TOXICOLOGICAL PROFILE FOR 1,2-DIBROMOETHANE

Agency for Toxic Substances and Disease Registry
U.S. Public Health Service

July 1992

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Resister on April 17, 1987; on October 20, 1988; on October 26, 1989; and on October 17, 1990. A revised list of 275 substances was published on October 17, 1991.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the lists. Each profile must include the following content:

(A) An examination, summary, and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects.

(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 which present a significant risk to human health of acute, subacute, and chronic health effects.

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

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and 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 is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described, Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but 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.

Foreword

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. 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 protection of public health will be identified by ATSDR, the National Toxicology Program (NTP) of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

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 our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control, the NTP, and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

William L. Roper

William L. Roper, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

CONTENTS

LIST OF FIGURES

LIST OF TABLES

1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about 1,2-dibromoethane (ethylene dibromide, EDB) and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,177 sites on its National Priorities List (NPL). 1,2-Dibromoethane has been found at 9 of these sites. However, we do not know how many of the 1,177 NPL sites have been evaluated for 1,2-dibromo-ethane. As EPA evaluates more sites, the number of sites at which 1,2-dibromoethane is found may change. The information is important to you because 1,2-dibromoethane may cause harmful health effects and because these sites are potential or actual sources of human exposure to 1,2-dibromoethane.

When a chemical is released from a large area such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment as a chemical emission. This emission, which is also called a release, does not always lead to exposure. You can be exposed to a chemical only when you come into contact with the chemical. You may be exposed to it in the environment by breathing, eating, or drinking substances containing the chemical or from skin contact with the chemical.

If you are exposed to a hazardous substance such as 1,2-dibromoethane, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

1.1 WHAT IS 1,2-DIBROMOETHANE?

1,2-Dibromoethane is a pesticide and gasoline additive. It is mostly man-made, but it may occur naturally in the ocean in very small amounts. In the 1970s and early 1980s, it was used in soil to kill insects and worms that get on fruits, vegetables, and grain crops. It was also used in soil to protect grass, such as on golf courses. Another use was to kill fruit flies on citrus fruits, mangoes, and papayas after they were picked. EPA stopped most of these uses in 1984. 1,2-Dibromoethane is added to leaded gasoline to produce better fuel efficiency. Because use of leaded gasoline has fallen, less 1,2-dibromoethane is made for this use. The chemical is a colorless liquid with a mild, sweet odor. It evaporates easily and can dissolve in water. 1,2-Dibromoethane stays in groundwater and in soil for a long time but breaks down quickly in the air. More information on the chemical and physical properties of 1,2-dibromoethane can be found in Chapter 3 and on its occurrence and fate in the environment in Chapter 5.

1.2 HOW MIGHT I BE EXPOSED TO 1,2-DIBROMOETHANE?

You can be exposed to low levels of 1,2-dibromoethane in drinking water (especially well water) and in air. Before EPA stopped the use of 1,2-dibromoethane as a pesticide, the most common way you would have been exposed was by eating food that had very small amounts of this chemical in it. You could still be exposed to low levels of 1,2-dibromoethane, particularly from groundwater (well water), in areas where the chemical was used in farming or from hazardous waste sites. Most of the 1,2-dibromoethane that enters the soil will get into the groundwater or evaporate into the air. Small amounts can remain in very tiny particles in soil near hazardous waste sites or in areas once used as farmland. The compound may be released from these particles slowly over time or if the soil is crushed or disturbed. You can be exposed to 1,2-dibromoethane in the air near production plants. Background levels in the environment are very low. The air most people breathe contains between 0.01-0.06 parts of 1,2-dibromoethane per billion parts of air (ppb). Because 1,2-dibromoethane easily evaporates, most surface waters do not contain detectable amounts. Groundwater is more likely to contain 1,2-dibromoethane with an average concentration of about 0.9 ppb. In foods, 1,2-dibromoethane has recently been found in 2 out of 549 samples at concentrations of 2 and 11 ppb. There is no information on background levels in surface water or soil. If you applied 1,2-dibromoethane on a farm or golf course, if you worked to pack fruits gassed with 1,2-dibromoethane, or if you worked in a factory that made 1,2-dibromoethane, you could be exposed to much higher than background levels. For more information on human exposure to 1,2-dibromoethane, see Chapter 5.

1.3 HOW CAN 1,2-DIBROMOETHANE ENTER AND LEAVE MY BODY?

1,2-Dibromoethane can enter your body after you eat or drink contaminated food and water. It can also enter your body through your skin when you bathe or swim in contaminated water. The 1,2-dibromoethane inside tiny soil particles may enter your body if you crush or eat contaminated soil. The chemical can enter your nose and lungs when you breathe air that contains 1,2-dibromoethane or when you shower with water that is contaminated. Near hazardous waste sites or near areas that once were farmed, the most likely way that you will be exposed is by drinking contaminated groundwater. 1,2-Dibromoethane will be rapidly taken into your bloodstream by any method of exposure. Most of it builds up in your liver and kidneys where it is rapidly broken down to different substances. These substances leave your body quickly in the urine, and smaller amounts are passed in liver bile into the stool. Small amounts of 1,2-dibromoethane that are not broken down can be breathed out of your lungs. Chapter 2 has more information on how 1,2-dibromoethane enters and leaves the body.

1. PUBLIC HEALTH STATEMENT

1.4 HOW CAN 1,2-DIBROMOETHANE AFFECT MY HEALTH?

The effects of breathing high levels of 1,2-dibromoethane in humans are unknown. Studies in animals show that they can die from breathing high concentrations of 1,2-dibromoethane for a short time while lower concentrations can cause liver and kidney damage. You can die if you swallow or have skin contact with large quantities of 1,2-dibromoethane. A woman who drank 40 milliliters (mL) of pure liquid 1,2-dibromoethane died within a day. Changes in the liver and kidney are reported in humans that died of ingestion of 1,2-dibromoethane. People who tried to commit suicide by swallowing concentrated 1,2-dibromoethane got ulcers inside their mouth and stomach. Laboratory rats and mice fed less-concentrated 1,2-dibromoethane for as little as 2 weeks had damage to the lining of their stomach. If you spill liquid 1,2-dibromoethane on your skin, you can get blisters.

Breathing 1,2-dibromoethane for moderately long periods damages the lining of the nose in rats. This effect has not been seen in humans. Animals that breathed or ate food containing 1,2-dibromoethane for short or long periods were less fertile or had abnormal sperms. Changes in the brain and behavior have occurred in young rats whose male parents had breathed 1,2-dibromoethane.

A worker who breathed 1,2-dibromoethane for several years developed bronchitis, headache, and depression, but his health improved after he stopped breathing air contaminated with 1,2-dibromoethane. 1,2-Dibromoethane is not known to cause birth defects in people. It can impair reproduction in males by damaging sperms in testicles. This type of damage has been seen in workers exposed to 1,2-dibromoethane for several years. Pregnant animals that are sick from exposure to 1,2-dibromoethane have had pups with birth defects. There are no reports of cancer in workers or other people exposed to 1,2-dibromoethane for several years. Rats and mice that repeatedly breathed, swallowed, or had skin contact with 1,2-dibromoethane for long periods had cancer in many organs. The Department of Health and Human Services has determined that 1,2-dibromoethane may reasonably be anticipated to be a carcinogen.

1.5 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO 1,2-DIBROMOETHANE?

There is no known reliable medical test to determine whether you have been exposed to 1,2-dibromoethane. For more information, see Chapters 2 and 6.

1. PUBLIC HEALTH STATEMENT

1.6 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government has set standards and guidelines to protect people from the potential health effects of 1,2-dibromoethane in drinking water, food, and air. EPA recommends that no more than 0.008 ppm of 1,2-dibromoethane should be present in drinking water that is consumed for up to 10 days. EPA does not allow any 1,2-dibromoethane to be in food. Companies must report to EPA if they spill 1,000 pounds or more of 1,2-dibromoethane.

The Occupational Health and Safety Administration (OSHA) has limited workers' exposure to 1,2-dibromoethane in air to an average of 20 ppm for an 8-hour workday. According to OSHA, short-term exposure of 15 minutes to 1,2-dibromoethane should not be more than 0.5 ppm. The National Institute for Occupational Safety and Health (NIOSH) has set an average limit for 1,2-dibromoethane of 0.045 ppm in workroom air during an 8-hour day. According to NIOSH, short-term exposure of 15 minutes to 1,2-dibromoethane should not be more than 0.13 ppm.

For more information on guidelines and standards for 1,2-dibromoethane exposure, see Chapter 7.

1.7 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns not covered here, please contact your state health or environmental department or:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, E-29
Atlanta, Georgia 30333

This agency can also provide you with information on the location of the nearest occupational and environmental health clinic. Such clinics specialize in recognizing, evaluating, and treating illness that result from exposure to hazardous substances.

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 of the toxicology of 1,2-dibromoethane and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for 1,2-dibromoethane based on toxicological studies and epidemiological investigations.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure--inhalation, oral, and dermal--and then by health effect--death, systemic, immunological, neurological, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods --acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more).

Levels of significant exposure 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. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with the carcinogenic effects of 1,2-dibromoethane are indicated in Figures 2-l and 2-2. Because cancer effects could occur at lower exposure levels, the figures also show a range for the upper bound of estimated excess risks, ranging from a risk of one in 10,000 to one in 10,000,000 ($10m^{4}$ to $10m^{7}$), as developed by EPA.

2. HEALTH EFFECTS

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability and to extrapolate from laboratory animal data to humans.

Although methods have been established to derive these levels (Barnes et al. 1988; EPA 1989a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels 'of significant human exposure improve, these MRLs will be revised.

2.2.1 Inhalation Exposure

2.2.1.1 Death

No studies were located regarding death in humans after inhalation exposure to 1,2-dibromoethane. However, inhalation exposure as well as dermal exposure may have played a role in the deaths of two pesticide workers exposed to 1,2-dibromoethane. For a discussion of this report by Letz et al. (1984), see Section 2.2.3.1.

Older studies have established lethal concentrations of inhalation exposure to 1,2-dibromoethane for experimental animals. Groups of rats were exposed to 1,2-dibromoethane at concentrations of l00-10,000 ppm and durations of 0.02-16 hours (Rowe et al. 1952). For each exposure concentration tested, several exposure durations were selected that were expected to encompass 0%-100% mortality. A total of 40 combinations of exposure concentration and duration were tested, using a total of 711 rats. Plots were constructed of concentration versus exposure duration expected to produce 99.99%, 50%, and 0.01% mortality. Selected points from the 50% plot are illustrated in Figure 2-l and recorded in Table 2-l.

Deaths in rats resulting from single-exposure concentration/duration combinations expected to produce 50%-90% mortality usually occurred within 24 hours. These deaths were attributed to cardiac or respiratory failure and were probably a direct effect of 1,2-dibromoethane toxicity. Deaths resulting from exposure concentration/duration combinations expected to produce 0.01%-50% mortality occurred as long as 12 days after exposure and were due to pneumonia. The authors attributed pneumonia to 1,2-dibromoethane-induced lung injury, but this lesion could also have been due to intercurrent bacterial or mycoplasmal pulmonary infection. Rats free of enzootic respiratory infections were not available in 1952. More contemporary inhalation studies of

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

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	Rat	1 d 12.0 hr				200 (LC_{50})	Rowe et al. 1952
2	Rat	1 d 2.0 hr				400 (16/25 died)	Rowe et al. 1952
3	Rat	1 d 0.1 hr				5,000 (9/10 died)	Rowe et al. 1952
4	Rat	1 d 0.05 hr				10,000 (LC_{50})	Rowe et al. 1952
5	Rat	9 d 7hr/d				100 (3/10 died)	Rowe et al. 1952
6	Rabbit	4 d 7 hr/d				100 (3/4 died)	Rowe et al. 1952
7	Gn pig	1d 7hr/d		200			Rowe et al. 1952
8	Gn pig	1 d 2hr/d		400			Rowe et al. 1952
9	Mouse	10 d 23hr/d Gd6-15				38 (10/17 died)	Short et al. 1978
10	Rat	10 d 23hr/d Gd6-15				80 (LC_{50})	Short et al. 1978
Systemic							
11	Rat	7 hr	Hepatic	50			Rowe et al. 1952
		4 hr	Hepatic		100 (histopathological changes)		

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
12	Rat	7d/9d 7hr/d	Resp		100 (leukocyte infiltration)		Rowe et al. 1952
			Hepatic		100 (cloudy swelling)		
			Renal		100 (increased weight)		
			Other		100 (spleen congestion)		
13	Rabbit	4 d 7hr/d	Hepatic		100 (fatty degeneration, necrosis)		Rowe et al. 1952
			Renal	100			
Developmental							
14	Rat	10 d 23hr/d Gd6-15				20 (skeletal anomalies)	Short et al. 1978
15	Mouse	10 d 23hr/d Gd6-15				20 (skeletal anomalies)	Short et al. 1978
INTERMEDIATE EXPOSURE							
Death							
16	Rat	3 wk 7d/wk 7hr/d				80 (10/50 females died)	Short et al. 1979
17	Rat	10 wk 5d/wk 7hr/d				89 (7/33 males died)	Short et al. 1979
Systemic							
18	Rat	13 wk 5d/wk 6hr/d	Resp	3	10 (hyperplasia)		Nitschke et al. 1981

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
19	Rat	13 wk 5d/wk 6hr/d	Resp	3	15 (hyperplasia)		Reznik et al. 1980
20	Rat	13 wk 5d/wk 6hr/d	Other	15	75 (vacuolization of cells)		NTP 1982
21	Rat	91 d 5d/wk 7hr/d	Hemato Hepatic Renal Other	50	 50 (increased weight) 50 (increased weight) 50 (decreased spleen weight)		Rowe et al. 1952
22	Rabbit	84 d 5d/wk 7hr/d	Hepatic Renal	50 50			Rowe et al. 1952
23	Rabbit	214 d 5d/wk 7hr/d	Other	25			Rowe et al. 1952
24	Gn pig	80 d 5d/wk 7hr/d	Resp Hepatic Renal	25 25 25	50 (increased weight) 50 (fatty degeneration) 50 (tubular degeneration)		Rowe et al. 1952
25	Mouse	13 wk 5d/wk 6hr/d	Resp Derm/oc	15 15	75 (megalocytic cells) 75 (eye irritation)		NTP 1982
26	Monkey	70 d 5d/wk 7hr/d	Hepatic Renal		50 (fatty degeneration) 50 (increased weight)		Rowe et al. 1952
27	Monkey	220 d 5d/wk 1hr/d	Other	25			Rowe et al. 1952

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
Reproductive							
28	Rat	10 wk 5d/wk 7hr/d		39		89 (infertility)	Short et al. 1979
29	Rat	3 wk 7d/wk 7hr/d		39		80 (reduced fertility)	Short et al. 1979
Cancer							
30	Mouse	6 mo 5d/wk 6hr/d				20 (CEL, lung tumors)	Adkins et al. 1986
CHRONIC EXPOSURE							
Death							
31	Rat	18 mo 5d/wk 7hr/d				20 (43/48 males died; 37/48 females died)	Wong et al. 1982
32	Rat	89-104 wk 5d/wk 6hr/d				40 (45/50 males died; 42/50 females died)	NTP 1982
33	Mouse	79-103 wk 5d/wk 6hr/d				10 (31/50 females died)	NTP 1982
Systemic							
34	Rat	89-104 wk 5d/wk 6hr/d	Renal	10	40 (nephropathy)		NTP 1982
			Hepatic	10	40 (hepatocellular necrosis)		
			Other	10	40 (degeneration of adrenal cortex)		

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
35	Rat	18 mo 5d/wk 7hr/d	Hemato		20 (splenic atrophy)		Wong et al. 1982
36	Mouse	79-103 wk 5d/wk 6hr/d	Resp		10 (hyperplasia in females)		NTP 1982
			Hepatic	40			
			Other	10	40 (decreased body weight)		
Reproductive							
37	Rat	89-104 wk 5d/wk 6hr/d			10 (testicular degeneration)		NTP 1982
Cancer							
38	Rat	18 mo 5d/wk 7hr/d				20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5d/wk 6hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79-103 wk 5d/wk 6hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a]The number corresponds to entries in Figure 2-1.

CEL = cancer effect level; d = day; Derm/oc = dermal/ocular; Gd = gestation day; Gn pig = guinea pig; Hemato = hematological; hr = hour; LOAEL = lowest-observed-adverse-effect level; LC_{50} = lethal concentration, 50% kill; mo = month; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week

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

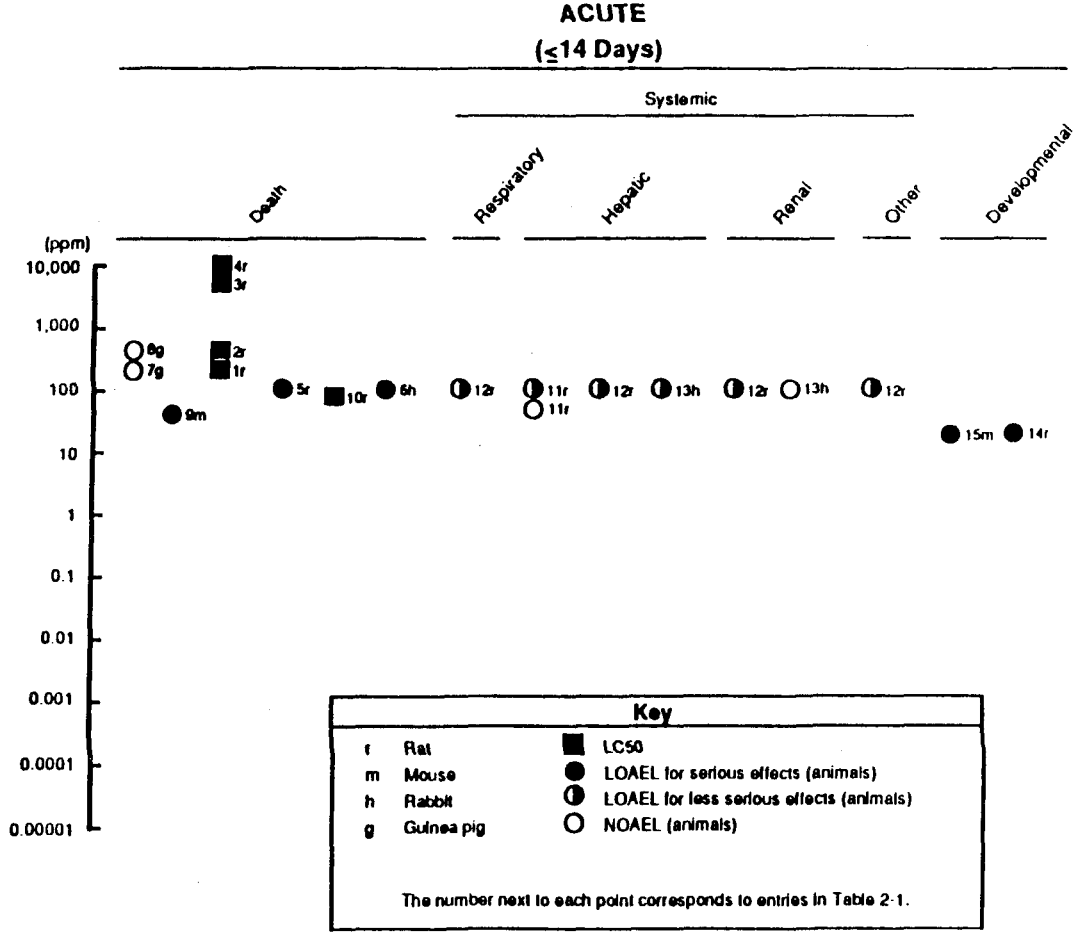


FIGURE 2-1 (Continued)

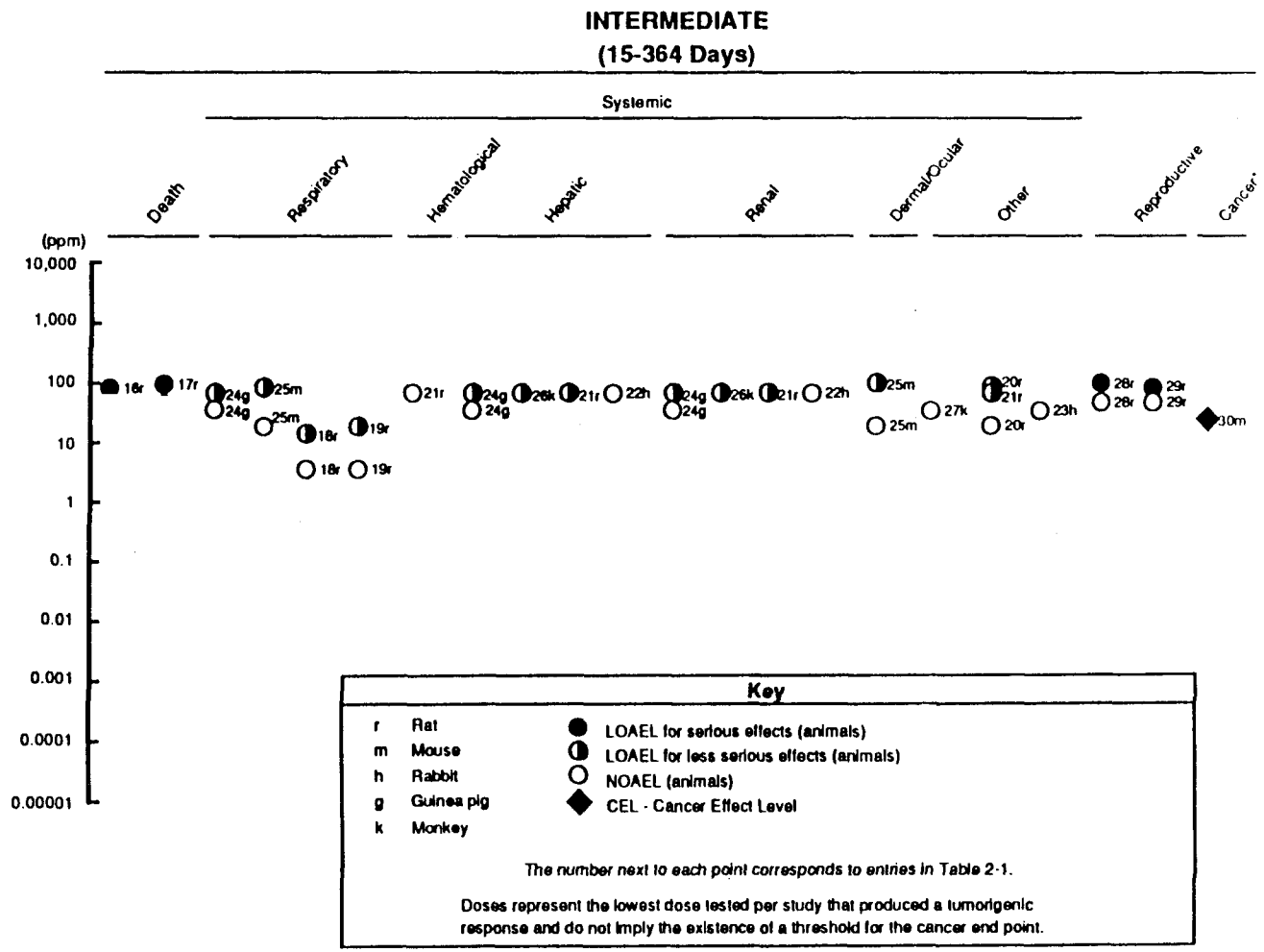
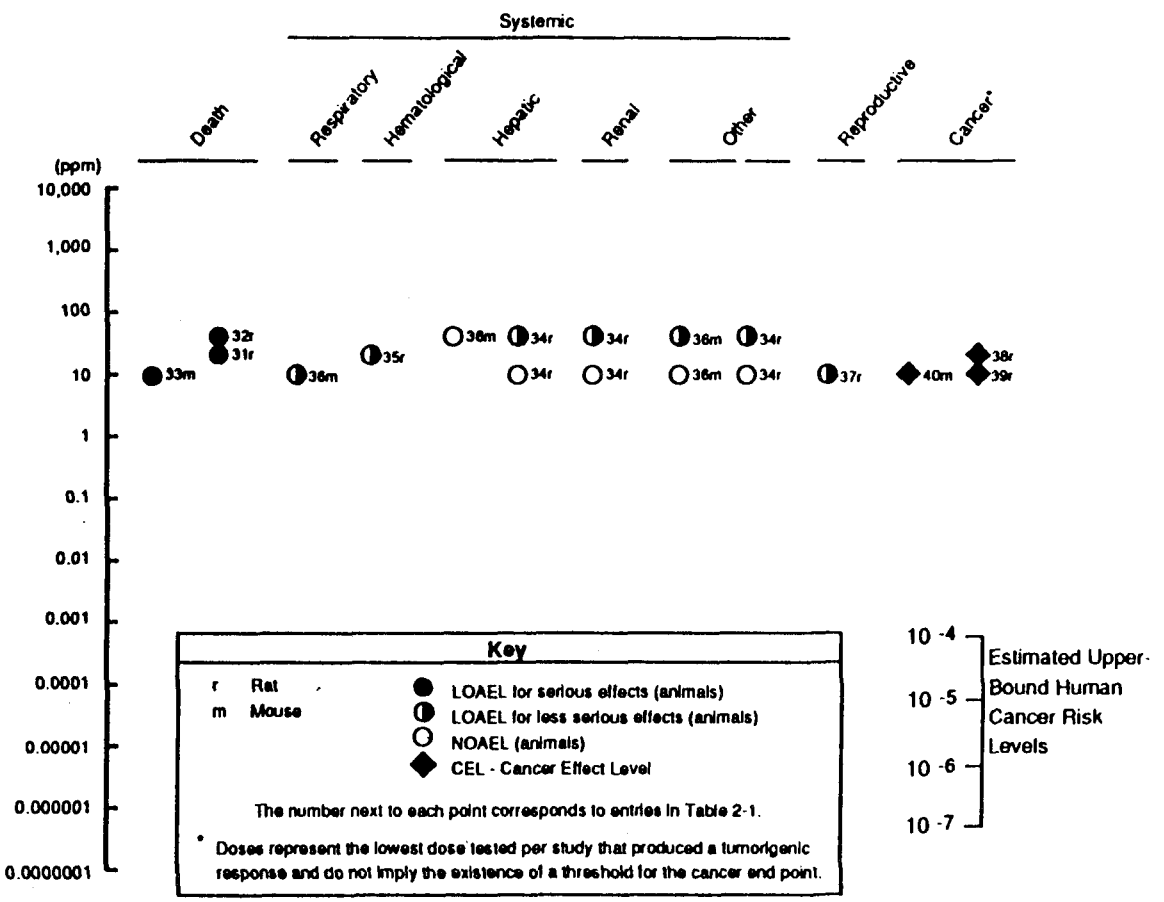


FIGURE 2-1 (Continued)

CHRONIC
(≥365 Days)



1,2-dibromoethane using commercially produced rats (Nitschke et al. 1981; NTP 1982) did not report pneumonic lesions or pneumonia-related mortality.

As the duration of exposure of the rats increased, the LC_{50} (lethal concentration, 50% kill) value decreased. Maximum nonfatal single exposures for rats were 1.2 minutes at 10,000 ppm, 2.4 minutes at 5,000 ppm, 6 minutes at 3,000 ppm, 12 minutes at 1,600 ppm, 36 minutes at 400 ppm, 2 hours at 200 ppm, and 16 hours at 100 ppm, the longest exposure tested. In other species exposed to 1,2-dibromoethane by Rowe et al. (1952), maximum nonfatal single exposures for guinea pigs were 2 hours at 400 ppm and 7 hours at 200 ppm, the longest exposure tested.

A group of albino rats heterogenous for weight (range of 190-604 grams) was exposed in a fumigation chamber to 1,040 ppm of 1,2-dibromoethane until death occurred (Akamine 1952). Clinical signs of toxicity were reddened nasal mucous membranes, epistaxis, ptyalism, anorexia, weight loss, and weakness. The lethal exposure times ranged from 5 to 165 minutes.

Deaths occurred in pregnant female Crl:CD rats and CD mice exposed to 1,2-dibromoethane for 23 hours per day over a 10-day period. Female rats and mice had increased mortality when exposed to 80 ppm of 1,2-dibromoethane while female mice also had significant mortality when exposed to concentrations of 38 ppm 1,2-dibromoethane (Short et al. 1978). Twenty percent mortality occurred in female Crl:CD rats exposed to 80 ppm 1,2-dibromoethane over a 3-week period; mortality did not occur at lower concentrations of 20 or 39 ppm. Male rats exposed to 89 ppm 1,2-dibromoethane over a 10-week period had 21% mortality but mortality did not occur at lower concentrations of 19 or 39 ppm (Short et al. 1979). There was no gross necropsy or histopathologic examination to establish the cause of death as related to chemical toxicity in either of these studies, which were focused primarily on development and reproduction.

Rats and mice exposed chronically to 1,2-dibromoethane by inhalation had high mortality (NTP 1982; Wong et al. 1982). The majority of deaths were related to cancer rather than direct toxic effects of 1,2-dibromoethane. Both studies are discussed further in Section 2.2.1.8.

The highest NOAEL value and the reliable lethal concentrations for each species for the acute-duration category, in rats for the intermediate-duration category and in rats and mice for the chronic-duration/category are recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-l and plotted in Figure 2-l.

2. HEALTH EFFECTS

No studies were located regarding cardiovascular, gastrointestinal, or musculoskeletal effects in humans or animals after inhalation exposure to 1,2-dibromoethane.

Respiratory Effects. The respiratory tract, particularly the nasal cavity, is the point-of-contact target organ affected by inhalation of 1,2-dibromoethane.

A possible case of chronic intoxication by 1,2-dibromoethane occurred in a worker involved in 1,2-dibromoethane production (Kochmann 1928). Symptoms were nonspecific. Upper respiratory symptoms consisted of pharyngitis and bronchitis; other symptoms were lymphadenopathy, conjunctivitis, anorexia, headache, and depression. The worker's condition improved upon cessation of exposure. No other studies were located regarding respiratory effects in humans after inhalation exposure to 1,2-dibromoethane.

Rats were exposed repeatedly to inhalation of 1,2-dibromoethane (Rowe et al. 1952). Of 10 female rats exposed to 100 ppm of 1,2-dibromoethane over a 9-day period, 30% did not survive. Survivors had increased lung weights and increased number of leukocytes in pulmonary septa. There was no description of nasal lesions; therefore, it is likely that the nasal cavity was not examined microscopically.

