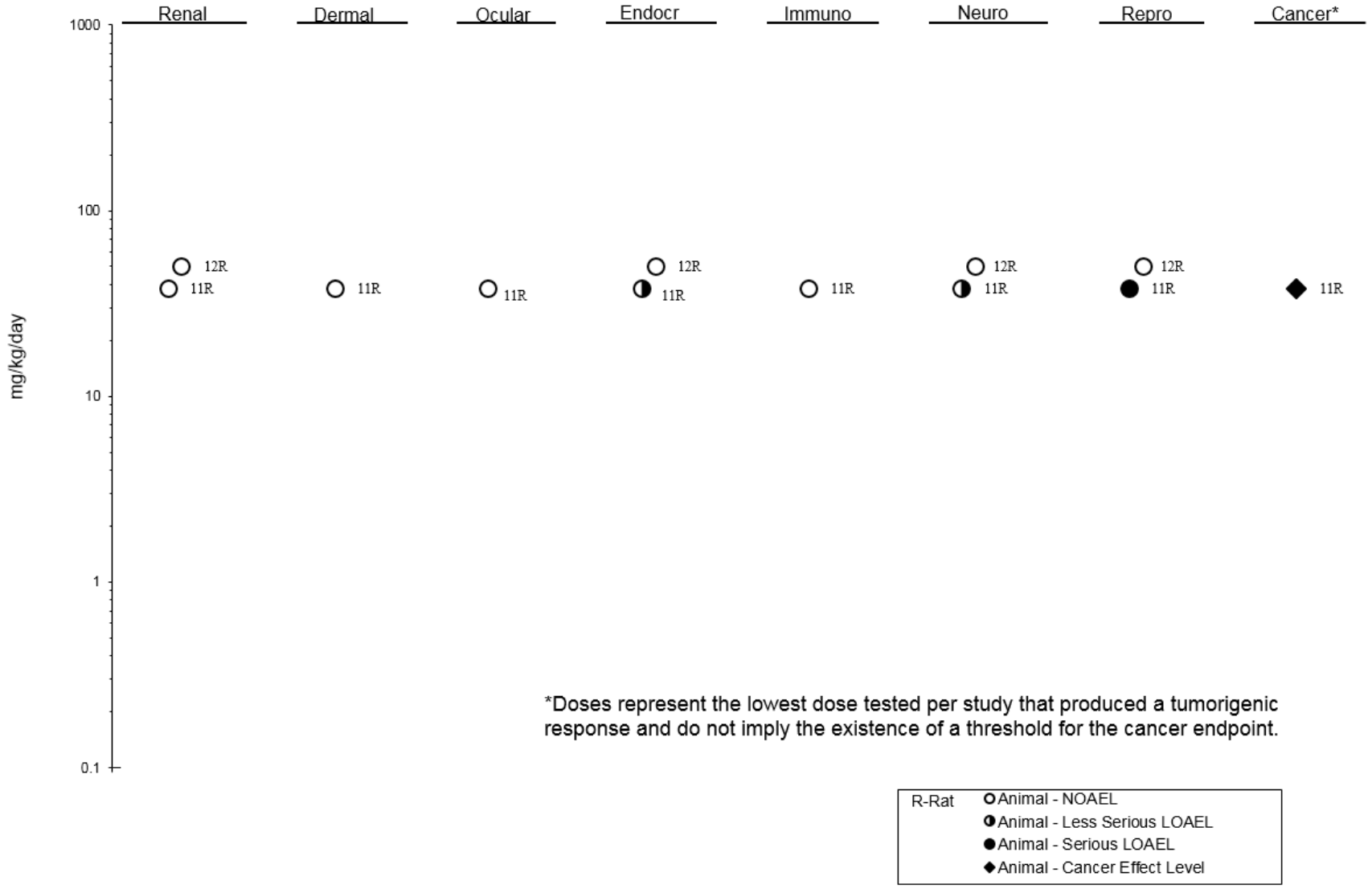


Figure 2-3. Levels of Significant Exposure to 1,2-Dibromoethane – Oral
Chronic (≥365 days)

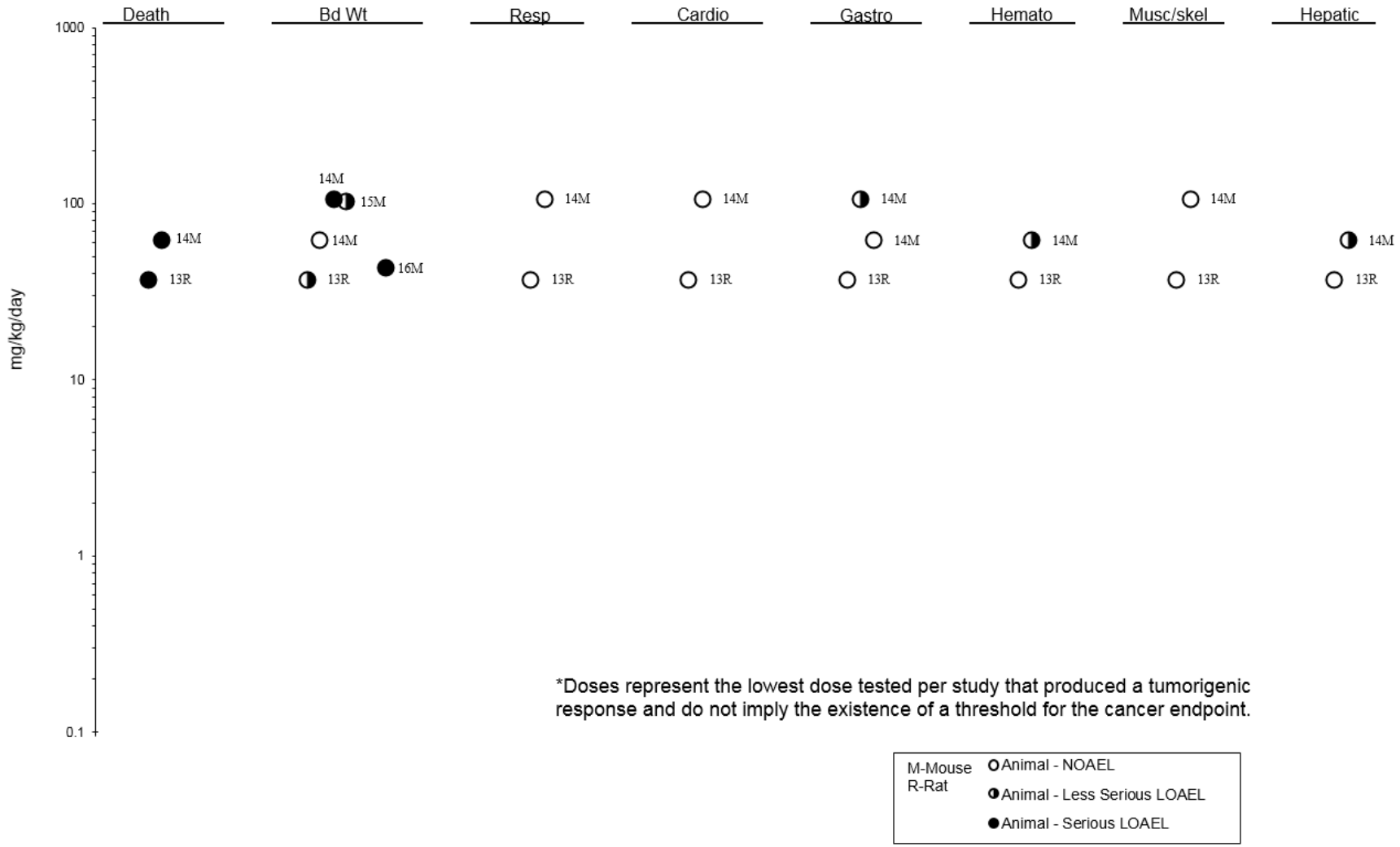


Figure 2-3. Levels of Significant Exposure to 1,2-Dibromoethane – Oral
Chronic (≥365 days)

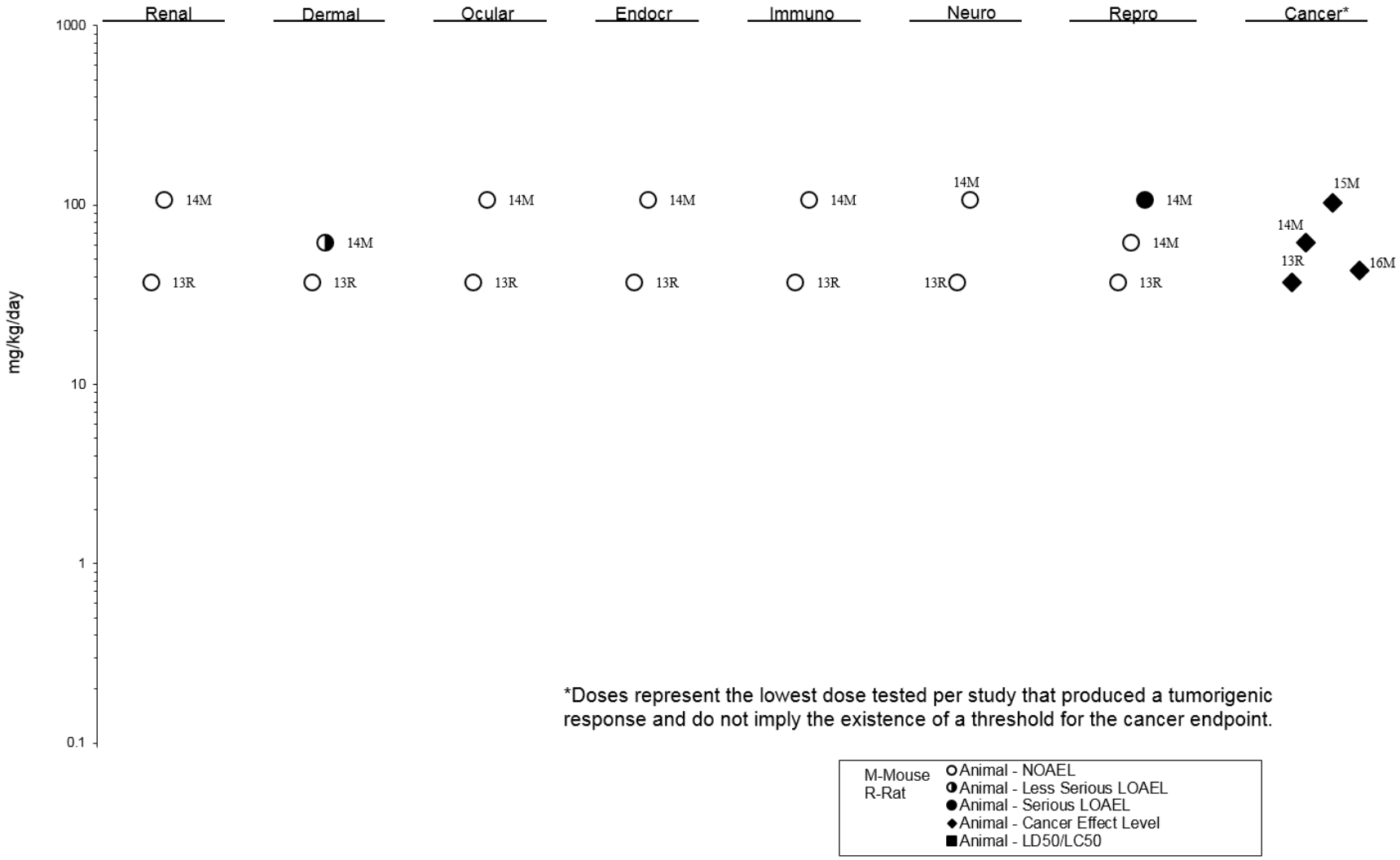


Table 2-3. Levels of Significant Exposure to 1,2-Dibromoethane – Dermal

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.

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

3.1 TOXICOKINETICS

Toxicokinetics of 1,2-dibromoethane has been studied in animal models and in *in vitro* models of animal and human tissues. These studies have revealed the following:

- Ingested 1,2-dibromoethane is rapidly absorbed (within 30 minutes in rats).
- Absorbed 1,2-dibromoethane and its metabolites are widely distributed. Based on studies with ^{14}C-labeled 1,2-dibromoethane, the highest concentrations of ^{14}C are found in kidney, liver, and spleen.
- Metabolism is the dominant mechanism of elimination of absorbed 1,2-dibromoethane. Major pathways of metabolism include oxidation mediated by CYP450 and conjugation with GSH mediated by GST.
- The two primary products of CYP450 and GST, 2-bromoacetaldehye and S-(2-bromoethyl)-glutathione, respectively, are both reactive and contribute to 1,2-dibromoethane toxicity.
- S-(2-Bromoethyl)glutathione forms adducts with protein and DNA, which is thought to contribute to genotoxicity and carcinogenicity of 1,2-dibromoethane.
- Absorbed 1,2-dibromoethane is rapidly eliminated (>99% in 1 day in rats).
- Metabolites of 1,2-dibromoethane (e.g., mercapturic acids) are excreted in urine.

3.1.1 Absorption

No studies were located in humans regarding the inhalation absorption of 1,2-dibromoethane. The available animal toxicity data indicate that absorption of 1,2-dibromoethane occurs in rats, mice, rabbits, guinea pigs, and monkeys exposed via inhalation for acute, intermediate, and chronic durations (Rowe et al. 1952; Stott and McKenna 1984). Based on the findings in animal studies, 1,2-dibromoethane is expected to be absorbed in humans exposed via the inhalation route.

No studies were located in humans regarding the oral absorption of 1,2-dibromoethane. However, there is evidence to suggest that oral absorption occurs in humans. Death and poisoning resulting from suicide attempts (Olmstead 1960; Saraswat et al. 1986) and from consumption of contaminated fruits, grains, and drinking water (EPA 1983) indicate that absorption occurred.

Uptake of 1,2-dibromoethane readily occurs in rats following oral dosing (Botti et al. 1982; Hissink et al. 2000; Nachtomi 1981; Plotnick et al. 1979; Van Bladeren et al. 1980). In rats, peak blood concentrations of 1,2-dibromoethane occurred within 30 minutes following gavage dosing (the earliest time of sampling of blood), suggesting that absorption was nearly complete within 30 minutes.