There have been several subchronic studies of 1,2-dibromoethane. In one, rats and guinea pigs were exposed to 50 ppm of 1,2-dibromoethane daily for as many as 63 (rats) or 57 (guinea pigs) exposures (Rowe et al. 1952). Experimental findings were complicated by upper respiratory infection and pneumonia.

To determine doses to be used in chronic inhalation studies, F344 rats and $B6C3F_1$ mice of both sexes were exposed to 0, 3, 15, or 75 ppm 1,2-dibromoethane for 13 weeks (NTP 1982; Reznik et al. 1980). Lesions occurred in respiratory turbinates in the dorsal portion of the nasal cavity of rats and mice exposed to 75 ppm. Respiratory epithelium was affected with cytomegaly of basal cells, focal hyperplasia, loss of cilia, and squamous metaplasia. Rats exposed to 15 ppm 1,2-dibromoethane had similar lesions but at lower incidence and with less severity; mice exposed to 15 ppm had no nasal lesions. Lung lesions were not described for rats; mice exposed to 75 ppm. developed megalocytic bronchiolar epithelial cells (NTP 1982).

A study was conducted to examine proliferative nasal epithelial lesions in F344 rats following subchronic inhalation of 1,2-dibromoethane at concentrations of 0, 3, 10, or 40 ppm (Nitschke et al. 1981). The study incorporated serial sacrifices and sacrifices after an 88-89-day postexposure period. Rats in the mid- and high-dose groups had hyperplasia of nasal turbinate epithelium; rats at the highest dose also exhibited nonkeratinizing squamous metaplasia of respiratory epithelium of the nasal turbinates.

Lesions in both dose groups reverted to normal after the postexposure interval. Although lesions did not progress and were essentially reversible during the recovery period, it is possible that such effects could progress in severity and result in neoplasia following long-term inhalation of 1,2-dibromoethane.

In a chronic inhalation study conducted by NTP (1982), carcinogenic end points were nasal tumors in rats and mice and pulmonary tumors in mice (see Section 2.2.1.8). A nonneoplastic lesion of epithelial hyperplasia occurring throughout the respiratory tract was a prominent histologic feature in the 1,2-dibromoethane-exposed mice.

Hematological Effects. No studies were located regarding hematologic effects in humans after inhalation exposure to 1,2-dibromoethane. Female rats exposed acutely to 100 ppm 1,2-dibromoethane for up to seven exposures (see Section 2.2.1.1) had splenic congestion and hemosiderosis; no changes in hematopoietic or lymphoid elements were described (Rowe et al. 1952).

Hematologic evaluation was performed on Sprague-Dawley rats that received 20 ppm 1,2-dibromoethane by inhalation and were fed either a control diet or a diet containing 0.05% disulfiram for 18 months (Wong et al. 1982). Hematologic evaluation of control rats with no exposure to 1,2-dibromoethane was not done. This study is discussed in Section 2.2.1.8. Moribund animals (males and females) that had exposure to the inhalation and dietary regimens for 10-12 months were evaluated. Rats exposed to 1,2-dibromoethane and fed 'a control diet had hematologic parameters within normal ranges. Atrophy of the spleen occurred in male rats. Both sexes of rats exposed to 1,2-dibromoethane and fed the 0.05% disulfiram diet had total erythrocyte counts, hematocrit, and hemoglobin values significantly lower than rats exposed to 1,2-dibromoethane and fed the control diet, with females most severely affected. Both sexes of rats on this latter regimen had splenic atrophy. Because there was no description of this splenic lesion, it is unclear whether atrophy referred to decreased extramedullary hematopoiesis in the red pulp, lymphoid depletion of the white pulp, or both changes.

Hepatic Effects. Two workers collapsed after entering a pesticide storage tank containing residues of 1,2-dibromoethane (Letz et al. 1984). Clinical chemistry prior to death for both men revealed acute hepatic failure along with other symptoms of toxicity. As with dermal exposure, inhalation exposure was also postulated to play a potentially important role. However, the exposure levels were not quantified.
The iiver is a target organ for toxic effects of 1,2-dibromoethane in experimental animals following exposure by a variety of routes.

2. HEALTH EFFECTS

Acute toxic hepatic effects of 1,2-dibromoethane consisting of hepatocellular cloudy swelling, centrilobular fatty change, and patchy necrosis were reported in animals after a single inhalation exposure (Rowe et al. 1952). Repeated inhalation exposures of rats and rabbits to 100 ppm 1,2-dibromoethane induced diffuse hepatocellular cloudy swelling in rats and centrilobular hepatocellular fatty change and necrosis in rabbits.

Rats in a subchronic inhalation study exposed to 50 ppm 1,2-dibromoethane had intercurrent infectious disease that severely complicated experimental results (see the discussion in this section on Respiratory Effects). No liver lesions were reported in surviving rats (Rowe et al. 1952). Guinea pigs exposed to 50 ppm 1,2-dibromoethane did not develop respiratory disease. Their liver lesions consisted of minimal centrilobular hepatocellular fatty change (Rowe et al. 1952). Liver lesions were not induced in F344 rats or $B6C3F_1$ mice following subchronic exposure to any concentrations of 1,2-dibromoethane used including the highest dose (75 ppm.) (NTP 1982).

In the chronic inhalation bioassay of 1,2-dibromoethane conducted by NTP (1982) (discussed in Section 2.2.1.8), increased incidence of focal and centrilobular hepatocellular necrosis occurred in male and female F344 rats exposed to the highest dose (40 ppm) of 1,2-dibromoethane. Compound-related degenerative or necrotizing hepatocellular lesions did not occur in $B6C3F_1$ mice following exposure to any concentration used. Liver lesions were not reported in rats after chronic inhalation exposure to 20 ppm 1,2-dibromoethane with or without 0.05% disulfiram in the diet; however, hepatocellular tumors (not otherwise classified) were induced in exposed rats fed dietary disulfiram (Wong et al. 1982). Also see Section 2.2.1.8.

Renal Effects. The clinical chemistry prior to death of two men who entered a pesticide tank that contained residues of 1,2-dibromoethane revealed acute renal failure (Letz et al. 1984). The exposure levels were not reported.

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 exposed acutely by inhalation (single exposure) to toxic concentrations greater than,100 ppm. Rats receiving several inhalation exposures to 100 ppm 1,2-dibromoethane had elevated kidney weights but no renal lesions. No evidence of kidney damage occurred in rabbits on a somewhat similar exposure regimen (Rowe et al. 1952). Blood urea nitrogen levels were not elevated in either species, indicating that renal function was not compromised.

Rats exposed subchronically to 50 ppm 1,2-dibromoethane had increased kidney weights but unremarkable kidney histology (Rowe et al. 1952). Guinea pigs similarly exposed had elevated absolute and relative kidney weights.

Histologically, the guinea pig kidneys had slight congestion, edema, and tubular epithelial degeneration (Rowe et al. 1952). Neither species exposed to 1,2-dibromoethane had elevated blood urea nitrogen levels.

Renal lesions did not occur in rats or mice exposed by inhalation to 0., 3, 15, or 75 ppm of 1,2-dibromoethane in a subchronic study to determine concentrations to be used for the chronic inhalation bioassay (NTP 1982).

Renal changes were not reported in rats, guinea pigs, or rabbits exposed to 25 ppm 1,2-dibromoethane over 205-214 days (Rowe et al. 1952). In the NTP chronic inhalation study (NTP 1982), toxic nephropathy (not otherwise characterized) was present in 4 low-dose (10 ppm) and 28 high-dose (40 ppm) male and 8 high-dose female F344 rats but was not present in any of the control animals. Compound-related renal lesions were not found in $B6C3F_1$ mice, although ascending suppurative urinary tract infections may have masked renal lesions as a result of early mortality and/or pyelonephritis.

Because neoplastic changes were emphasized in the study of Wong et al. (1982), (see Section 2.2.1.8), it is unclear whether nonneoplastic lesions were recognized by the investigators.

Dermal/Ocular Effects. No studies were located regarding dermal or ocular effects in humans after inhalation exposure to 1,2-dibromoethane:

No studies were located regarding dermal effects in animals after inhalation exposure to 1,2-dibromoethane.

In the subchronic inhalation study of 1,2-dibromoethane in rodents conducted by NTP (1982), eye irritation was noted at study conclusion (weeks 12 and 13) in mice receiving the highest concentration (75 ppm).

Other Systemic Effects. Mild nonspecific endocrine lesions were observed after inhalation exposure to 1,2-dibromoethane. After subchronic exposure to 75 ppm, rats had adrenal lesions consisting of swelling and/or cytoplasmic vacuolization of cells in the zona fasciculata of the cortex and thyroid lesions consisting of slight decreases in follicular size. Degenerative changes in the adrenal cortex occurred at elevated incidence in female Fischer 344 rats after chronic exposure to 40 ppm 1,2-dibromoethane. This may represent a secondary, stress-related effect because there was poor survival at this high dose with the majority of rats dying or sacrificed when moribund during the study (NTP 1982).

2.2.1.3 Immunological Effects

No studies were located regarding immunologic effects in humans after inhalation exposure to 1,2-dibromoethane. Lymphoid neoplasia putatively

associated with exposure of grain milling workers to various chemicals including 1,2-dibromoethane is discussed in Section 2.9.3.

As discussed in Section 2.2.1.2, splenic atrophy occurred in rats exposed by inhalation to 20 ppm 1,2-dibromoethane and fed diets with or without 0.05% disulfiram. Whether atrophy referred to lymphoid or hematopoietic tissue was not specified (Wong et al. 1982).

2.2.1.4 Neurological Effects

In an old case report by Kochmann (1928), a worker exposed by inhalation during 1,2-dibromoethane production had nonspecific neurologic signs of headache and depression; these signs resolved after cessation of exposure. Also, see Section 2.2.1.2,

There are no studies in animals focusing specifically on the nervous system. In the lethality studies of Rowe et al. (1952) discussed in Section 2.2.1.1, rats and guinea pigs exposed by inhalation to higher concentrations of 1,2-dibromoethane had central nervous system depression (exact clinical signs not specified). Brain tissue apparently was not examined histologically.

2.2.1.5 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to 1,2-dibromoethane.

1,2-Dibromoethane can induce developmental effects in rodents (Short et al. 1978, 1979; Smith and Goldman 1983). The results of these studies indicate that 1,2-dibromoethane is more toxic to pregnant mice than pregnant rats (Short et al. 1978). It produces maternal toxicity as evidenced by decreases in food consumption, body weight gain, and survival (Short et al. 1978, 1979). Developmental effects observed include anatomical and skeletal defects and reduced survival of fetuses. However, these adverse developmental effects have been observed in animals at doses that induce maternal toxicity.

Inhalation exposure of pregnant Sprague-Dawley (Crl:CD) rats to 1,2-dibromoethane for 10 days during gestation resulted in significant reduction in food consumption at 20 ppm, weight loss at 32, 38, and 80 ppm, and 50% mortality at 80 ppm (Short et al. 1978). A significant reduction in the viability of embryos and fetuses was also evident at 80 ppm, Skeletal anomalies, primarily incomplete ossification, were common in the fetuses at concentrations as low as 20 ppm. Using the same protocol, the authors reported similar observations in CD-1 mice, although the maternal effects were more pronounced (Short et al. 1978). The maternal mortality was 100% in the 80-ppm exposure group. Reduction in food consumption and maternal body weight were noted at concentrations as low as 20 ppm. Fetotoxic effects consisted of

significantly increased resorptions and reduced fetal body weight. The skeletal anomalies, primarily incomplete ossification, observed in fetuses may have been the result of malnourishment rather than the direct effect of 1,2-dibromoethane-induced toxicity. However, the number of fetal mice was insufficient to draw this conclusion.

The reliable LOAEL values for developmental effects in rats and mice for the acute-duration category are reported in Table 2-l and plotted in Figure 2-l.

2.2.1.6 Reproductive Effects

Antispermatogenic effects of 1,2-dibromoethane have been observed in humans occupationally exposed to 1,2-dibromoethane (Ratcliffe et al. 1987; Takahashi et al. 1981; Ter Haar 1980). These effects include changes in sperm velocity and count. Whether or not these effects are associated with reduced fertility in humans cannot be totally addressed, since the epidemiologic study (Wong et al. 1979) was not capable of detecting such a sensitive effect. Although this study had several limitations, it indicates a potential for adverse effects of 1,2-dibromoethane on fertility.

Two types of human studies have been reported in the literature: one that assessed fertility differences between groups of workers (Wong et al. 1979) and others that assessed the potential antispermatogenic effects in male workers (Ratcliffe et al. 1987; Ter Haar 1980). These studies provided little or equivocal evidence that 1,2-dibromoethane exposure was associated with adverse fertility or antispermatogenic effects in exposed workers. All studies lacked sufficient statistical power to detect an association due to small sample size, inadequate exposure assessment or histories, inappropriate control groups, and a general methodological weakness in assessing fertility status and antispermatogenic effects. Nevertheless, they do provide some indication of potential adverse effects of 1,2-dibromoethane on fertility and sperm production.

A decrease in male fertility to 49% below expected values (significant at $p=0.05$) was reported in one of four 1,2-dibromoethane manufacturing plants (Wong et al. 1979). After adjustment for workers who had vasectomies and one whose wife had a hysterectomy, the reduction in fertility was 29% and no longer significant at that level.

Occupational exposure to 1,2-dibromoethane has been reported to produce adverse effects both on spermatogenesis (sperm concentration) and seminal fluid production (semen volume) in human males (Ratcliffe et al. 1987; Takahashi et al. 1981, Ter Haar 1980).

The study by 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. In the low-exposure group (less than

0.5 ppm 1,2-dibromoethane in air), 20% of the individuals had sperm counts below 40 million while 42% of the high-exposure group (between 0.5 and 5 ppm 1,2-dibromoethane in the air) had sperm counts below 40 million. As discussed by Dobbins (1987), there was no concurrent unexposed control group; sperm counts were compared to several published values for the U.S. population. While the differences between the low- and high-exposure groups were significant, the absence of a control group was a serious defect.

The semen quality of 46 papaya workers with chronic exposure to 1,2-dibromoethane was examined (Ratcliffe et al. 1987). These men were employed for an average of 5 years and worked in six plants as sorters, packers, forklift drivers, and fumigators. The time-weighted average 1,2-dibromoethane exposure level was estimated at 0.088 ppm, with peak exposures as high as 0.226 ppm. After adjusting data for several variables, statistically significant decreases in sperm count, decreases in the percentages of viable and motile sperm, and increases in sperm abnormalities were evident when compared with a control population of unexposed sugar refinery workers. Chronic exposure to 1,2-dibromoethane affected sperm motility, but not velocity.

A significant reduction in sperm count of agricultural workers was also reported in earlier studies by Takahashi et al. (1981). They examined sperm counts, volume, morphology, and motility in a small sample of agricultural workers in Molokai, Hawaii. Agricultural worker exposure to 1,2-dibromoethane could not be estimated. A significant reduction in sperm count occurred in the workers as compared to reference controls and to fertile controls. Confounding factors were additional worker exposure to dibromochloropropane and marijuana use.

The direct effect of inhalation exposure to 1,2-dibromoethane on spermatogenesis in animals has not been studied. Nonetheless, the available data from animal studies indicate that the male reproductive system in rats is affected by exposure to 1,2-dibromoethane at high doses. In all studies discussed below, however, rats had high mortality associated with chemical toxicity and/or chemically-induced neoplasia. It is therefore difficult to attribute effects on the reproductive organs to a direct result of 1,2-dibromoethane toxicity. Male Sprague-Dawley (Crl:CD) rats exposed by inhalation to 1,2-dibromoethane at concentrations as high as 89 ppm in air for 10 weeks developed atrophy of the testis, epididymis, prostate, and seminal vesicles (Short et al. 1979). None of the rats from the 89-ppm exposure group were able to impregnate female rats during a 2-week mating period following termination of exposure. Mortality and morbidity also occurred among rats exposed at the high concentration. Testicular degeneration and testicular atrophy in dosed F344 rats in NTP's chronic inhalation study (NTP 1982) occurred in association with spontaneous interstitial cell tumors and chemically-induced mesotheliomas. In the study by Wong et al. (1982), testicular atrophy occurred in Sprague-Dawley rats exposed to

1,2-dibromoethane (20 ppm) in combination with disulfiram in the diet, a regimen that resulted in 100% mortality by 14 months.

The highest NOAEL and reliable LOAEL values for reproductive effects in rats for intermediate durations and a LOAEL value for chronic duration are recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.7 Genotoxic Effects

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). Neither study revealed any genotoxic effect. In a study conducted on workers involved in spraying 1,2-dibromoethane 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 (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 vitro in lymphocytes obtained from these workers. 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).

Other genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

There have been two epidemiological studies regarding carcinogenic effects in workers exposed occupationally to 1,2-dibromoethane, primarily by the respiratory route (Ott et al. 1980; Turner and Barry 1979).

Cancer mortality and mortality due to respiratory disease were studied in 161 male employees exposed to 1,2-dibromoethane in two 1,2-dibromoethane manufacturing plants located in Texas and Michigan (Ott et al. 1980). Because the Texas and Michigan plants ceased operations in 1969 and 1976, respectively, environmental assessments were based on existing records and discussions with workers formerly associated with the plants. No statistically significant increase in deaths was observed when data were examined in terms of duration of exposure or interval since first exposure. Although there was an increase in cancer mortality among employees with more than 6 years of exposure to 1,2-dibromoethane in both plants, this increase was not statistically significant. The authors suggested that the observed incidence of cancer in the study population was lower than that which would be

predicted from animal studies. They concluded that there was a need for continued surveillance of the cohort of 161 employees and an industry-wide study of mortality among workers in 1,2-dibromoethane manufacturing plants. Although this study has a number of limitations, results of the study neither confirm nor refute the possibility that 1,2-dibromoethane is a human carcinogen. Study limitations include not controlling for confounding factors such as smoking, incomplete identification of exposure levels of 1,2-dibromoethane, concomitant exposure of workers to other chemicals, lack of a matched control group, and lack of completeness of report data.

In another epidemiological study, the mortality of workers exposed to 1,2-dibromoethane in two manufacturing plants in Britain was evaluated (Turner and Barry 1979). The manufacturing operation of each plant involved the extraction of bromine from sea water and its subsequent reaction with ethylene to form 1,2-dibromoethane. Although the size of the group studied was too small to analyze mortality rates on a year-by-year basis, a comparison of rates was done by grouping person-years of follow-up into four age ranges over the period of the study (23 years). No increase in mortality from any cause, including neoplasia, was identified in the 1,2-dibromoethane workers.

Chronic inhalation exposure of rodents to 1,2-dibromoethane has been associated with neoplasms in the respiratory tract, as well as in other organ systems. Two studies have examined the carcinogenic potential of 1,2-dibromoethane in rodents after inhalation exposure (NTP 1982; Wong et al. 1982). There was also an A strain mouse assay (Adkins et al. 1986).

A chronic inhalation study (18 months) in Sprague-Dawley (Crl:CD) rats examined the carcinogenicity of 20 ppm 1,2-dibromoethane alone and with simultaneous exposure to 0.05% disulfiram in the diet (Wong et al. 1982). Male rats exposed to 1,2-dibromoethane had significantly higher incidences of splenic hemangiosarcomas and subcutaneous mesenchymal tumors. Female rats exposed to 1,2-dibromoethane had significantly higher incidences of splenic hemangiosarcomas and mammary tumors (combined adenoma, fibroadenoma, carcinoma, or adenocarcinoma). In both sexes of rats, the combination of 1,2-dibromoethane and disulfiram resulted in significantly higher incidences of hepatocellular tumors (percentage of adenoma or carcinoma not identified); splenic hemangiosarcoma; kidney adenoma and adenocarcinoma; thyroid follicular epithelial adenoma; and hemangiosarcoma of the omentum or mesentery. It was unclear whether hemangiosarcoma of the mesentery (omentum) and of the lung. were primary sites or metastatic from spleen. Female rats had increased incidence of mammary gland tumors.

Because the nasal cavity of the animals was not examined histologically, it cannot be determined whether nasal cavity tumors were induced. Also, because the authors tested animals at only one concentration, the doseresponse cannot be characterized.

2. HEALTH EFFECTS

The carcinogenicity of 1,2-dibromoethane in F344 rats and $B6C3F_1$ mice was examined in an inhalation bioassay (NTP 1982). Doses tested were 0, 10, and 40 ppm; study duration was 79-103 weeks. Mortality related to chemicallyinduced malignant tumors and to toxic lesions was high in high-dose rats of both sexes. Both sexes of rats had significant compound-related increases in nasal epithelial tumors. EPA (IRIS 1991) has derived a unit risk value of. $2.2x10^{-4}$ $\mu g/m^3$ for cancer risk associated with inhalation exposure to 1,2-dibromoethane from this study based on the incidence of nasal tumors in male rats. EPA also estimated that 1,2-dibromoethane concentrations of $5x10^{-1}$, $5x10^{-2}$, and $5x10^{-3}$ $\mu g/m^3$ ($6.5x10^{-5}$, $6.5x10^{-6}$, and $6.5x10^{-7}$ ppm) in air are associated in humans with excess lifetime cancer risks of 10^{-4}, 10^{-5}, and 10^{-6}, respectively. These values correspond to 1 excess cancer death in 10,000, 100,000, or 1 million persons exposed continuously for their lifetime (estimated as 70 years) to these respective levels of 1,2-dibromoethane by inhalation. These estimated concentrations associated'with cancer risk were converted into ppm and plotted in Figure 2-l.

Exposed rats also had elevated incidences of splenic hemangiosarcomas (both sexes), mesothelioma of the tunica vaginalis (males), pulmonary alveolar/bronchiolar adenoma or carcinoma (females), and fibroadenoma of the mammary gland (females).

Exposed female mice had significant compound-related increases in nasal carcinomas (NTP 1982; Stinson et al. 1981). The incidences of combined alveolar/bronchiolar carcinoma and adenoma were significantly increased in the lungs of high-dose male and female mice as compared with control animals. In addition to these tumors, adenomatous polyps were present in tracheal, bronchial, and bronchiolar lumens (NTP 1982).

There was a statistically significant compound-related increase in incidence of several other tumors in female mice: hemangiosarcoma of the abdominal retroperitoneum, particularly involving the area of the ovaries, uterus, kidneys, and adrenal; subcutaneous fibrosarcomas; and mammary adenocarcinoma (NTP 1982). A limitation of the study was poor survival in male mice from ascending suppurative urinary tract infections.

A/J strain mice exposed by inhalation to 20 and 50 ppm 1,2-dibromoethane for 6 months had a significant increase in the frequency and incidence of alveolar-bronchiolar adenomas (Adkins et al. 1986).

In summary, two epidemiological studies have not identified an increased risk of cancer in people occupationally exposed by inhalation to 1,2-dibromoethane. In experimental animals exposed by the inhalation route, 1,2-dibromoethane is a potent carcinogen, producing cancer at the point-of-contact--the upper respiratory tract--as well as in numerous organs and tissues throughout the body.

2.2.2 Oral Exposure

2.2.2.1 Death

There are two case reports of death in humans following oral administration of 1,2-dibromoethane in suicide attempts.

A white 43-year-old female died 54 hours after ingestion of 9 "Fumisoil" capsules each containing 4.5 mL 1,2-dibromoethane (140 mg/kg/day) (Olmstead 1960). Clinical signs prior to death were emesis, diarrhea, oliguria progressing to anuria, tachypnea, and agitation. Pathologic findings were in liver and kidney. The liver had extensive centrilobular hepatocellular necrosis with sinusoidal dilatation and a minimal cellular reaction. The kidney had patchy areas of either acute tubular necrosis or autolysis, mild cytoplasmic vacuolization of proximal cortical tubules, and proteinaceous casts in tubules near the cortico-medullary junction.

Ingestion of one ampule of commercial 1,2-dibromoethane occurred in six additional human cases of attempted suicide (Saraswat et al. 1986). The patients were all teenagers or young adults; two out of six died. One female patient was admitted in a moribund condition and died approximately 36 hours after admission. Pathologic findings were oropharyngeal ulceration, gastric mucosal erosions, massive hepatocellular necrosis, icterus, and renal lesions (hemorrhage, tubular swelling, and occasional necrosis). A second female was admitted with nausea, emesis, and a burning sensation in her throat. She became hypotensive, unconscious, and died approximately 15 hours after admission. Pathologic findings were oropharyngeal ulcers, gastric hyperemia, and centrilobular hepatocellular necrosis. Four other patients who survived after ingesting 1,2-dibromoethane (three female, one male) had nausea and emesis and three out of four had labial and oral erosions and ulcers.

In a study using large domestic animals because of concern over soil nematocide residues in treated forage, 1,2-dibromoethane was administered orally in a gelatin capsule to a small number of animals (Schlinke 1969). 1,2-Dibromoethane at 50 mg/kg body weight caused mortality in one calf, while one calf given 25 mg/kg body weight and one calf given 10 mg/kg body weight survived. Sheep were similarly treated; one given 50 mg/kg body weight died, one out of two given 25 mg/kg died, and one given 10 mg/kg survived. Interpretation of these studies was complicated by use of a ruminant species, a very small number of animals, and lack of necropsy data.

Single-dose oral LD_{50} values in rats, guinea pigs, rabbits, and mice were determined by Rowe et al. (1952) in a gavage study using 1,2-dibromoethane in olive oil. All reliable LD_{50} values (lethal dose, 50% kill) for each species for the acute-duration category are recorded in Table 2-2 and plotted in

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

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
ACUTE EXPOSURE								
Death								
1	Rat	(GO)	1 d 1x/d				117 (LD_{50}; female)	Rowe et al. 1952
2	Rat	(GO)	1 d 1x/d				146 (LD_{50}; males)	Rowe et al. 1952
3	Rabbit	(GO)	1 d 1x/d				55 (LD_{50}; female)	Rowe et al. 1952
4	Gn pig	(GO)	1 d 1x/d				110 (LD_{50})	Rowe et al. 1952
5	Mouse	(GO)	1 d 1x/d				420 (LD_{50}; female)	Rowe et al. 1952
Systemic								
6	Rat	(GO)	1 d 1x/d	Hepatic Renal	100 100			Short et al. 1979
7	Rat	(GO)	1 d 1x/d	Hepatic			110 (necrosis)	Broda et al. 1976
8	Rat	(G)	2 wk 5d/wk	Gastro	40	80 (forestomach cell proliferation and hyperkeratosis)		Ghanayem et al. 1986
9	Rat	(GO)	1 d 1x/d	Hepatic		107 (fat degeneration)		Botti et al. 1986

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
Reproductive								
10	Rat	(GO)	5 d 1x/d		30			Teramoto et al. 1980
11	Mouse	(GO)	5 d 1x/d		150			Teramoto et al. 1980
INTERMEDIATE EXPOSURE								
Reproductive								
12	Bull	(C)	20 d 1x/2d			4 (transient sperm anomalies)		Amir 1975
13	Bull	(GO)	20 d 1x/2d			4 (transient sperm anomalies)		Amir et al. 1977
CHRONIC EXPOSURE								
Cancer								
14	Rat	(GO)	49-61 wk 5d/wk 1x/d				38 (CEL; stomach tumor male) 37 (CEL; stomach tumor female)	NCI 1978
15	Mouse	(W)	15-18 mo 7d/wk 1x/d				103 (CEL, forestomach tumor female) 116 (CEL, forestomach tumor male)	Van Duuren et al. 1985
16	Mouse	(W)	18 mo 7d/wk 24h/d				50 (CEL, gastrointestinal tumors male)	Van Duuren et al. 1986

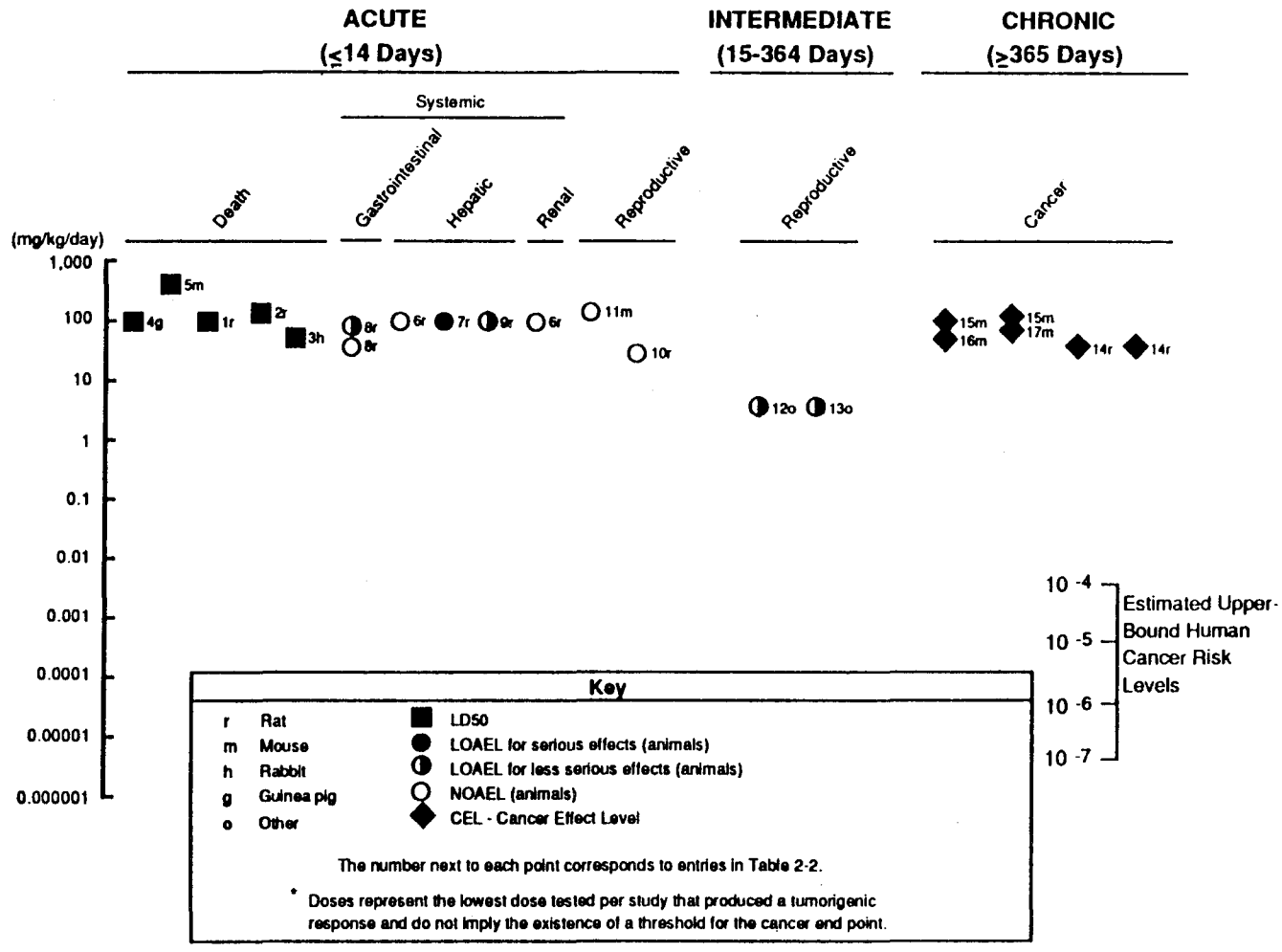
TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
17	Mouse	(GO)	53-78 wk 5d/wk 1x/d				62 (CEL, forestomach, lung tumors)	NCI 1978

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

(C) = capsule; CEL = cancer effect level; CNS = central nervous system; d = day; (G) = gavage; Gastro = gastrointestinal; Gn pig = guinea pig; (GO) = oral by gavage; LOAEL = lowest-observed-adverse-effect level; LD_{50} = lethal dose, 50% kill; mo = month; NOAEL = no-observed-adverse-effect level; (W) = water; wk = week; (x) = times.