No studies were located regarding the dermal absorption of 1,2-dibromoethane in humans. However, two occupational case reports suggest that dermal absorption of 1,2-dibromoethane (versus inhaled) was the major route of exposure to 1,2-dibromoethane that resulted in death (Letz et al. 1984). Dermal absorption does occur in animals but has not been quantified. Absorption of 1,2-dibromoethane was demonstrated in guinea pigs whose blood levels were monitored during dermal exposure to 1 mL of 1,2-dibromoethane (Jakobson et al. 1982). Following dermal application, the blood level of 1,2-dibromoethane increased rapidly, reaching a maximum level of approximately 2.1 µg/mL at 1 hour and 1.8 µg/mL at 6 hours.

3.1.2 Distribution

No studies were located in humans or animals regarding the distribution of 1,2-dibromoethane after inhalation exposure. Although occupational cases of inhalation exposure of humans have been reported (Letz et al. 1984), there were no data on 1,2-dibromoethane levels in tissues.

No studies were located in humans regarding the distribution of 1,2-dibromoethane after oral exposure. In humans intentionally ingesting 1,2-dibromoethane, kidney lesions and centrilobular necrosis of the liver were found (Olmstead 1960; Saraswat et al. 1986). This is indirect evidence of distribution of 1,2-dibromoethane to these tissues.

The tissue distribution of 1,2-dibromoethane has been studied in rats following exposure by the oral route. The kidneys, liver, and spleen appear to retain the highest amounts of the administered dose (Plotnick et al. 1979) as illustrated in Table 3-1. Rats received an oral dose of 15 mg/kg/day of labeled 1,2-dibromo-ethane in corn oil. Twenty-four hours later, 3% of radioactivity was detected in fat, brain, kidney, liver, spleen, testes, blood, and plasma, 72.38% was detected in the urine, and 1.65% was detected in the feces (Plotnick et al. 1979). By 48 hours after administration, 73% of the radiolabeled dose was accounted for in the urine, 1.1% in the liver, and 2.4% in the feces. Total recovery was 77.8% of the administered radioactivity. 1,2-Dibromoethane in the expired air was not measured. In rats, 1,2-dibromoethane and its

metabolites can bind covalently to serum albumin (Kaphalia and Ansari 1992). As shown in Table 3-1, blood also has a high concentration of radiolabeled 1,2-dibromoethane.

Table 3-1. Distribution of ^{14}C in Selected Tissues and Body Fluids of Male Rats 24 and 48 Hours After a Single Oral Dose of 15 mg/kg [U-^{14}C]-1,2-Dibromoethane

	Tissue concentration[a]		Percentage of dose[b]	
Tissue	24 Hours	48 Hours	24 Hours	48 Hours
Liver	4.78±0.24	2.87±0.33	1.79±0.07	1.10±0.21
Kidneys	3.32±0.42	1.06±0.16	0.21±0.02	0.08±0.01
Spleen	1.00±0.03	0.66±0.03	0.02±<0.01	0.01±<0.01
Blood[c]	0.90±0.05	0.64±0.07	0.59±0.03	0.43±0.04
Testes	0.49±0.05	0.19±0.02	0.04±<0.01	0.01±<0.01
Brain	0.41±0.04	0.17±0.02	0.02±<0.01	0.01±<0.01
Fat[d]	0.35±0.04	0.44±0.06	0.15±0.02	0.20±0.03
Plasma	0.46±0.04	0.22±0.02	No data	No data
Urine	No data	No data	72.38±0.98[e]	73.54±2.80[f]
Feces	No data	No data	1.65±0.28[e]	2.42±0.54[f]
Total recovery	No data	No data	76.85	77.8

[a]Values represent mean concentration in µg/g or µg/mL (expressed as parent compound) plus or minus the standard error of the mean of duplicate determinations on six animals.
[b]Values represent the mean percentage of the administered radioactivity plus or minus the standard error of the mean of duplicate determinations on six animals.
[c]Assumed 9% of body weight.
[d]Assumed 6% of body weight.
[e]n=12 (includes 24-hour samples obtained from rats killed 48 hours after compound administration).
[f]Cumulative 48-hour excretion.

Source: Plotnick et al. 1979

The retention of 1,2-dibromoethane in tissues and body fluids can be altered by concurrent exposure to modifiers of enzyme activity, such as disulfiram (Plotnick et al. 1979). The concentration of radiolabeled 1,2-dibromoethane in the liver, kidneys, spleen, testes, and brain increased significantly in rats fed disulfiram in the diet for 12 days before an oral dose of 15 mg ^{14}C-1,2-dibromoethane/kg compared with rats not fed disulfiram. Disulfiram, an inhibitor of cytochrome P-450 metabolism (via action on acetaldehyde dehydrogenase), was found to increase the uptake of ^{14}C into liver nuclei. These observations correlate well with the results of chronic studies (Wong et al. 1982) that demonstrated enhanced tumorigenic effects in the liver and testes following combined 1,2-dibromoethane and disulfiram exposure.

No studies were available in humans or animals regarding the distribution of 1,2-dibromoethane following dermal exposure. However, toxic effects observed in humans and animals after dermal exposure indicate that the compound is widely distributed throughout the body.

Tissue distribution of 1,2-dibromoethane following intraperitoneal administration was studied in mice (Edwards et al. 1970) and guinea pigs (Plotnick and Conner 1976). The kidney and liver retained the highest amounts of the administered 1,2-dibromoethane dose across all of the observation periods (see Tables 3-2 and 3-3). Autoradiographic studies of mice injected intraperitoneally with ^{14}C-1,2-dibromoethane (40 mg/kg) revealed radioactivity primarily in the intestines, kidneys, liver, blood, fat, and spleen. Only 1% of the administered dose (per gram of wet tissue) was detected in the kidney and in the stomach tissue, 6.2% was detected in whole blood, and 2.6% was detected in plasma 24 hours posttreatment (Edwards et al. 1970).

Following a single intraperitoneal injection of 30 mg/kg ^{14}C-1,2-dibromoethane in corn oil to guinea pigs, the majority of the dose was accounted for in the urine (65.9%), liver (2.16%), and feces (3%) by the end of the 72-hour period. Approximately 10–12% of the administered dose was excreted via the lungs (Plotnick and Conner 1976). Plotnick and Conner (1976) investigated tissue distribution of 1,2-dibromoethane in guinea pigs because they found similarities in metabolism and biotransformation pathways between guinea pigs and humans. The authors reported that target organs for tissue distribution in guinea pigs were the same as those in rats, although the percentage of dose recovered was higher in guinea pig tissues.

Table 3-2. Distribution of 1,2-Dibromoethane in Mice

	Percentage of dose[a]		
Organ	1 Hour	3 Hours	24 Hours
Small intestine	34.0	5.8	0.39
Kidney	13.0	12.0	1.0
Liver	12.0	6.6	0.42
Lung	0.9	1.0	0.14
Spleen	4.1	4.7	0.61
Plasma	12.0	12.0	2.6

[a]Intraperitoneal injection of 40 mg/kg body weight.

Source: Edwards et al. 1970

Table 3-3. Percentage of Administered ^{14}C in Selected Tissues and Body Fluids of Male Guinea Pigs at Various Time Intervals Following Intraperitoneal Administration of 30 mg/kg of ^{14}C-1,2-Dibromoethane[a]

Organ	4 Hours	8 Hours	12 Hours	24 Hours	48 Hours	48 Hours
Liver	16.29±2.42	13.65±0.39	10.50±2.13	4.72±0.21	2.12±0.07	2.16±0.21
Kidneys	6.00±0.42	5.69±0.43	3.31±0.17	1.64±0.45	0.31±0.01	0.24±0.02
Stomach[b]	1.14±0.44	0.52±0.20	0.62±0.08	0.18±0.02	0.18±0.02	0.18±0.04
Lungs	0.35±0.06	0.38±0.09	0.37±0.01	0.24±0.01	0.12±0.01	0.10±0.01
Pancreas	0.31±0.10	0.36±0.06	0.33±0.02	0.20±0.03	0.07±0.01	0.06±0.01
Testes	0.16±0.04	0.17±0.01	0.12±0.01	0.12±0.01	0.07±0.01	0.06±0.01
Heart	0.13±0.02	0.16±0.02	0.12±0.01	0.10±0.01	0.04±0.01	0.03±0.01
Brain	0.12±0.02	0.16±0.02	0.14±0.01	0.13±0.01	0.07±0.01	0.05±0.00
Adrenals	0.08±0.02	0.10±0.04	0.04±0.01	0.03±0.01	0.01±0.01	0.02±0.01
Spleen	0.07±0.01	0.06±0.01	0.07±0.01	0.08±0.02	0.03±0.00	0.02±0.01
Urine[c]	14.9±1.0	26.3±10.1	43.2±8.1	46.0±4.8	54.3±3.4	65.9±4.6

[a]Values represent the mean plus or minus the standard error of the mean of duplicate determinations on three animals at each time interval.
[b]Including stomach contents.
[c]Cumulative excretion.

Source: Plotnick and Conner 1976

These results are similar to those after oral administration and suggest that 1,2-dibromoethane is rapidly absorbed and distributed but retained to only a limited extent mainly in the kidneys and liver, regardless of the route of exposure and the species tested.

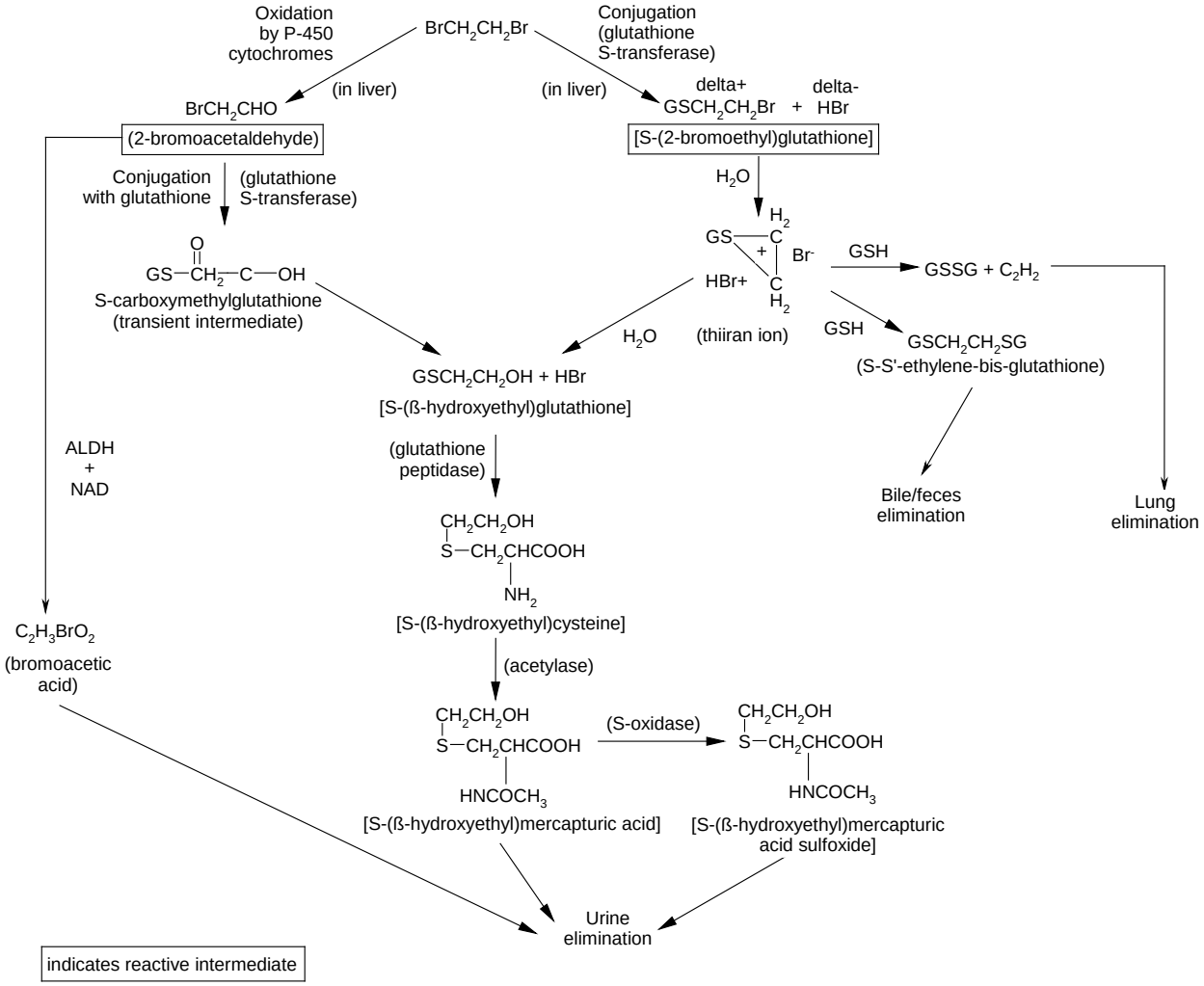
3.1.3 Metabolism

No human studies were located that provided information on metabolism of 1,2-dibromoethane from inhalation or oral exposures. However, 1,2-dibromoethane is metabolized by enzyme systems known to be present in humans. 1,2-Dibromoethane is metabolized to active forms capable of inducing toxic effects by either of two systems: the microsomal monooxygenase system (cytochrome P-450 oxidation, CYP450) or the cytosolic activation system (glutathione conjugation). Figure 3-1 provides an overview of the metabolism of 1,2-dibromoethane by the two systems. The pathway of biotransformation for 1,2-dibromoethane appears to be the controlling factor for its biological activity. Two reactive intermediates, 2-bromoacetaldehyde and S-(2-bromoethyl) glutathione, are formed. The 2-bromoacetaldehyde is responsible for tissue damage caused by covalent binding to cellular macromolecules. S-(2-Bromoethyl)glutathione is responsible for genotoxicity of 1,2-dibromoethane and, perhaps its carcinogenic effect observed in laboratory animals. These two systems and their relative importance are discussed in detail below.