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



2.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, hematological, musculoskeletal, or dermal/ocular effects in humans or animals after oral exposure to 1,2-dibromoethane.

The highest NOAEL and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Gastrointestinal Effects. Oral and/or pharyngeal ulceration occurred in five out of six humans who ingested commercial 1,2-dibromoethane ampules (Saraswat et al. 1986). This report was discussed in detail in Section 2.2.2.1.

Because 1,2-dibromoethane given chronically by gavage induced a high incidence of squamous cell tumors of the forestomach of rodents, a short-term study was conducted to identify forestomach lesions following 2-week repeated gavage administration of 40 or 80 mg/kg/day 1,2-dibromoethane to F344 rats (Ghanayem et al. 1986). A significant increase in forestomach mucosal cell proliferation and hyperkeratosis occurred in rats exposed to 80 mg/kg/day. These proliferative lesions, which in themselves are not preneoplastic, could suggest the potential for development of neoplastic lesions. The authors concluded that forestomach mucosal hyperplasia resulting from chronic gavage of 1,2-dibromoethane may provide a favorable environment for tumor development.

Nonneoplastic proliferative lesions of the forestomach were observed i.n high-dose Osborne-Mendel rats in the chronic gavage study of 1,2-dibromoethane conducted by the National Cancer Institute (NCI 1978). These consisted of acanthosis and hyperkeratosis of forestomach squamous epithelium. Similar lesions occurred in high-dose B6C3F_1 mice. These dose levels are not plotted and recorded in Figure 2-2 and Table 2-2, respectively, since these doses also caused forestomach squamous cell tumors.

Hepatic Effects. Severe liver necrosis occurred in three humans who ingested commercial 1,2-dibromoethane in order to commit suicide (Olmstead 1960; Saraswat et al. 1986). Necrosis was massive in one of these individuals; the other two had centrilobular hepatocellular necrosis.

1,2-Dibromoethane is considered to be a weak hepatotoxin in animals. Hepatocellular fatty change (degeneration) is one of the common lesions in experimental animals associated with acute oral exposure to 1,2-dibromoethane (Botti et al. 1986). When administered to rats by gavage at a dosage of 110 mg/kg/day, this lesion is corroborated by an increase in liver

triglyceride levels that begins within 8 hours of treatment (Nachtomi and Alumot 1972).

Using light microscopy, Broda et al. (1976) did not observe hepatocellular fatty change in livers of rats exposed by gavage to 110 mg/kg 1,2-dibromoethane in olive oil. Rats developed 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.

Following gavage administration of 107 mg/kg 1,2-dibromoethane to rats, 1,2-dibromoethane depleted both cytosolic and mitochondrial glutathione; ultrastructurally, some mitochondria had abnormal shapes (Botti et al. 1986). When rats were pretreated 30 minutes prior to 1,2-dibromoethane administration with diethylmaleate, a cytoplasmic glutathione-depleting agent, hepatocytes had generalized vacuolization due to mitochondria with severe ultrastructural abnormalities and swelling. These findings demonstrated the importance of glutathione in maintenance of mitochondrial membrane integrity. With reduced glutathione levels and the concomitant formation of glutathione disulfides, the mitochondrial membrane became altered and permeable to calcium ions (Botti et al. 1986).

Liver was not examined histologically in the subchronic study used to set concentrations for the NCI chronic gavage bioassay of 1,2-dibromoethane (NCI 1978). In the NCI (1978) gavage bioassay (discussed in detail in Section 2.2.2.8), a nonneoplastic hepatic lesion, peliosis hepatis, occurred in a small number of treated male and female Osborne-Mendel rats and had an equivocal relationship to 1,2-dibromoethane exposure.

Renal Effects. Renal lesions have been reported in humans dying acutely after acute oral exposure to 1,2-dibromoethane. In the case report by Olmstead (1960), the patient's kidneys had equivocal necrotizing tubular lesions, proximal convoluted tubular cytoplasmic vacuolization, and proteinaceous casts in tubules near the corticomedullary junction. In the report of Saraswat et al. (1986), one of two fatalities had renal hemorrhage, tubular swelling, and occasional necrotic tubular cells.

Cell proliferation, predominantly in the proximal tubules, occurred in Wistar 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 8-48 hours after treatment indicates that such proliferation was not a regenerative response (Ledda-Columbano et al. 1987b).

Toxic nephropathy of the type seen after inhalation exposure of rats (see Section 2.2.1.2) was not identified in rats or mice in the NCI (1978) gavage bioassay of 1,2-dibromoethane.

Other Systemic Effects. Endocrine lesions related to 1,2-dibromoethane exposure were reported in the NCI (1978) gavage bioassay. These consisted of adrenal cortical cell degeneration in a small number of exposed male and female Osborne-Mendel rats. The possibility exists that this adrenal change represents a secondary (stress-related) effect rather than a primary effect of 1,2-dibromoethane exposure.

2.2.2.3 Immunological Effects

No studies were located regarding immunologic effects in humans or animals after oral exposure to 1,2-dibromoethane.

2.2.2.4 Neurological Effects

No clinical signs specific to primary neurologic effects were described in humans following ingestion of 1,2-dibromoethane (Saraswat et al. 1986) (see Section 2.2.2.1). One of the patients who became unconscious and died after ingestion of 1,2-dibromoethane had nonspecific brain lesions--meningeal congestion and interstitial cortical edema. Of the four patients who survived, three had symptoms of confusion upon admission although they were conscious.

Sheep and calves dying after toxic oral doses of 1,2-dibromoethane (Schlinke 1969) had nonspecific clinical signs of stiffness, prostration, and anorexia.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans and animals after oral exposure to 1,2-dibromoethane.

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans, although oral exposure via drinking water and contaminated food has been documented in the literature.

Reproductive effects from oral exposure to 1,2-dibromoethane have been investigated in various animals including bulls, rats, and mice over intermediate and chronic exposure durations (Amir 1973; Amir and Ben-David 1973; Amir and Lavon 1976; Amir and Volcani 1965; Amir et al. 1983; NCI 1978). These studies indicate species differences in sperm damage resulting from exposure to 1,2-dibromoethane.

A high percentage (up to 79%) of abnormal spermatozoa in bull ejaculates was reported as early as two weeks following oral administration of 10 doses of 4 mg/kg 1,2-dibromoethane on alternate days (Amir and Ben-David 1973).

Radioactivity (^{3}H or ^{14}C-1,2-dibromoethane) was detected in spermatozoa collected approximately 1 week following the initial oral dose (Amir 1973). These results indicate that 1,2-dibromoethane exerts spermicidal action during the process of spermiogenesis and sperm maturation. This conclusion was supported by the evidence that the percentage of sperm abnormalities was highest when little 1,2-dibromoethane radioactivity could be detected in sperm. In addition, reduction in sperm concentration was more pronounced in adult bulls than in young bulls, and the period of recovery was longer in adult animals (Amir 1975). In another study, bulls were fed 2 mg/kg/day 1,2-dibromoethane for 12 months followed by 4 mg/kg 1,2-dibromoethane every other day ,until they reached the age of 14-16 months. The semen samples examined revealed low sperm density, structural abnormalities, and low mobility (Amir and Volcani 1965). Sperm production returned to normal as early as 10 days postexposure (Amir and Lavon 1976; Amir et al. 1977).

In the chronic gavage study of 1,2-dibromoethane conducted by NCI (1978), high-dose male Osborne-Mendel rats and $B6C3F_1$ mice developed testicular atrophy. Because study animals had high compound- and gavagerelated mortality and early onset of forestomach squamous cell carcinomas, it is difficult to determine from these results whether testicular atrophy (degeneration) was a primary (compound-induced) or secondary (nonspecific) event.

The highest NOAEL values for reproductive effects in rats and mice for acute exposure duration and a reliable LOAEL in bulls for the intermediate-duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to 1,2-dibromoethane. Repeated oral administration of 1,2-dibromoethane to rats at 100 mg/kg/day (Epstein et al. 1972) and to mice at doses as high as 150 mg/kg/day (Teramoto et al. 1980) did not induce dominant lethal mutations. Females mated to these males did not show a significant increase in the number of dead implants, indicating a lack of genotoxic effect. Liver and sperm cells from rats gavaged once with 1,2-dibromoethane at doses ranging from 10 to 100 mg/kg were not found to have higher rates of unscheduled DNA synthesis than those from untreated rats (Working et al. 1986). In contrast, oral administration of approximately 3 mg/kg to rats resulted in the formation of DNA adducts in all tissues examined (kidney, liver, spleen, intestine, stomach, testes, heart, brain, and muscle, listed in decreasing order of amount detected) (Hill et al. 1978). 1,2-Dibromoethane induced DNA damage in rat liver cells when administered as a single dose by gavage at doses ranging from 75-220 mg/kg (Nachtomi and Sarma 1977). Hepatocellular DNA damage caused at the 75-mg/kg dose level was completely repaired 96 hours after administration.

Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

No studies were located regarding carcinogenic effects in humans following oral exposure to 1,2-dibromoethane.

The rat liver foci assay is a short-term in vivo test to predict carcinogenic potential of a chemical. In this assay, 1,2-dibromoethane has both initiating and promoting activity, which correlates well with its carcinogenic effects in animals.

1,2-Dibromoethane was administered orally in corn oil to Sprague-Dawley rats in doses up to 120 mg/kg body weight in an initiation protocol that included partial hepatectomy (Milks et al. 1982). This treatment did not cause an increase in γ-glutamyl transpeptidase (GGT) positive foci after 2 months. When 1,2-dibromoethane was orally administered in corn oil at doses of 10 or 30 mg/kg in a promotion protocol with N-nitrosodiethylamine as an initiator, there was a significant increase in production of GGT positive foci after 2 months. Based on their results, the authors speculated that 1,2-dibromoethane had epigenetic (promoter) activity, which could contribute to the compound's carcinogenic effect. Promotion effects may have been related to hepatocellular mitogenesis. Such a promotional effect was not detected when 1,2-dibromoethane was used to induce hepatocellular mitogenesis in the absence of partial hepatectomy following initiation by diethylnitrosamine (Ledda-Colwnbano et al. 1987a).

In another liver foci study using Sprague-Dawley (Crl:CD) rats, 1,2-dibromoethane in corn oil given by gavage was used as an initiator. Two dose regimens were used: 75 mg/kg 1,2-dibromoethane at 0 and 24 hours or corn oil at 0 hours and 75 mg/kg 1,2-dibromoethane at 24 hours. Partial hepatectomies and phenobarbital in drinking water also were part of the protocol. With this system, at 16 months, 1,2-dibromoethane-exposed rats had increased numbers of foci of hepatic cellular alteration. Rats that received the two doses of 1,2-dibromoethane had increased numbers of nodules on hematoxylin and eosin-stained sections as well as increased number and size of GGT positive foci (Moslen 1984). These results indicate that 1,2-dibromoethane can act as an initiator.

Oral exposure of rodents to 1,2-dibromoethane either via gavage or drinking water has resulted in neoplasms of the forestomach and other organs.

The carcinogenicity of 1,2-dibromoethane by the oral route has been examined in a chronic bioassay conducted by NCI (1978). The chemical was administered by gavage in corn oil to rats and mice. Because of dose adjustments during the study, doses were expressed as time-weighted average (TWA) as follows: high doses for rats were 41 mg/kg/day (males) and 39 mg/kg/day (females); low doses for rats were 38 mg/kg/day (males) and 37 mg/kg/day (females); the high dose for male and female mice was 107 mg/kg/day; and the low dose for male and female mice was 62 mg/kg/day.

2. HEALTH EFFECTS

Under test conditions, 1,2-dibromoethane was carcinogenic to Osborne-Mendel rats and B6C3F_1 mice resulting in squamous cell carcinomas of the forestomach in rats and mice of both sexes and lung adenomas in male and female mice. There were also two equivocal endpoints in rats: hepatocellular tumors in females and hemangiosarcomas in males. It should be noted that there were a number of problems associated with this study. High mortality as a result of incorrect determination of the maximum tolerated dose necessitated discontinuation of dosing from weeks 17 to 30 in the high-dose rats. Periodic adjustments of dose were made for male and female mice. There may have been errors in laboratory gavage procedures. Finally, the rat and mouse studies were terminated early. However, these limitations do not diminish the conclusion that 1,2-dibromoethane is carcinogenic to rats and mice following chronic gastric intubation exposure.

EPA (1987a) has derived a q_1* value of 85 $(mg/kg/day)^{-1}$ for cancer risk associated with oral exposure to 1,2-dibromoethane based on the study by NCI (1978) in rats. IRIS (1991) also estimated that 1,2-dibromoethane concentrations of $4x10^{-2}$, $4x10^{-3}$, and $4x10^{-4}$ μg/L ($5x10m^{-6}$, $5x10^{-7}$, and $5x10^{-8}$ mg/kg/day) in water are associated in humans with excess lifetime cancer risks of 10^{-4}, 10^{-5}, and 10^{-6}, respectively. These values correspond to 1 excess cancer death in 10,000, 100,000, or 1 million persons, exposed continuously. for their lifetime (estimated as 70 years) to these respective levels of 1,2-dibromoethane by ingestion. These estimated concentrations associated with cancer risk were converted into mg/kg/day and plotted in Figure 2-2.

There are two drinking water studies of 1,2-dibromoethane that further support the conclusion that oral exposure to 1,2-dibromoethane results in forestomach tumors in mice.

A dose of 103 mg/kg/day for females and 116 mg/kg/day for males of 1,2-dibromoethane in drinking water induced squamous cell tumors (primarily carcinomas) of the forestomach in male and female B6C3F_1 mice (Van Duuren et al. 1985). It should be noted that the male and female mice were sacrificed before the completion of the chronic study because of excessive morbidity. Because only one dose of 1,2-dibromoethane was used, a dose-response could not be characterized.

In another drinking water study, 50 mg/kg/day 1,2-dibromoethane was used as a positive control for a study on humic acids (Van Duuren et al. 1986). Both sexes of B6C3F_1 mice exposed to 1,2-dibromoethane had statistically significant increases in squamous cell tumors of the forestomach: squamous cell carcinomas in males and papillomas or carcinomas in females. Male 1,2-dibromoethane-treated mice also had a significant increase over control animals in the incidence of papilloma and squamous carcinoma of the esophagus. Animals were tested at only one dose; therefore, dose-response could not be characterized.

2.2.3 Dermal Exposure

2.2.3.1 Death

Two fatal cases of occupational exposure to 1,2-dibromoethane were reported by Letz et al. (1984). A worker collapsed shortly after entering a pesticide storage tank containing residues of 1,2-dibromoethane; he remained in the tank for 45 minutes. A supervisor attempting to rescue the worker also collapsed and was exposed for 20-30 minutes prior to rescue. Both men died 12 and 64 hours after collapse, respectively. The primary route of exposure was postulated to be dermal, with inhalation also playing a potentially important role. Neither worker had been wearing protective clothing or respirators.

Clinical chemistry prior to death for both men revealed metabolic acidosis, acute renal and hepatic failure, skeletal muscle necrosis, and damage to other organ systems. Autolysis of viscera prevented complete characterization of lesions associated with mortality from these 1,2-dibromoethane exposures.

Lethal amounts of topically applied 1,2-dibromoethane were rapidly absorbed through the intact skin of rabbits. When evaporation was prevented for 24 hours by occlusive dressing, mortality occurred within 4 days (Rowe et al. 1952).

The reliable LOAEL for death in rabbits from acute dermal exposure to 1,2-dibromoethane is recorded in Table 2-3.

2.2.3.2 Systemic Effects

No studies were located regarding hematologic effects in humans or animals after dermal exposure to 1,2-dibromoethane.

Respiratory Effects. In the case report of Letz et al. (1984) (see Section 2.2.3.1), one patient had bilateral pulmonary edema and cyanosis at necropsy. These lesions, however, are nonspecific and can occur with any type of agonal death. No studies were located regarding respiratory effects in animals after dermal exposure to 1,2-dibromoethane.

Cardiovascular Effects. One of the patients described by Letz et al. (1984) (see Section 2.2.3.1) who had a terminal cardiopulmonary arrest had acute myocardial interstitial edema, myocardial inflammation, and Grampositive sporulating rods at necropsy. The second patient initially had a

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

Species	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
ACUTE EXPOSURE						
Death						
Rabbit	24 hr				300 (approximate LD_{50})	Rowe et al. 1952
Systemic						
Rabbit	24 hr	Derm/oc		210 (erythema, necrosis)		Rowe et al. 1952
Neurological						
Rabbit	24 hr			210 (CNS depression)		Rowe et al. 1952
CHRONIC EXPOSURE						
Cancer						
Mouse	440-594 d 3d/wk 1x/d				833 (CEL, lung adenoma)	Van Duuren et al. 1979

CEL = cancer effect level; CNS = central nervous system; d = day; Derm/oc = dermal/ocular; hr = hour; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; wk = week

normal electrocardiogram, but as his renal and hepatic function deteriorated, eventually developed supraventricular tachycardia and asystole.

No studies were located regarding cardiovascular effects in animals after dermal exposure to 1,2-dibromoethane.

Gastrointestinal Effects. Both patients described by Letz et al. (1984) (see Section 2.2.3.1) vomited shortly after removal from the tank; one complained of a burning throat. Both patients later developed diarrhea.

No studies were located regarding gastrointestinal effects in animals after dermal exposure to 1,2-dibromoethane.

Musculoskeletal Effects. Both patients described by Letz et al. (1984) (see Section 2.2.3.1) had greatly elevated levels of serum creatinine phosphokinase after 1,2-dibromoethane exposure; this enzyme increases in the event of skeletal muscle necrosis. There was no report of skeletal muscle being examined at necropsy or histologically in either individual.

No studies were located regarding musculoskeletal effects in animals after dermal exposure to 1,2-dibromoethane.

Hepatic Effects. Both patients described by Letz et al. (1984) (see Section 2.2.3.1) had elevated serum aspartate aminotransferase and lactic dehydrogenase, indicating severe hepatic damage. These enzymes were elevated 5 hours after exposure in one man who died 12 hours after exposure and 24 hours after exposure in the second patient who died 64 hours following exposure. Liver from the patient dying first had intrasinusoidal nuclear fragmentation consistent with Kupffer cell damage; autolysis precluded examination of the second patient's liver.

No studies were located regarding hepatic effects in animals after dermal exposure to 1,2-dibromoethane.

Renal Effects. The patient described by Letz et al. (1984) (see Section 2.2.3.1) who lived for 64 hours after exposure to toxic levels of 1,2-dibromoethane had acute renal failure as evidenced by severe oliguria 24 hours after exposure and abnormal clinical chemistry values (blood urea nitrogen, creatinine, and serum uric acid). Severe metabolic acidosis was present despite two hemodialysis procedures.

No studies were located regarding renal effects in animals after dermal exposure to 1,2-dibromoethane.

Dermal/Ocular Effects. Volunteers including the report's author were exposed topically to liquid from a remote water gauge; this liquid contained 1,2-dibromoethane as well as other chemicals (Pflesser 1938). Follow-up tests

were formed with 1,2-dibromoethane. No dermal changes occurred when the liquid or 0.5 cc of 1,2-dibromoethane was applied to uncovered skin. A burning sensation, inflammation and vesiculation occurred when a cloth dressing saturated with the liquid was applied for 1-2 hours. Skin lesions resolved with treatment after 7-13 days.

Erythema and blisters developed within 24 hours on the trunk and legs of a worker exposed to residues of 1,2-dibromoethane in a pesticide tank (Letz et al. 1984). This patient, immediately after rescue, complained of burning eyes, but ocular lesions did not develop.

When rabbits were exposed topically to 1,2-dibromoethane, all animals with occlusive dressings, irrespective of concentration, had moderate to severe cutaneous erythema, edema, and necrosis with sloughing (Rowe et al. 1952). When evaporation was not inhibited, slight erythema but no additional damage occurred. Lethality associated with this exposure was discussed in Section 2.2.3.1.

Undiluted 1,2-dibromoethane applied topically to rabbit eyes caused pain, conjunctival irritation, and superficial cornea1 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 cornea1 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).

The LOAEL for dermal effects in rabbits from acute dermal exposure to 1,2-dibromoethane is recorded in Table 2-3.

2.2.3.3 Immunological Effects

No studies were located regarding immunologic effects in humans or animals after dermal exposure to 1,2-dibromoethane.

2.2.3.4 Neurological Effects

Two male workers collapsed very shortly after entering a storage tank that contained toxic 1,2-dibromoethane residues (Letz et al. 1984). After 45 minutes of exposure prior to rescue, one patient was comatose then became combative and incoherent in the ambulance. One hour later, he was lethargic; as metabolic acidosis developed, he became semicomatose. When the second patient was rescued from the tank after 20-30 minutes of exposure; he became delirious and combative. His neurological symptoms then ameliorated until he developed hepatorenal failure.

In the study of Rowe et al. (1952) discussed in Section 2.2.3.1, rabbits exposed dermally to 1,2-dibromoethane at all dosage levels had central nervous system depression (not otherwise specified).

The reliable LOAEL for neurological effects in rabbits from acute dermal exposure is recorded in Tible 2-3.

No studies were located regarding the following health effects in humans or animals after dermal exposure to 1,2-dibromoethane:

2.2.3.5 Developmental Effects
2.2.3.6 Reproductive Effects
2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

2.2.3.8 Cancer

No studies were located regarding carcinogenic effects in humans following exposure to 1,2-dibromoethane by the dermal route alone. However, occupational exposures to 1,2-dibromoethane are likely to involve dermal as well as respiratory exposure. Two epidemiologic studies concerning occupational exposure are discussed in Section 2.2.1.8 and an abstract is discussed in Section 2.9.3.

Dermal exposure of mice to 1,2-dibromoethane has resulted in cutaneous neoplasms and increased incidences of primary lung tumors.

Repeated topical application of 1,2-dibromoethane (0, 833, or 1,666 mg/kg/day) to Ha:ICR Swiss mice resulted in a statistically significant increase in skin papillomas at the high dose (Van Duuren et al. 1979). In addition, the number of mice with distant tumors (lung tumors) was significantly higher at both doses applied. Because the mice in the study were housed six to a cage with no restraining collars to prevent licking the application site, aspiration to the lungs could have occurred during grooming. 1,2-Dibromoethane did not initiate skin tumors after a single topical application, even when treatment by phorbol myristate (a potent tumor promoter) followed the dermal application of 1,2-dibromoethane (Van Duuren et al. 1979). The cancer effect level causing lung tumors in mice from chronic dermal exposure is reported in Table 2-3.

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located in humans regarding the inhalation absorption of 1,2-dibromoethane. The available animal toxicity data (see Section 2.2.1) 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.

2.3.1.2 Oral Exposure

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 intubation (Botti et al. 1982; Nachtomi 1981; Plotnick et al. 1979; Van Bladeren et al. 1980). The presence of 1,2-dibromoethane residues in the kidney, liver, and spleen of rats following ingestion is also evidence of its absorption (Plotnick et al. 1979). It may be inferred that uptake from the gastrointestinal tract of rats is extensive, since 73% of a radiolabeled ^{14}C-1,2-dibromoethane dose was excreted in the urine (Plotnick et al. 1979; Van Bladeren et al. 1980) and about 2% was excreted in the feces by 24-48 hours (Plotnick et al. 1979).

2.3.1.3 Dermal Exposure

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 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.

The available data suggest that 1,2-dibromoethane may be absorbed dermally by humans. Thus, contact with water contaminated with 1,2-dibromoethane may result in absorption.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

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.

2.3.2.2 Oral Exposure

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. The tissue distribution of 1,2-dibromoethane has been studied in rats following exposure by the oral route. Although retention was limited, the kidneys, liver, and spleen appear to retain the highest amounts of the administered dose (Plotnick et al. 1979) as illustrated in Table 2-4. Rats received an oral dose of 15 mg/kg/day of labeled 1,2-dibromoethane in corn oil. Twenty-four hours later 3% of radioactivity was detected in fat, brain, kidney, liver, spleen, testes, blood, and plasma, 72.38% in the urine, and 1.65% 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.

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 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.

2.3.2.3 Dermal Exposure

No studies were available in humans or animals regarding the distribution of 1,2-dibromoethane following dermal exposure. However, toxic

TABLE 2-4. 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[a]

	Tissue concentration[b]		Percentage of dose[c]	
Tissue	24 Hours	48 Hours	24 Hours	48 Hours
Liver	4.78 ± 0.24	2.87 ± 0.33	1.79 ± 0.07	1.10 ± 0.12
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
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
Blood[e]	0.90 ± 0.05	0.64 ± 0.07	0.59 ± 0.03	0.43 ± 0.04
Plasma	0.46 ± 0.04	0.22 ± 0.02	No data	No data
Urine	No data	No data	72.38 ± 0.98[f]	73.54 ± 2.80[g]
Feces	No data	No data	1.65 ± 0.28[f]	2.42 ± 0.54[g]
Total recovery	No data	No data	76.85	77.8

[a]Source: Plotnick et al. 1979

[b]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.

[c]Values represent the mean percentage of the administered radioactivity plus or minus the standard error of the mean of duplicate determinations on six animals.

[d]Assumed 6% of body weight

[e]Assumed 9% of body weight

[f]n = 12 (includes 24-hour samples obtained from rats killed 48 hours after compound administration)

[g]Cumulative 48-hour excretion

effects observed in humans and animals after dermal exposure indicate that the compound is widely distributed throughout the body.

2.3.2.4 Other Routes of Exposure

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, liver, and stomach retained the highest amounts of the administered 1,2-dibromoethane dose across all the observation periods (see Tables 2-5 and 2-6). 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% in whole blood, and 2.6% 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.

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, liver, and stomach, regardless of the route of exposure and the species tested.

2.3.3 Metabolism

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) and the cytosolic activation system (glutathione conjugation). Figure 2-3 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 1,2-dibromoethane's proven genotoxic effect and, perhaps, its carcinogenic effect observed in laboratory animals. These two systems and their relative importance are discussed in detail below.

TABLE 2-5. Distribution of 1,2-Dibromoethane in Mice[a]

Organ	Percentage of dose[b]		
	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

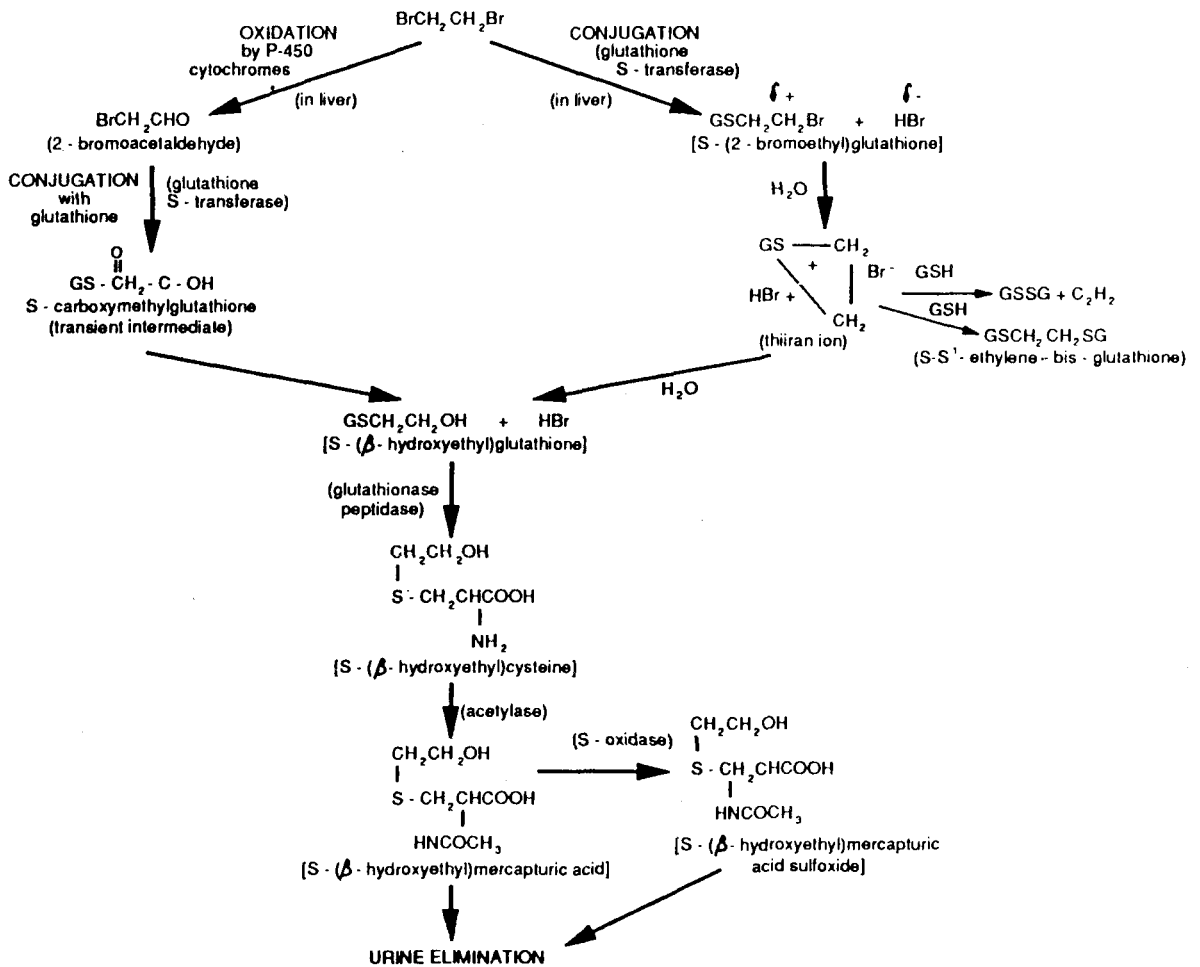
[a]Source: Edwards et al. 1970
[b]Intraperitoneal injection of 40 mg/kg body weight

TABLE 2-6. 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,b]

Organ	4 Hours	8 Hours	12 Hours	24 Hours	48 Hours	72 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[c]	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[d]	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]Source: Plotnick and Conner 1976
[b]Values represent the mean plus or minus the standard error of the mean of duplicate determinations on three animals at each time interval.
[c]Including stomach contents
[d]Cumulative excretion

FIGURE 2-3. Proposed Metabolic Pathways for 1,2-Dibromoethane*



*Adapted from Lawrence and Michaels 1984

1,2-Dibromoethane is metabolized in various tissues through microsomal oxidation by cytochrome P-450 to form 2-bromoacetaldehyde (Tamura et al. 1986; Van Duuren et al. 1985). This metabolite can produce histopathological changes such as liver damage, by binding to cellular proteins (Hill et al. 1978). 2-Bromoacetaldehyde can be metabolized further by aldehyde dehydrogenase in the presence of nicotinamide adenine dinucleotide dehydrogenase to 2-bromoethanol which is highly toxic and causes genotoxicity. 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-carboxymethylcysteine 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 a hypoxic condition suggesting a new metabolic pathway for 1,2-dibromoethane.

As shown in Figure 2-3, 1,2-dibromoethane can be conjugated with glutathione through the action of glutathione transferases to form S-(2-bromoethyl) glutathione (Peterson et al. 1988). This reactive intermediate can react to form ethylene and glutathione disulfide through further action of glutathione transferases. These are detoxification products. The ethylene is 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 (Van Bladeren et al. 1981). This ion 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-(N^7-guanyl)ethyl]glutathione (Ozawa and Guengerich 1983; Koga et al. 1986; Peterson et al. 1988). A recent study suggests that S-(2-bromoethyl) glutathione is the main genotoxic metabolite that binds to DNA to form the complex S-[2-(N^7-guanyl)ethyl]cysteine (Bolt 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 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 conjugation reaction of 1,2-dibromoethane with glutathione, a molecule present in mammalian cells. This suggests that the primary pathway of 1,2-dibromoethane metabolism (i.e., activation and detoxification) in rats is via the microsomal monooxygenase system. An in vivo study (Van Duuren et al. 1985) provides evidence that microsomal oxidation 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 (Van Bladeren 1983). The reactive metabolites formed by these two systems 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-(N^7-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.

Evidence from animal bioassays supports the hypothesis that it is the cytosolic system and not the microsomal oxidative system that is responsible for the carcinogenicity of 1,2-dibromoethane. Metabolism of 1,2-dibromoethane by glutathione conjugation was demonstrated in vitro in rat hepatocytes (Sundheimer et al. 1982). 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 microsomal 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 (Kowalski et al. 1985a; Sipes et al. 1986a; Wiersma and Sipes 1983).

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

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

2.3.4.2 Oral 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 2-4. Unmetabolized 1,2-dibromoethane may be excreted via the lungs; fecal excretion of metabolites accounts for approximately 3% of the administered dose (Plotnick et al. 1979).

Based on the rapid and extensive metabolism seen in all animals, the fate of 1,2-dibromoethane in humans would be expected to be similar. Seventy percent of the administered parent compound is excreted in the urine and feces by 48 hours. 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.

2.3.4.3 Dermal Exposure

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

2.3.4.4 Other Routes of Exposure

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.

2.4 RELEVANCE TO PUBLIC HEALTH

No MRLs were derived for 1,2-dibromoethane because of a lack of quantitative exposure data.

Humans are susceptible to the acute toxic effects of 1,2-dibromoethane from various routes of exposure. Except for adverse reproductive effects in

men after occupational exposure, chronic effects of 1,2-dibromoethane exposure have not been documented in humans. Based on data derived from animal studies, mechanisms of action of 1,2-dibromoethane at a cellular level, toxicokinetics, and genotoxicity tests, there is a potential for certain adverse health effects in humans exposed chronically to low environmental levels of 1,2-dibromoethane that could exist near hazardous waste sites or areas of former agricultural use.

Clinical signs in humans and animals related to acute toxic exposure to 1,2-dibromoethane are depression and collapse, indicative of neurologic effects, and erythema and necrosis of tissue at the point of contact (oral and pharyngeal ulcers for ingestion, skin blisters and sloughing for dermal exposure). Neurologic signs are not seen in animals exposed to nonlethal doses.

Target organs of 1,2-dibromoethane are of two types. The first is the point of contact with the chemical, i.e., skin for dermal exposure (humans and animals), oropharynx for ingestion (humans), stomach for gavage administration (rodents), and upper respiratory tract for inhalation exposure (humans, rodents). Although there is little information on toxicity of 1,2-dibromoethane in humans after inhalation, the testis was a target organ in exposed workers; the liver and kidney have been identified as target organs after dermal and oral exposure in humans. The liver, kidney, and testis are target organs in experimental animals irrespective of the exposure route.

Death. 1,2-Dibromoethane can be fatal to humans after oral or dermal exposure. Acute deaths following toxic doses are related to cardiopulmonary arrest or, if affected individuals survive for a period of time, to hepatic and renal failure. These results are supported by animal studies in which acute death occurred after oral, dermal, and inhalation exposure.

Doses that cause acute death in humans and animals are relatively large. For humans, reports of death following oral exposure were a result of intentional ingestion of a high concentration of 1,2-dibromoethane. Human death following dermal and inhalation exposure occurred in two accidentally-exposed workers. It is therefore highly unlikely that there would be a risk to humans of death under conditions of low-level, long-term exposure from contaminated food or water.

Systemic Effects

Respiratory Effects. Nonspecific respiratory symptoms were reported in a worker involved in 1,2-dibromoethane production and presumably chronically exposed by inhalation (Kochmann 1928). One of the workers exposed in a storage tank by dermal and inhalation routes to 1,2-dibromoethane had bilateral pulmonary edema, a nonspecific agonal finding, at necropsy (Letz et al. 1984). Similar results occurred in rats exposed acutely to toxic concentrations by inhalation (Rowe et al. 1952). Abnormal respiratory effects have been well documented in experimental animals after inhalation exposure; respiratory effects did not occur after dermal or oral exposure. Many of the respiratory tract lesions in animal inhalation studies consist of proliferation, particularly in the upper respiratory tract. Animal studies also identify the upper respiratory tract as a site for 1,2-dibromoethane binding and metabolism. These animal studies are relevant to humans because they suggest a possibility for adverse effects in the human respiratory system following low-level exposure to 1,2-dibromoethane by inhalation.

Cardiovascular Effects. Cardiovascular effects as terminal events were reported in patients dying after dermal and inhalation exposure to 1,2-dibromoethane. One individual also had acute myocardial lesions (Letz et al. 1984). Cardiovascular effects were not identified in humans who died after 1,2-dibromoethane ingestion. These findings in humans were not supported by studies in experimental animals exposed by inhalation, oral, or dermal routes. It is unlikely that humans exposed to low levels of 1,2-dibromoethane will experience adverse cardiovascular effects.

Gastrointestinal Effects. Gastrointestinal effects of labial, oral, and pharyngeal ulcers occurred in humans intentionally ingesting high concentrations of 1,2-dibromoethane (Saraswat et al. 1986). Nausea and emesis occurred in humans exposed to high concentrations by the oral or dermal and inhalation routes; the latter patients also developed diarrhea (Letz et al. 1984). Results of adverse gastrointestinal effects in humans were supported by animal studies using the oral route of exposure (Ghanayem et al. 1986; NCI 1978). No gastrointestinal effects were present in animals exposed dermally or by inhalation. While adverse gastrointestinal effects are not likely in humans exposed orally to low levels of 1,2-dibromoethane, the upper gastrointestinal tract is a potential site of 1,2-dibromoethane binding and metabolism (Kowalski et al. 1985a).

Hematologic Effects. Effects of 1,2-dibromoethane on the hematopoietic system of humans exposed by inhalation, oral, or dermal routes have not been described. Results of animal studies are equivocal except that, based on a study in rats, individuals taking disulfiram for alcoholism might be a susceptible human subpopulation at higher risk for adverse hematopoietic effects (Wong et al. 1982) (See Sections 2.6 and 2.7).

Musculoskeletal Effects. Dramatic musculoskeletal effects as evidenced by elevated muscle enzymes in serum occurred in two patients exposed by the dermal and inhalation routes (Letz et al. 1984). No musculoskeletal effects were reported in humans exposed by other routes or in experimental animals. Risks appear to be negligible for adverse musculoskeletal effects in humans exposed to low levels of 1,2-dibromoethane.

Hepatic Effects. Hepatic effects have been reported in humans exposed orally or by the dermal and inhalation routes to toxic doses of 1,2-dibromoethane (Letz et al. 1984; Olmstead 1960; Saraswat et al. 1986). These effects consist of hepatocellular and Kupffer cell necrosis. Results in humans are supported by animal studies in which the liver is also a target organ for toxic effects of 1,2-dibromoethane following exposure by a variety of routes (Botti et al. 1986; Brandt et al. 1987; Broda 1976; NTP 1982; Rowe et al. 1952). 1,2-Dibromoethane, as well as inducing necrosis, can also act as a hepatocellular mitogen in rats (Ledda-Columbano et al. 1987a).

Liver toxicity related to 1,2-dibromoethane depends on the metabolic pathway utilized and the amount of damage induced in cellular protein and membrane structures. Humans exposed to low levels of 1,2-dibromoethane are at potential risk of having toxic events occurring within hepatocytes; whether these effects will be subcellular or result in cell necrosis may depend on internal dose and a variety of factors. Liver damage that is severe enough to cause clinical disease in humans from low-level exposure is unlikely.

Intraperitoneal administration of 1,2-dibromoethane to male B6C3F1 mice induced hepatic DNA damage (genotoxicity) at doses lower than those that caused other signs of acute toxicity such as increased liver weights, elevated serum enzyme levels, or mortality (Storer and Conolly 1983). Thus, *in vivo* and *in vitro* studies suggest that there is a potential for humans to develop subcellular damage after exposure by various routes to low levels of 1,2-dibromoethane.

Renal Effects. The kidney is a target organ in humans for 1,2-dibromoethane toxicity (Letz et al. 1984; Olmstead 1960). In humans exposed acutely to toxic concentrations of 1,2-dibromoethane either by oral or dermal routes, renal damage was described, with one of the exposed individuals dying of acute renal failure despite attempts at hemodialysis. Results in humans are supported by animal studies. Renal effects occurred in male Fischer 344 rats exposed to 1,2-dibromoethane by intraperitoneal injection. Lesions were evenly distributed among renal proximal tubules and consisted of cellular swelling and cytoplasmic vacuolization but not necrosis (Kluwe et al. 1982). Nonprotein sulfhydryl levels were initially reduced, then increased; this is suggestive of changes in tubular glutathione levels. 1,2-Dibromoethane also acts as a renal mitogen in rats in the absence of tubular cell necrosis (Ledda-Columbano et al. 1987b).

Renal lesions or changes in renal function in humans chronically exposed to 1,2-dibromoethane have not been identified. Following chronic inhalation exposure to 1,2-dibromoethane, rats developed toxic nephropathy (NTP 1982).

1,2-Dibromoethane can be activated in the kidney of rodents by a glutathione-dependent pathway to toxic metabolites, as well as having such metabolites reach the kidney via the enterohepatic circulation (Rush et al. 1984; Working et al. 1986). Because similar metabolic pathways exist in humans, animal studies suggest that there is a possibility for adverse renal effects at a subcellular level to occur in humans exposed to low levels of 1,2-dibromoethane such as might occur near areas of former agricultural use or hazardous waste sites. Such low-level exposure is very unlikely to result in clinically detectable renal damage.

Dermal/Ocular Effects. Adverse dermal effects occur in humans following topical exposure of relatively high concentrations of 1,2-dibromoethane. These effects consist of inflammation, blister formation, and necrosis (Letz et al. 1984; Pflesser 1938). Effects were most severe when 1,2-dibromoethane applied to the skin was not allowed to evaporate (Pflesser 1938). Rapid absorption of 1,2-dibromoethane through the skin can also result in systemic toxicity (Letz et al. 1984). These results in humans are supported by studies in animals (Rowe et al. 1952). Humans exposed to low levels of 1,2-dibromoethane in contaminated water such as during bathing or swimming, are unlikely to have any local irritant effects but may be susceptible to absorption of the compound.

Ocular effects have not been reported in humans exposed dermally or orally to toxic doses of 1,2-dibromoethane. Animal studies have identified adverse ocular effects such as irritation and cornea1 damage after exposure to relatively high concentrations (NTP 1982; Rowe et al. 1952). While it appears that humans would be susceptible to development of ocular damage if a high concentration of 1,2-dibromoethane were splashed in the eyes, adverse ocular effects of exposure to low levels of environmental 1,2-dibromoethane would not be expected.

Immunological Effects. No studies were located that specifically investigated immunological effects in humans or animals after exposure to 1,2-dibromoethane.

Neurological Effects. Depression, disorientation, and collapse have been reported in humans with acute exposure to toxic doses of 1,2-dibromoethane by oral (Saraswat et al. 1986) or dermal (Letz et al. 1984) routes. Residues of 1,2-dibromoethane were detected in the brain tissue of one fatality (Letz et al. 1984). The fact that the nervous system is at risk when humans are acutely exposed to lethal doses is supported by animal studies (Rowe et al. 1952).

No neurological effects have been described in humans exposed in an occupational setting except for one report of nonspecific signs of headache and depression (Kochmann 1928). Neurologic signs were not reported in animals exposed by various routes and for intermediate and chronic durations. It is therefore unlikely that neurologic effects will occur in humans chronically exposed to low levels of 1,2-dibromoethane.

Neurological effects as evidenced by alterations in brain neurotransmitter enzymes occurred in the F_1 progeny of male Fischer 344 rats exposed to 1,2-dibromoethane by intraperitoneal injection (Hsu et al. 1985). Choline acetyltransferase and acetylcholinesterase levels had reversible changes in various parts of the brain while glutamic acid decarboxylase levels remained depressed at 90 days post-partum. This study raises some concerns about the progeny of men with occupational exposure since adverse effects of 1,2-dibromoethane on spermatogenesis have been reported in humans. In addition, testicular binding and sperm damage in animals can occur by various routes of exposure.

Developmental Effects. Adverse effects on fetal development have not been documented in humans.

In rats and mice exposed to 1,2-dibromoethane by inhalation, most developmental effects have been observed at doses that produced maternal toxicity. This raises the possibility that the fetuses of pregnant women who were exposed to doses high enough to cause clinical illness would be at risk for development toxicity, depending on the trimester when exposure occurred.

Since overt toxicity would not be expected in pregnant women exposed to low environmental levels of 1,2-dibromoethane, fetuses would not appear to be at serious risk of developmental effects. However, the remote possibility that behavioral effects in the fetus could occur as a result of exposure of either the female or male parent to 1,2-dibromoethane should be considered. Although the possibility of behavioral effects has not been investigated in humans, this is a sensitive effect and would require a large study population to detect. One animal study suggesting this possibility is the previously discussed study of Hsu et al. (1985) in which the progeny of exposed male rats had alterations in brain neurotransmitter enzymes. Another study (Fanini et al. 1984) investigated the behavioral effects of paternal exposure to 1,2-dibromoethane in rat progeny. Male F344 rats injected intraperitoneally daily for 5 consecutive days with doses of 1,2-dibromoethane in saline ranging from 1.25 to 10 mg/kg were mated with untreated females 4 or 9 weeks following exposure. Pups fathered by males from the dosed groups and conceived at 4 or 9 weeks post-exposure showed dose-dependent impairment in an open-field activity test. Although the swimming performance of pups was significantly impaired, it was dependent upon the time of breeding and the particular component of swimming behavior analyzed.

Reproductive Effects. Antispermatogenic effects and possible effects on fertility have been reported in humans occupationally exposed to 1,2-dibromoethane (Heinrichs 1983; Ratcliffe et al. 1987; Ter Haar 1980; Wong et al, 1979). However, many of these studies lacked sufficient statistical power to detect an association between parameters measured and exposure.

Adverse reproductive effects are supported by animal studies. However, in some of the oral and inhalation studies in animals, chemical toxicity and/or neoplasia made it difficult to ascribe testicular lesions to direct toxicity. In other studies, antispermatogenic effects of 1,2-dibromoethane were documented directly in bovines exposed via feed; these effects were reversible after chemical withdrawal (Amir and Ben-David 1973; Amir and Volcani 1965). Effects were more severe in adult bulls compared to young bulls (Amir 1975).

The effects on reproduction of 1,2-dibromoethane administered to animals by parenteral routes corroborate the findings of other investigations in animals conducted via inhalation and oral routes. Sperm damage occurred in rams after a single intratesticular injection of 1,2-dibromoethane (Amir et al. 1983). A dose-response was observed with less acute effects on spermatids noted at doses as low as 6.37 mg/kg. Some effects on morphology of sperm were reversible. Transient sperm abnormalities were reported in Columbian rams that received 12 consecutive, daily subcutaneous injections of 1,2-dibromoethane at various doses ranging from 7.8 to 13.5 mg/kg (Eljack and Hrudka 1979a). A dose-related decline in sperm motility and acrosome abnormalities were evident during the 5th week following initiation of treatment.

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). Antispermatogenic effects in exposed workers and this preferential binding of 1,2-dibromoethane in the testis of rodents and ruminants suggest that similar effects on spermatozoa could occur in men exposed to low levels of 1,2-dibromoethane.

Genotoxic Effects. 1,2-Dibromoethane has been tested extensively to assess its genotoxic potential in prokaryotic, eukaryotic, and mammalian systems. Tables 2-7 and 2-8 present the results of *in vivo* and *in vitro* genotoxicity studies, respectively. The results of these studies indicate that 1,2-dibromoethane is a potent mutagen, producing a broad spectrum of mutations in various test systems.

In bacterial systems, 1,2-dibromoethane is a direct-acting mutagen and primarily causes mutations of the base-pair substitution type (Barber et

al. 1981; McCann et al. 1975; Moriya et al. 1983; Principe et al. 1981; Rosenkranz 1977). The mutagenicity of 1,2-dibromoethane in bacteria was not influenced by mammalian metabolizing systems in four out of five studies (Barber et al. 1981; Moriya et al. 1983; Principe et al. 1981; Stolzenberg and Hine 1980). However, detection of its mutagenic activity is influenced by the amount of glutathione present (Kerklaan et al. 1985; Zoetemelk et al. 1987). 1,2-Dibromoethane tested positive for mutagenicity with or without metabolic activation in fungi and mammalian cell lines in in vitro assay systems (Brimer et al. 1982; Clive et al. 1979; Crespi et al. 1985; Ferreri et al. 1983; Malling 1969; Principe et al. 1981; Tan and Hsie 1981). It has been tested for its ability to induce heritable mutations in vivo using fruit flies (Drosophila melanogaster), mice, and rats. 1,2-Dibromoethane caused heritable mutations in male fruit flies (Kale and Baum 1979, 1981, 1982, 1983; Vogel and Chandler 1974) but not in mice (Epstein et al. 1972; Teramoto et al. 1980) or rats (Teramoto et al. 1980).

Chromosomal abnormalities and sister chromatid exchanges have been observed in mice following intraperitoneal administration of 1,2-dibromoethane (Krishna et al. 1985). Such chromosomal aberrations were also detected in vitro using human lymphocytes (Tucker et al. 1984); however, in studies which use cells from animals and humans with prior exposure to 1,2-dibromoethane, these abnormalities were unreliable or were not detected (Krishna et al. 1985; Steenland et al. 1985, 1986).

1,2-Dibromoethane has been shown to bind covalently to DNA both in vitro (Banerjee and Van Duuren 1979, 1983; DiRenzo et al. 1982; Inskeep and Guengerich 1984; Koga et al. 1986; Ozawa and Guengerich 1983; Prodi et al. 1986) and in vivo (Hill et al. 1978; Inskeep et al. 1986; Koga et al. 1986; Prodi et al. 1986), forming a stable adduct. Such adducts have been observed in rat testicular cells following in vivo exposure to 1,2-dibromoethane (Hill et al. 1978) and DNA repair activity was increased in rat spermatocytes treated in vitro with 1,2-dibromoethane (Working et al. 1986). Preincubation of rat hepatocytes or spermatocytes with inhibitors of cytochrome P-450-mediated oxidation did not affect 1,2-dibromoethane-induced unscheduled DNA synthesis (UDS) in vitro. In contrast, depletion of cellular glutathione inhibited 1,2-dibromoethane-induced UDS in both cell types in vitro (Working et al. 1986). This observation indicates that conjugation of 1,2-dibromoethane to glutathione and its subsequent metabolism results in the formation of genotoxic metabolites.

Thus, interaction of 1,2-dibromoethane with DNA can result in a mutation that is passed on to offspring. In conclusion, sufficient evidence exists to indicate that 1,2-dibromoethane presents potential genotoxic risks for humans. These effects may occur in humans living in areas surrounding hazardous waste sites or areas of former agricultural use where they may be exposed to 1,2-dibromoethane.

TABLE 2-7. Genotoxicity of 1,2-Dibromoethane In Vivo

Species (test system)	End point	Results	Reference
Eukaryotic organisms:			
Drosophila melanogaster/inhalation exposure	Recessive lethal	+	Kale and Baum 1979, 1981, 1982, 1983
D. melanogaster/dietary exposure	Recessive lethal	+	Vogel and Chandler 1974; NTP 1989
Mammalian cells:			
Mouse/oral exposure	Dominant lethal	-	Epstein et al. 1972
Mouse/oral exposure	Dominant lethal	-	Teramoto et al. 1980
Mouse/intraperitoneal administration	Dominant lethal	-	Epstein et al. 1972
Rat inhalation exposure	Dominant lethal	-	Short et al. 1979
Rat oral exposure	Dominant lethal	-	Teramoto et al. 1980
Mouse/intraperitoneal administration	Sister chromatid exchange	-	Krishna et al. 1985
Human/occupational exposure	Sister chromatid exchange	-	Steenland et al. 1985, 1986
Mouse/intraperitoneal administration	Micronuclear formation	-	Krishna et al. 1985
Mouse/intraperitoneal administration	Chromosomal aberrations	-	Krishna et al. 1985
Rat/intraperitoneal administration	Unscheduled DNA synthesis	-	Bentley and Working 1988

DNA = deoxyribonucleic acid; + = positive result; - = negative result

TABLE 2-8. Genotoxicity of 1,2-Dibromoethane *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium/plate incorporation	Reverse mutation	No data	+	Ames and Yanofasky 1971
		+	No data	McCann et al. 1975; Zoetemelk et al. 1987
S. typhimurium/plate incorporation	Reverse mutation	+	+	Stolzenberg and Hine 1980; Principe et al. 1981; NTP 1989; Moriya et al. 1983
S. typhimurium/plate incorporation	Reverse mutation	-	No data	Shiau et al. 1980
		+	No data	Kerklaan et al. 1985
Escherichia coli (WP2 uvrA)/plate incorporation	Reverse mutation	No data	+	Hemminki et al. 1980
E. coli (WP2 her)/plate incorporation	Reverse mutation	+	No data	Moriya et al. 1983
S. typhimurium/vapor exposure	Reverse mutation	+	No data	Hughes et al. 1987
S. typhimurium/vapor phase	Reverse mutation	+	+	Barber et al. 1981
S. typhimurium/spot test	Reverse mutation	+	-	Shiau et al. 1980
S. typhimurium/spot test	Reverse mutation	No data	+	Rosenkranz 1977; Brem et al. 1974a; Buselmaier et al. 1972, 1976; Buijs et al. 1984
Serratia marcescens (a21)/host mediated assay	Reverse mutation	-	No data	Buselmaier et al. 1972, 1976
Bacillus subtilis/spot test	Forward mutation	+	-	Shiau et al. 1980
E. coli/spot test	Forward mutation	No data	+	Izutani et al. 1980
B. subtilis/spot test	Forward mutation	+	-	Shiau et al. 1980
E. coli/spot test	DNA damage	No data	+	Rosenkranz 1977; Brem et al. 1974a
B. subtilis/spot test	DNA damage	No data	-	Shiau et al. 1980
Eukaryotic organisms:				
Neurospora crassa/liquid incubation	Recessive lethal	No data	+	Malling 1969
Streptomyces coelicolor/plate incorporation	Forward mutation	No data	-	Principe et al. 1981
Aspergillus nidulans/plate incorporation	Forward mutation	No data	+	Principe et al. 1981
S. coelicolor/spot test	Forward mutation	No data	+	Principe et al. 1981
A. nidulans/spot test	Forward mutation	No data	+	Principe et al. 1981

TABLE 2-8 (Continued)

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Mammalian cells:				
Chinese hamster ovary cells liquid media	Forward mutation	+	+	Tan and Hsie 1981; Brimer et al. 1982
Mouse lymphoma L5178Y/liquid media	Forward mutation	+	+	Clive et al. 1979; NTP 1989
Human epithelial cells liquid media	Forward mutation	No data	+	Ferreri et al. 1983
Human lymphoblasts Tk6	Forward mutation	No data	+	Crespi et al. 1985
Human lymphoblasts AAH-1	Forward mutation	No data	+	Crespi et al. 1985
Chinese hamster V79 cells: CH5	Sister chromatid exchange	+	+	Tezuka et al. 1980; NTP 1989
Chinese hamster V79 cells	Chromosomal abberations	+	+	NTP 1989
Peripheral lymphocytes from oyster toadfish and American eel	Sister chromatid exchange	No data	+	Ellingham et al. 1986
Human peripheral lymphocytes	Sister chromatid exchange	+	No data	Tucker et al. 1984
Opossum lymphocytes	Unscheduled DNA synthesis	No data	+	Meneghini 1974
Primary rat hepatocytes	DNA repair	No data	+	Williams et al. 1982; Working et al. 1986
Human lymphocytes	DNA repair	+	-	Peroco and Prodi 1981

DNA = deoxyribonucleic acid; + = positive result; - = negative result

Cancer. There are no reports of cancer in humans associated with occupational exposure to 1,2-dibromoethane, although the negative epidemiologic studies have some limitations.

1,2-Dibromoethane has been positive in short-term tests in animals used to predict carcinogenic potential of a chemical (Milks et al. 1982; Moslen 1984). In addition, there is dramatic tissue-specific binding of metabolites in experimental animals. Radiolabeled 1,2-dibromoethane was administered parenterally (intravenously or intraperitoneally) to C57BL mice, Sprague-Dawley rats and F344 rats. Both species had binding of high levels of 1,2-dibromoethane metabolites in the epithelium of the entire respiratory tract, the upper gastrointestinal tract, the vagina, and subepithelial glands of the nasal olfactory mucosa. .Lower levels of metabolites were bound in the liver, kidney, adrenal cortex, and testicular interstitium (Kowalski et al. 1985a). DNA synthesis in the nasal mucosa of mice was inhibited (Hellman and Brandt 1986). This tissue-specific metabolism correlates well with toxic and/or carcinogenic lesions observed in experimental studies of inhalation and oral exposure to 1,2-dibromoethane. The possibility exists that similar binding and metabolism could occur in humans.

1,2-Dibromoethane is a potent carcinogen in rats and mice, causing malignant and benign neoplasms of epithelial and mesenchymal origin in multiple organ systems when administered by inhalation, oral, or dermal routes. Cancer was also induced at initial point of contact with 1,2-dibromoethane--nasal cavity for inhalation exposure, forestomach for oral (gavage and drinking water) exposure, and skin for dermal exposure.

The weight of evidence for carcinogenicity of 1,2-dibromoethane includes induction of malignant neoplasms in two species of rodents and in multiple organ systems by inhalation', oral, and dermal exposure. In addition, 1,2-dibromoethane and a number of its metabolites are electrophiles, and form adducts with cell proteins and nucleic acid. Of two potential 1,2-dibromoethane metabolites tested in a drinking water study in mice, bromoethanol induced squamous papillomas of the forestomach in male and female mice while bromacetaldehyde did not induce a significant incidence of tumors. Based on these findings, Van Duuren et al. (1985) determined that it was unlikely that bromoethanol or bromoacetaldehyde were the active carcinogenic metabolites of 1,2-dibromoethane. 1,2-Dibromoethane is a potent mutagen in numerous <u>in vitro</u> test systems. Based on these findings, exposure of humans to levels of 1,2-dibromoethane such as found in agricultural areas or near hazardous waste sites presents a potentially serious public health risk.

EPA has classified 1,2-dibromoethane in the Carcinogen Assessment Group's Group B2 (EPA 1987a). Group B2 includes chemicals for which evidence for carcinogenicity is adequate in animals but inadequate in humans. The q_1*

value developed by EPA for humans exposed orally is 85 $(mg/kg/day)^{-1}$ based on data from the NCI (1978) gavage bioassay. For humans exposed by inhalation, the unit risk value is $2.2x10^{-4}$ $\mu g/m^3$ based on data from the NTP (1982) inhalation bioassay (IRIS 1991).

2.5 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers 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 or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to 1,2-dibromoethane are discussed in Section 2.5.1.

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 often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by 1,2-dibromoethane are discussed in Section 2.5.2.

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, biologically effective dose, or target tissue response. If

biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

2.5.1 Biomarkers Used to Identify and/or Quantify Exposure to 1,2-Dibromoethane

Primary biomarkers of exposure are the presence of 1,2-dibromoethane in blood or exhaled breath or excretion of specific metabolites in urine. In humans exposed to toxic levels of 1,2-dibromoethane (Letz et al. 1984), the parent compound was not measured in blood samples collected before death. However, two exposed individuals had elevated levels of serum bromide ions. This elevation is likely to have resulted from debromination of 1,2-dibromoethane during its metabolism. Elevated serum bromide is not specific to 1,2-dibromoethane exposure, but, rather, it is indicative of exposure to classes of brominated chemicals.