Results of animal studies show that 1,2-dibromoethane is metabolized in various tissues through oxidation by CYP450 to form 2-bromoacetaldehyde (Guengerich et al. 1991; Tamura et al. 1986; Van Duuren et al. 1985; Wormhoudt et al. 1996a, 1996b). Although various isoforms of CYP450 can utilize 1,2-dibromoethane as a substrate, the dominant contributor to metabolism of 1,2-dibromoethane appears to be CYP2E1 (Wormhoudt et al. 1996a, 1996b). The metabolic product of CYP450, 2-bromo-acetaldehyde, can produce histopathological changes such as liver damage, by binding to cellular proteins (Hill et al. 1978; Kaphalia and Ansari 1992). 2-Bromoacetaldehyde can also be metabolized by aldehyde dehydrogenase in the presence of nicotinamide adenine dinucleotide to bromoacetic acid, which is excreted in the urine. In addition, 2-bromoacetaldehyde can also be conjugated with glutathione. The conjugated metabolite is reduced to S-carboxymethylglutathione. This compound can form S-carboxy-methylcysteine, which may be metabolized to thioglycolic acid and excreted in the urine or can be metabolized to S-(β-hydroxyethyl) cysteine. The latter is excreted in the urine following action by N-acetyl transferase in the presence of acetyl CoA enzyme and subsequent sulfoxidation to form mercapturic acids (Nachtomi et al. 1966; Van Bladeren 1983). Mercapturic acids are the primary urinary metabolites of 1,2-dibromoethane. Tomasi et al. (1983) demonstrated that 1,2-dibromoethane can form a

free radical intermediate under hypoxic conditions, suggesting a new metabolic pathway for 1,2-dibromoethane.

Figure 3-1. Proposed Metabolic Pathways for 1,2-Dibromoethane



ALDH = aldehydehydrogenase; GSH = glutathione; NAD = nicotinamide adeinine dinucleotide

Source: Lawrence and Michaels 1984

As shown in Figure 3-1, 1,2-dibromoethane can be conjugated with glutathione through the action of GSTs to form S-(2-bromoethyl) glutathione (Peterson et al. 1988). Although various isoforms of GST can utilize 1,2-dibromoethane as a substrate, the alpha and theta isoforms (GSTA2 and GST T1) appear to be major contributors (Cmarik et al. 1990; Ploemen et al. 1997; Sherratt et al. 1998). The GSH conjugate, S-(2-bromoethyl) glutathione, can react to form ethylene and glutathione disulfide through further action of glutathione transferases. These are considered to be detoxification pathways. Ethylene can be exhaled, and the glutathione disulfide is eliminated in the feces via the bile.

S-(2-Bromoethyl)glutathione is considered to be the genotoxic, and probably the carcinogenic, intermediate of 1,2-dibromoethane metabolism (Cho and Guengerich 2013; DeLeve 1997; Thomas et al. 2001; Van Bladeren et al. 1981); for additional information, see the discussion on mechanisms in Section 2.20 (Genotoxicity). It has also been implicated as a contributor to mitochondrial toxicity by alkylating mitochondrial DNA (Thomas et al. 2001). S-(2-Bromoethyl)glutathione is a highly reactive alkylating agent that can bind to DNA either through direct nucleophilic substitution (Van Bladeren 1983) or substitution through the ethylene-S-glutathionyl-episulfonium ion to form S-[2-(N7-guanyl)ethyl] glutathione (Cho and Guengerich 2013; Koga et al. 1986; Ozawa and Guengerich 1983; Peterson et al. 1988). S-(2-Bromoethyl) glutathione is the main genotoxic metabolite that binds to DNA to form the complex S-[2-(N7-guanyl)ethyl]mercapturic acid (Bolt et al. 1986; Guengerich et al. 1995; Koga et al. 1986). The ethylene-S-glutathionyl-episulfonium ion can also react with water and be detoxified to form S-(β-hydroxyethyl)glutathione, or react with glutathione to form S,S'-ethylene-bis-(glutathione). The latter is excreted in the feces via the bile. S-(β-hydroxyethyl)glutathione can form S-(β-hydroxyethyl)-glutathione-S-oxide by sulfoxidation or react with peptidases to form S-(β-hydroxyethyl)cysteine. The former is excreted in the feces via the bile. The latter forms S-(β-hydroxyethyl)mercapturic acid by the action of N-acetyl transferase and is excreted in the urine (EPA 1985; Nachtomi 1970; Van Bladeren 1983).

In animals, 1,2-dibromoethane is rapidly metabolized after oral administration and is ultimately converted into mercapturic acid derivatives that appear in urine (Kirby et al. 1980; Nachtomi 1970; Nachtomi et al. 1965). The principal mercapturic acid derivative, N-acetyl-S-(2-hydroxyethyl-)L-cysteine, and other related metabolites are derived from the metabolism of GSH conjugates formed with 1,2-dibromoethane or its CYP450 metabolites (Figure 3-1). An *in vivo* study (Van Duuren et al. 1985) provides evidence that CYP450 of 1,2-dibromoethane in rodents can produce adducts that bind preferentially to protein. In a study using tetradeutero-1,2-dibromoethane, only about 20% of the mercapturic acid excreted was formed via direct glutathione conjugation for 1,2-dibromoethane (Van Bladeren 1983). The reactive metabolites formed by these the CYP450 and GST pathways may bind to protein (2-bromoacetaldehyde) or DNA (S-[2-bromoethyllglutathione) producing either cytotoxicity or genotoxicity, respectively. Adducts formed via cytosolic glutathione conjugation, identified as S-[2-(N7-guanyl)ethyl]glutathione by Ozawa and Guengerich (1983), have been associated with genotoxic, and perhaps carcinogenic, effects (Van Bladeren et al. 1982; White et al. 1983). Edwards et al. (1970) also identified metabolites after oral administration.

3.1.4 Excretion

No studies were located-in humans or animals regarding the excretion of 1,2-dibromoethane after inhalation exposure.

No studies were available in humans regarding the excretion of 1,2-dibromoethane after oral exposure. Oral administration of 1,2-dibromoethane to rats primarily results in mercapturic acid derivatives excreted in the urine (approximately 74% of the administered dose) (Plotnick et al. 1979) as shown in Table 3-1. Unmetabolized 1,2-dibromoethane or its metabolites (e.g., ethylene) may be excreted via the lungs; fecal excretion of metabolites accounts for approximately 3% of the administered dose (Plotnick et al. 1979). In rats, absorbed 1,2-dibromoethane is rapidly eliminated from blood, primarily by metabolism, although excretion in exhaled air may also be a contributing elimination pathway. Biphasic elimination of 1,2-dibromoethane from blood was observed following an oral dose of 50 mg/kg, with half-times estimated to be approximately 25 and 121 minutes. The terminal half-time of 121 minute predicts elimination of approximately >99% of absorbed 1,2-dibromoethane in 24 hours. Systemic clearance, as measured by blood 1,2-dibromoethane kinetics, was considerably slower following a 150 mg/kg oral dose (55 mL/minute/kg) compared to a 50 mg/kg dose (125 mL/minute/kg). Dose-dependence of systemic clearance has been attributed to a capacity limitation of metabolism. Kinetics of blood 1,2-dibromoethane observed following an intravenous dose were similar to kinetics observed following an oral dose (Hissink et al. 2000). Following an intravenous injection of 1,2-dibromoethane, elimination from blood exhibited biphasic kinetics, with half-times estimated to be approximately 15 and 85 minutes following a dose of 10 mg/kg and 38 and 77 minutes following a dose of 50 mg/kg (Hissink et al. 2000). Systemic clearance was slower (28 mL/minute/kg) following a 50 mg/kg intravenous dose compared to a 10 mg/kg dose (75 mL/minute/kg; Hissink et al. 2000).

Based on the rapid and extensive metabolism and systemic clearance seen in animals, the fate of 1,2-dibromoethane in humans would be expected to be similar. The lack of persistence of metabolites in the tissues indicate that 1,2-dibromoethane is readily removed from the body. Low-level exposure would not be expected to result in accumulation of 1,2-dibromoethane or its metabolites in human tissue. However, theoretically, acute high-level exposure may saturate metabolic pathways and consequently allow 1,2-dibromoethane to accumulate in the tissues for a longer period of time (Hissink et al. 2000).

Plotnick and Conner (1976) reported that 10–12% of a dose is excreted via the lungs 72 hours after intraperitoneal injection of 30 mg/kg ^{14}C-1,2-dibromoethane to guinea pigs. The majority of the dose was accounted for in the urine (65.9%), liver (2.16%), and feces (3%).

Intraperitoneal administration of 37.6, 75, or 113 mg 1,2-dibromoethane/kg/day (0.2, 0.4, or 0.6 mmol/kg) to rats resulted in metabolic biotransformation into mercapturic acid, which was strongly indicative of saturable metabolism (Goyal et al. 1989). Administration of L-2-oxothiazolidine-4-carboxylic acid (OTCA) (4±5 mmol/kg) enhanced glutathione availability and increased excretion of urinary mercapturic acid at the higher doses. These results suggest that OTCA increases the capacity for detoxification via the glutathione pathway.

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

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

Hissink et al. (2000) Model for Rats and Humans

Model Structure. Hissink et al. (2000) reported a PBPK model of 1,2-dibromoethane in rats and humans. The model includes compartments representing blood, lung, stomach and intestines, fat, kidneys, liver, skeletal muscle, testes, and lumped compartments representing other rapidly or slowly perfused tissues. Absorption of ingested 1,2-dibromoethane is simulated as a series of first-order transfers through and out of the gastrointestinal tract, which are governed by rate coefficients (hour^{-1}). These include transfer coefficients for stomach lumen to small intestine lumen, small intestine lumen to liver, stomach lumen to stomach tissue, and small intestine lumen to small intestine tissue. Absorption of inhaled 1,2-dibromo-ethane is simulated as flow-limited transfer from inhaled air to blood governed by a ventilation rate (L/hour), a blood:air partition coefficient, and cardiac output (L/hour). Transfers of 1,2-dibromoethane between blood and each tissue compartment are simulated as flow-limited transfers governed by

tissue:blood partition coefficients and tissue blood flows (L/hour). Elimination of absorbed 1,2-dibromoethane is attributed entirely to metabolism, which is assumed to occur in all tissues, except fat, and rapidly and slowly perfused tissues. Two metabolism pathways are included in the model: (1) capacity limited oxidation mediated by CYP450, assumed to be entirely P450E1, governed by a V_{max} (µmol/hour/kg) and K_m (µM); and (2) conjugation with GSH mediated by GST, governed by a rate coefficient. The CYP450 pathway is assumed to active in kidney, liver, and lung of rats and in liver and lung of humans. The GST pathway is assumed to be active in kidney, liver, lung, stomach and small intestines, skeletal muscle, and testes of both rats and humans.

Parameter Values. Parameter values for the model and literature sources of the estimates are reported in Table 1 of Hissink et al. (2000). Metabolic parameters were derived from *in vitro* studies that estimated enzyme or pathway kinetics parameters in rat or human tissues (Ploemen et al. 1997). Some parameters were indicated as having been derived from *in vivo* data, with no further explanation (e.g., gastrointestinal absorption parameters). Absorption parameters were assigned different values for oral dosing at 50 and 150 mg/kg.

Model Evaluation. Hissink et al. (2000) compared model predictions of blood 1,2-dibromoethane kinetics in rats following a single gavage dose of 1,2-dibromoethane (50 or 150 mg/kg) or a single intravenous dose (10 or 50 mg/kg). Inclusion of extrahepatic metabolism improved agreement between observations and predictions for blood 1,2-dibromoethane concentrations following both the oral and intravenous dose. Hissink et al. (2000) explored the impact of including active extrahepatic metabolism in the performance of the model. In general, assigning all metabolism to the liver resulted in predictions of blood 1,2-dibromoethane that were higher than when extrahepatic metabolism was assumed to occur (see Figure 2 of Hissink et al. 2000). This effect resulted from greater metabolic clearance of 1,2-dibromoethane when extrahepatic metabolism was active. Including active extrahepatic metabolism improved agreement between predicted and observed blood 1,2-dibromoethane time profiles for both oral and intravenous dosing. However, the model has not been evaluated for predicting blood 1,2-dibromoethane kinetics in rats repeatedly dosed or exposed by inhalation and was not evaluated for making dosimetry predictions in humans; therefore, a figure depicting this model has not been included.

Model Applications. Hissink et al. (2000) applied the model to predicting blood concentration of 1,2-dibromoethane and cumulative metabolism through the CYP450 and GST pathways for 8-hour inhalation exposures to 40 ppm 1,2-dibromoethane in rats and humans (see Figure 3 of Hissink et al. 2000). The model predicted a rapid decline in blood 1,2-dibromoethane concentrations following

cessation of inhalation exposures. Higher cumulative metabolism through both the CYP450 and GST pathways was predicted in rats compared to humans. Inclusion of active extrahepatic metabolism in the model increased cumulative metabolism. The relative amounts of metabolites predicted to be formed from the CYP450 and GST pathways depended on assumptions regarding the relative activities of the two pathways. Alternative parameter values for the two pathways were explored based on expression ratios obtained from human liver samples (Ploeman et al. 1997). High P450E1/GST activity ratios resulted in greater contributions of CYP450 metabolism to overall elimination from metabolism. No reports describing risk assessment applications of the Hissink et al. (2000) model were located (e.g., dose-response assessment or dosimetry extrapolation).

3.1.6 Animal-to-Human Extrapolations

PBPK models for 1,2-dibromoethane in rats and human have been reported and used to make dosimetry comparisons between rats and humans exposed by the inhalation route (Hissink et al. 2000). However, the models have not been evaluated for accuracy of predictions of toxicokinetics in humans, or of toxicokinetics of inhalation dosing or repeated dosing in rats or humans. Therefore, use of these models for extrapolating internal dosimetry in rats to humans is not recommended without further verification of the model for these types of applications.

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

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

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

No data are available on the toxicity of 1,2-dibromoethane in children, but it is assumed that effects will be similar to those seen in adults. Developmental studies in animals observed incomplete ossification of the skeleton following gestational exposure to inhaled 1,2-dibromoethane (see study details in Section 2.17). However, no information on developmental effects in humans was identified.

1,2-Dibromoethane produces damage to the respiratory tract, gastrointestinal system, liver, kidneys, or male reproductive system in humans and animals. Individuals with underlying diseases of the systems may be more sensitive to the toxicity of 1,2-dibromoethane.

As discussed in Section 2.20 (Genotoxicity), the major mechanism of genotoxicity of 1,2-dibromoethane is conjugation 1,2-dibromoethane with GSH to an active genotoxic metabolite. This reaction is catalyzed by GST, which exists as isozymes. Thus, polymorphisms in GST may alter toxicity of glutathione. For example, in a study in human fibroblasts from individuals with decreased GSH levels due to a hereditary deficiency, the number of sister chromatid exchanges was significantly lower than in fibroblast from individuals without this deficiency (DeLeve 1997).