Because a proportion of unmetabolized 1,2-dibromoethane is excreted from the lungs of guinea pigs (Plotnick and Conner 1976), measurement of the chemical in exhaled breath of humans is another potential method of monitoring human exposure. This has been done in a study using university student volunteers from a petrochemical plant area and a nonindustrial area. 1,2-Dibromoethane in exhaled breath was not found in either group of volunteers (Wallace et al. 1982).

Rats exposed acutely by gavage to 110 mg/kg of 1,2-dibromoethane in olive oil had elevated concentrations of the parent compound in the blood up to 30 minutes after exposure. At 2 and 4 hours postexposure, only trace amounts were detected and by 13 hours after exposure, 1,2-dibromoethane concentrations were not detected in the blood. Serum bromide levels were not measured (Nachtomi and Alumot 1972). Metabolites of 1,2-dibromoethane in urine from rats receiving a comparable dose were characterized chromatographically (Nachtomi et al. 1965). Urine had increased concentrations of bromide ion, S(β-hydroxyethyl) mercapturic acid, and S(β-hydroxyl)cysteine. These latter two metabolites are formed via the cytosolic rather than the microsomal pathway and, therefore, may not be present as biomarkers for humans of 1,2-dibromoethane exposure. However, urine of exposed humans has not been tested for the metabolites listed, including bromide ion.

Two DNA adducts of 1,2-dibromoethane metabolites have been found in in vitro studies (Bolt et al. 1986; Ozawa and Guengerich 1983; Peterson et al. 1988). These adducts are S-[2-(N^7-guanyl)ethyl]glutathione and S-[2-N^7-guanyl)ethyl] cysteine. These adducts are potential biomarkers of exposure to 1,2-dibromoethane and could be tested for in biopsy or autopsy tissue specimens.

A less invasive procedure that could provide a indication of DNA adduct formation is measurement in the urine of the mercaptic acid S-[2-N^7-guanl)ethyl]-N-acetylcysteine. Excretion of this metabolite into the urine of

rats occurs in a dose-dependent, linear manner after intraperitoneal administration of 1,2-dibromoethane (Kim and Guengerich 1989). This biomarker has not been looked for to date in humans suspected to have exposure to 1,2-dibromoethane.

2.5.2 Biomarkers Used to Characterize Effects Caused by 1,2-Dibromoethane

The liver, kidney, and testis are the major visceral target organs for toxic effects of 1,2-dibromoethane.

Hepatocellular necrosis related to covalent binding of metabolites to cell and plasma proteins and to mitochondrial membrane damage results in release of intracellular enzymes into the bloodstream, providing biomarkers of liver cell damage. Biomarkers of hepatocellular necrosis are not specific to 1,2-dibromoethane but are a general indication of damage. Increased serum enzymes include aspartate aminotransferase (AST), glutamate oxalacetic transaminase (GOT), alanine aminotransferase (ALT), glutamate pyruvate transaminase (GPT), and lactic dehydrogenase (LDH) (Botti et al. 1986; Letz 1984) in humans and rats as well as leakage of LDH from exposed, isolated rodent hepatocytes (Albano et al. 1984; Van Iersel et al. 1988). Plasma prothrombin time was also measured by Rowe et al. (1952) in rodents exposed to 1,2-dibromoethane; this test, however, is of minimal diagnostic value in detection of mild hepatocellular dysfunction (Berkow 1987).

Kidney effects can range from mild tubular damage to life-threatening renal damage, i.e., tubular nephropathy. Severe toxic renal lesions can result in compromised renal function with changes in urinalysis, oliguria, or anuria (renal shutdown) and increases in blood urea nitrogen, serum creatinine, and uric acid. While biomarkers of renal damage have been identified in humans exposed to toxic doses of 1,2-dibromoethane by oral or dermal routes, these findings have not been duplicated in animal experiments.

Chemically-induced testicular damage can be recognized by changes in sperm concentration, sperm motility, and sperm morphology (Wyrobek 1984). Reduced fertility, a highly sensitive biomarker, may also be associated with chemical exposure of humans. For example, Ratcliffe et al. (1987) evaluated spermatogenic parameters in papaya fumigation industry employees exposed for an average length of 5 years to 1,2-dibromoethane and unexposed workers in the sugar industry. The route of exposure to 1,2-dibromoethane was primarily inhalation. They identified decreased sperm count per ejaculate, decreases in the percentage of viable and motile sperm, and increases in numbers of sperm with abnormal morphology in 1,2-dibromoethane-exposed workers. For additional discussion of the study, see Section 2.2.1.6.

An epidemiological study on 1,2-dibromoethane has identified equivocal effects of reduced fertility in exposed workers (Wong et al. 1979).

2.6 INTERACTIONS WITH OTHER CHEMICALS.

Disulfiram is the generic name for Antabuse, a drug used in the treatment of chronic alcoholism. Disulfiram potentiates the toxic and carcinogenic effects of 1,2-dibromoethane in experimental animals. Presumably, this occurs by blocking conversion of the aldehyde metabolite as with acetaldehyde from ethanol. There is no evidence that similar effects occur in humans. Based on animal data, however, Ayerst Laboratories, producers of Antabuse (disulfiram), recommended the following in the package insert: "Patients taking Antabuse tablets should not be exposed to ethylene dibromide or its vapors" (PDR 1991).

In rats treated with disulfiram prior to oral dosing with 1,2-dibromoethane (Plotnik et al. 1979), there was decreased clearance of radiolabeled 1,2-dibromoethane from the body with increased concentration in tissues (liver, kidney, spleen, testis, and brain). In the liver of the disulfiram-1,2-dibromoethane. group, there was preferential uptake of labeled 1,2-dibromoethane in hepatocyte nuclei, indicative of DNA binding.

The mechanism of synergism between the compounds is not known. Slower clearance of 1,2-dibromoethane or increased tissue levels of a toxic intermediate metabolite (likely the aldehyde) in disulfiram-exposed individuals may be responsible for enhancement of toxic and neoplastic lesions in exposed rodents (Plotnik et al. 1979).

As discussed in Section 2.2.1 under the various systemic effects and cancer, rats exposed by inhalation to 1,2-dibromoethane and fed a diet containing 0.05% disulfiram (Wong et al. 1982), compared to rats exposed to 1,2-dibromoethane alone, had significantly elevated incidences of certain neoplastic and toxic lesions. Neoplasms elevated in the disulfiram-1,2-dibromoethane group were hepatocellular tumors, renal adenoma and adenocarcinoma, and thyroid follicular cell adenoma. Toxic lesions were testicular degeneration (atrophy) and splenic atrophy. Rats receiving the 1,2-dibromoethane-disulfiram regimen also had high mortality at a significantly earlier date compared to control rats, rats exposed to disulfiram alone, or rats exposed to 1,2-dibromoethane alone.

1,2-Dibromoethane did not potentiate the hepatotoxic effects of carbon tetrachloride in rats (Danni et al. 1988).

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Certain populations may have a higher risk for developing toxic effects from low-level 1,2-dibromoethane exposure.

A biological difference that could increase susceptibility of fetuses and premature or perinatal infants to 1,2-dibromoethane toxicity is developmental immaturity of the P-450 (microsomal enzyme) system. Biotransformation of xenobiotics occurs predominantly by glutathione conjugation (Benet and Sheiner 1985; Sipes and Gandolfi 1986). This pathway is known to generate a number of toxic intermediate metabolites of 1,2-dibromoethane. In addition, fetal mice have selective binding of 1,2-dibromoethane metabolites in epithelial lining of the upper alimentary tract and the entire respiratory tract after 1,2-dibromoethane was administered parenterally to pregnant females (Kowalski et al. 1986).

As discussed in Section 2.6, chronic alcoholics receiving Antabuse (disulfiram) therapy are potentially more susceptible to toxic and neoplastic effects of 1,2-dibromoethane. It also follows that individuals with compromised liver or renal function or with asthma or other chronic respiratory diseases may have increased susceptibility to the toxic effects of 1,2-dibromoethane; however, chemical-specific effects have not been identified.

2.8 MITIGATION OF EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to 1,2-dibromoethane. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to 1,2-dibromoethane. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

Human exposure to 1,2-dibromoethane may occur by inhalation, ingestion or by dermal contact. Mitigation approaches to reduce absorption of 1,2-dibromoethane have included general recommendations of separating contaminated food, water, air, clothing from the exposed individual. Externally, exposed eyes and skin are flushed with a clean neutral solution such as water or normal saline. Water or milk is administered after ingestion of 1,2-dibromoethane to wash residual chemical through the esophagus if the patient can swallow (Bronsten and Currance 1988). Residual chemical remaining in the stomach is removed by gastric lavage after precautions have been taken to protect the respiratory tract from aspiration of gastric contents. Activated charcoal is administered to bind unabsorbed chemical that has passed out of the stomach and into the lower gastrointestinal tract. Administration of a cathartic is thought to be unnecessary since diarrhea frequently follows ingestion of this agent.

Once absorbed, 1,2-dibromoethane is rapidly metabolized. Its metabolism may induce effects by either of two systems, the microsomal monooxygenase system or the cytosolic activation system. Animal research has shown that seventy percent of 1,2-dibromoethane is excreted in the urine and feces within 48 hours. The lack of persistent metabolites in the tissues indicate that 1,2-dibromoethane is readily removed from the body. Methods for reducing body burden were not found.

Two reactive intermediates are formed through 1,2-dibromoethane metabolism, 2-bromoacetaldehyde and S-(2-bromoethyl) glutathione. The 2-bromoacetaldehyde causes tissue damage by covalent binding to cellular macromolecules. The S-(2-bromoethyl) glutathione is responsible for genotoxic effects and possibly its carcinogenic effect observed in laboratory animals.

No specific antidote has been shown to be effective in treating 1,2-dibromoethane intoxication once absorption into the bloodstream has occurred (Ellenhorn and Barceloux 1988). Intravenous infusions of glucose may limit the hepatotoxicity of 1,2-dibromoethane (EPA 1989b). During the recovery phase, a diet rich in vitamin B and carbohydrates may limit liver damage (Dreisbach and Robertson 1987; Lawrence and Michaels 1984). Hemodialysis may be needed to regulate extracellular fluid and electrolyte balance and to remove metabolic waste products if renal failure occurs (EPA 1989b).

Clinical or experimental methods to interfere with the mechanisms of action for 1,2-dibromoethane are not well understood. Using P-450 inhibitors may be possible to prevent the formation of the reactive metabolites, however this may not be feasible since it would not be specific for 1,2-dibromoethane and it would also affect the detoxification of other substances. Also, for this approach to work the glutathione pathway must also be inhibited. Otherwise, carcinogenicity would be increased due to the diversion of 1,2-dibromoethane from the oxidative pathway to the conjugative pathway, which forms S-(2-bromoethyl) glutathione, a more potent mutagen and carcinogen (EPA, 1985).

The carcinogenic and mutagenic effects of 1,2-dibromoethane is due to its ability to bind to DNA and RNA with metabolic activation. The mechanism of action for the antispermatogenic effects is probably related to the removal of sulphur from cysteine in the nucleus of the spermatozoa. Clinical intervention to interfere with these mechanisms has yet to be developed.

2.9 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 the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed

to determine the health effects (and techniques for developing methods to determine such health effects) of 1,2-dibromoethane.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

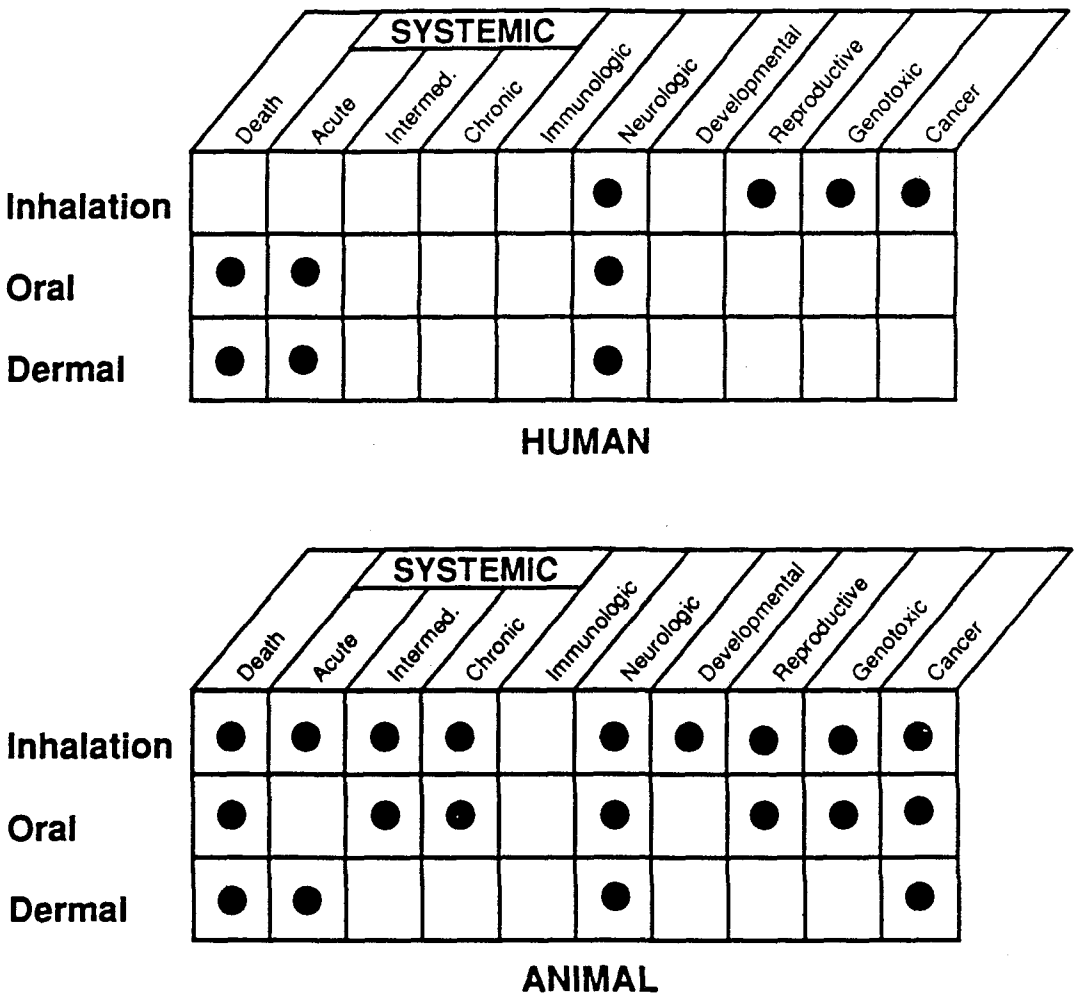
2.9.1 Existing Information on Health Effects of 1,2-Dibromoethane

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,2-dibromoethane are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of 1,2-dibromoethane. 'Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information (i.e., data gaps that must necessarily be filled).

Figure 2-4 graphically depicts the information that currently exists on the health effects of 1,2-dibromoethane in humans and animals by various routes of exposure. The vast majority of literature reviewed concerning the, health effects of 1,2-dibromoethane in humans described case reports and longer-term studies of pesticide workers and case reports of accidental or intentional ingestion of 1,2-dibromoethane. The predominant route of exposure in the occupational studies is believed to be inhalation, with dermal exposure also implied. In a case report of fatalities, dermal exposure was considered the primary route (Letz et al. 1984). The information on human exposure is limited in that the possibility of concurrent exposure to other pesticides or other toxic substances cannot be excluded, and the duration and level of exposure to 1,2-dibromoethane generally cannot be quantified from the information presented in these reports.

The database for the health effects of 1,2-dibromoethane after inhalation and ingestion in experimental animals is substantial. However, as can be seen in Figure 2-4, only limited information is available on the effects of dermal exposure to 1,2-dibromoethane in animals. Furthermore, the health effects associated with intermediate and chronic exposure durations are more fully characterized than those associated with acute exposure.

FIGURE 2-4. Existing Information on Health Effects of 1,2 - Dibromoethane



2.9.2 Data Needs

Acute-Duration Exposure. The toxic effects of inhalation exposure to 1,2-dibromoethane have been investigated in various species of animals but no data are available in humans. Acute inhalation of 1,2-dibromoethane has been shown to cause lethal effects in rats, rabbits, guinea pigs, and monkeys which result primarily from respiratory and cardiac failure (Akamine 1952; Short et al. 1978; Rowe et al. 1952). The lungs, liver, kidney, and spleen are the target organs of inhaled 1,2-dibromoethane (Rowe et al. 1952). Central nervous system (CNS) effects are more pronounced at high vapor concentrations (Rowe et al. 1952). However, behavioral effects have been reported in rats and mice at lower exposure concentrations (Rowe et al. 1952). Acute oral exposures have. resulted in death in humans and animals (Olmstead 1960; Rowe et al. 1952; Saraswat et al. 1986; Schlinke 1969). Hepatotoxicity has been the primary effect in both humans and animals (Olmstead 1960; Rowe et al. 1952; Saraswat et al. 1986). The limited data from human studies show that dermal exposure causes blisters and death (Letz et al. 1984); similar effects occur in animals (Rowe et al. 1952). Thus, acute effects of 1,2-dibromoethane in animals have been characterized, and additional studies do not appear to be necessary at this time.

Intermediate-Duration Exposure. Effects of repeated exposures in humans have not been investigated. The animal studies described predominantly renal, respiratory, hepatic, gastrointestinal tract, developmental, and reproductive or dermal/ocular effects (Amir 1975; Amir et al. 1977; Nitschke et al. 1981; NTP 1982; Rowe et al. 1952; Short et al. 1979). Little or no reliable information on cardiovascular, hematological, musculoskeletal, neurological, and immunological effects in animals is available. Since all three routes (inhalation, oral, and dermal) are significant means of exposure for individuals living near hazardous waste sites, more information on the health effects (specifically neurological, immunological, hematological, and cardiac effects) associated with repeated-dose, low-level exposure to 1,2-dibromoethane would be useful.

Chronic-Duration Exposure and Cancer. Limited epidemiological studies have been conducted involving occupational exposure in workers, primarily by the respiratory route (Ratcliffe et al. 1987; Takahashi et al. 1981; Ter Haar 1980; Wong et al. 1979). These studies did not identify chronic adverse effects in organ systems other than the male reproductive system (refer to the subsequent discussion on reproductive toxicity). Chronic bioassays have been conducted in animals via the inhalation, oral, and dermal routes of exposure (NCI 1978;'NTP 1982; Van Duuren et al. 1979, 1985, 1986; Wong et al. 1982). These studies have found predominantly respiratory, forestomach, hepatic, renal, and testicular effects. Thus, the chronic effects of 1,2-dibromoethane in animals appear to be characterized, and additional studies do not appear to be necessary. Because the use of 1,2-dibromoethane has diminished

dramatically since its registration was canceled in 1984, there is lower potential for additional long-term exposure. However, based on the Wong et al. (1982) study, additional chronic studies on the interactions between 1,2-dibromoethane and other chemicals may be warranted.

Limited epidemiological studies have been conducted involving occupational exposure in workers, primarily by the respiratory route (Ratcliffe et al. 1987; Takahashi et al. 1981; Ter Haar 1980; Wong et al. 1979). These studies neither confirm nor refute the possibility of 1,2-dibromoethane as a human carcinogen. Carcinogenicity bioassays have been conducted in animals via the inhalation, oral, and dermal routes of exposure (NCI 1978; NTP 1982; Van Duuren et al. 1979, 1985, 1986; Wong et al. 1982). These studies have found cancer in multiple organ systems in two species of rodents. Thus, the carcinogenic effects of 1,2-dibromoethane appear to be well characterized, and additional studies are not necessary. Because the use of 1,2-dibromoethane has diminished considerably since its registration was canceled in 1984, the potential for additional long-term exposure is lower.

Genotoxicity. 1,2-Dibromoethane has been tested for mutagenic activity in a battery of in vitro and in vivo assay systems. It is mutagenic in bacteria, fungi, fruit flies, and cultured mammalian cells (Ames and Yanofasky 1971; Barber 1981; Brimer et al. 1982; Crespi et al. 1985; Moriya et al. 1983; NTP 1989; Principe et al. 1981; Shiau et al. 1980). In the dominant lethal assay, 1,2-dibromoethane failed to elicit a positive response (Epstein et al. 1972; Short et al. 1979; Teratomoto et al. 1980). In addition, there is limited evidence that it may cause sister chromatid exchanges and chromosomal aberrations (Ellingham et al. 1986; NTP 1989; Tezuka et al. 1980; Tucker et al. 1984). However, conflicting results have been reported for chromosomal aberration studies in human lymphocytes from exposed workers and in human and animal cell lines treated with 1,2-dibromoethane in vitro (Krishna et al. 1985; Steenland et al. 1985, 1986). A number of in vitro and in vivo studies demonstrate that 1,2-dibromoethane can interact with DNA resulting in genotoxic events (Bentley and Working 1988; Meneghini 1974; Peroco and Prodi 1981; Williams et al. 1982; Working et al. 1986). In view of the limited and somewhat conflicting evidence for the carcinogenicity of 1,2-dibromoethane in exposed human populations, data on the clastogenic and genotoxic effects in humans could offer insight into potential human health risks from 1,2-dibromoethane.

Reproductive Toxicity. Epidemiologic evidence concerning antispermatogenic and antifertility effects of inhalation exposure to 1,2-dibromoethane has been documented in the literature (Heinrichs 1983; Ratcliffe et al. 1987; Ter Haar 1980; Wong et al. 1979). However, results of these studies are limited by the small sample size and confounding factors. In rats, inhalation exposure results in impaired reproductive performance (NTP 1982; Short et al. 1979). Although no information on the reproductive toxicity of 1,2-dibromoethane is available in humans by oral exposure,

antispermatogenic effects have been well demonstrated in various animal species including the bull, rat, and mouse following oral exposure (Amir 1973; Amir and Ben-David 1973; Amir and Lavon 1976; Amir and Volcani 1965; Amir et al. 1983; NCI 1978). No studies are available in humans or animals to assess reproductive toxicity resulting from the dermal route of exposure. The toxicokinetic data indicate that 1,2-dibromoethane is absorbed through the skin (Jakobson et al. 1982; Letz et al. 1984). Therefore, additional information on the effects via the dermal route of exposure would be useful.

Developmental Toxicity. The developmental effects of inhalation exposure to 1,2-dibromoethane have not been investigated in humans. The studies in animals clearly indicate that fetotoxic and behavioral effects occur in mice and/or rats at concentrations that are toxic to maternal welfare as well (Fanini et al. 1984; Hsu et al. 1985; Short et al. 1978). No data are available for humans or animals regarding developmental toxicity resulting from oral and dermal routes of exposure. Since human exposure to 1,2-dibromoethane can occur via inhalation and dermal exposures at hazardous waste sites and also from ingestion of contaminated drinking water, additional epidemiological studies in populations around hazardous waste sites to investigate the developmental hazard posed by 1,2-dibromoethane would be useful. Such studies would also be useful in areas where groundwater was contaminated by 1,2-dibromoethane from prior use of the pesticide in agriculture.

Immunotoxicity. No information on specific immunological effects of 1,2-dibromoethane is available for humans or animals exposed via inhalation, oral, or dermal routes. Some effect on the immune system can be inferred from a report of lymphoid neoplasia associated with exposure of workers to various chemicals including 1,2-dibromoethane (Alavanja et al. 1988). Epidemiological and animal studies would be useful to investigate the immunotoxic potential of 1,2-dibromoethane. Furthermore, if 1,2-dibromoethane proves to be a potential immunosuppressant, further research into this area could help identify populations at higher risk because of pre-existing permanent immunosuppression.

Neurotoxicity. Evidence for neurological effects in humans and experimental animals after oral or inhalation exposure is limited. Acute inhalation exposure of a worker resulted in transient depression (Kochmann 1928). Animal data show that acute inhalation of high concentrations causes CNS depression in animals (Rowe et al. 1952). Behavioral effects have been reported in offspring following inhalation exposure of rats during gestation (Fanini et al. 1984; Hsu et al. 1985). Acute oral exposures have been reported to cause death and brain lesions in humans (Saraswat et al. 1986) and stiffness, prostration, and anorexia in animals (Schlinke 1969). No information is available to assess neurological effects resulting from dermal exposure to 1,2-dibromoethane in humans and animals. Further studies of

neurological effects following inhalation and/or dermal exposure in both the newborn and adult would be valuable, as there are so few data available.

Epidemiological and Human Dosimetry Studies. Most of the available information on the effects of 1,2-dibromoethane in humans comes from cases of acute poisoning following accidental or intentional ingestion and from occupational exposures in agricultural industries (Alavanja et al. 1988; Kochmann 1928; Letz et al. 1984; Olmstead 1960; Ott et al. 1980; Ratcliffe et al. 1987; Saraswat et al. 1986; Takahashi et al. 1981; Ter Haar 1980; Turner and Barry 1979; Wong et al. 1979). Limitations inherent in these studies include unquantified exposure concentrations and durations, small sample size, as well as concomitant exposure to other pesticides and marijuana use. In addition, developmental and systemic effects following inhalation, oral, and dermal exposures in humans have not been studied. Well-controlled epidemiological studies that focused on exposure levels and health effects (e.g., systemic effects, developmental and immunological effects, genotoxicity, and cancer) of persons living in areas near hazardous waste sites would be useful in monitoring other affected populations. A common problem in such studies is acquisition of reliable dosimetry data on the exposed populations. For this reason, efforts to improve estimates of past exposure and to define more accurately current exposure levels to 1,2-dibromoethane would be valuable. Follow-up of exposed workers would be useful.

Biomarkers of Exposure and Effect. There appears to be no biological indicator for 1,2-dibromoethane toxicity that is entirely adequate when considered alone. Biomarkers of acute exposure to potentially toxic levels are residues of 1,2-dibromoethane in target tissues such as liver and brain, elevated serum bromide levels, and the presence of bromide ions and certain metabolites of 1,2-dibromoethane in urine (Letz et al. 1984; Nachtomi et al. 1965). Tissue specimens also could be examined for the presence of 1,2-dibromoethane metabolites covalently bound to protein or DNA (Bolt et al. 1986; Ozawa and Guengerich 1983; Peterson et al. 1988).

Results of studies in humans and animals suggest that sperm abnormalities, evidence of DNA damage such as chromosomal anomalies, and tests for liver and kidney dysfunction may serve as biomarkers of the effects of 1,2-dibromoethane (Ellingham et al. 1986; Heinrichs 1983; NTP 1982, 1989; Ratcliffe et al. 1987; Rowe et al. 1952; Ter Haar 1980; Wong et al. 1979). More quantitative data on chronically exposed individuals would provide a good database for use with screening protocols. These data could include tests of urine for 1,2-dibromoethane metabolites, monitoring of serum and urinary bromide ions, periodic monitoring of semen samples for abnormalities in sperm concentration, motility and morphology, and serum aspartate aminotransferase for liver cell damage.

Absorption, Distribution, Metabolism, and Excretion. Quantitative evidence on the absorption of 1,2-dibromoethane in humans is not available. However, it is known that workers,exposed to 1,2-dibromoethane experience toxic effects following inhalation, oral, and dermal exposure (Alavanja et al. 1988; Kochmann 1928; Letz et al. 1984; Ott et al. 1980; Ratcliffe et al. 19.87; Takahashi et al. 1981; Ter Haar 1980; Turner and Barry 1979; Wong et al. 1979). Animal studies clearly indicate that 1,2-dibromoethane is absorbed (Botti et al. 1982; Jakobson et al. 1982; Letz et al. 1984; Rowe et al. 1952). Reports that specifically evaluate the compound's rate or extent of absorption would be useful.

No studies were located regarding the distribution of 1,2-dibromoethane in humans. Animal studies regarding its distribution following oral absorption are available (Plotnick et al. 1979; Wong et al. 1982). Based on similar pathologic findings in humans and animals, the distribution in humans seems to be similar. Studies that investigate the distribution of 1,2-dibromoethane following inhalation or dermal exposures would be useful in order to evaluate whether 1,2-dibromoethane behaves similarly across all routes of exposure. Information was not available regarding the metabolism of 1,2-dibromoethane following inhalation, oral, or dermal exposure in humans. Its metabolism in humans probably occurs via the microsomal monooxygenase system because glutathione conjugation is less prominent in man. Metabolism of 1,2-dibromoethane in animals has been investigated via oral exposure (Lawrence and Michaels 1984; Tamura et al. 1986; Van Duuren et al. 1985). Mercapturic acids are identified as the primary metabolites of microsomal oxidation (Kirby et al. 1980; Nachtomi 1970; Nachtomi et al. 1965). The reactive metabolites formed by the microsomal oxidation or glutathione conjugation of 1,2-dibromoethane may bind to protein or DNA, producing either cytotoxicity or genotoxicity, respectively (Ozawa and Guengerich 1983; Van Bladeren 1983; White et al. 1983). Quantitative information regarding the metabolites formed would suggest which biodegradation pathways are favored and would also provide insight into the enzyme kinetics. Information regarding the overall rate of metabolism and rates of specific reaction following inhalation and dermal exposures would be useful, as well as how metabolism is affected by chemical interactions.

No studies in humans were found regarding excretion of 1,2-dibromoethane. Animal studies regarding the excretion of 1,2-dibromoethane following inhalation and dermal exposures are unavailable, but information is available for excretion following oral exposures (Plotnick et al. 1979). Since metabolites may contribute to the toxic effects attributed to 1,2-dibromoethane, it would be beneficial to conduct studies that would establish elimination rates for each metabolite or similar metabolic products. In addition, such studies may also provide information to facilitate the rapid removal of 1,2-dibromoethane and its metabolites in exposed people.

Comparative Toxicokinetics. Generally, target organs and adverse effects of 1,2-dibromoethane exposure are similar across species. Toxicokinetic studies have been performed in rats, mice, and guinea pigs. There are no major differences in distribution patterns. Humans would be expected to metabolize 1,2-dibromoethane in a manner qualitatively similar to animals. However, the disposition of 1,2-dibromoethane in humans remains to be determined.

Mitigation of Effects. Data are needed on mechanisms that may be used to decrease the effects of 1,2-dibromoethane once it has entered the bloodstream. Currently, the only available data are regarding treatment of clinical effects of 1,2-dibromoethane intoxication. Data are also needed on the chronic effects of low-level exposure to 1,2-dibromoethane to assess its long-term effects in humans.

2.9.3 On-going Studies

A recent abstract reported an excessive mortality from non-Hodgkin's lymphoma during the 1970s and 1980s in grain millers in the grain processing industry (Alavanja et al. 1988). Such workers had been exposed to 1,2-dibromoethane as well as aluminum phosphide, ethylene dichloride, malathion, and methyl bromide.

Additional on-going studies regarding the health effects of 1,2-dibromoethane were reported in the Directory of On-Going Research in Cancer Epidemiology (Parkin and Wahrendorf 1987). T. Meinhardt (NIOSH, Cincinnati, Ohio) is conducting epidemiological studies to investigate carcinogenic and cytogenetic changes in two separate populations exposed occupationally to 1,2-dibromoethane. J. Ratcliffe, formerly of NIOSH, was investigating cytogenetic and reproductive effects of exposure to 1,2-dibromoethane during occupational exposure to workers engaged in fumigating papaya.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

The chemical formula, structure, synonyms, and identification numbers for 1,2-dibromoethane are listed in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Important physical and chemical properties of 1,2-dibromoethane are listed in Table 3-2.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of 1,2-Dibromoethane

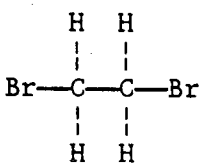
Characteristic	Information	Reference
Chemical name	1,2-Dibromoethane	Windholz 1983
Synonyms	Ethylene dibromide; dibromoethane; ethylene bromide; ethane, 1,2-dibromo-; EDB; α-, β-dibromoethane; sym-dibromoethane; glycol bromide; glycol dibromide; 1,2-dibromoethano (Italian); bomoro ei etile (Italian); 1,2-dibroomethaan (Dutch); althylenbromid (German); dibromure d'ethylene (French); dwubromoetan (Polish)	HSDB 1989; Weiss 1986; Windholz 1983
Trade names	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	HSDB 1989; Weiss 1986; Windholz 1983
Chemical Formula	$C_2H_4Br_2$	Windholz 1983
	$BrCH_2CH_2Br$	Windholz 1983
Chemical structure		

TABLE 3-1 (Continued)

Characteristic	Information	Reference
Identification numbers:		
CAS registry	106-93-4	Weiss 1986
NIOSH RTECS	NIOSH/KH 9275000	NIOSH 1985
EPA hazardous waste	U067	HSDB 1989
OHM/TADS	7216716	HSDB 1989
DOT/UN/NA/IMCO shipping	DOT 1605; UN 1605; IMO 6.1	HSDB 1989
HSDB	536	HSDB 1989
NCI	C00522	HSDB 1989

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/ Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemicals Substances

TABLE 3-2. Physical and Chemical Properties of 1,2-Dibromoethane

Property	Information	Reference
Molecular weight	187.86	Weiss 1986
	187.88	Windholz 1983
	188.0	NIOSH 1985
Color	Colorless	Weiss 1986
Physical state at 15°C, 1 atm	Liquid	Weiss 1986
Melting point (centigrade)	10°C	NIOSH 1978
Boiling point (centigrade)	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	NIOSH 1978
Water at 25°C	0.429 g/100 g water	Parrish 1983
Organic solvents	Miscible with alcohol, ether	Windholz 1983
Partition coefficients:		
Octanol/water	86	Steinberg et al. 1987
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	

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 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 to 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; as a result, 1,2-dibromoethane production plants are generally located near major sources of bromine, such as in Arkansas (Fishbein 1980). Current facilities that manufacture or process 1,2-dibromoethane are listed in Table 4-l.

4.2 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). Worldwide producers of 1,2-dibromoethane include the United Kingdom, Benelux, France, Spain, Italy, and Switzerland; collectively they produce lo-66 million pounds per year (Fishbein 1980).

A major market for U.S. 1,2-dibromoethane production has been overseas, although export levels have been declining. 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).

4.3 USE

1,2-Dibromoethane has been and is still used in a variety of ways. The main use is as an additive in leaded gasoline where 1,2-dibromoethane acts as a "scavenger" that converts lead oxides in cars to lead halides; these are

TABLE 4-1. Facilities That Manufacture or Process 1,2-Dibromoethane[a]

Facility	Location	Maximum Amount on site (lbs)	Use
Great Lakes Chemical Co. El Dorado-Main Plant	El Dorado, AR	1,000,000-9,999,999	Produce; for sale/distribution
Great Lakes Chemical Corp. South Plant	El Dorado, AR	100,000-999,999	As a reactant
Ethyl Corporation	Magnolia, AR	1,000,000-9,999,999	Produce; for sale/distribution
Texaco Ref. 7 Mktg., Inc.	Bakersfield, CA	10,000-99,999	
Exxon Co. USA. Benicia Refinery	Benicia, CA	No Data	As a formulation component
Arco Products Company Los Angeles Refinery	Carson, CA	10,000-99,999	As a formulation component
Shell Oil Company	Carson, CA	10,000-99,999	As a formulation component
Shell Oil Company	Carson, CA	10,000-99,999	As a formulation component
Chevron U.S.A. Inc.	El Segundo, CA	10,000-99,999	As a formulation component
Tosco Corporation	Martinez, CA	10,000-99,999	As a formulation component
Chevron Research Company Richmond Research Center	Richmond, CA	0-99	As a formulation component; in ancillary or other uses
Chevron U.S.A. Inc. Richmond Refinery	Richmond, CA	1,000-9,999	As a formulation component
Mobil Oil Corporation Torrance Refinery	Torrance, CA	1,000-9,999	As a formulation component
Texaco Ref. & Mktg., Inc.	Wilmington, CA	10,000-99,999	As a formulation component
Chevron U.S.A. Inc. Hawaiian Refinery	Ewa Beach, HI	100,000-999,999	As a formulation component
Shell Oil Company	Roxana, IL	10,000-99,999	As a formulation component
Rock Island Refining Corporation	Indianapolis, IN	10,000-99,999	As a formulation component
Ethyl Process Development Center	Baton Rouge, LA	100-999	As a formulation component; in repackaging
Exxon Baton Rouge Refinery	Baton Rouge, LA	100,000-999,999	As a formulation component
Alliance Refinery - Bp America	Belle Chasse, LA	100-999	As a formulation component
Tenneco Oil Company	Chalmette, LA	0-99	As a formulation component
Marathon Petroleum Company	Garyville, LA	10,000-99,999	As a formulation component
Placid Refining Company	Port Allen, LA	1,000-9,999	Import; as a formulation component
Marathon Petroleum Company	Detroit, MI	1,000-9,999	As a formulation component
Koch Refining Company	Saint Paul, MN	1,000-9,999	In ancillary or other uses
Chevron U.S.A. Inc. Pascagoula Refinery	Pascagoula, MS	100,000-999,999	As a formulation component
Du Pont Chambers Works	Deepwater, NJ	1,000,000-9,999,999	As a formulation component
Diaz Chemical Corporation	Holley, NY	10,000-99,999	As a byproduct; as a reactant

TABLE 4-1 (Continued)

Facility	Location	Maximum Amount on site (lbs)	Use
Shell Chemical Company	Belpre, OH	10,000-99,999	As a reactant
Sun Refinery And Marketing Co.	Oregon, OH	10,000-99,999	As a formulation component
Sun Refining And Marketing Co.	Tulsa, OK	1,000-9,999	As a formulation component
Kerr-Mcgee Refining Corp.	Wynnewood, OK	1,000-9,999	Import; as a formulation component
Chevron U.S.A. Inc.	Philadelphia, PA	10,000-99,999	As a formulation component
Exxon Baytown Refinery	Baytown, TX	10,000-99,999	As a formulation component
Du Pont Beaumont Works	Beaumont, TX	10,000-99,999	In re-packaging
Chevron U.S.A. Inc. El Paso Refinery	El Paso, TX	0-99	As an impurity
Ethyl Corporation Houston Plant	Pasadena, TX	100,000-999,999	As a formulation component; in repackaging
Chevron U.S.A. Inc. Port Arthur Refinery	Port Arthur, TX	10,000-99,999	As a formulation component
Diamond Shamrock Refining And Marketing Company	Sunray, TX	10,000-99,999	As a formulation component
Phillips 66 Company Sweeny Refinery And Petrochemical	Sweeny, TX	10,000-99,999	As a formulation component
Marathon Petroleum Company	Texas City, TX	10,000-99,999	As a formulation component
Diamond Shamrock Refining And Marketing Company	Three Rivers, TX	10,000-99,999	As a formulation component

[a]Derived from TRI87 1989

released more easily with engine exhaust (Fishbein 1980; Stenger 1978). In 1978, 90% of the 1,2-dibromoethane produced went into leaded gasoline for this purpose (Santodonato et al. 1985). Due to the increased regulation of leaded gasoline, the production and consumption of 1,2-dibromoethane has been and will continue to decrease in the future (Fishbein 1980; Santodonato et al. 1985).

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). Currently, other minor applications 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, and as a chemical intermediate for dyes, resins, waxes, and gums (HSDB 1989).

4.4 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 emissions of the incineration process must meet the requirements of the Clean Air Act of 1970 relating to gaseous emissions. Similarly, combustible containers of organic pesticides should be disposed of in a pesticide incinerator or be buried in a specially designated landfill. The noncombustible containers should be triple-rinsed and then returned to the manufacturer to be recycled. Residues and rinse liquids should be used in conjunction with the 1,2-dibromoethanecontaining product where possible, otherwise they should be disposed of as described above (HSDB 1989).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

1,2-Dibromoethane has historically been released to .the environment mainly as a result of its use as a gasoline additive and fumigant. 1,2-Dibromoethane partitions to the atmosphere and groundwater. The compound can be transported over long distances in the atmosphere, and is very mobile in soils. 1,2-Dibromoethane is transformed in the atmosphere by reaction with hydroxyl radicals and in soils by biodegradation. As a result of its high water solubility, the compound is not expected to bioconcentrate or biomagnify in food chains. 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.

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

EPA has identified 1,177 NPL sites. 1,2-Dibromoethane has been found at 9 of the total number of sites evaluated for that compound. We do not know how many of the 1,177 sites have been evaluated for 1,2-dibromoethane. As more sites are evaluated by EPA; this number may change (View 1989). The frequency of these sites within the United States can be seen in Figure 5-1.

5.2 RELEASES TO THE ENVIRONMENT

1,2-Dibromoethane has been 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 has also been released from industrial processing facilities. For example, 1,2-dibromoethane was found in air, water, soil, and sediment samples taken near industrial bromine facilities in El Dorado and Magnolia, Arkansas, in 1977 (Pellizzari et al. 1978).

According to the SARA Section 313 Toxics Release Inventory (TRI), an estimated total of at least 152,634 pounds of 1,2-dibromoethane were released to the environment from manufacturing and processing facilities in the United States in 1987 (see Table 5-l). This total includes an estimated 44 pounds that were released through underground injection. The TRI data should be used with caution since the 1987 data represent first-time reporting by these facilities. Only certain types of facilities were required to report. This is not an exhaustive list.

TABLE 5-1. Releases to the Environment from Facilities That Manufacture or Process 1,2-Dibromoethane[a]

Facility	Location	Total (lbs)						
		Air	Underground injection	Water	Land	Environment	POTW[b] transfer	Off-site transfer
Great Lakes Chemical Co. El Dorado-Main Plant	El Dorado, AR	9,700	0	0	0	9,700	0	14,000
Great Lakes Chemical Corp. South Plant	El Dorado, AR	3,700	44	0	0	3,744	0	0
Ethyl Corporation	Magnolia, AR	18,100	0	0	0	18,100	0	23,300
Texaco Ref. 7 Mktg., Inc.	Bakersfield, CA	150	0	0	0	150	0	0
Exxon Co. USA. Benicia Refinery	Benicia, CA	0	0	0	0	0	0	0
Arco Products Company Los Angeles Refinery	Carson, CA	60	0	0	0	60	0	0
Shell Oil Company	Carson, CA	145	0	0	0	145	0	0
Shell Oil Company	Carson, CA	71	0	0	0	71	0	0
Chevron U.S.A. Inc.	El Segundo, CA	13	0	90	250	353	1	1
Tosco Corporation	Martinez, CA	500	No Data	250	250	1,000	No Data	0
Chevron Research Company Richmond Research Center	Richmond, CA	0	0	0	0	0	0	0
Chevron U.S.A. Inc. Richmond Refinery	Richmond, CA	500	0	0	0	500	No Data	0
Mobil Oil Corporation Torrance Refinery	Torrance, CA	500	0	0	0	500	250	0
Texaco Ref. & Mktg., Inc.	Wilmington, CA	50	0	2	0	52	2	0
Chevron U.S.A. Inc. Hawaiian Refinery	Ewa Beach, HI	500	No Data	250	0	750	0	0
Shell Oil Company	Roxana, IL	0	0	0	0	0	0	0
Rock Island Refining Corporation	Indianapolis, IN	250	0	0	250	500	0	250
Ethyl Process Development Center	Baton Rouge, LA	5,500	0	250	0	5,750	0	0
Exxon Baton Rouge Refinery	Baton Rouge, LA	18	0	0	0	18	0	0

TABLE 5-1 (Continued)

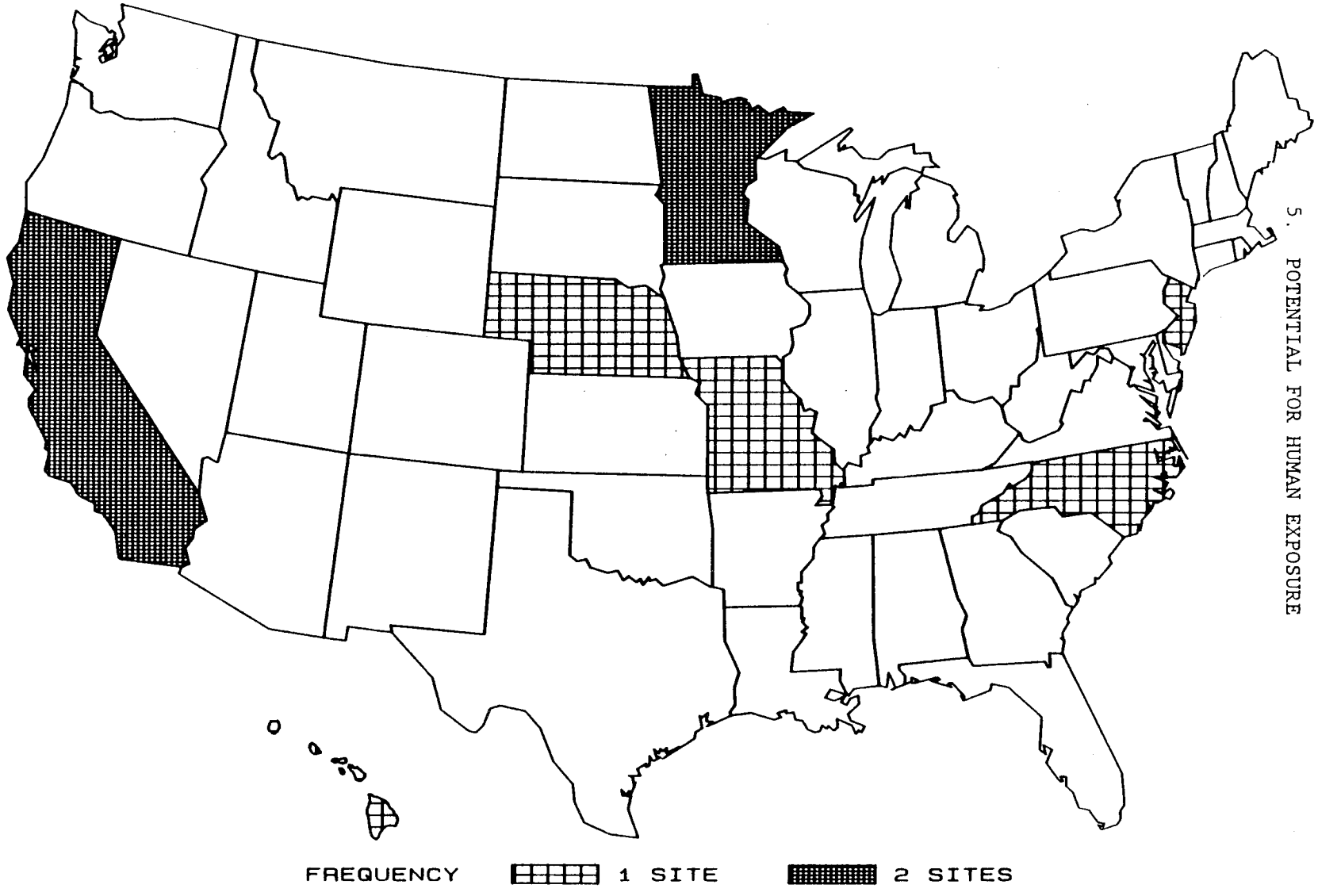
Facility	Location	Total (lbs)						
		Air	Underground injection	Water	Land	Environment	POTW[b] transfer	Off-site transfer
Alliance Refinery - Bp America	Belle Chasse, LA	750	0	0	0	750	0	0
Tenneco Oil Company	Chalmette, LA	4	0	0	0	4	No Data	0
Marathon Petroleum Company	Garyville, LA	750	0	0	0	750	0	0
Placid Refining Company	Port Allen, LA	4	No Data	0	0	4	0	0
Marathon Petroleum Company	Detroit, MI	0	0	0	0	0	0	0
Koch Refining Company	Saint Paul, MN	12	0	0	0	12	0	0
Chevron U.S.A. Inc. Pascagoula Refinery	Pascagoula, MS	500	0	92	250	842	0	0
Du Pont Chambers Works	Deepwater, NJ	6,060	0	0	700	6,760	No Data	No Data
Diaz Chemical Corporation	Holley, NY	500	0	0	0	500	250	1,700
Shell Chemical Company	Belpre, OH	13,000	0	0	0	13,000	0	360
Sun Refinery And Marketing Co.	Oregon, OH	250	0	0	0	250	0	0
Sun Refining And Marketing Co.	Tulsa, OK	0	0	0	0	0	0	0
Kerr-Mcgee Refining Corp.	Wynnewood, OK	250	0	0	0	250	0	0
Chevron U.S.A. Inc.	Philadelphia, PA	500	0	0	0	500	0	0
Exxon Baytown Refinery	Baytown, TX	0	0	0	0	0	0	0
Du Pont Beaumont Works	Beaumont, TX	400	0	0	No Data	400	No Data	200
Chevron U.S.A. Inc. El Paso Refinery	El Paso, TX	250	0	0	0	250	0	0
Ethyl Corporation Houston Plant	Pasadena, TX	1,200	0	0	0	1,200	0	250
Chevron U.S.A. Inc. Port Arthur Refinery	Port Arthur, TX	250	0	0	0	250	0	0
Diamond Shamrock Refining And Marketing Company	Sunray, TX	0	0	0	0	0	0	0

TABLE 5-1 (Continued)

Facility	Location	Total (lbs) Air	Underground injection	Water	Land	Environment	POTW[b] transfer	Off-site transfer
Phillips 66 Company Sweeny Refinery And Petrochemical	Sweeny, TX	2	0	0	0	2	0	37
Marathon Petroleum Company	Texas City, TX	1,300	0	0	0	1,300	0	0
Diamond Shamrock Refining And Marketing Company	Three Rivers, TX	1	0	0	2	3	0	2
Totals		65740	44	934	1702	68420	503	40100

[a]Derived from TRI87 1989
[b]POTW -- publicly owned treatment works

FIGURE 5-1. FREQUENCY OF NPL SITES WITH 1,2-DIBROMOETHANE CONTAMINATION *



* Derived from View 1989

5. POTENTIAL FOR HUMAN EXPOSURE

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

5.2.1 Air

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

An estimated total of at least 149,854 pounds of 1,2-dibromoethane was released to the atmosphere from manufacturing and processing facilities in the United States in 1987 (TR187 1989) (see Table 5-l).

5.2.2 Water

The 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).

An estimated total of at least 1,034 pounds of 1,2-dibromoethane was released to surface waters from manufacturing and processing facilities in the United States in 1987 (TR187 1989) (see Table 5-l).

1,2-Dibromoethane has been detected in an estimated 0.23% of the groundwater samples analyzed for the 2,783 hazardous waste sites participating in the Contract Laboratory Program (CLP); a positive geometric mean concentration value was not reported. 1,2-Dibromoethane has not been detected in surface water samples taken at hazardous waste sites (CLPSD 1988). Note that the CLP Statistical Database (CLPSD) includes data from both NPL and non-NPL sites.

5.2.3 Soil

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.

An estimated total of at least 1,702 pounds of 1,2-dibromoethane was released to soils from manufacturing and processing facilities in the United States in 1987 (TR187 1989) (see Table 5-l).

1,2-Dibromoethane has been detected in an estimated 0.12% of the soil samples collected from the 2,783 hazardous waste sites that have had samples analyzed by the CLP; a positive geometric concentration value was not reported (CLPSD 1988). Note that the CLPSD includes data from both NPL and non-NPL sites.

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

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. As the data in Section 5.4.1 indicate, 1,2-dibromoethane can be transported for long distances in the atmosphere before removal in wet and dry deposition or degradation.

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).

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 (half-life = years) from micropore sites to contaminate groundwater.

As a result of its high water solubility, 1,2-dibromoethane is not expected to bioconcentrate or biomagnify in terrestrial and aquatic food chains.

5.3.2 Transformation and Degradation

5.3.2.1 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).

5.3.2.2 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 leached to groundwater is expected to persist for years.

5.3.2.3 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.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

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, although the latest available, 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. The data may reflect ambient concentrations of a decade or more ago, but 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.

5.4.1 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: rural and remote areas--less than detection limit; urban and suburban areas--2.6 parts per trillion (ppt); and source-dominated areas--1.9 ppt. Typical daily concentrations at four sites in the metropolitan Los Angeles area in 1983 were reported to range from less than 5 ppt to 17 ppt (KOwalski et al. 1985b). Ambient air concentrations for other metropolitan areas in the United States in 1980 were reported by Singh et al. (1981) as follows:

	1,2-Dibromoethane (ppt)	
Location	Mean	Range
Houston, TX	59	10-368
St. Louis, MO	16	8-26
Denver, CO	31	10-78
Riverside, CA	22	10-47

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 less than 0.001-0.003 ppt.

5.4.2 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 greater than 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. States with reported 1,2-dibromoethane groundwater contamination problems include Wisconsin (Krill et al. 1986), Hawaii (Oki and Giambelluca 1987), New Jersey (maximum concentration of 48,800 ppt in 34 of 421 samples) (Page 1981), and Georgia (l,OOO-94,000 ppt) (Marti et al. 1984). According to the interim data available in the Pesticides in Ground Water Data Base, 1,2-dibromoethane detection in groundwater has been confirmed in six states: California, Connecticut, Georgia, Massachusetts, New York, and Washington. 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.

5.4.3 Soil

No information was found in the literature regarding current ambient concentrations of 1,2-dibromoethane in surface soils in the United States.

5.4.4 Other Environmental 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 in a recent survey. 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).

5.5 GENERAL POPULATION AND OCCUPATIONAL 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. According to EPA (1985), daily intake from drinking water has been estimated to range from 0 to 16 μg/kg/day. 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. No information was found in the available literature regarding the size of the human population potentially exposed to 1,2-dibromoethane through contact with contaminated waste site media.

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. Current exposure levels are also 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).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Members of the general population with potentially high exposure to 1,2-dibromoethane include individuals living near the nine 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.

5.7 ADEQUACY OF.TIiE 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 the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,2-dibromoethane.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

5.7.1 Data Needs

Physical and Chemical Properties. The physical/chemical properties of 1,2-dibromoethane, described in Table 3-2, are sufficiently well characterized to enable assessment of the environmental fate of the compound.

Production, Import/Export, Use, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxic Release Inventory (TRI), which contains this information for 1987, became available in May of 1989. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

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). The most recent information on the annual U.S. production of 1,2-dibromoethane is for 1982 (169.8 million pounds); this is lower than the average for the 1970s (280 million pounds) (Santodonato et al. 1985). The most recent import and export data are for 1980 (0.861 million pounds) and 1981 (29.8 million pounds), respectively; import volumes reportedly fluctuated between 1977 and 1981 and the 1981 export volume is substantially lower than that for 1978 (84.8 million pounds) (Santodonato et al. 1985). 1,2-Dibromoethane may be found in air and water as a result of its use, e.g., as a chemical intermediate, although its uses as a lead scavenger in gasoline and as a soil and grain fumigant have been decreased or eliminated by governmental regulation (Fishbein 1979, 1980; HSDB 1989; Santodonato et al. 1985; Stenger 1978). In addition, the general regulations governing organic pesticide disposal developed by EPA are applicable to 1,2-dibromoethane. It is disposed of mainly by incineration and by burial; however, the amounts disposed of by each method are not reported (HSDB 1989). Therefore, more recent production, import, export, use, and disposal volumes of 1,2-dibromoethane would be useful in assessing the potential for the release of, and exposure to, this chemical.

Information regarding the various modes of production, use, and disposal of 1,2-dibromoethane is well documented. 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). 1,2-Dibromoethane is volatilized from surface waters before it can undergo degradation (EPA 1987b). 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 at hazardous waste sites. 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 abioavailability 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; EPA 1983; Ewing et al. 1977; Daft 1989; Page 1981; Pellizzari et al. 1978; Singh et al. 1981; Williams et al. 1988). However, the monitoring data for these media are not current. Estimates of human intake have been made on the basis of these older data. Additional information is needed on the current levels of 1,2-dibromoethane in ambient air, soils, and groundwater and on human intake levels, particularly at the nine hazardous waste sites known to be contaminated with the compound. This information will be helpful in estimating human exposure to the compound via contact with contaminated media.

Exposure Levels in Humans. 1,2-Dibromoethane can be measured in blood 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.

Exposure Registries. No exposure registries for 1,2-dibromoethane were located. This compound is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The

compound will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to this compound.

5.7.2 On-going Studies

As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environmental Health Laboratory Sciences Division of the National Center for Environmental Health and Injury Control, Centers for Disease Control, will be analyzing human blood samples for 1,2-dibromoethane and other volatile organic compounds. These data will give an indication of the frequency of occurrence and background levels of these compounds in the general population.

On-going remedial investigations and feasibility studies conducted at the nine NPL sites known to be contaminated with 1,2-dibromoethane will add to the available database on exposure levels in environmental media, exposure levels in humans, and exposure registries.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring 1,2-dibromoethane in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify 1,2-dibromoethane. Rather, the intention is to identify well established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect 1,2-dibromoethane in environmental samples are the methods approved by federal agencies such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL MATERIALS

Gas chromatography (GC) equipped with a flame ionization detector has been employed for measuring the concentration of 1,2-dibromoethane in the tissues of two workers following exposure (Letz et al. 1984). A detection limit of 0.5 μg of 1,2-dibromoethane per gram of tissue was achieved. In the same report, Letz et al. (1984) detected ppm (mg/L) levels of bromide ion (a metabolite of 1,2-dibromoethane) in the serum and whole blood before and after the death of two individuals, respectively. Detection limits of 50 mg of bromide ion per liter of serum and 8 mg of bromide ion per liter of whole blood were obtained using gold chloride calorimetry and high-performance liquid chromatography, respectively. GC has also been used for quantifying ppm levels of 1,2-dibromoethane in blood and liver of rats and chicks (Nachtomi and Alumot 1972). See Table 6-l for details.

6.2 ENVIRONMENTAL SAMPLES

High-resolution GC equipped with an appropriate detector is the most common analytical technique for determining the concentrations of 1,2-dibromoethane in air, water, wastewater, soil, leaded gasoline, and various foods (e.g., grains, grain-based foods, beverages, and fruits). The choice of a particular detector will depend on the nature of the sample matrix, the detection limit, and the cost of the analysis. Because volatile organic compounds in environmental samples may exist as complex mixtures or at very low concentrations, concentrations of these samples prior to quantification are usually necessary.

Gas purging and trapping is the most commonly used method for the preconcentration of 1,2-dibromoethane from water, waste water, soil, and various foods. This method also provides a preliminary separation of 1,2-dibromoethane from other less volatile and nonvolatile components in the

TABLE 6-1. Analytical Methods for Determining 1,2-Dibromoethane in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Biological tissues	Add water to tissue sample (at 50°C) and homogenise; extract with carbon disulfide and analyze	Gas chromatography flame ionization detector	0.5 µg/g	No data	Letz et al. 1984
Bromide ion in serum (before death of workers)	No data	Gold chloride colorimetry	50 mg/L	No data	Letz et al. 1984
Bromide ion in whole-blood (after death of workers)	No data	High-performance liquid chromatography	8 mg/L	3.6% coefficient of variation	Letz et al. 1984
Blood and liver (rats and chicks)	No data	Gas chromatography	ppm levels	No data	Nachtomi and Alumot 1972

samples, thereby alleviating the need for extensive separation of the components by a chromatographic column prior to quantification.

The best sensitivity for 1,2-dibromoethane quantification is obtained by either electron capture detector (ECD) or Hall electrolytic conductivity detector (HECD) in the halide detection mode, since these detectors are relatively insensitive to nonhalogenated species and very sensitive to halogenated species. Another common detection device is a mass spectrometer (MS) connected to a GC. The GC/MS combination provides unequivocal identification of 1,2-dibromoethane in samples containing multiple components having similar GC elution characteristics (see Table 6-2). To date, GC equipped with either ECD or HECD has provided the greatest sensitivity for detecting 1,2-dibromoethane. However, GC/MS employing the techniques of selective ion monitoring and isotope dilution have produced sensitivities in the parts-per-quadrillion range for some organic pollutants (Patterson et al. 1987), and could be used for 1,2-dibromoethane analysis.

The primary method of analyzing 1,2-dibromoethane in air is by adsorption on a solid phase (i.e., activated charcoal tube or Tenax adsorbent followed by thermal or solvent elution for subsequent quantification. GC/ECD and GC/MS are the most commonly used analytical techniques for 1,2-dibromoethane after elution from the solid phase (Clark et al. 1982; Collins and Barker 1983; Erikson and Pellizzari 1978; Girish and Kumar 1975; NIOSH 1987; Scott et al. 1987). NIOSH has recommended GC/ECD (method 1008) for determining 1,2-dibromoethane in air (NIOSH 1987). The range of quantification is 0.3-1,000 ppb for a 25-L air sample.