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

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

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to 1,2-dibromoethane are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for 1,2-dibromoethane from this report are discussed in Section 5.6, General Population Exposure.

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

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

3.3.1 Biomarkers of Exposure

Precluding the detection of 1,2-dibromoethane in blood or urine, there are no specific exposure biomarkers. In a 2007-2008 survey of 2,577 individuals, 1,2-dibromoethane in blood was below the limits of detection (<0.015 ng/mL) (CDC 2017). Urinary mercapturic acids have been considered as possible biomarkers of exposures of electrophilic chemicals, including 1,2-dibromoethane (Calafat et al. 1999; De Rooij et al. 1998; van Welie et al. 1992). Because various electrophilic chemicals share common pathway for conjugation with GSH, urinary mercapturic acids would not specific for 1,2-dibromoethane. For example, 2-hydroxyethyl mercapturic acid is a urinary metabolite for a variety of electrophilic hydrocarbons, including 1,2-dibromoethane, acrylonitrile, 2-brompropanol, 2-chloroethylnitroso ureas, ethene, ethylene oxide, and vinyl chloride (De Rooij et al. 1998). Data on urinary levels of 2-hydroxyethyl mercapturic acid (N-acetyl-S-(2-hydroxyethyl)-L-cysteine) in the U.S. non-institutionalized population are collected as part of the National Health and Nutrition Examination Survey (NHANES) (Calafat et al. 1999; CDC 2017). Based on data for the period 2011–2012, the 2-hydroxyethyl mercapturic acid geometric mean and 95th percentile in children (6–11 years of age) were 1.69 and 5.11 µg/g creatinine, respectively (CDC 2017). The 95th percentile for adults (≥20 years of age) was 6.87 µg/g creatinine; the geometric mean for adults was not reported. These levels reflect exposures to all chemicals that are metabolized to 2-hydroxyethyl mercapturic acid, including 1,2-dibromoethane.

3.3.2 Biomarkers of Effect

There are no adverse effects that are specific for or unique to 1,2-dibromoethane. However, some biochemical markers may indicate effects of 1,2-dibromoethane. Biochemical markers of effect are typically measured in tissues collected by methods that are non-invasive (e.g., urine, exhaled air) or minimally invasive (e.g., blood). Protein or DNA adducts could potentially provide biomarkers of effective (e.g., genotoxic) dose or long-term exposure because they are retained form longer periods of time (Van Welie et al. 1992). The DNA adduct, S-[2-(N7-guanyl)ethyl]mercapturic acid, would be of potential importance as a biomarker for 1,2-dibromoethane because it is thought to represent the dose of reactive metabolite formed from 1,2-dibromoethane, and has been implicated in 1,2-dibromoethane genotoxicity and carcinogenicity (Bolt et al. 1986; Guengerich et al. 1995; Koga et al. 1986). However, formation of S-[2-(N7-guanyl)ethyl]mercapturic acid is not unique to 1,2-dibromoethane; it is also formed in association with exposures to other electrophiles metabolized through the GST pathway (Guengerich 2005). Adducts with serum albumin may also be potential biomarkers of reactive metabolites produced from 1,2-dibromoethane, as 1,2-dibromoethane and its metabolites can bind covalently to serum albumin (Kaphalia and Ansari 1992).

3.4 INTERACTIONS WITH OTHER CHEMICALS

Exposure to chemicals that modify activity of GST have the potential to alter the toxicity of 1,2-dibromoethane. Agents that inhibit GST have been shown to increase hepatotoxicity of 1,2-dibromoethane. These chemicals include ethanol and its metabolite (i.e., acetaldehyde), the acetaldehyde inhibitor disulfiram (Wong et al. 1982), diethylmaleate (Botti et al. 1986), and carbon tetrachloride (Aragno et al. 1996; Chiarpotto et al. 1995a, 1995b; Danni et al. 1991). This effect is thought to occur as the result of increasing metabolism through the CYP450 pathway and increased formation of 2-bromacetaldehyde, a reactive product of CYP450 in liver and other tissues (Guengerich et al. 1991; Tamura et al. 1986; Van Duuren et al. 1985; Wormhoudt et al. 1996a, 1996b).

Chemicals that deplete cellular GSH have been shown decrease the formation of 1,2-dibromoethane-DNA adducts and genotoxicity of 1,2-dibromoethane. These chemicals include diethylmaleate and butathione sulfoxamine (Cho and Guengerich 2013; Cmarike et al. 1990). This effect is thought to occur as the result of decreasing metabolism through the GST and decreased formation of S-(2-bromoethyl)-glutathione, a reactive product of GST which can form DNA adducts (Cho and Guengerich 2013; DeLeve 1997; Thomas et al. 2001; Van Bladeren et al. 1981).

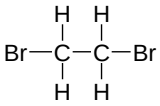
Consistent with the effect of depletion of GST, hereditary deficiency in GST has been associated with decreased genotoxicity of 1,2-dibromoethane in cultured human fibroblasts (DeLeve 1997). In the opposite direction, chemicals that induce GST increase metabolism of 1,2-dibromoethane through the GST pathway. These include coumarin, ethoxyquin, and phenobarbital (Sherratt et al. 1998). This suggests the possibility that chemical exposures that result in GST induction could also potentiate the genotoxicity of 1,2-dibromoethane.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

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

Table 4-1. Chemical Identity of 1,2-Dibromoethane

Characteristic	Information	Reference
Chemical name	1,2-Dibromoethane	Windholz 1983
Synonym(s) and registered trade name(s)	Ethylene dibromide; dibromoethane; ethylene bromide; ethane, 1,2-dibromo-; EDB; α-, β-dibromoethane; sym-dibromoethane; glycol bromide; glycol dibromide; 1,2-dibromoethano (Italian); bomoro ei etile (Italian); 1,2-dibroomethaan (Dutch); althylenbromid (German); dibromure d'ethylene (French); dwubromoetan (Polish); Bromofume; Dowfume W85; Dowfume EDB; Dowfume 40, W-10, W-15, W-40; Dowfume MC-2; Iscobrome D; ENT 15, 349; Netis; Pestmaster EDB-85; Santryuum; Unifume; EDB-85; Fumogas; Icopfume soilbrom-85; soilfume; DBE	HSDB 1989; Weiss 1986; Windholz 1983
Chemical formula	$C_2H_4Br_2$; $BrCH_2CH_2Br$	Windholz 1983
Chemical structure		
CAS Registry Number	106-93-4	Weiss 1986

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

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

Table 4-2. Physical and Chemical Properties of 1,2-Dibromoethane

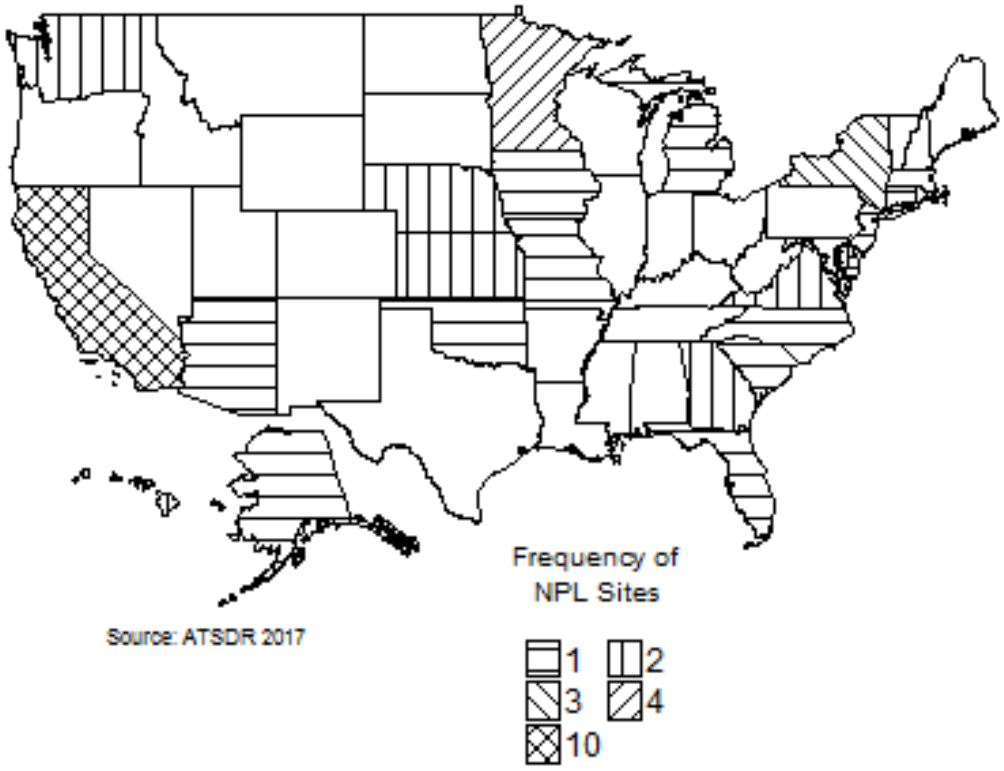
Property	Information	Reference
Molecular weight	187.86 187.88 188.0	Weiss 1986 Windholz 1983 NIOSH 1985
Color	Colorless	Weiss 1986
Physical state at 15°C, 1 atm	Liquid	Weiss 1986
Melting point	10°C	NIOSH 1978
Boiling point	131–132°C	Windholz 1983
Density at 25°C	2.172 g/cm^3	Windholz 1983
Odor	Mild sweet odor, like chloroform	Weiss 1986
Odor threshold:		
Water	No data	
Air	No data	
Solubility:		
Water at 20°C	0.4 g/100 g water	Weiss 1986
Water at 25°C	0.429 g/100 g water	Parrish 1983
Organic solvents	Miscible with alcohol, ether	Windholz 1983
Partition coefficients:		
Log K_{ow}	86	Steinberg et al. 1987
Log K_{oc}	66	Rogers and Mcfarlane 1981
Vapor pressure at 25°C	11 mmHg	Windholz 1983
Henry's law constant at 20°C	8.2x10^{-4} atm m^3/mol	Rathbun and Tai 1986
Autoignition temperature	Not flammable	Weiss 1986
Flashpoint	Not flammable	Weiss 1986
Flammability limits	Not flammable	Weiss 1986
Conversion factors	No data	
Explosive limits	No data	

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

1,2-Dibromoethane has been identified in at least 43 of the 1,854 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2017). However, the number of sites in which 1,2-dibromoethane has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 42 are located within the United States and 1 is located in Puerto Rico (not shown).

Figure 5-1. Number of NPL Sites with 1,2-Dibromoethane Contamination



- 1,2-Dibromoethane is used as an intermediate in the production of dyes, resins, gums, and waxes, and as a pesticide treatment of felled logs. Previously, 1,2-dibromoethane was used as an additive to leaded gasoline and as a fumigant; however, these uses are historical only.

- 1,2-Dibromoethane can enter the air and surface waters from industrial releases into air or effluent discharges into water. 1,2-Dibromoethane is highly mobile in soil, yet may persist in it. It is water soluble and may be found in groundwater.

- Residual 1,2-dibromoethane bound to soil micropores is relatively immobile and resistant to degradation. This material is present in ppb concentrations and may be slowly leached from soil micropores over years to contaminate groundwater. If the micropores are disturbed and crushed, there is a greater likelihood of releasing the bound 1,2-dibromoethane. The compound persists in soils and groundwater.

- 1,2-Dibromoethane is transformed in the atmosphere by reaction with hydroxyl radicals and in soils by biodegradation. Volatilization is the most important removal process for 1,2-dibromoethane released to surface waters.

- The most important route of exposure to 1,2-dibromoethane for most members of the general population is ingestion of contaminated drinking water or through inhalation of 1,2-dibromoethane released into air. Individuals living in the vicinity of 1,2-dibromoethane processing facilities or hazardous waste sites contaminated with 1,2-dibromoethane may be exposed to higher concentrations of the compound.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

1,2-Dibromoethane is a halogenated aliphatic hydrocarbon produced when gaseous ethylene comes in contact with bromine. The mixing of ethylene and bromine is accomplished in a variety of ways. One of the more common manufacturing processes involves a liquid-phase bromination of ethylene at 35–85°C. After the bromination of ethylene, the mixture is neutralized to free acid and then purified by distillation. Other methods of 1,2-dibromoethane formation include the hydrobromination of acetylene and a reaction of 1,2-dibromoethane with water (Fishbein 1980; HSDB 1989).

In the 1970s, production of 1,2-dibromoethane in the United States remained stable, averaging 280 million pounds per year; production peaked in 1974 at 332.1 million pounds. In 1979, the production volume averaged 285.9 million pounds (Santodonato et al. 1985). Since then, production has consistently decreased. This decrease was primarily due to increased government regulation and restriction on products using 1,2-dibromoethane. Consequently, by 1982, the U.S. production of 1,2-dibromoethane reached a low of 169.8 million pounds (Santodonato et al. 1985). Data on production of 1,2-dibromoethane are not available after 1984.

1,2-Dibromoethane production constitutes one of the largest single uses of bromine. Table 5-1 summarizes information on U.S. companies that manufactured or used 1,2-dibromoethane in 2016 (TRI16 2017).

Table 5-1. Facilities that Produce, Process, or Use 1,2-Dibromoethane

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
CA	2	0	49,999,999	7, 12
LA	2	0	999	1, 5, 7
MN	1	1,000	9,999	7, 9
MS	1	10,000	99,999	7
MT	1	10,000	99,999	2, 3, 4, 7, 9, 10
NY	1	100	999	12
OH	1	1,000	9,999	12
TX	3	10,000	99,999	2, 4, 7, 9

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

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

Source: TRI16 2017 (Data are from 2016)

5.2.2 Import/Export

The U.S. import levels of 1,2-dibromoethane fluctuated between 1977 and 1981, reaching a peak in 1980 of 0.861 million pounds and a low in 1979 of 0.079 million pounds (Santodonato et al. 1985). Previous producers of 1,2-dibromoethane include the United Kingdom, Benelux, France, Spain, Italy, and Switzerland; collectively they produce 10–66 million pounds per year (Fishbein 1980).

The U.S. export level of 1,2-dibromoethane in 1981 was 29.8 million pounds. This was substantially lower than in 1978 when the U.S. export level was 84.8 million pounds (Santodonato et al. 1985).