1,2-Dibromoethane is usually isolated from aqueous media by the purgeand-trap method or liquid-liquid extraction. GC/ECD or GC/MS is the technique employed for measuring 1,2-dibromoethane in water and waste water at ppt levels (Kroneld 1985; Marti et al. 1984; Simmonds 1984). GC/ECD is also the technique (method 8011) recommended by the EPA Office of Solid Waste and Emergency Response for determining 1,2-dibromoethane in drinking water and groundwater at ppt levels (EPA 1987b).

1,2-Dibromoethane can be isolated from soil samples by liquid-liquid extraction and subsequent quantification by GC/MS (Sawhney et al. 1988). Low ppb levels of 1,2-dibromoethane in soil were reported using this technique. Sample collection and preparation for the analysis of 1,2-dibromoethane in foods includes the purge-and-trap method, headspace gas analysis, liquid-liquid extraction, and steam distillation (Alleman et al. 1986; Anderson et al. 1985; Bielorai and Alumot 1965, 1966; Cairns et al. 1984; Clower et al. 1985; Pranoto-Soetardhi et al. 1986; Scudamore 1985). GC equipped with either ECD or HECD is the technique used for measuring 1,2-dibromoethane in foodstuffs at ppt levels (Clower et al. 1985; Entz and Hollifield 1982; Heikes and Hopper 1986; Page et al. 1987; Van Rillaer and Beernaert 1985).

TABLE 6-2. Analytical Methods for Determining 1,2-Dibromoethane in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Adsorb air sample onto charcoal tube; extract sample and analyze	GC/ECD	0.0003-1 ppm (for a 25-L air sample)	No data	NIOSH 1987 (Method 1008)
	Collect air sample on Tenax adsorbent; desorb thermally and analyze	GC/ECD or GC/FID	No data	1.4% RSD	Clark et al. 1982
	No data	GC/PID	0.019 ppm	No data	Dumas and Bond 1982
Water	Purge and cryotrap on adsorbent	GC/ECD	0.01-0.004 µg/L	12.1% RSD	Simmonds 1984
	Purge and trap on adsorbent	GC/MS	0.05 µg/L	95%	Marti et al. 1984
	Add sodium chloride to sample and extract with hexane	GC/ECD	0.01 µg/L	95%-114%	EPA 1987b (Method 8011)
Water and waste water	Purge and trap on adsorbent	GC/MS	1 µg/L (drinking water)	68% (drinking water)	Michael et al. 1988
Soil	Extract sample with methanol	GC/MS	≤0.0018 µg/g	No data	Sawhney et al. 1988
	Decompose 1,2-dibromoethane in sample by distillation and cooling in acetone:isooctane (1:1); analyze resulting hydrogen bromide at 376 nm	MEC	<0.5 µg/g	>96%	Abdel-Kader et al. 1979
Leaded gasoline	Derivatize 1,2-dibromoethane in sample with silica-supported silver picrate column; analyze derivative	HPLC/ED	0.28 µg/L	No data	Colgan et al. 1986

TABLE 6-2 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Various foods (e.g., grains, grain-based foods, fruits, and beverages)	Ground sample in water (water-soluble foods or sulfuric acid (water-immiscible foods) and introduce in headspace analyzer	GC/MS	<0.001 µg/g (water-soluble foods) 0.01-0.05 µg/g (lipid-containing foods)	90%-100%	Entz and Hollifield 1982
	Ground sample in water or sulfuric acid and introduce in headspace analyzer	GC/ECD	0.001 µg/g	70%-82%	Pranoto-Soetardhi et al. 1986
	Extract 1,2-dibromoethane from sample by steam distillation	GC/ECD	0.0005-0.1 µg/g	95.1%-117%	Page et al. 1987; Van Rillaer and Beernaert 1985
	Add isooctane and sodium chloride solution to sample and shake; extract with methanol and analyze	GC/ECD or HECD	0.002 µg/g	62%	Daft 1988
	Extract sample by soaking in acetone: water (5:1) and dry (calcium chloride)	GC/ECD	low ng/g levels	90%-100%	Daft 1988
	Purge-and-trap on adsorbent	GC/ECD or HECD	0.0009 µg/g	82%-99%	Heikes and Hopper 1986
	Extract with acetone-water, or by triple hexane codistillation	GC/ECD	0.0004-0.005 µg/g	94%-106%	Clower et al. 1985

ECD = electron capture detector; ED = electrochemical detector; FID = flame ionization detector; GC = gas chromatography; HECD = Hall's electrolytic conductivity detector; HPLC = high performance liquid chromatography; MEC = molecular emission cavity analysis; MS = mass spectrometry; PID = photo-ionization detector

6. ANALYTICAL METHODS

A highly sensitive and specific liquid chromatographic method for determining 1,2-dibromoethane in leaded gasoline has been developed by Colgan et al. (1986). The method involves the reaction between silver picrate adsorbed on silica gel and 1,2-dibromoethane to form 1-bromo-2-(picryloxy)-ethane and/or 1,2-bis(picryloxy)ethane. The derivatives formed were analyzed by high-performance liquid chromatography (HPLC) equipped with an oxidative electrochemical detector (ED). A detection limit of 280 ppt of 1,2-dibromoethane was reported (Colgan et al. 1986).

6.3 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 the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,2-dibromoethane,

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that, if met, would reduce or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Data Needs

Methods for Determining Biomarkers of Exposure and Effect. GC, HPLC, and gold chloride calorimetry have been used for measuring low ppt levels of 1,2-dibromoethane and bromide ion. These techniques are sensitive for measuring background levels of 1,2-dibromoethane in the population (Letz et al. 1984). However, it is not known whether these techniques are sensitive for measuring levels of 1,2-dibromoethane at which health effects may begin to occur. Although analytical methods are available to detect exposures to 1,2-dibromoethane, it is difficult to monitor for exposure to 1,2-dibromoethane in humans. This is because 1,2-dibromoethane is volatile and has a short half-life in biological materials (Plotnick et al. 1979; Windholz 1983). Monitoring for bromide ion in biological media is also problematic in that the presence of this metabolite may result from the metabolism of other brominated hydrocarbons (see Chapter 2). Furthermore, information on the precision and accuracy of the gas chromatographic technique would be useful for interpreting monitoring data in biological tissues and fluids.

Biochemical assays have been employed to measure changes in enzyme levels (e.g., aspartate aminotransferase, lactic dehydrogenase) as an indication of exposure to 1,2-dibromoethane in humans and animals (Albano et al. 1984; Botti et al. 1989; Letz et al. 1984; Van Iersel et al. 1988). Decreased sperm counts per ejaculate and increased numbers of sperm with abnormal morphology have also been identified in workers following exposure to 1,2-dibromoethane (Ratcliffe et al. 1987; Wyrobek 1984). In general, these techniques are nonspecific for 1,2-dibromoethane exposure (see Chapter 2). There are no data to indicate whether a biomarker, if available, would be preferred over chemical analysis for monitoring exposure to 1,2-dibromoethane.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. GC equipped with either ECD, HECD, or MS and HPLC/ED are the analytical techniques used for measuring low levels of 1,2-dibromoethane in air, water, waste water, soil, leaded gasoline, and foodstuffs (Colgan et al. 1986; Daft 1988; EPA 1987b; Marti et al. 1984; Michael et al. 1988; NIOSH 1987; Sawhney et al. 1988; Simmonds 1984). The media of most concern for potential human exposure to 1,2-dibromoethane are drinking water, air, and foodstuffs. Gas chromatographic techniques are sensitive for measuring background levels of 1,2-dibromoethane in these media and levels of 1,2-dibromoethane at which health effects might begin to occur. GC/ECD is the technique (method 8011) recommended by EPA for measuring ppt levels of 1,2-dibromoethane in water (EPA 1987b). NIOSH has also recommended GC/ECD as the method (method 1008) for measuring low-ppm to sub-ppb levels of 1,2-dibromoethane in air (NIOSH 1987). GC/HECD or ECD has been employed for detecting 1,2-dibromoethane in various foodstuffs at low- to sub-ppb levels. No additional analytical methods for measuring 1,2-dibromoethane in environmental media appear to be necessary at this time.

6.3.2 On-going Studies

The Environmental Health Laboratory Sciences Division of the National Center for Environmental Health and Injury Control, Centers for Disease Control, is developing methods for the analysis of 1,2-dibromoethane and other volatile organic compounds in blood. These methods use high resolution gas chromatography and magnetic sector mass spectrometry which gives detection limits in the low parts-per- trillion range.

7. REGULATIONS AND ADVISORIES

1,2-Dibromoethane is on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986" (EPA 1987f).

The international, national, and state regulations and guidelines regarding 1,2-dibromoethane in air, water, and other media are summarized in Table 7-1.

7. REGULATIONS AND ADVISORIES

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

Agency	Description	Information	References
INTERNATIONAL			
IARC	Carcinogenic classification	Group 2A[a]	IARC 1987
NATIONAL			
Regulations:			
a. Air:			
OSHA (Transitional Values)	PEL TWA (8 hr)	20 ppm	OSHA 1974 (29 CFR 1910.1000)
	Ceiling level (CL)	30 ppm	OSHA 1974 (29 CFR 1910.1000)
	Acceptable maximum peak above CL (5 min for 8 hr shift)	50 ppm	OSHA 1974 (29 CFR 1910.1000)
	STEL (15 min)	0.5 ppm	EPA 1987a
b. Water:			
EPA ODW	Monitoring for organic chemicals: Groundwater monitoring requirement for EDB if the state determines they are vulnerable to EDB contamination	Yes	EPA 1987d (40 CFR 141.40)
EPA OWRS	NPDES permit application requirements: Toxic pollutants and hazardous substances to be identified by existing discharges if expected to be present	Yes	EPA 1983 (40 CFR 122, Appendix D)
c. Other:			
DOT	Label	Poison	DOT 1980 (49 CFR 172.102)
EPA OERR	CERCLA reportable quantity	1000 lbs (454 kg)	EPA 1986 (40 CFR 117.3)
EPA OPP	Decision and emergency order suspending registrations of pesticide products containing 1,2-dibromoethane for use as a grain and spot milling fumigant		EPA 1984b
EPA OSW	Designation of hazardous substances	Yes	EPA 1978 (40 CFR 116.4)
	Listing as toxic waste from specific sources: Wastewater from the reactor vent gas scrubber in the production of EDB via bromination of ethene; spent adsorbent solids and still bottoms from purification of EDB in its production via bromination of ethene	Yes	EPA 1981b (40 CFR 261.32)
EPA OSW	Listing as toxic waste: Discarded commercial chemical products off-specifications species container residues, and spill residues thereof	Yes	EPA 1988a
	Listing as hazardous waste constituent	Yes	EPA 1988b (40 CFR 261, Appendix VIII)
	Groundwater monitoring list	Yes	EPA 1987e (40 CFR 264, Appendix IX)

7. REGULATIONS AND ADVISORIES

TABLE 7-1 (Continued)

Agency	Description	Information	References
NATIONAL (Cont.)			
EPA OTS	Toxic chemical release reporting; Community right-to-know (proposed)	Yes	EPA 1987f
OSHA	Meets criteria for OSHA medical records rule	Yes	OSHA 1980 (29 CFR 1910.20)
RCRA	Handling and report/recordkeeping requirements--limit	1000 kg	CESARS 1989
USDA	Removal of provisions that mangoes be treated with EDB before entry into the United States	Yes	USDA 1988
Guidelines:			
a. Air:			
ACGIH	Carcinogenicity	A2[b]	ACGIH 1987-88
	Skin designation	Yes	ACGIH 1987-88
NIOSH	REL TWA (8-hr)	0.045 ppm	NIOSH 1985
	CL (15-min)	0.13 ppm (1.0 mg/m^3)	NIOSH 1985
	Designated as NIOSH occupational carcinogen	Yes	NIOSH 1985
b. Water:			
EPA ODW	Health Advisories:		IRIS 1991
	1-day	8.0 µg/L	
	10-day	8.0 µg/L	
c. Other:			
EPA	Carcinogen classification	B2[c]	IRIS 1991
	Unit risk (air)	2.2 x 10^{-4} µg/m^3	IRIS 1991
	Unit risk (water)	2.5 x 10^{-3} µg/L	IRIS 1991
	Oral cancer potency factor	85 mg/kg/day	IRIS 1991
STATE			
Regulations and Guidelines:			
a. Air:	Acceptable ambient air concentrations (µg/m^3)		NATICH 1988
Connecticut	8-hr	755	
Indiana	8-hr	720	
North Carolina	24-hr	1.90	
Pennsylvania (Philadelphia)	1-yr	2.47	
Virginia	24-hr	1500	
	Point source emissions limits for BACT		
North Dakota		No data	Rydell 1990
Wisconsin		250.0 lbs/yr	State of Wisconsin Department of Natural Resources 1988a

TABLE 7-1 (Continued)

Agency	Description	Information	References
STATE (Cont.)			
b. Water:	Drinking water quality standards and guidelines (μg/L)		FSTRAC 1988
Arizona		0.010	
California		0.02	
Connecticut		0.1	
Kansas		0.005	
Massachussetts		0.04	
Maine		1	
Minnesota		0.008	
New Mexico		0.1	
Washington		0.02	
Vermont		0.01	State of Vermont Agency of Natural Resources
Wisconsin		0.5	
	Public health groundwater quality standards (μg/L)		State of Wisconsin Department of
Wisconsin	Enforcement standard	0.010	Natural
Wisconsin	Preventive action limit	0.001	Resources 1988b

[a]Group 2A: Inadequate evidence of carcinogenicity in humans; sufficient evidence in animals
[b]A2: Suspected human carcinogen
[c]B2: Probable human carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; BACT = Best Available Control Technology; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CL = Ceiling Level; DOT = Department of Transportation; EDB = 1,2-Dibromoethane; EPA = Environmental Protection Agency; NIOSH = National Institute for Occupational Safety and Health; NPDES = National Pollutant Discharge Elimination System; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OPP = Office of Pesticide Programs; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; OTS = Office of Toxic Substances; OWRS = Office of Water Regulations and Standards; PEL = Permissible Exposure Limit; RCRA = Resource Conservation Recovery Act; REL = Recommended Exposure Limit; TWA = Time-Weighted Average; USDA = United States Department of Agriculture.

8. REFERENCES

*Abdel-Kader MHK, Peach ME, Stiles DA. 1979. Determination of ethylene dibromide in fortified soils by molecular emission cavity analysis using a modified extraction process. J Assoc Off Anal Chem 62:114-118.

*ACGIH. 1987-1988. TLV's - Threshold limited values and biological indices for 1987-1988. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, 21.

Adams PM, Legator MS, Fanini D. 1983. The effect of paternal exposure to ethylene dibromide on the behavior of the F_1 progeny [Abstract]. Teratology 27:27A.

*Adkins B Jr, Van Stee EW, Simmons JE, et al. 1986. Oncogenic response of strain A/J mice to inhaled chemicals. J Toxicol Environ Health 17:311-322.

*Akamine EK. 1952. Toxicity of ethylene dibromide to white rats. Hawaii Agricultural Experiment Station of the University of Hawaii, Progress Notes No. 83, July 1984. l-4.

*Alavanja MCR, Blair A, Masters M. 1988. Mortality study of workers in the grain industry [Abstract]. Am J Epidemiol 128:900.

*Albano E, Poli G, Tomasi A, et al. 1984. Toxicity of 1,2-dibromoethane in isolated hepatocytes: Role of lipid peroxidation. Chem Biol Interact 50:255-266.

*Alleman TG, Sanders RA, Madison BL. 1986. Simultaneous analysis of grain and grain-based products for ethylene dibromide, carbon tetrachloride, and ethylene dichloride. J Assoc Off Anal Chem 69:575-580.

Alumot E, Chalutz E. 1972. Fumigation of citrus fruit with ethylene dibromide. Desorption of residues and ethylene evolution. Pestic Sci 3:539-544.

Aman J, Farkas L, Ben-Shamai MH, et al. 1946. Experiments on the use of ethylene dibromide as a fumigant for grain and seed. Annals of Applied Biology 33:389-395.

*Ames BN, Yanofsdy C. 1971. The detection of chemical mutagens with enteric bacteria. In: Hollander A, ed. Chemical mutagens: Principles, and methods for their detection. Vol. 1, Plenum Press, New York: 267-282.

*Amir D, Volcani R. 1965. Effect of dietary ethylene dibromide on bull semen. Nature 206:99-100.

---

* Cited in text

8. REFERENCES

Amir D, Volcani R. 1967. The effect of dietary ethylene dibromide (EDB) on the testes of bulls: A preliminary report. Fertil and Steril 18:144-148.

*Amir D. 1973. The sites of the spermicidal action of ethylene dibromide in bulls. J Reprod Fert 35:519-525.

*Amir D, Ben-David E. 1973. The pattern of structural changes induced in bull spermatozoa by oral or injected ethylene dibromide (EDB). Ann Biol Anim Bioch Biophys 13:165-170.

*Amir D. 1975. Individual and age differences in the spermicidal effect of ethylene dibromide in bulls. J Reprod Fert 44:561-565.

*Amir D, Lavon U. 1976. Changes in total nitrogen, lipoproteins and amino acids in epididymal and ejaculated spermatozoa of bulls treated orally with ethylene dibromide. J Reprod Fert 47:73-76.

*Amir D, Esnault C, Nicolle JC, et al. 1977. DNA and protein changes in the spermatozoa of bulls treated orally with ethylene dibromide. J Reprod Fert 51:453-456.

Amir D, Nicolle JC, Courot M. 1979. Changes induced in bull spermatids and testicular spermatozoa by a single peritesticular injection of ethylene dibromide. Int J Androl 2:162-170.

*Amir D, Gledhill BL, Garner DL, et al. 1983. Spermiogenic, epididymal, and spermatozoa1 damage induced by a peritesticular injection of ethylene dibromide to rams. Anim Reprod Sci 6:35-50.

Amir D. 1984. The spermicidal effect of ethylene dibromide in bulls and rams: A comparative study. Congressional Proceedings - 10th International Congress on Animal Reproduction and Artificial Insemination 2:33-34.

Amuh IRA. 1975. Persistence of ethylene dibromide residues in fumigated maize. Ghana J Sci 15:59-63.

*Anders MW, Livesey JC. 1980. Metabolism of 1,2-dihaloethanes. In: Ames B, Infante P, Reitz R, ed. Ethylene dichloride: A potential health risk. Banbury Report 5. Cold Spring Harbor Laboratory, 331-341.

*Anderson RA, Peplinski AJ, Storey CL, et al. 1985. Distribution of ethylene dibromide residues in whole corn and milled corn products. Cereal Chem 62:198-200.

Anonymous. 1980. Carcinogenesis bioassay of 1,2-dibromoethane. Vet Hum Toxicol 22:101-103.

8. REFERENCES

Anonymous. 1982, Ethylene dibromide (EDB) revised. Vet Hum Toxicol 24:175-176.

Anonymous, 1987. Analytical technique reveals pesticide hazards. Agric Eng 68:18.

ANSI. 1970. American national standard acceptable concentrations of ethylene dibromide (1,2-dibromoethane). American National Standards Institute, Inc., New York, NY. ANSI 237.31-1970, 5-8.

Arfellini G, Bartoli S, Colacci A, et al. 1984. In vivo and in vitro binding of 1,2-dibromoethane and 1,2-dichloroethane to macromolecules in rat and mouse organs. J Cancer Res Clin Oncol 108:204-213.

Armstrong D, Kutob R, Sipes I. 1985. Deuterium isotope effect on the expiration and tissue distribution of 1,2-dibromoethane [Abstract]. Toxicologist 5:174.

*Banerjee S, Van Durren BL. 1979. Binding of carcinogenic halogenated hydrocarbons to cell macromolecules. J Nat1 Cancer Inst 63:707-711.

*Barber ED, Donish WH, Mueller KR. 1981. A procedure for the quantitative measurement of the mutagenicity of volatile liquids in the Ames Salmonella/microsome assay. Mutat Res. 90:31-48.

*Barnes D, Bellin J, DeRosa C, et al. 1988. Reference dose (RfD): Description and use in health risk assessments. Appendix A: Integrated risk information system supportive documentation. Washington, D.C.: US Environmental Protection Agency, Office of Health and Environmental Assessment. EPA/600/8-86-032a.

Basile M. 1981. [Bromine residues in strawberries produced on soil fumigated with ethylene dibromide (EDB)]. Inf Tore Fitopatol 29:11-14. (Italian)

*Benet LZ, Sheiner LB. 1985. Pharmacokinetics: The dynamics of drugs absorption, distribution, and elimination. In: 7th ed. Goodman's and Gilman's: The pharmaceutical basis of therapeutics. New York, NY: MacMillan Publishing Company.

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

Berck B. 1962. Polarographic determination of methyl bromide, ethyl dibromide, acrylonitrile, chloropicrin, and carbon tetrachloride in air. J Agric Food Chem 10:158-162.

8. REFERENCES

Berck B. 1974. Fumigant residues of carbon tetrachloride, ethylene dichloride, and ethylene dibromide in wheat, flour, bran, middlings, and bread. J Agric Food Chem 22:977-984.

*Berkow R, ed. 1987. The Merck manual of diagnosis and therapy. 15th ed. Rahway, NJ: Merck, Sharpe & Dohme Research Laboratories.

*Bielorai R, Alumot E. 1965. Determination of ethylene dibromide in fumigated feeds and foods by gas-liquid chromatography. J Sci Food Agric 16:594-596.

*Bielorai R, Alumot E. 1966. Determination of residues of a fumigant mixture in cereal grain by electron-capture gas chromatography. J Agric Food Chem 14:622-625.

Bignami M, Cardamone, G, Comba P, et al. 1977. Relationship between chemical structure and mutagenic activity in some pesticides: The use of Salmonella typhimurium and Aspergillus nidulans. Mutat Res 46:243-244.

*Bolt HM, Laib RJ, Peter H, et al. 1986. DNA adducts of halogenated hydrocarbons. J Cancer Res Clin Oncol 112:92-96.

*Botti B, Moslen MT, Trieff NM, et al. 1982. Transient decrease of liver cytosolic glutathione S-transferase activity in rats given 1,2-dibromoethane or CC14. Chem Biol Interact 42:259-270.

*Botti B, Bini A, Calligaro A, et al. 1986. Decrease of hepatic mitochondrial glutathione and mitochondrial injury induced by 1,2-dibromoethane in the rat in vivo: Effect of diethylmaleat pretreatment. Toxicol Appl Pharmacol 83:494-505.

*Botti B, Franceschini V, Tomasi A, et al. 1989. Mechanistic aspects of 1,2-dibromoethane-induced mitochondrial GSH depletion in vitro. Adv Biosci 76:99-105.

*Bouwer EJ, McCarty PL. 1983. Transformations of halogenated organic compounds under dinitrification conditions. Appl Environ Microbial 45:1295-1299.

*Brandt I, Brittebo EB, Kowalski B, et al. 1987. Tissue binding of 1,2-dibromoethane in the cynomolgus monkey (Macaca fascicularis). Carcinogenesis 8:1359-1361.

*Brem H, Stein AB, Rosenkranz HS. 1974a. The mutagenicity and DNA-modifying effect of haloalkanes. Cancer Res 34:2576-2579.

8. REFERENCES

Brem H, Coward JE, Rozenkrantz HS. 1974b. 1,2-Dibromoethane: Effect on the metabolism and ultrastructure of Escherichia coli. Biochem Pharmacol 23:2345-2347.

Bridges RG. 1956. The fate of labelled insecticide residues in food products. V. The nature and significance of ethylene dibromide residues in fumigated wheat. J Sci Food Agric 7:305-313.

Brimer PA, Tan EL, Hsie AW. 1981. Effect of metabolic activation on the mutagenicity and cytotoxicity of ethylene dibromide in the Chinese hamster ovary hypoxanthine guanine phosphoribosyl transferase [Abstract]. Environ Mutagen 3:317-318.

*Brimer PA, Tan EL, Hsie AW. 1982. Effect of metabolic activation on the mutagenicity and cytotoxicity of ethylene dibromide in the CHO/HGPRT system. Mutat Res 95:377-388.

*Broda C, Nachtomi E, Alumot (Olomucki) E. 1976. Differences in liver morphology between rats and chicks treated with ethylene dibromide. Gen Pharmac 7:345-348.

*Brodzinsky R, Singh HB. 1983. Volatile organic chemicals in the atmosphere: An assessment of available data. Research Triangle Park, NC: US Environmental Protection Agency, Office of Research and Development, Environmental Sciences Research Laboratory. EPA-600/3-83-027a; NTIS PB83-195503.

*Bronstein AC, Currance PL. 1988. Emergency care for hazardous materials exposure. St. Louis, MO: Mosby Company, 143-144.

*Buijs W, Van der Gen A, Mohn GR, et al. 1984. The direct mutagenic activity of alpha, omega-dihalogenoalkanes in Salmonella typhimurium. Strong correlations between chemical properties and mutagenic activity. Mutat Res 141:11-14.

*Buselmaier W, Roehrborn G, Propping P. 1972. [Mutagenicity investigations with pesticides in host-mediated assay and dominant lethal test in mice]. Biol Zbl 91:311-325.

*Buselmaier W, Roehrborn G, Propping P. 1976. Comparative investigations pn the mutagenicity of pesticides in mammalian test systems. Mutat Res 21:25-26.

*Cairns T, Siegmund EG, Doose GM, et al. 1984. Confirmation of ethylene dibromide in fruits and grains by mass spectrometry. Anal Chem 56:2138-2141.

Call F. 1957. The mechanism of sorption of ethylene dibromide on moist soils. J Sci Food Agric 8:630-639.

8. REFERENCES

Capewell S. 1987. Patients presenting with lung cancer in South East Scotland. Thorax 42:853-857.

Castro CE. 1988. Rebuttal on photohydrolysis of ethylene dibromide. J Agric Food Chem 36:873-874.

Castro CE, Belser NO. 1985. Photohydrolysis of ethylene dibromide. J Agric Food Chem 33:536-538.

*CESARS. 1989. Chemical evaluation search retrieval system. Chemical Information System.

Cheeseman KH, Albano EF, Tomasi A, et al. 1985. Biochemical studies on the metabolic activation of halogenated alkanes. Environ Health Perspect 64:85-101.

*Clark AI, McIntyre AE, Lester JN, et al. 1982. Evaluation of a Tenax GC sampling procedure for collection and analysis of vehicle-related aromatic and halogenated hydrocarbons in ambient air. J Chromatogr 252:147-157.

Clark AI, McIntyre AE, Perry R, et al. 1984. Monitoring and assessment of ambient atmospheric concentrations of aromatic and halogenated hydrocarbons at urban, rural, and motorway locations. Environmental Pollution (Series B) 7:141-158.

*Class T, Balls&miter K. 1986. Chemistry of organic traces in air. V. Determination of halogenated C, -C2-hydrocarbons in clean marine air and ambient continental air and rain by high resolution gas chromatography using different stationary phases. Fresenius' Z Anal Chem 325:107.

*Class TH, Ballschmitter K. 1988. Chemistry of organic traces in air. VIII. Sources and Distribution of bromo and bromochloromethanes in marine air and surface water of the Atlantic Ocean. J Atmos Chem 6:35-46.

Clive D. 1977. A linear relationship between tumorigenic potency in vivo and mutagenic potency at the heterozygous thymidine kinase (TK+/-) locus of L5178Y mouse lymphoma cell coupled with mammalian metabolism. Dev Toxicol Environ Sci 2:241-247.

*Clive D, Johnson KO, Spector JFS, et al. 1979. Validation and characterization of the L5178Y/TK+/- mouse lymphoma mutagen assay system. Mutat Res 59:61-108.

Clive D, McCuen R, Spector JFS, et al. 1983. Specific gene mutations in L5178Y cells in culture: A report of the US Environmental Protection Agency Gene-Tox Program. Mutat Res 115:225-251.

8. REFERENCES

*Glower M, McCarthy JP, Rains DM. 1985. Effect of cooking on levels of ethylene dibromide residues in rice. J Assoc Anal Chem 68:710-711.

Clower M Jr, McCarthy JP, Carson LJ. 1986. Comparison of methodology for determination of ethylene dibromide in grains and grain-based foods. J Assoc Off Anal Chem 69:87-90.

*CLPSD. 1988. CLP Statistical Database. Viar & Co., August 10, 1988.

Colacci A, Mazzullo M, Arfellini G, et al. 1985. In vitro microsome- and cytosol-mediated binding of 1,2-dichloroethane and 1,2-dibromoethane with DNA. Cell Biology and Toxicology 1:45-55.

*Colgan ST, Krull IS, Dorschel C, et al. 1986. Derivatization of ethylene dibromide with silica-supported silver picrate for improved high-performance liquid chromatographic detection. Anal Chem 58:2366-2372.

*Collins M, Barker NJ. 1983. Direct monitoring of ambient air for ethylene oxide and ethylene dibromide. Am Lab 15:72, 74-76, 78-81.

Cone MV, Ferguson M, Powers CD, et al. 1986. National body-burden database chemicals identified in human biological media 1984. Washington, DC: US Environmental Protection Agency, Office of Toxic Substances, Exposure Evaluation Division. EPA 560/5-84-003-Vol. 7-Pt.-l.

Cone MV, Ferguson M, Powers CD, et al. 1986. National body-burden database chemicals identified in human biological media 1984. Washington, DC: US Environmental Protection Agency, Office of Toxic Substances, Exposure Evaluation Division. EPA 560/5-84-003-Vol. 7-Pt.-2.

Cone MV, Ferguson M, Powers CD, et al. 1986. National body-burden database chemicals identified in human biological media 1984. Washington, DC: US Environmental Protection Agency, Office of Toxic Substances, Exposure Evaluation Division. EPA 560/5-84-003-Vol. 7-Pt.-3.

Cordle MK. 1988. USDA regulation of residues in meat and poultry products. J Anim Sci 66:413-433.

Costa AK, Trudell JR. 1988. Toxicity of 1,2-dibromoethane in primary hepatocyte monolayer cultures: Lack of dependence on oxygen concentration. Toxicol Appl Pharmacol 95:241-247.

*Crespi CL, Seixas GM, Turner TR, et al. 1985. Mutagenicity of 1,2-dichloroethane and 1,2-dibromoethane in two human lymphoblastoid cell lines. Mutat Res 142:133-140.