5.2.3 Use

The main historical use of 1,2-dibromoethane was as an anti-knock additive in leaded gasoline, where 1,2-dibromoethane acted as a "scavenger" that converted lead oxides to lead halides. In the 1970s and early 1980s, the second largest application of 1,2-dibromoethane was as a soil fumigant to protect against insects, pests, and nematodes in citrus, vegetable, and grain crops and as a fumigant for turf, particularly on golf courses (HSDB 1989). However, in 1984, EPA banned the use of 1,2-dibromoethane as a soil

and grain fumigant, thus eliminating this market for 1,2-dibromoethane manufacturers (Santodonato et al. 1985).

Current uses of 1,2-dibromoethane include treatment of felled logs for bark beetles, termite control, control of wax moths in beehives, spot treatment of milling machinery, Japanese beetle control in ornamental plants, as a chemical intermediate for dyes, resins, waxes, and gums, and precursor in the synthesis of vinyl chloride (EPA 2004; HSDB 1989).

5.2.4 Disposal

Disposal methods of 1,2-dibromoethane fall under the general regulation for organic pesticide disposal developed by EPA. The two main methods of disposal are incineration and burial. Incineration is the preferred method; disposal by burial, in a specially designated landfill, is used only if no appropriate incineration facilities are available. All incinerator emissions must meet the requirements of the Clean Air Act of 1970 relating to gaseous emissions. Similarly, dispose of combustible organic pesticide containers in a pesticide incinerator or bury in a specially designated landfill. Triple rinse noncombustible containers and recycle them.

5.3 RELEASES TO THE ENVIRONMENT

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

1,2-Dibromoethane was widely released to the environment mainly as a result of the historical use of the compound as a gasoline additive and a fumigant (Fishbein 1979). The compound was also released from industrial processing facilities. For example, in 1977, 1,2-dibromoethane was found in air, water, soil, and sediment samples taken near industrial bromine facilities in Arkansas (Pellizzari et al. 1978).

Class and Ballschmitter (1988) suggested that 1,2-dibromoethane may be produced naturally in seawater from a dibromomethane precursor via a halogen exchange reaction. The dibromoethane is produced by brown algae via haloperoxidase enzymes and released to seawater.

5.3.1 Air

Estimated releases of 783 pounds (~0.36 metric tons) of 1,2-dibromoethane to the atmosphere from 12 domestic manufacturing and processing facilities in 2016, accounted for about 92% of the estimated total environmental releases from facilities required to report to the TRI (TRI16 2017). These releases are summarized in Table 5-2.

Historically, 1,2-dibromoethane releases to the atmosphere have been due to fugitive emissions from leaded gasolines, automobile exhaust, and the former use of the compound as a fumigant (Fishbein 1979).

5.3.2 Water

No 1,2-dibromoethane was released to surface water or publicly owned treatment works from 12 domestic manufacturing and processing facilities in 2016 (TRI16 2017). These releases are summarized in Table 5-2.

Historical use of 1,2-dibromoethane as a solvent and chemical intermediate has led to release of the compound to surface waters in industrial process effluents (Fishbein 1979).

5.3.3 Soil

Estimated releases of 69 pounds (~0.03 metric tons) of 1,2-dibromoethane to soil from 12 domestic manufacturing and processing facilities in 2016, accounted for about 8% of the estimated total environmental releases from facilities required to report to the TRI (TRI16 2017). No 1,2-dibromoethane was released via underground injection (TRI16 2017). These releases are summarized in Table 5-2.

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

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
CA	2	2	0	0	10	0	2	10	12
LA	2	740	0	0	0	0	740	0	740
MN	1	6	0	0	1	0	6	1	7
MS	1	18	0	0	58	0	18	58	76
MT	1	ND	ND	ND	ND	ND	ND	ND	ND
NY	1	1	0	0	0	0	1	0	1
OH	1	1	0	0	0	0	1	0	1
TX	3	15	0	0	0	0	15	0	15
Total	12	783	0	0	69	0	783	69	852

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

ND = no data; RF = reporting facilities; UI = underground injection

Source: TRI16 2017 (Data are from 2016)

The main sources of 1,2-dibromoethane release to soils appear to be the historical use of the compound as a soil fumigant and land disposal of wastes containing the compound.

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Air. The vapor pressure (11 mmHg at 25°C) of 1,2-dibromoethane suggests that the compound readily partitions to the atmosphere following release to surface water and soils. 1,2-Dibromoethane can be transported for long distances in the atmosphere before removal in wet and dry deposition or degradation.

Water. Volatilization is the most important removal process for 1,2-dibromoethane released to surface waters. Volatilization half-lives of 1–16 days have been estimated for flowing and standing surface waters. Sorption to sediment or suspended particulate material is not expected to be an important process (EPA 1987a, 1987b; HSDB 1989).

Sediment and Soil. As a result of its low sorption potential, high vapor pressure, and high water solubility, 1,2-dibromoethane is rapidly lost from soils by volatilization to the atmosphere or leaching to surface water and groundwater (EPA 1987a). In studies with two silty clay loam soils and cation saturated montmorillonite clays, a maximum of only 4% of applied 1,2-dibromoethane was found to be sorbed to soil particulates; an experimental soil sorption coefficient (K_{oc}) value of 66 was reported (Rogers and McFarlane 1981). However, Steinberg et al. (1987) have reported that a small fraction of 1,2-dibromoethane released to soils (that is not rapidly volatilized, leached, or degraded) is sorbed strongly to soil micropores where it persists for long periods of time, resistant to mobilization and degradation. This residual 1,2-dibromoethane may slowly leach from micropore sites to contaminate groundwater, with a leaching half-life of years.

Other Media. As a result of its high water solubility, 1,2-dibromoethane is not expected to bioconcentrate or biomagnify in terrestrial and aquatic food chains. Low-exposure bioconcentration factors suggest that 1,2-dibromoethane has limited bioaccumulation potential in organisms (ECHC 2013).

5.4.2 Transformation and Degradation

Air. Direct photolysis of 1,2-dibromoethane in the troposphere is not expected to occur (Jaber et al. 1984). 1,2-Dibromoethane reacts with hydroxyl radicals in the atmosphere; the half-life for the reaction has been estimated to be about 40 days (EPA 1987a).

Water. Biotic and abiotic degradation of 1,2-dibromoethane in surface waters is slow relative to volatilization of the compound to the atmosphere (EPA 1987b). 1,2-Dibromoethane is resistant to hydrolysis (Jaber et al. 1984); the hydrolytic half-life of the compound has been reported to range from 2.5 years (Vogel and Reinhard 1982) to 13.2 years (HSDB 1989). As a result of its hydrolytic stability and the limited biological activity in subsurface soils, 1,2-dibromoethane in groundwater is expected to persist for years.

Sediment and Soil. 1,2-Dibromoethane undergoes biodegradation in aerobic surface soils; the rate has been reported to decrease with increasing concentrations of the compound (Pignatello 1986). Biodegradation appears to be limited under anaerobic conditions (Bouwer and McCarty 1983). Residual 1,2-dibromoethane sorbed to soil micropores is resistant to biodegradation, chemical transformation, and mobilization; Steinberg et al. (1987) detected the compound in a surface soil 19 years after 1,2-dibromoethane had been applied for the last time as a fumigant.

5.5 LEVELS IN THE ENVIRONMENT

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

As a result of its persistence in soil and groundwater, and past widespread use as a gasoline additive and fumigant, 1,2-dibromoethane has been detected in ambient air, soils, groundwater, and food. However, most of the monitoring data reported in this section are not current. Volatilization is the most important removal process for 1,2-dibromoethane released to surface waters. Since only a small fraction of the compound is sorbed to soil, sorption to sediment and subsequent persistence in sediment is not expected to be an important process in the removal of 1,2-dibromoethane from the environment. Because of the phaseout of the use of leaded gasoline and the ban on fumigant uses of 1,2-dibromoethane, current ambient media concentrations, with the potential exception of groundwater concentrations, are expected to be much lower than the levels reported here.

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

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

Media	Detection limit	Reference
Air	0.0003–1 ppm	NIOSH 1987
Water	0.01 µg/L	EPA 1987b
Soil	≤0.018 µg/g	Sawhney et al. 1988
Biological tissues	0.5 µg/g	Letz et al. 1984

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

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

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

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (ppb)	2.4	2.53	15,800	30	16
Soil (ppb)	118,000	65,600	47,400	5	3
Air (ppbv)	0.01	0.029	4,503.15	5	4

[a]Concentrations found in ATSDR site documents from 1981 to 2017 for 1,832 NPL sites (ATSDR 2017). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

1,2-Dibromoethane has been detected in ambient air samples collected at a number of sites in the United States. In a review of available monitoring data for volatile organic compounds, Brodzinsky and Singh (1983) reported the following median concentrations of 1,2-dibromoethane in ambient air samples in the United States: less than detection limit in rural and remote areas; 2.6 parts per trillion (ppt) in urban and suburban areas; and 1.9 ppt in source-dominated areas. Typical daily concentrations at four sites in the metropolitan Los Angeles area in 1983 were reported to range from <5 to 17 ppt (Kowalski et al. 1985b). Ambient air concentrations of 1,2-dibromoethane for other metropolitan areas in the United States in 1980 were reported by Singh et al. (1981) as follows (mean [range]): 15 ppt [10–368 ppt] in Houston, Texas; 16 ppt [8–26 ppt] in St. Louis, Missouri; 31 ppt [10–78 ppt] in Denver, Colorado; and 22 ppt [10–47 ppt] in Riverside, California.

1,2-Dibromoethane has also been detected in ambient air samples collected at two hazardous waste sites in New Jersey at geometric mean concentrations of 20–50 ppt; the maximum value reported was 6,710 ppt (La Regina et al. 1986).

Long-range transport of 1,2-dibromoethane from industrialized areas may have been the source of the compound found in ambient air samples collected in the Arctic by Rasmussen and Khalil (1984). 1,2-Dibromoethane concentrations in the 1983 study were reported to range from 1.0 to 1.9 ppt.

Natural production was speculated to be the source of 1,2-dibromoethane found in ambient air samples collected from open areas of the North and South Atlantic Ocean by Class and Ballschmitter (1988); concentration levels were reported to be <0.001–0.003 ppt.

5.5.2 Water

As a result of its volatility, 1,2-dibromoethane has been detected at only low levels in surface water samples collected in the United States. Ewing et al. (1977) reported that 1,2-dibromoethane was detected (i.e., concentrations >1,000 ppt) in only 2 of 204 surface water samples collected near heavily industrialized sites throughout the country. 1,2-Dibromoethane was detected at a maximum concentration of 200 ppt in 11 of 175 surface water samples collected in New Jersey from 1977 to 1979 (Page 1981). However, the compound has been widely detected in groundwater samples collected in the United States. In the late 1980s, the states with reported 1,2-dibromoethane groundwater contamination problems included Wisconsin (Krill et al. 1986), Hawaii (Oki and Giambelluca 1987), New Jersey (Page 1981), and Georgia (1,000–94,000 ppt) (Marti et al. 1984). California, Connecticut, Georgia, Massachusetts, New York, and Washington have historically been identified with 1,2-dibromoethane in groundwater. The median and maximum concentrations reported were 900 and 14,000 ppt, respectively (Williams et al. 1988).

Class and Ballschmitter (1988) suggested that brown algae may be the source of the <0.01–0.03 ppt of 1,2-dibromoethane found in the marine water samples collected from the North and South Atlantic Oceans.

5.5.3 Sediment and Soil

This section has not been updated with new information. No information was found in the literature regarding historical ambient concentrations of 1,2-dibromoethane in surface soils in the United States.

5.5.4 Other Media

1,2-Dibromoethane residues in foods have decreased since the use of the compound as a fumigant was banned by EPA. For example, Daft (1989) reported finding 1,2-dibromoethane in only 2 of 549 samples of fatty and nonfatty foods analyzed for fumigant residues. 1,2-Dibromoethane was detected in samples of peanut butter and whiskey at a mean concentration of 7 µg/g (range 2–11 ng/g). Historical foodstuff residue levels have been reviewed by EPA (1983).

5.6 GENERAL POPULATION EXPOSURE

Current human exposure to 1,2-dibromoethane for most members of the general population appears to be limited to ingestion of low levels of the compound in contaminated drinking water. Data from the early 1980s indicate that daily intake from drinking water has been estimated to range from 0 to 16 µg/kg/day (EPA 1985). Ingestion of contaminated foodstuffs does not appear to be an important source of exposure; EPA (1983) estimated that the maximum intake of 1,2-dibromoethane from contaminated foods was 0.09 µg/kg/day. Average inhalation of ambient air also appears to be of less importance than ingestion of groundwater, although the available data are not current and variable. Daily respiratory intake was estimated by EPA (1985) to range from 0 to 79 µg/kg/day. Average inhalation exposures in four metropolitan areas of the United States in 1980 were estimated by Singh et al. (1981) to range from 2.8 to 9.9 µg/day (or 0.04–0.14 µg/kg/day for a 70-kg human). However, inhalation of 1,2-dibromoethane released to indoor air from contaminated groundwater (e.g., during showering) may be an important source of human exposure. For example, McKone (1987) modeled the mass transfer of several volatile organic compounds, including 1,2-dibromoethane, from water to air and calculated a maximum concentration of 1,2-dibromoethane in household air of 2.4×10^{-4} mg/L, assuming a tap water concentration of 1 mg/L.

Exposure of the general population to higher concentrations of 1,2-dibromoethane may result from contact with contaminated hazardous waste site media, principally soils and groundwater. The human population potentially exposed to 1,2-dibromoethane through contact with contaminated waste site media is unknown.

In occupational settings, current exposures are expected to be substantially reduced from historical levels (Santodonato et al. 1985). The large numbers of people exposed to 1,2-dibromoethane in the workplace through its manufacture and use as a gasoline additive and fumigant have decreased as these uses of the

compound have been limited. NIOSH (1977) estimated that as many as 108,000 workers were potentially exposed to 1,2-dibromoethane during production and fumigant related uses, and an additional 875,000 workers were exposed to lower levels of the compound through its use in leaded gasoline. Exposure levels are expected to be substantially reduced from the historical inhalation and dermal exposures reported in manufacturing and processing facilities by Rumsey and Tanita (1978) and in fumigation operations reviewed by EPA (1983).

Data from the Fourth National Report on Human Exposure to Environmental Chemical are summarized in Table 5-5. Blood 1,2-dibromoethane measurements were below of limit of detection (CDC 2017).

Table 5-5. Blood 1,2-Dibromoethane Levels (ng/mL) in the NHANES U.S. Population

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	2007–2008	ND	<LOD	<LOD	<LOD	<LOD	2,577
Age group							
12–19 years	2007–2008	ND	<LOD	<LOD	<LOD	<LOD	409
20–59 years	2007–2008	ND	<LOD	<LOD	<LOD	<LOD	1,389
≥60 years	2007–2008	ND	<LOD	<LOD	<LOD	<LOD	779
Sex							
Males	2007–2008	ND	<LOD	<LOD	<LOD	<LOD	1,270
Females	2007–2008	ND	<LOD	<LOD	<LOD	<LOD	1,307
Race/ethnicity							
Mexican Americans	2007–2008	ND	<LOD	<LOD	<LOD	<LOD	471
Non-Hispanic blacks	2007–2008	ND	<LOD	<LOD	<LOD	<LOD	532
Non-Hispanic whites	2007–2008	ND	<LOD	<LOD	<LOD	<LOD	1,165

CI = confidence interval; LOD = level of detection = 0.015 ng/mL; ND = not detected; NHANES = National Health and Nutrition Examination Survey

Source: CDC 2017

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Members of the general population with potentially high exposure to 1,2-dibromoethane include individuals living near the NPL sites currently known to be contaminated with the compound. The size of the population and the concentrations of 1,2-dibromoethane in all of the contaminated media to which these people are potentially exposed have not been completely characterized. Other populations with potentially high exposures to 1,2-dibromoethane include individuals in the six states with confirmed

groundwater contamination, and workers involved in the manufacture and continued use of 1,2-dibromoethane.

CHAPTER 6. ADEQUACY OF THE DATABASE

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

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

6.1 Information on Health Effects

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

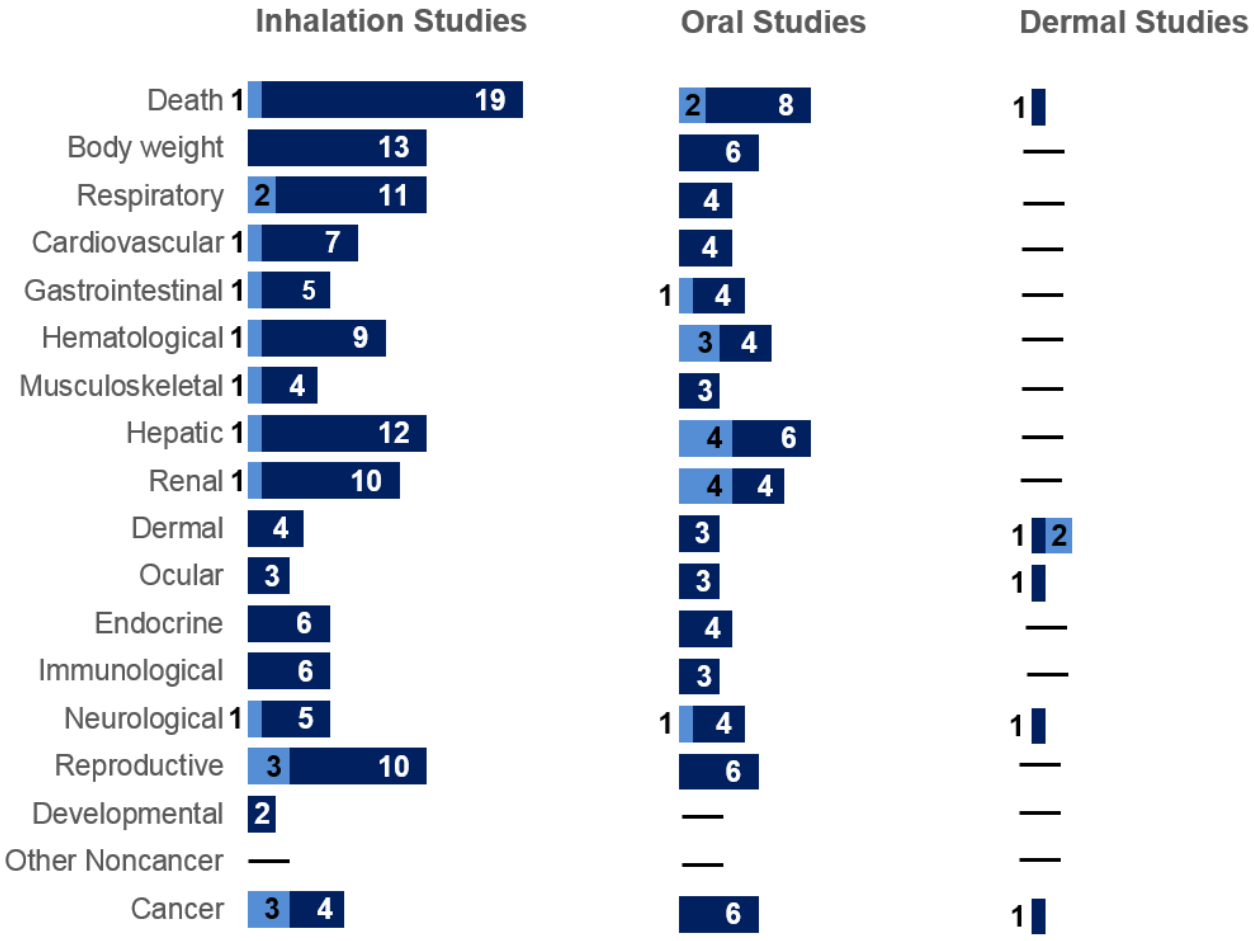
6.2 Identification of Data Needs

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

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

Potential body weight, respiratory, hepatic, and reproductive effects were the most studied endpoints

The majority of the studies examined oral exposure in **animals** (versus **humans**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect.

MRLs. No MRLs have been derived for 1,2-dibromoethane. For acute and chronic inhalation exposure, severe effects and mortality were observed at the lowest exposures tested and, therefore, acute- and chronic-duration inhalation MRLs were not derived. For intermediate-duration oral exposure, effects observed at the lowest exposure tested (hyperplasia of nasal turbinates) is a potentially precarcinogenic effect; thus, an intermediate-duration inhalation MRL was not derived. For oral exposure, severe effects and mortality observed at the lowest exposures tested for all exposure duration categories preclude derivation of oral MRLs. More detailed discussions of the rationale for not deriving MRLs for 1,2-dibromoethane are provided in the MRL worksheets (Appendix A). Acute-, intermediate-, and chronic-duration inhalation and oral studies conducted at lower exposures (nonlethal) could provide data to identify the most sensitive, non-serious endpoints for 1,2-dibromoethane.

Health Effects. Available studies show that 1,2-dibromoethane damages several organ systems. However, as noted above, inhalation and oral studies conducted in laboratory animals at lower (nonlethal) exposures are needed to identify NOAEL and LOAEL values for effects for comprehensive toxicological endpoints. Other specific data needs are as follows.

Reproductive. Occupational exposure studies have evaluated effects to the male reproductive system (Ratcliffe et al. 1987; Schrader et al. 1988; Ter Haar 1980; Wong et al. 1979). Several studies in laboratory animals have identified the male reproductive system as a target for 1,2-dibromoethane (NCI 1978; NTP 1982; Short et al. 1979). Very little information is available regarding reproductive performance, although one study did not observe adverse effects on fertility in rats (Shivanandappa et al. 1987). Additional studies would be important to more fully explore potential reproductive effects of 1,2-dibromoethane in males and females.

Developmental. Only one study has evaluated the potential developmental effects of 1,2-dibromoethane, with results showing incomplete skeletal ossification in rats and mice (Short et al. 1978). Additional studies investigating developmental effect are needed to fully evaluate the potential for 1,2-dibromoethane to adversely affect the developing organism.

Epidemiology and Human Dosimetry Studies. Available data in humans exposed to 1,2-dibromoethane consists of a few case reports at lethal and near-lethal exposures and a few studies in workers, with only one occupational study providing exposure data and appropriate controls (Ratcliffe et al. 1987). Additional well-controlled studies in workers or the general population would be helpful in

evaluating the chronic human health risk from 1,2-dibromoethane exposure, including the potential for 1,2-dibromoethane to induce cancer in humans.

Biomarkers of Exposure and Effect. Use of 1,2-dibromoethane biomarkers has not been well-investigated or applied.

Absorption, Distribution, Metabolism, and Excretion. Few studies have quantitatively evaluated the absorption of 1,2-dibromoethane. No studies on the distribution of dermally administered 1,2-dibromoethane in animals were identified. Studies evaluating the toxicokinetics of 1,2-dibromoethane provide information on the absorption, distribution, metabolism, and excretion of 1,2-dibromoethane in animal models with no data available in humans. A single PBPK model has been developed for rats and humans (Hissink et al. 2000). However, the model has not been evaluated for predicting toxicokinetics in humans, or for predicting toxicokinetics in rats following inhalation exposure or repeated oral exposures. Additional toxicokinetic data are important to conduct these evaluations.

Comparative Toxicokinetics. Although a PBPK model has been developed for rats and humans (Hissink et al. 2000), it has not been evaluated for use in dosimetry extrapolation. Therefore, additional toxicokinetic data to allow for dosimetry extrapolations would be useful.

Children's Susceptibility. No studies have evaluated the toxicity of 1,2-dibromoethane in children or young animals. Studies in young animals would be useful to address potential concerns that children may be more susceptible to the toxicity of 1,2-dibromoethane than adults.

Physical and Chemical Properties. The physical/chemical properties of 1,2-dibromoethane, described in Table 4-2, are sufficiently well characterized to enable assessment of the environmental fate of the compound.

Production, Import/Export, Use, Release, and Disposal. Although 1,2-dibromoethane is currently produced and used in the United States, increased government regulation and restriction on products containing the compound probably have decreased the potential for exposure of the U.S. population (Fishbein 1980; Santodonato et al. 1985). 1,2-Dibromoethane is used as a chemical intermediate. Previous uses as a gasoline additive and soil fumigant are no longer permitted (Fishbein 1979, 1980; HSDB 1989; Santodonato et al. 1985; Stenger 1978). Incineration and burial are the main disposal methods; however, there is no accounting of disposal amounts by each method (HSDB 1989).

However, more recent data describing present domestic production levels, the proportions of 1,2-dibromoethane consumed by the various uses, as well as data on export levels and the countries to which these exports are made would be helpful in providing a broader, more up-to-date picture of the U.S. 1,2-dibromoethane industry as a whole.

Environmental Fate. 1,2-Dibromoethane partitions to the atmosphere and groundwater (Windolz 1983). It is transported in the atmosphere where it undergoes degradation by hydroxyl radicals (EPA 1987a). 1,2-Dibromoethane is mobile and biodegradable in soils, although 1,2-dibromoethane sorbed to soil micropores is immobile and persistent (Pignatello 1986; Steinberg et al. 1987). Additional information is needed on the persistence of 1,2-dibromoethane in groundwater and sorbed to soil micropores. This information will be helpful in establishing the half-life of the compound in the media of most concern for human exposure.

Bioavailability from Environmental Media. 1,2-Dibromoethane can be absorbed by inhalation of contaminated ambient air, dermal contact, and ingestion of contaminated drinking water and foodstuffs (EPA 1983; Jakobson et al. 1982; Letz et al. 1984; Rowe et al. 1952; Saraswat et al. 1986; Stott and McKenna 1984). Ingestion of contaminated groundwater is the exposure route of concern. Additional information is needed on the absorption of 1,2-dibromoethane from soil following ingestion or dermal contact. This information will be useful in determining the bioavailability of residual 1,2-dibromoethane in soils.

Food Chain Bioaccumulation. 1,2-Dibromoethane is not expected to bioconcentrate in plants, aquatic organisms, or animals, or biomagnify in terrestrial or aquatic food chains as a result of its high water solubility (NIOSH 1978; Parrish 1983). Additional information is needed on bioconcentration and biomagnification of the compound to confirm this predicted environmental behavior.

Exposure Levels in Environmental Media. 1,2-Dibromoethane has been detected in ambient air, groundwater, soils, and foodstuffs (Brodzinsky and Singh 1983; Daft 1989; EPA 1983; Ewing et al. 1977; Page 1981; Pellizzari et al. 1978; Singh et al. 1981; Williams et al. 1988). However, new monitoring data are currently needed.

Exposure Levels in Humans. As of 2008, NHANES reported that 1,2-dibromoethane in blood is less than the detection limit (0.015 ng/mL) for 2,577 individuals. 1,2-Dibromoethane can be measured in

6blood and metabolites can be detected in urine (Letz et al. 1984; Nachtomi et al. 1965). However, since the compound is rapidly and extensively metabolized in mammals, and 1,2-dibromoethane metabolites do not persist in tissues, these biomarkers have not been useful in identifying or quantifying human exposure to the compound.

Exposures of Children. No studies are available to assess whether children are at a higher exposure risk than adults to 1,2-dibromoethane. Studies examining potential exposure sources for children would be useful.

6.3 Ongoing Studies

One ongoing study was identified in NIH Reporter (2017); this study is summarized in Table 6-1.

Table 6-1. Ongoing Studies on 1,2-Dibromoethane

Investigator	Affiliation	Research description	Sponsor
Guengerich, F Peter	Vanderbilt University	Mechanism of action study on 1,2-dibromoethane crosslinks with DNA	NIEHS

DNA = deoxyribonucleic acid; NIEHS = National Institute of Environmental Health Sciences

Source: NIH Reporter 2017

CHAPTER 7. REGULATIONS AND GUIDELINES

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

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

Table 7-1. Regulations and Guidelines Applicable to 1,2-Dibromoethane

Agency	Description	Information	Reference
	Air		
EPA	RfC	$9x10^{-3}$ mg/m^3	IRIS 2004
WHO	Air quality guidelines	No data	WHO 2010
	Water & Food		
EPA	RfD	$9x10^{-3}$ mg/kg/day	IRIS 2004
	Drinking water standards and health advisories		EPA 2012
	1-Day health advisory (10-kg child)	0.008 mg/L	
	10-Day health advisory (10-kg child)	0.008 mg/L	
	DWEL	0.3 mg/L	
	National primary drinking water regulations		EPA 2009
	MCL	0.00005 (mg/L)	
WHO	Drinking water quality guidelines	0.0004 mg/L (0.4 µg/L) (provisional)	WHO 2004, 2017
FDA	EAFUS	No data[a]	FDA 2013
	Allowable level in bottled water	0.00005 mg/L	FDA 2017
	Cancer		
HHS	Carcinogenicity classification	Reasonably anticipated to be a human carcinogen	NTP 2016
EPA	Carcinogenicity classification	Likely to be carcinogenic to humans	IRIS 2004
	Inhalation unit risk, 95% upper bound	$6x10^{-4}$ $(µg/m^3)^{-1}$	
	Oral slope factor, 95% upper bound	$2x10^{0}$ $(mg/kg\text{-}day)^{-1}$	
IARC	Carcinogenicity classification	Group 2A[b]	IARC 1999

Table 7-1. Regulations and Guidelines Applicable to 1,2-Dibromoethane

Agency	Description	Information	Reference
	Occupational		
OSHA	PEL for general industry		OSHA 2016b
	8-hour TWA	20 ppm	
	Acceptable ceiling concentration	30 ppm	
	Maximum peak (5-minute)[c]	50 ppm	
	PEL (ceiling limit) for shipyards and construction	(C)25 ppm[d]	OSHA 2016a, 2017
NIOSH	REL		NIOSH 2016
	TWA (up to 10 hours)	0.045 ppm	
	Ceiling (15-minute)	0.13 ppm	
	IDLH	100 ppm	NIOSH 1994
	Emergency Criteria		
EPA	AEGLs-air		EPA 2016
	AEGL 1		
	10 minute	52 ppm	
	30 minute	26 ppm	
	60 minute	17 ppm	
	4 hour	7.1 ppm	
	8 hour	4.6 ppm	
	AEGL 2		
	10 minute	73 ppm	
	30 minute	37 ppm	
	60 minute	24 ppm	
	4 hour	10 ppm	
	8 hour	6.5 ppm	
	AEGL 3		
	10 minute	170 ppm	
	30 minute	76 ppm	
	60 minute	46 ppm	
	4 hour	17 ppm	
	8 hour	10 ppm	
DOE	PACs-air		DOE 2016b
	PAC-1[e]	17 ppm	
	PAC-2[e]	24 ppm	
	PAC-3[e]	46 ppm	

[a]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[b]Group 2A: probably carcinogenic to humans.
[c]Acceptable maximum peak, for a maximum duration of 5 minutes, above the acceptable ceiling concentration for an 8-hour shift.
[d]Skin designation.

Table 7-1. Regulations and Guidelines Applicable to 1,2-Dibromoethane

Agency	Description	Information	Reference

[e]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2016a).

AEGL = acute exposure guideline levels; DOE = Department of Energy; DWEL = Drinking Water Equivalent Level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; IDLH = Immediately Dangerous to Life or Health; IRIS = Integrated Risk Information System; MCL = Maximum Contaminant Level; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TWA = time-weighted average; WHO = World Health Organization

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

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

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

APPENDIX A

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

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dibromoethane
CAS Numbers: 106-93-4
Date: July 1992
March 2017—Updated literature search
Profile Status: Final
Route: Inhalation
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration inhalation MRL for 1,2-dibromoethane.

Rationale for Not Deriving an MRL: The available acute-duration inhalation studies were designed to assess lethality (Rowe et al. 1952) or developmental effects (Short et al. 1978) and did not evaluate comprehensive toxicological endpoints. At the lowest exposure level tested in acute-duration inhalation studies (20 ppm, 23 hours/day for gestational days 6–15), skeletal anomalies, a serious effect, were observed (Short et al. 1978). Therefore, data are not suitable for derivation of an acute-duration inhalation MRL.

Agency Contacts (Chemical Managers): Rae T. Benedict

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dibromoethane
CAS Numbers: 106-93-4
Date: July 1992
March 2017—Updated literature search
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration inhalation MRL for 1,2-dibromoethane.

Rationale for Not Deriving an MRL: Several studies have investigated effects of intermediate-duration inhalation exposure to 1,2-dibromoethane (Nitchke et al. 1981; NTP 1982; Reznik et al. 1980; Rowe et al. 1952; Short et al. 1979). Of these studies, NTP (1982) is the only study that conducted histopathological evaluations of comprehensive tissues. Two studies conducted histopathological assessments of selected tissues (Nitchke et al. 1981; Rowe et al. 1952), and other studies focused on specific endpoints, including respiratory effects (Reznik et al. 1980) and reproductive effects (Short et al. 1979). The lowest LOAELs for noncancer effects of intermediate-duration inhalation exposure to 1,2-dibromoethane for each system are summarized in Table A-1.

Changes in body weight in female mice were observed in all treatment groups, with a LOAEL value of 3 ppm. However, effects on body weight were inconsistent, with increases of 30 and 15% in the 3 and 15 ppm groups, respectively, and a 36% decrease in the 75 ppm group (NTP 1982). Therefore, alterations in body weight were not considered as the basis for the intermediate-duration MRL. Hyperplasia of nasal turbinates was observed in male and female rats, with NOAEL and LOAEL values of 3 and 10 ppm, respectively, for a 13-week exposure (Nitchke et al. 1981). Although hyperplasia is not a carcinogenic lesion, it is a proliferative lesion that is important in the development of cancer (EPA 2005). Since chronic-duration inhalation exposure to 10 ppm 1,2-dibromoethane produced adenomas and carcinomas in the nasal cavity in male and female rats (NTP 1982), it is possible that nasal cavity hyperplasia observed following 13 weeks of exposure may represent a precancerous event. Given this uncertainty, an intermediate-duration inhalation based on nasal cavity hyperplasia is not considered appropriate. Although hepatic and renal effects were observed in guinea pigs exposure to 50 ppm (NOAEL 25 ppm) (Rowe et al. 1952), these effects could not be used to derive an intermediate-duration MRL because death was observed in mice exposed to 20 ppm for 6 months (Adkins et al. 1986). Therefore, an intermediate-duration inhalation MRL has not been derived.

Table A-1. Effects in Rats and Mice Exposed to Inhaled 1,2-Dibromoethane for Intermediate Durations

Effect	Species (sex)	NOAEL (ppm)	LOAEL (ppm)	Reference
Respiratory, hyperplasia of nasal turbinates	Rat (M,F)	3	10	Nitchke et al. 1981
Body weight gain change	Rat (F)	-	3	NTP 1982
Death	Mouse (F)	ND	20	Adkins et al. 1986
Hepatic, fatty degeneration	Guinea pig (M)	25	50	Rowe et al. 1952
Renal, tubular degeneration, interstitial congestion, edema	Guinea pig (M,F)	25	50	Rowe et al. 1952

Table A-1. Effects in Rats and Mice Exposed to Inhaled 1,2-Dibromoethane for Intermediate Durations

Effect	Species (sex)	NOAEL (ppm)	LOAEL (ppm)	Reference
Ocular, irritation	Mouse (M,F)	15	75	NTP 1982
Endocrine, thyroid, decreased follicular size	Rat (M/F) Mouse (M,F)	15	75	NTP 1982
Endocrine, adrenal cortex, swelling and/or vacuolization	Rat (M,F)	15	75	NTP 1982
Reproductive, reduced fertility, degeneration of uterine epithelium	Rat (F)	39	80	Short et al. 1979
Reproductive, infertility, testicular atrophy	Rat (M)	39	89	Short et al. 1979

F = female; M = male; ND = not determined

Agency Contacts (Chemical Managers): Rae T. Benedict

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dibromoethane
CAS Numbers: 106-93-4
Date: July 1992
March 2017—Updated literature search
Profile Status: Final
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of an chronic-duration inhalation MRL for 1,2-dibromoethane.

Rationale for Not Deriving an MRL: The lowest nonlethal exposure level associated with adverse effects is for male reproductive effects in an occupational exposure of 46 fruit fumigation workers exposed 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 these workers. Compared to controls (n=43), significant decreases in sperm count (42% decrease; $p<0.01$) and the percentages of viable (11% decrease; $p<0.01$) and motile (24% decrease; $p<0.01$) sperm, and increases in abnormal sperm [tapered heads (69% increase; $p<0.001$), absent heads (45% increase; $p<0.001$), abnormal tails (14% increase; $p<0.001$)] were observed. Although the study report infers that the only chemical exposure was to 1,2-dibromoethane, the study report did not specifically state this. However, even with this uncertainty, a chronic-duration MRL could not be derived based on these data because effects are classified as a serious LOAEL.

All studies in laboratory animals were conducted at exposures levels of 10, 20, and 40 ppm, which are markedly higher than exposure levels in the human occupational studies (NTP 1982; Wong et al. 1982). Non-neoplastic effects observed at 10 ppm included nasal inflammation (female mice), spleen hemosiderosis (female mice), hepatic necrosis (male and female rats), adrenal cortical degeneration (female rats), retinal degeneration (female rats), and testicular degeneration (male rats) (NTP 1982). However, because excessive treatment-related deaths (31/50) also occurred in female mice at 10 ppm and a serious adverse effect (testicular degeneration) occurred in male rats exposed to 10 ppm, these data could not be used to derive a protective MRL. Data from male mice exposed to 10 ppm were not considered in the identification of adverse because of high mortality from urinary tract infections in control and treatment groups; this was not related to treatment (NTP 1982). The Wong et al. (1982) study saw effects at a higher concentration (20 ppm) and, therefore, was not considered further.

Agency Contacts (Chemical Managers): Rae T. Benedict

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dibromoethane
CAS Numbers: 106-93-4
Date: July 1992
March 2017—Updated literature search
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL for 1,2-dibromoethane.

Rationale for Not Deriving an MRL: The available acute-duration oral exposure studies were designed to assess death (Rowe et al. 1952), gastrointestinal (Ghanayem et al. 1986), hepatic (Botti et al. 1986; Broda et al. 1979), or reproductive effects (Teramoto et al. 1980). As such, comprehensive toxicological endpoints were not examined in acute-duration oral exposure studies. The lowest lethality value reported was an LD_{50} value of 55 mg/kg (single dose) in rabbits (Rowe et al. 1952). Gastrointestinal and hepatic effects occurred at higher acute exposures. Fatty degeneration of the liver was observed in male rats exposed to 107 mg/kg (single dose) and forestomach proliferation and hyperkeratosis were observed in rats administered 80 mg/kg/day (5 days/week for 2 weeks). Dominant lethal mutagenicity tests were the only reproductive endpoint studied and there was no observable effect in male rats exposed up to 30 mg/kg/day or male mice exposed to up to 150 mg/kg/day. Because lethality was observed at the lowest acute oral exposure tested, data are not suitable for derivation of an acute-duration oral MRL.

Agency Contacts (Chemical Managers): Rae T. Benedict

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dibromoethane
CAS Numbers: 106-93-4
Date: July 1992
March 2017—Updated literature search
Profile Status: Final
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration oral MRL for 1,2-dibromoethane.

Rationale for Not Deriving an MRL: Two studies evaluated the effects of intermediate-duration oral exposure to 1,2-dibromoethane (NCI 1978; Shivanandappa et al. 1987). The NCI (1978) study conducted histopathological examinations of comprehensive tissues in male rats exposed to 38 mg/kg/day for 47 weeks. Although the exposure duration for this study was intended to be 2 years, treatment of male rats was terminated after 47 weeks due to excessive mortality (31/50 deaths); early mortality was not observed in control rats. NCI (1978) reported the following noncancerous adverse effects: hepatic peliosis, adrenal cortical degeneration, and testicular atrophy. The Shivananappa et al. (1987) study examined several tissues in a small number of male rats (5/group) exposed to 5–50 mg/kg/day for 90 days; no adverse effects were observed in any treatment group. An intermediate-duration oral MRL was not derived because excessive mortality occurred at the lowest dose tested (38 mg/kg/day) (NCI 1978).

Agency Contacts (Chemical Managers): Rae T. Benedict

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** 1,2-Dibromoethane
CAS Numbers: 106-93-4
Date: July 1992
March 2017—Updated literature search
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL for 1,2-dibromoethane.

Rationale for Not Deriving an MRL: Only one study evaluated noncancer effects of chronic-duration oral (gavage) exposure to 1,2-dibromoethane (NCI 1978); other chronic-duration studies evaluated body weight and cancer endpoints only (Van Duuren et al. 1985, 1986). Exposures in the NCI (1978) study were 37 mg/kg/day for 57 weeks in female rats and 62 and 107 mg/kg/day in male and female mice exposed for 53 weeks. Excessive mortality was observed in the NCI study; no early mortality was observed in controls. In female rats, 48/50 deaths occurred before treatment week 57; no noncancer effects were observed. In mice exposed to 62 mg/kg/day, 30/50 males died by week 58 and 22/50 females died by week 70. Effects observed in mice administered 62 mg/kg/day were depressed body weight gain (males and females), splenic hematopoiesis (females), liver inflammation (males), and alopecia and skin sores (males and females). However, due to excessive mortality at the lowest dose tested (37 mg/kg/day), a chronic-duration oral MRL was not derived.

Agency Contacts (Chemical Managers): Rae T. Benedict

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR 1,2-DIBROMOETHANE

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

B.1 LITERATURE SEARCH AND SCREEN

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

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

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

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

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

B.1.1 Literature Search

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

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

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

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

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

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
03/2017	((106-93-4[rn] OR 1N41638RNO[rn] OR "Ethylene Dibromide"[MeSH] OR "Ethylene Dibromide"[nm]) AND (1990/01/01 : 3000[dp] OR 1990/01/01 : 3000[mhda])) OR

Table B-2. Database Query Strings

Database search date	Query string
	((("Ethylene dibromide"[tw] OR "1,2-Dibromaethan"[tw] OR "1,2-Dibromoetano"[tw] OR "1,2-Dibromoethane"[tw] OR "1,2-Dibroomethaan"[tw] OR "1,2-Ethylene dibromide"[tw] OR "Aadibroom"[tw] OR "Aethylenbromid"[tw] OR "alpha, beta-Dibromoethane"[tw] OR "alpha, omega-Dibromoethane"[tw] OR "Bromofume"[tw] OR "Bromuro di etile"[tw] OR "Celmide"[tw] OR "Dibromoethane"[tw] OR "Dibromure d'ethylene"[tw] OR "Dowfume 40"[tw] OR "Dowfume EDB"[tw] OR "Dowfume W-100"[tw] OR "Dowfume W-8"[tw] OR "Dowfume W-85"[tw] OR "Dowfume W-90"[tw] OR "Dwubromoetan"[tw] OR "E-D-Bee"[tw] OR "Edabrom"[tw] OR "EDB-85"[tw] OR "Ethylene bromide"[tw] OR "Ethylene dibromide"[tw] OR "Fumo-gas"[tw] OR "Glycol dibromide"[tw] OR "Iscobrome D"[tw] OR "Kopfume"[tw] OR "Nefis"[tw] OR "Nephis"[tw] OR "Pestmaster edb-85"[tw] OR "Sanhyuum"[tw] OR "Soilbrom"[tw] OR "Soilbrom-100"[tw] OR "Soilbrom-40"[tw] OR "Soilbrom-85"[tw] OR "Soilbrom-90"[tw] OR "Soilbrom-90EC"[tw] OR "Soilfume"[tw] OR "sym-Dibromoethane"[tw] OR "Unifume"[tw]) NOT medline[sb]) AND (1990/01/01 : 3000[dp] OR 1990/01/01 : 3000[crdat] OR 1990/01/01 : 3000[edat]))
Toxline	
03/2017	("ethylene dibromide" OR "1 2-dibromaethan" OR "1 2-dibromoetano" OR "1 2-dibromoethane" OR "1 2-dibroomethaan" OR "1 2-ethylene dibromide" OR "aadibroom" OR "aethylenbromid" OR "alpha beta-dibromoethane" OR "alpha omega-dibromoethane" OR "bromofume" OR "bromuro di etile" OR "celmide" OR "dibromoethane" OR "dibromure d'ethylene" OR "dowfume 40" OR "dowfume edb" OR "dowfume w-100" OR "dowfume w-8" OR "dowfume w-85" OR "dowfume w-90" OR "dwubromoetan" OR "e-d-bee" OR "edabrom" OR "edb-85" OR "ethylene bromide" OR "ethylene dibromide" OR "fumo-gas" OR "glycol dibromide" OR "iscobrome d" OR "kopfume" OR "nefis" OR "nephis" OR "pestmaster edb-85" OR "sanhyuum" OR "soilbrom" OR "soilbrom-100" OR "soilbrom-40" OR "soilbrom-85" OR "soilbrom-90" OR "soilbrom-90ec" OR "soilfume" OR "sym-dibromoethane" OR "unifume" OR 106-93-4 [rn]) AND 1990:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
Toxcenter	
03/2017	FILE 'TOXCENTER' ENTERED AT 15:52:34 ON 30 MAR 2017 L1 4912 SEA 106-93-4 L2 4881 SEA L1 NOT TSCATS/FS L3 4009 SEA L2 NOT PATENT/DT L4 1872 SEA L3 AND PY>=1990 ACTIVATE TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)

Table B-2. Database Query Strings

Database search date	Query string
	L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L20 QUE (ENDOCRIN? AND DISRUPT?)
	L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L27 QUE (NEPHROTOX? OR HEPATOTOX?)
	L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29
	L31 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L33 QUE L30 OR L31 OR L32
	L34 QUE (NONHUMAN MAMMALS)/ORGN
	L35 QUE L33 OR L34

Table B-2. Database Query Strings

Database search date	Query string
	L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L37 QUE L35 OR L36 --------- L38 1234 SEA L4 AND L37 L39 1066 SEA L38 NOT DEVELOPMENT L40 1017 DUP REM L38 (217 DUPLICATES REMOVED) L41 137 SEA L38 AND MEDLINE/FS L42 160 SEA L38 AND BIOSIS/FS L43 848 SEA L38 AND CAPLUS/FS L44 89 SEA L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L45 1016 DUP REM L41 L42 L44 L43 (218 DUPLICATES REMOVED) L*** DEL 137 S L38 AND MEDLINE/FS L*** DEL 137 S L38 AND MEDLINE/FS L46 137 SEA L45 L*** DEL 160 S L38 AND BIOSIS/FS L*** DEL 160 S L38 AND BIOSIS/FS L47 98 SEA L45 L*** DEL 848 S L38 AND CAPLUS/FS L*** DEL 848 S L38 AND CAPLUS/FS L48 721 SEA L45 L*** DEL 89 S L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L*** DEL 89 S L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L49 60 SEA L45 L50 879 SEA (L46 OR L47 OR L48 OR L49) NOT MEDLINE/FS D SCAN L50

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS[a]	
03/2017	Compound searched: 106-93-4
NTP	
03/2017	106-93-4 ethylene dibromide 1,2-dibromoethane
NIH RePORTER	
11/2017	Active projects, "Ethylene dibromide" OR "1,2-Dibromaethan" OR "1,2-Dibromoetano" OR "1,2-Dibromoethane" OR "1,2-Dibroomethaan" OR "1,2-Ethylene dibromide" OR "Aadibroom" OR "Aethylenbromid" OR "alpha,beta-Dibromoethane" OR "alpha,omega-Dibromoethane" OR "Bromofume" OR "Bromuro di etile" OR "Celmide" OR "Dibromoethane" OR "Dibromure d'ethylene" OR "Dowfume 40" OR "Dowfume EDB" OR "Dowfume W-100" OR "Dowfume W-8" OR "Dowfume W-85" OR "Dowfume W-90" OR "Dwubromoetan" OR "E-D-Bee" OR "Edabrom" OR "EDB-85" OR "Ethylene bromide" OR "Ethylene dibromide" OR "Fumo-gas" OR "Glycol dibromide" OR

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	"Iscobrome D" OR "Kopfume" OR "Nefis" OR "Nephis" OR "Pestmaster edb-85" OR "Sanhyuum" OR "Soilbrom" OR "Soilbrom-100" OR "Soilbrom-40" OR "Soilbrom-85" OR "Soilbrom-90" OR "Soilbrom-90EC" OR "Soilfume" OR "sym-Dibromoethane" OR "UN 1605" OR "Unifume"
Other	Identified throughout the assessment process

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

The 2017 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 1,576
- Number of records identified from other strategies: 43
- Total number of records to undergo literature screening: 1,619

B.1.2 Literature Screening

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

- Title and abstract screen
- Full text screen

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

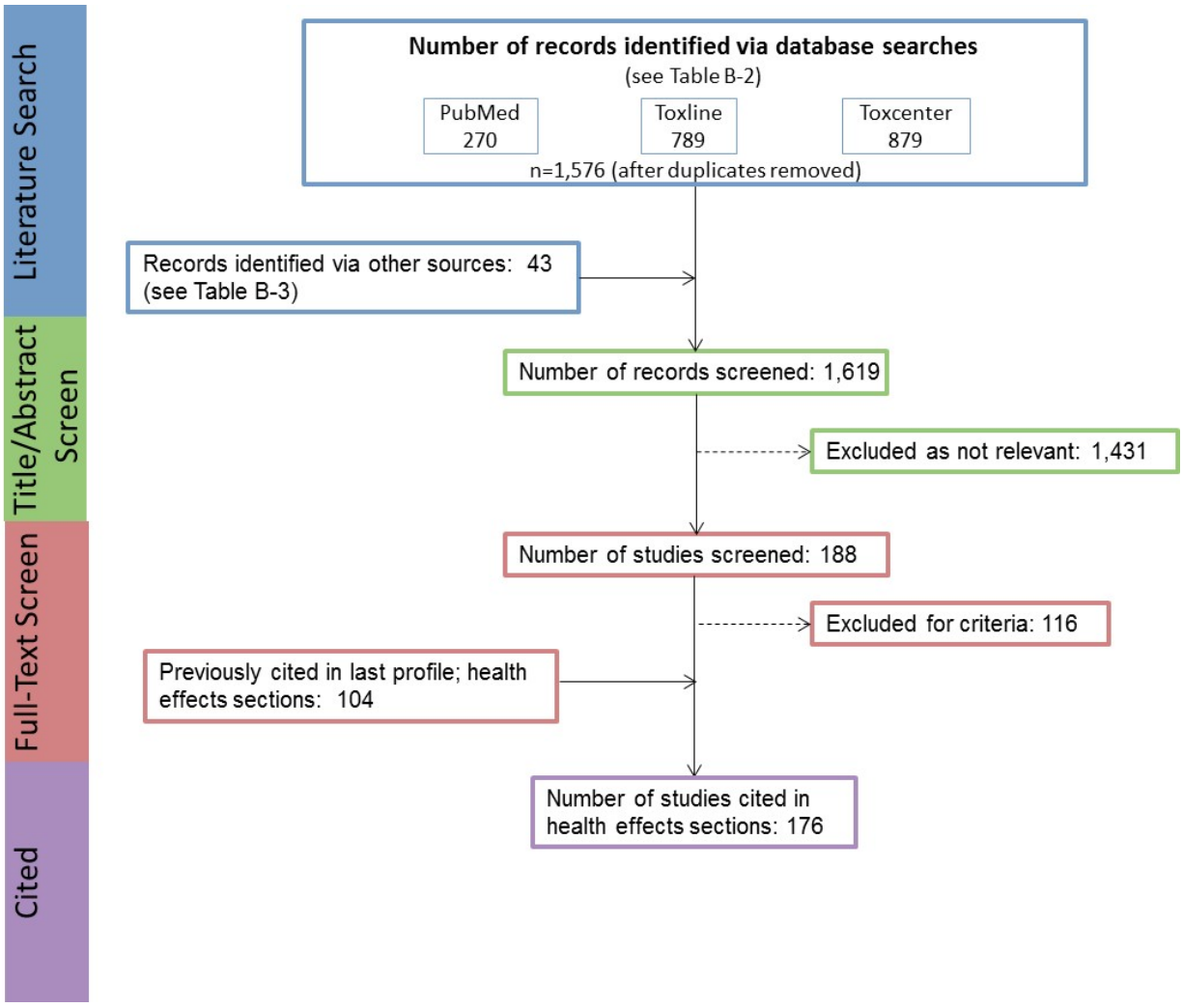
- Number of titles and abstracts screened: 1,619
- Number of studies considered relevant and moved to the next step: 188

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

- Number of studies undergoing full text review: 188
- Number of studies cited in the pre-public draft of the toxicological profile: 104
- Total number of studies cited in the profile: 176

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

Figure B-1. March 2017 Literature Search Results and Screen for 1,2-Dibromoethane



APPENDIX C. USER'S GUIDE

Chapter 1. Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

Minimal Risk Levels (MRLs)

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

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

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

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

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

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

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

TABLE LEGEND

See Sample LSE Table (page C-5)

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

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

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

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

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

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

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

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

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

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

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

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

FIGURE LEGEND

See Sample LSE Figure (page C-6)

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

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

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

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

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

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

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

APPENDIX C

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

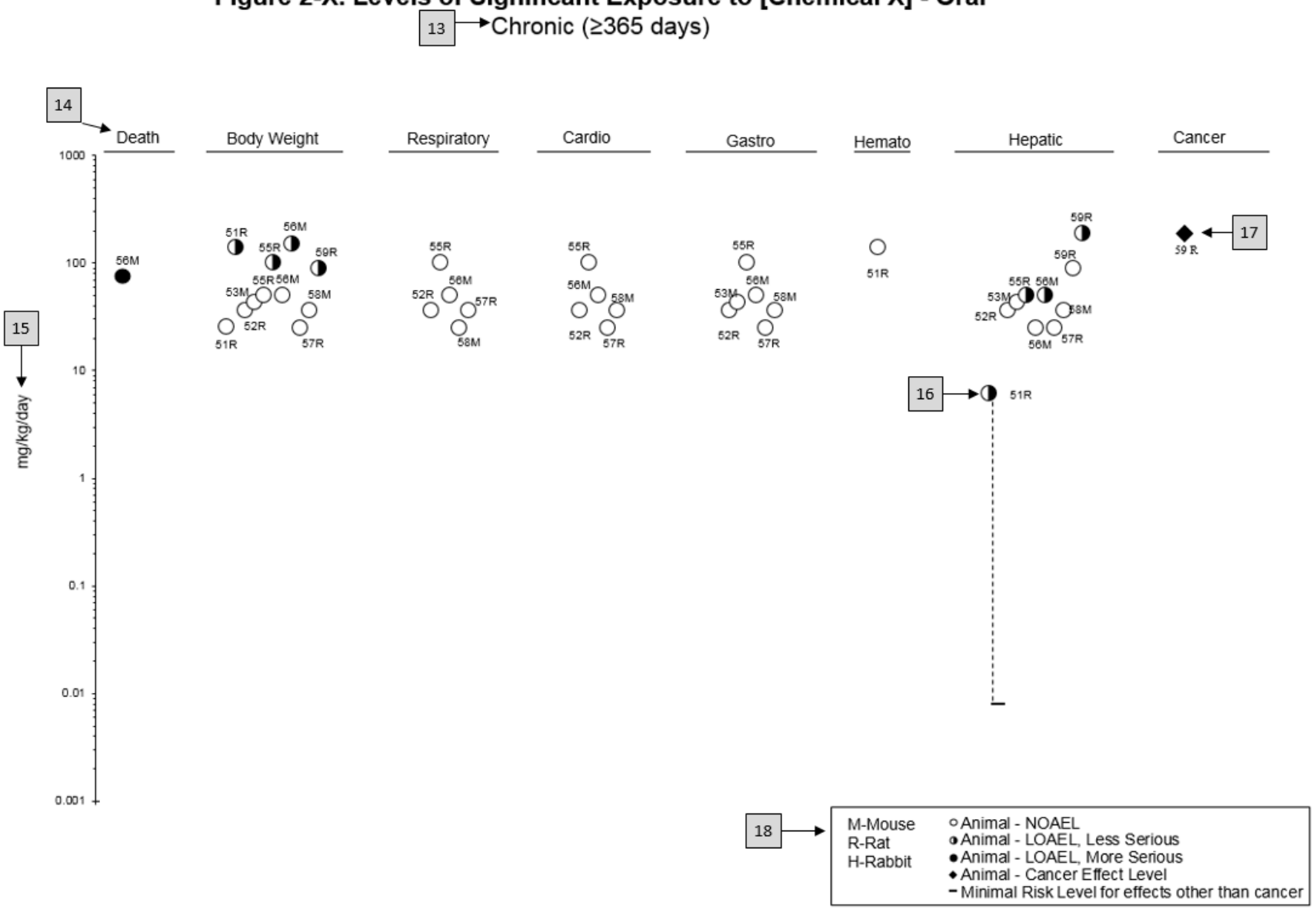
Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
CHRONIC EXPOSURE (2)									
51 (3)	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7,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

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

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

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

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



APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

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

ATSDR Information Center

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

The following additional materials are available online:

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

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

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

Other Agencies and Organizations

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

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

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

Clinical Resources (Publicly Available Information)

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

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

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

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

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

APPENDIX E. GLOSSARY

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

Ceiling Value—A concentration that must not be exceeded.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

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

APPENDIX F

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

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

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

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