Crider WL, Slater RW Jr. 1969, Flame-luminescence intensification and quenching detector (FLIQD) in gas chromatography. Anal Chem 41:531-533.

8. REFERENCES

Cumming RB, Walton MF. 1973. Modification of the acute toxicity of mutagenic and carcinogenic chemicals in the mouse by prefeeding with antioxidants. Food Cosmet Toxicol 11:547-553.

Daft JL. 1983. Gas chromatographic determination of fumigant residues in stored grains, using isooctane partitioning and dual column packings. J Assoc Off Anal Chem 66:228-233.

Daft JL. 1987. Determining multifumigants in whole grains and legumes, milled and low-fat grain products, spices, citrus fruit, and beverages. J Assoc Off Anal Chem 70:734-739.

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

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

*Danni 0, Aragno M, Ugazio G. 1988. In vivo studies on halogen compound interactions. I. Effects of carbon tetrachloride plus 1,2-dibromoethane on liver necrosis. Res Commun Chem Pathol Pharmacol 61:377-390.

Decarlo VJ. 1979. Studies on brominated chemicals in the environment. Annuals of the New York Academy Sciences 320:678-681.

Deichmann WB, Gerarde HW, ed. 1969. Toxicology of drugs and chemicals. 4th ed. New York Academic Press, 257.

*DiRenzo AB, Gandolfi AJ, Sipes IG. 1982. Microsomal bioactivation and covalent binding of aliphatic halides to DNA. Toxicol Lett 11:243-252.

*Dobbins JG. 1987. Regulation and the use of "negative" results from human reproductive studies: The case of ethylene dibromide. Am J Ind Med 12:33-45.

*DOT. 1980. US Department of Transport. Code of Federal Regulations. 49 CFR 172.102.

*Dreisbach RH, Robertson WO. 1987. Handbook of Poisoning: Prevention, Diagnosis and Treatment. Norwalk, CT: Appleton & Lange, 148-165.

Dumas T. 1962. Determination of 1,2-dibromoethane in air and as residue in fruits. J Agric Food Chem 10:476-477.

*Dumas T, Bond EJ. 1982. Microdetermination of ethylene dibromide in air by gas chromatography. J Assoc Off Anal Chem 65:1379-1381.

8. REFERENCES

Dunkel VC, Zeiger E, Brusick D, et al. 1985. Reproducibility of microbial mutagenicity assays. II. Testing of carcinogen and noncarcinogens in Salmonella typhimurium and Escherichia coli. Environ Mutagen (Suppl 5) 7:1-248.

*Edwards K, Jackson H, Jones Ar. 1970. Studies with alkylating esters-II: A chemical interpretation through metabolic studies of the antifertility effects of ethylene dimethanesulphonate and ethylene dibromide. Biochem Pharmacol 19:1783-1789.

ElJack A, Hrudka F. 1978. Morphogenesis of the acrosomic defects in the ram induced experimentally by ethylene dibromide [Abstract]. Anat Histol Embryo1 7:350.

*ElJack AH, Hrudka F. 1979a. Pattern and dynamics of teratospermia induced in rams by parenteral treatment with ethylene dibromide. J Ultrastruct Res 67:124-134.

ElJack AH, Hrudka F. 1979b. Spermatogenesis upset by 1,2-dibromoethane. Food Cosmet Toxicol 18:743-744.

*Ellenhorn MJ, Barceloux DG. 1988. Medical Toxicology. New York, NY: Elsevier, 974-976.

*Ellingham Tj, Christensen A, Maddock MB. 1986. In vitro induction of sister chromatid exchanges and chromosomal aberrations in peripheral lymphocytes of the oyster toadfish and american eel. Environ Mutagen 8:555-569.

Elliott BM, Ashby J. 1980. Ethylene dibromide and disulfiram: Studies in vivo and in vitro on the mechanism of the obsenred synergistic carcinogenic response. Carcinogenesis 1:1049-1058.

*Entz RC, Hollifield HC. 1982. Headspace gas chromatographic analysis of foods for volatile halocarbons. J Agric Food Chem 30:84-88.
EPA. 1977. US Environmental Protection Agency. Federal Register 42:63134-63148.

*EPA 1978. US Environmental Protection Agency. Code of Federal Regulations. 40 CFR 116.4

*EPA 1981a. US Environmental Protection Agency. Code of Federal Regulations. 40 CFR 180.397

*EPA 1981b. US Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.32

8. REFERENCES

*EPA. 1983. Ethylene dibromide (EDB). Washington, DC: US Environmental Protection Agency, Office of Pesticide Programs. Position Dot #4

*EPA. 1984a. Health and environmental effects profile for 1,2-dibromoethane. Cincinnati, OH: US Environmental Protection Agency, Environmental Criteria and Assessment Office. EPA 600/X-84/173. NTIS no. PB88-131107

*EPA. 1984b. US Environmental Protection Agency. Federal Register 49:4452-4457.

EPA. 1984c. US Environmental Protection Agency. Federal Register 49:17147-17150.

*EPA. 1985. Drinking water criteria document for ethylene dibromide (EDB) (Draft). Cincinnati, OH: US Environmental Protection Agency, Environmental Criteria and Assessment Office. EPA-600/X-84/181. NTIS no. PB86-118247

*EPA. 1986. US Environmental Protection Agency. Code of Federal Regulations. 40 CFR 117.3

*EPA. 1987a. Health effects assessment for ethylene dibromide. Cincinnati, OH: US Environmental Protection Agency, Environ. Criter. Assess. Off. EPA 600/8-88/037. NTIS no. PB88-180245

*EPA. 1987b. Drinking water criteria document for ethylene dibromide (EDB). Final. Cincinnati, OH: US Environmental Protection Agency, Environmental Criteria and Assessment Office. NTIS no. PB89-192181.

*EPA. 1987c. National primary drinking water regulations; synthetic organic chemicals; monitoring for unregulated contaminants. Federal Register 52:25690-25717.

*EPA. 1987d. US Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.40

*EPA. 1987e. US Environmental Protection Agency. Code of Federal Regulations. 40 CFR 264, Appendix IX

*EPA. 1987f. US Environmental Protection Agency. Federal Register 52:21152

*EPA. 1988a. US Environmental Protection Agency. Federal Register 53:13382

*EPA. 1988b. US. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261, Appendix VIII

*EPA. 1989a. Interim methods for development of inhalation references doses. Washington, DC: US Environmental Protection Agency, Office of Health and Environmental Assessment. EPA 600/8-88/066F

8. REFERENCES

*EPA. 1989b. Recognition and Management of Pesticide Poisonings. Washington, DC: U.S. Environmental Protection Agency. EPA-540/9-88-001.

*EPA. 1989c. Final Draft of the Drinking Water Criteria Document for Ethylene. Dibromide. Washington, D.C.: US Environmental Protection Agency, Office of Drinking Water.

*Epstein SS, Arnold E, Andrea J, et al. 1972. Detection of chemical mutagens by the dominant lethal assay in the mouse. Toxicol Appl Pharmacol 23:288-325.

*Erickson MD, Pellizzari Ed. 1978. Analysis of organic air pollutants in the Kanawha Valley, WV, and the Shanandoah Valley, VA. Philadelphia, PA: US Environmental Protection Agency, Region III. EPA 903/9-78-007. NTIS no. PB-286141.

Erickson SJ, Hawkins CE. 1980. Effects of halogenated organic compounds on photosynthesis in estuarine phytoplankton. Bull Environ Contam Toxicol 24:910-915.

*Ewing BB, Chian ESK, Cook JC, et al. 1977. Monitoring to detect previously unrecognized pollutants in surface waters. Washington, DC: US Environmental Protection Agency, Office of Toxic Substances. EPA 560/6-77-015

Fabricant JD, Chalmers JH Jr. 1980. Evidence of the mutagenicity of ethylene dichloride and structurally related compounds. In: Ames B., Infante P., Reitz R, ed. Ethylene Dichloride: A Potential Health Risk. Banbury Report No. 5. Cold Spring Harbor Laboratory, 309-322.

Fahrig R. 1974. Comparative mutagenicity studies with pesticides. IARC Sci Pub 10:161-181.

*Fanini D, Legator MS, Adams PM. 1984. Effects of paternal ethylene dibromide exposure on Fl generation behavior in the rat. Mutat Res 139:133-138.

*FDA. 1975a. US Food and Drug Administration, Human Health Services. Code of Federal Regulations. 21 CFR 193.225

*FDA. 1975b. US Food and Drug Administration, Human Health Services. Code of Federal Regulations. 21 CFR 193.230

*Ferreri AM, Rocchi P, Capucci A, et al. 1983. Induction of diphtheria toxin-resistant mutatants in human cells by halogenated compounds. J Cancer Res Clin Oncol 105:111-112.

*Fishbein L. 1979. Potential halogenated industrial carcinogenic and mutagenic chemicals: III. Alkane halides, alkanols and ethers. Sci Total Environ 11:223-257.

8. REFERENCES

*Fishbein L. 1980. Production, uses, and environmental fate of ethylene dichloride and ethylene dibromide. In: Ames B., Infante P., Reitz R., ed. Ethylene Dichloride: A Potential Health Risk? Banbury Report 5. Cold Spring Harbor, NY: Cold Spring Laboratory 227-238.

Fisher-Fischbein J. 1987. New frontiers in male reproductive toxicology? Am J Ind Med 11:611-614.

Foster PL, Wilkinson WG, Miller JK, et al. 1988. An analysis of the mutagenicity of 1,2-dibromoethane to Escherichia coli: Influence of DNA repair activities and metabolic pathways. Mutat Res 194:171-183.

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

Geddes AD. 1982. Sister-chromatid exchange (SCE) induction in human lymphocytes in vitro by 1,2-dibromoethane with and without metabolic activation. Mutat Res 97:188-189.

*Ghanayem BI, Maronpot RR, Matthews HB. 1986. Association of chemicallyinduced forestomach cell proliferation and carcinogenesis. Cancer Lett 32:271-278.

*Girish GK, Kumar A. 1975. Studies on the residues in wheat and wheat products fumigated with ethylene dibromide. Bull Grain Technol 13:131-135.

Going J, Long S. 1975. Sampling and analysis of selected toxic substances. Task II--ethylene dibromide. Final Report. Washington, DC: US Environmental Protection Agency, Office of Toxic Substances. EPA 560/6-75-001.

Gold LS, Slone TH, Berstein L. 1989, Summary of carcinogenic potency and positivity for 492 rodent carcinogens in the carcinogenic potency database. Environ Health Perspect 79:259-272.

*Goyal R, Tardif R, Brodeur J. 1989. Influence of a cysteine prodrug, L-2-oxothiazolidine-4-carboxylic acid, on the urinary elimination of mercapturic acids of ethylene oxide, dibromoethane, and acrylonitrile: A dose-effect study. Can J Physiol Pharmacol 67:207-212.

Graf U, Wurgler FE, Katz AL, et al. 1984. Somatic mutation and recombination test in Drosophila melanogaster. Environ Mutagen 6:153-188.

Grant WM. 1986. Toxicology of the Eye. 3rd ed. Springfield, IL: Charles C. Thomas, 316.

Grimmer G, Schmidt W. 1986. Model experiments on the phytotoxicity of halogenated hydrocarbons. Angew Chem Int Ed Engl 25:808-809.

8. REFERENCES

Guengerich FP, Peterson LA, Cmarik JL, et al. 1987. Activation of dihaloalkanes by glutathione conjugation and formation of DNA adducts. Environ Health Perspect 76:15-18.

Gupta RC, Dave SK, Shah MP, et al. 1980. A monitoring study of pesticide applicators employed by pest control agencies. Prog Ecol 5/7:297-304.

*Haddad LM, Winchester JF. 1990. Clinical Management of Poisoning and Drug Overdose. Philadelphia, PA: W.B. Saunders Co., 1242-1243.

Hardin BD, Bond GP, Sikov MR, et al. 1981. Testing of selected workplace chemicals for teratogenic potential. Stand J Work Environ Health 7(Suppl 4):66-75.

Harkov R, Kebbekus B, Bozzelli JW, et al. 1983. Measurement of selected volatile organic compounds at three locations in New Jersey during the summer season. J Air Pollut Control Assoc 33:1177-1183.

Harkov R, Kebbekus B, Bozzelli JW, et al. 1984. Comparison of selected volatile organic compounds during the summer and winter at urban sites in New Jersey. Sci Tot Environ 38:259-274.

Hauser TR, Bromber SM. 1982. EPA's monitoring program at Love Canal 1980. Env Monit Assess 2:249-271.

*Heikes DL, Hopper ML. 1986. Purge and trap method for determination of fumigants in whole grains, milled grain products, and intermediate grain-based foods. J Assoc Off Anal Chem 69:990-998.

*Heinrichs WL. 1983. Reproductive hazards of the workplace and the home. Clin Obstet Gynecol 26:429-436.

*Hellman B, Brandt I. 1986. Effects of carcinogenic halogenated aliphatic hydrocarbons on [^{3}H]thymidine incorporation into various organs of the mouse: A comparison between 1,2-dibromoethane and 1,2-dichloroethane. Mutat Res 163:193-199.

*Hemminki K, Falck K, Vainio H. 1980. Comparison of alkylation rates and mutagenicity of directly acting industrial and laboratory chemicals. Arch Toxicol 46:277-285.

Herring CO, Adams JA, Wilson BA, et al. 1988. Dose-response studies using ethylene dibromide (EDB) in Hydra olizactis. Bull Envir Contam Toxicol 40:35-40.

*Hill DL, Tzu-Wen S, Johnson TP, et al. 1978. Macromolecular binding and metabolism of the carcinogen 1,2-dibromoethane. Cancer Res 38:2438-2442.

8. REFERENCES

Hirsch. 1988. Ethyl bromide and ethyl bromide narcosis. Therapeutische Monatshefte 2:556-557.

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

*Hsu LL, Adams PM, Fanini D, et al. 1985. Ethylene dibromide: Effects of paternal exposure on the neurotransmitter enzymes in the developing brain of F_1, progeny. Mutat Res 147:197-203.

Huff JE. 1983. 1,2-Dibromoethane (ethylene dibromide). Environ Health Perspect 47:359-363.

Huff JE, McConnell EE, Haseman JK, et al. 1988. Carcinogenesis studies results of 398 experiments on 104 chemicals from the U.S. National Toxicology Program. In: Maltoni C., Selikoff I.J., ed. Annals of the New York Academy of Sciences. Living in a Chemical World: Occupational and Environmental Significance of Industrial Carcinogens. Vol. 534, New York, NY: New York Academy of Sciences, l-30.

*Hughes TJ, Simmons DM, Monteith LG, et al. 1987. Vaporization technique to measure mutagenic activity of volatile organic chemicals in the Ames/ Salmonella assay. Environ Mutagen 9:421-441.

Hughes TJ, Simmons DM, Monteith LG, et al. 1987. Mutagenicity of 31 organic compounds in a modified preincubation Ames assay with Salmonella typhimurium strains TA100 and TA102. Environ Mutagen 9:49.

Hunder G, Schmid A. 1988. In vivo metabolism of 1,2-dibromoethane (DBE). Arch Pharmacol 337(suppl):R18.

IARC. 1977. Ethylene dibromide. IARC monographs on the evaluation of the carcinogenic risk of chemicals to man: Some fumigants, the herbicides 2,4-D and 2,4,5-T, chlorinated dibenzodioxins and miscellaneous industrial chemicals, Vol. 15. International Agency for Research on Cancer., 195-209.

* IARC. 1987. IARC monographs on the evaluation of carcinogenic risks to humans. Lyon, France: International Agency for Research on Cancer. supp 7.

Igwe OJ, Que Hee SS, Wagner WD. 1986. Interaction between 1,2-dichloroethane and disulfiram. I. Toxicologic effects. Fundam Appl Toxicol 6:733-746.

Infante PF, Tsongas TA. 1982. Mutagenic and oncogenic effects of chloromethanes, chloroethanes, and halogenated analogues of vinyl chloride. Environmental Science Research 25:301-327.

8. REFERENCES

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

*Inskeep PG, Koga N, Cmarid JL, et al. 1986. Covalent binding of 1,2-dihaloalkanes to DNA and stability of the major DNA adduct, S-[2-(N^7-guanyl)ethyl]glutathione. Cancer Res 46:2839-2844.

*IRIS. 1991. Integrated Risk Information System. Database. Washington, D.C.: US Environmental Protection Agency, Environmental Criteria and Assessment Office.

Ivanetich KM, Thumser AE, A. 1987. Reversible inhibition and activation of hepatic GSH S-transferases by ethylene dibromide. Pharmac Ther 33:85-88.

Ivanetich KM, Ziman MR, Mennie REM, et al. 1984. Inhibition of rat GSH S-transferases by ethylene dibromide. Res Commun Chem Pathol Pharmacol 45:233-242.

*Izutani K, Nakata A, Shinagawa H, et al. 1980. Forward mutation assay for screening carcinogens by alkaline phosphatase constitutive mutations in Escherichia coli K-12. Biken J 23:69-75.

*Jaber HM, Mabey WR, Liu AT, et al. 1984. Data acquisition for environmental transport and fate screening for compounds of interest to the Office of Emergency and Remedial Response. Washington, D.C.: US Environmental Protection Agency. EPA-600/6-84-011. NTIS no. PB84-245281, 147.

Jackson RJ, Goldman L. 1985. Pesticide residues in food. Pediatrics 76:473-474.

*Jakobson I, Wahlberg JE, Holmberg B, et al. 1982. Uptake via the blood and elimination of 10 organic solvents following epicutaneous exposure of anesthetized guinea pigs. Toxicol Appl Pharmacol 63:181-187.

Johns R. 1976. Air pollution assessment of ethylene dibromide. Gov Rep Announce Index 76:131.

Jones CJ, Hudson BC, McGugan PJ, et al. 1978. The leaching of some halogenated organic compounds from domestic waste. J Hazardous Materials 2:227-233.

Jurinak JJ. 1957. The effect of clay minerals and exchangeable cations on the adsorption of ethylene dibromide vapor. Soil Science Society Proceedings 21:599-602.

8. REFERENCES

Jury WA, Focht DD, Farmer WJ. 1987. Evaluation of pesticide groundwater pollution potential from standard indices of soil-chemical adsorption and biodegradation. J Environ Qua1 16:422-428.

*Kale PG, Baum JW. 1979. Sensitivity of Drosophila melanogaster to low concentrations of gaseous mutagens: II. Chronic exposures. Mutat Res 68:59-68.

*Kale PG, Baum JW. 1981. Sensitivity of Drosophila melanogaster to low concentrations of gaseous mutagens: III. Dose-rate effects. Environ Mutagen 3:65-70.

*Kale P, Baum JW. 1982. Genetic effects of ethylene dibromide in Drosophila melanogaster. Environ Sci Res 25:291-300.

*Kale PG, Baum JW. 1983. Sensitivity of Drosophila melanogaster to low concentrations of gaseous mutagens: IV. Mutations in embryonic spermatogonia. Mutat Res 113:135-143.

*Kerklaan PRM, Zoetemelk CEM, Mohn GR. 1985. Mutagenic activity of various chemicals in Salmonella strain TA100 and glutathione-deficient derivatives: On the role of glutathione in the detoxification or activation of mutagens inside bacterial cells. Biochem Pharmacol 34:2151-2156.

*Kim DH, Guengerich FP. 1989. Excretion of the mercapturic acid S-[2-N^7-guanyl)ethyl]-N-acetylcysteine in urine following administration of ethylene dibromide to rats. Can Res 49:5843-5847.

*Kirby KW, Tremmel H, Keiser JE. 1980. Determination and metabolism of ethylene dibromide in minipigs. Bull Environ Contam Toxicol 25:774-777.

*Kluwe WM, McNish R, Hook JB. 1981. Acute nephrotoxicities and hepatoctoxicities of 1,2-dibromo-3-chloropropane and 1,2-dibromoethane in male and female F344 rats. Toxicol Lett 8:317-321.

*Kluwe WM, Harrington FW, Cooper SE. 1982. Toxic effects of organohalide compounds on renal tubular cells in vivo and in vitro. J Pharmacol Exp Ther 220:597-603.

*Kochmann VM. 1928. [Possible industrial poisonings with ethylene dibromide]. Munchener Medizinische Wochenschrift 75:1334-1336. (German).

*Koga N, Inskeep PB, Harris TM, et al. 1986. S-[2-(N^7-Guanyl)-ethyl]glutathione, the major DNA adduct formed from 1,2-dibromoethane. Biochemistry 25:2192-2198.

8. REFERENCES

*Kowalski B, Brittebo EB, Brandt I. 1985a. Epithelial binding of 1,2-dibromoethane in the respiratory and upper alimentary tracts of mice and rats. Cancer Res 45:2616-2625.

*Kowalski B, Brittebo EB, d'Argy R, et al. 1986. Fetal epithelial binding of 1,2-dibromoethane in mice. Carcinogenesis 7:1709-1714

*Kowalski JD, Shikiya JM, Tsou G. 1985b. Ambient sampling and analysis to halogenated hydrocarbons and benzene. Proc APCA Annu Meet 2:85-17.1, Kowalski J, Tsou G, Daymon D, et al. 1987. A method to prepared ambient concentrations of gas standards for halogenated hydrocarbons. Proc APCA Annu Meet 4:87/62.10, 13.

Kraybill HF. 1978. Carcinogenesis induced by trace contaminants in potable water. Bull NY Acad Med 54:413-427.

*Krill RM, Sonzogni WC. 1986. Chemical monitoring of Wisconsin's groundwater. J Am Water Works Assoc 78:70-75.

*Krishna G, Xu J, Nath J, et al. 1985. In vivo cytogenetic studies on mice exposed to ethylene dibromide. Mutat Res 158:81-87.

*Kroneld R. 1985. Recovery and reproducibility in determination of volatile halocarbons in water and blood. Bull Environ Contam Toxicol 34:486-496. La1 M, Monig J, Asmus K-D. 1986. Free radical induced degradation of 1,2-dibromoethane. Generation of free Br atoms. Free Rad Res Comms 1:235-241.

La1 M, Schoneich C, Monig J, et al. 1988. Rate constants for the reaction of halogenated organic radicals. Int J Radiat Biol 54:773-785.

*LaRegina J, Bozzelli JW, Harkov R, et al. 1986. Volatile organic compounds at hazardous waste sites and a sanitary landfill in New Jersey: An up-to-date review of the present situation. Environ Prog 5:18-27.

*Lawrence FH, Michaels RA. 1984. Ethylene dibromide (EDB): A guide for decision makers. Envirologic Data. Portland, ME: Envirologic Data, Inc., 122.

*Ledda-Columbano GM, Columbano A, Coni P, et al. 1987a. Liver cell proliferation induced by the mitogen ethylene dibromide, unlike compensatory cell proliferation, does not achieve initiation of rat liver carcinogenesis by diethylnitrosoamine. Cancer Lett 36:247-252.

*Ledda-Columbano GM, Columbano A, Coni P, et al. 1987b. Cell proliferation in rat kidney induced by 1,2-dibromoethane. Toxicol Lett 37:85-90.

8. REFERENCES

Leenhouts HP, Sijsma MJ, Cebulska-Wasilewska A, et al. 1986. The combined effect of DBE and x-rays on the induction of somatic mutations in tradescantia. Int J Radiat Biol Relat Stud Phys Chem Med 49:109-119.

Lehning E, Polin D, Whalen T. 1986. Ethylene dibromide EDB residues in chicken tissues and eggs during and after feeding EDB-contaminated diet. Poult Sci 65(Suppl 1):77.

*Letz GA, Pond SM, Osterloh JD, et al. 1984. Two fatalities after acute occupational exposure to ethylene dibromide. J Am Med Assoc 252:2428-2431.

Lipsett MJ, Carmelli D, Winship-Ball A, et al. 1982. Quantitative cancer risk assessment for occupational exposure to ethylene dibromide. Govt Reports Announcements & Index (GRA&I). Cincinnati, OH: Robert A. Taft Labs. NTIS/PB83-184325

Loague KM, Green RE, Liu CC, K., et al. 1989. Simulation of organic chemical movement in Hawaii soils with PRZM: 1. Preliminary results for ethylene dibromide. Pat Sci 43:67-95.

Loper JC. 1980. Mutagenic effects of organic compounds in drinking water. Mutat Res 76:241-268.

Ma TH, Sparrow AH, Schairer LA, et al. 1978. Effect of 1,2-dibromoethane (DBE) on meiotic chromosomes of tradescantia. Mutat Res 58:251-258.

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

Mackison FW, Stricoff RS, Partridge LJ Jr. 1978. Occupational Health Guidelines for ethylene dibromide. NIOSH/OSHA-Occupational health guidelines for chemical hazards. DHHS (NIOSH) Publication, 3.

Maiorino RM, Gandolfi AJ, Brendel K, et al. 1982. Chromatographic resolution of amino acid adducts of aliphatic halides. Chem Biol Interact 38:175-188.

*Mailing HV. 1969. Ethylene dibromide: A potent pesticide with high mutagenic activity [Abstract]. Genetics 61:39.

Mandel HG. 1971. Pathways of Drug Biotransformation. Biochemical conjuctions. In: LaSu B.N., Mandel H.G., Way E.L., ed. Fundamentals of drug metabolism and drug disposition. 167-168.

Mann AM, Darby FJ. 1985. Effects of 1,2-dibromoethane on glutathione metabolism in rat liver and kidney. Biochem Pharmacol 34:2827-2830.

8. REFERENCES

Maronpot RR, Shimkin MB, Witschi HP, et al. 1986. Strain A mouse pulmonary tumor test results for chemical previously tested in the National Cancer Institute carcinogenicity tests. J Nat1 Cancer Inst 76:1101-1112.

*Marti LR, DeKanel J, Dougherty RC. 1984. Screening for organic contamination of groundwater: Ethylene dibromide in Georgia irrigation wells. Environ Sci Technol 18:973-974.

*McCall SN, Jurgens P, Ivanetich KM. 1983. Hepatic microsomal metabolism of the dichloroethanes. Biochem Pharmacol 32:207-213.

*McCann J, Choi E, Yamasaki E, et al. 1975. Detection of carcinogens as mutagens in the Salmonella/microsome test: Assay of 300 chemicals. Proc Nat1 Acad Sci 72:5135-5139.

McKenry MV. 1974. The behavior of pesticides containing 1,3-dichloropropene and 1,2-dibromoethane in soils. Diss Abstr Int 3433034B.

*McKone TE. 1987. Human exposure to volatile organic compounds in household tap water: The indoor inhalation pathway. Environ Sci Technol 21:1194-1201.

Melnikov NN. 1971. Chemistry of pesticides. In: Gunther F.A., Gunther J.D., ed. University of Moscow. New York, Heidelberg, Berlin: Springer-Verlag, 38-39.

*Meneghini R. 1974. Repair replication of opossum lymphocyte DNA: Effect of compounds that bind to DNA. Chem Biol Interact 8:113-126.

*Michael LC, Pellizzari ED, Wiseman RW. 1988. Development and evaluation of a procedure for determining volatile organics in water. Environ Sci Technol 22:565-570.

*Milks MM, Wilt SR, Ali I, et al. 1982. Dibromoethane effects on the induction of γ-glutamyl-transpeptidase positive foci in rat liver. Arch Toxicol 51:27-35.

Millar JD. 1984. Occupational safety and health administration proposed rule: Occupational exposure to ethylene dibromide. Gov Rep Announce Index. Cincinnati, OH: National Institute for Occupational Safety and Health. PB85-164713/GAR, 62.

Minor JL, Short RD, Seifter J, et al. 1978. Effects of ethylene dibromide inhaled by rats and mice during gestation. Toxicol Appl Pharmacol 45:347.

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

8. REFERENCES

*Moslen MT. 1984. Increased incidence of hepatic foci and nodules in rats given one or two doses of 1,2-dibromoethane. Toxicol Pathol 12:307-314.

Moye HA, Weintraub R. 1988. Comment on "Reaction products and rates of disappearance of simple bromoalkanes, 1,2-dibromopropane, and 1,2-dibromoethane in water." Environ Sci Technol 22:231.

*Nachtomi E. 1970. Metabolism of ethylene dibromide in the rat: The enzymic reaction with glutathione in vitro and in vivo. Biochem Pharmacol 19:2853-2860.

*Nachtomi E. 1981. Role of diethyldithiocarbamate in ethylene dibromide metabolism and covalent binding. Toxicol Appl Pharmacol 57:247-253.

*Nachtomi E, Alumot E. 1972. Comparison of ethylene dibromide and carbon tetrachloride toxicity in rats and chicks: Blood and liver levels; lipid peroxidation. Exp Mol Pathol 16:71-78.

*Nachtomi E, Sarma DS. 1977. Repair of rat liver DNA in vivo damaged by ethylene dibromide. Biochem Pharmacol 26:1941-1945.
Nachtomi E, Farber E. 1978. Ethylene dibromide as a mitogen for liver. Lab Invest 38:279-283.

*Nachtomi E, Alumot E, Bondi A. 1965. The metabolism of ethylene dibromide (EDB) and related compounds in the rat. Israel J Chem 3:119-120.

*Nachtomi E, Alumot E, Bondi A. 1966. The metabolism of ethylene dibromide in the rat. I. Identification of detoxification products in urine. Israel Journal of Chemistry 4:239-246.

Naik MN Jr. 1971. Fate of pesticides in soil. Pestic 5:24-26.

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

*NATICH. 1988. National Air Toxics Information Clearinghouse. Research Triangle Park, NC: US Environmental Protection Agency, Office of Air Quality Planning and Standards.

*NCI . 1978. Bioassay of 1,2-dibromoethane for possible carcinogenicity. Bethesda, MD: National Cancer Institute. NTIS no. PB 288428

Nguyen T, Ollis DF. 1984. Complete heterogeneously photocatalyzed transformation of l,l-and 1,2-dibromoethane to CO_2 and HBr. J Phys Chem 88:3386-3388.

8. REFERENCES

*NIOSH. 1977. Criteria for a recommended standard....occupational exposure to ethylene dibromide. US Department of Health, Education, and Welfare. Cincinnati, OH: US Department of Health and Human Services. DHEW (NIOSH) 77-221

NIOSH. 1978. NIOSH Current intelligence bulletin reprints; Bulletins 1 through 18. US National Institute for Occupational Safety and Health,. Cincinnati, OH: Surveillance Hazard Evaluations, and Field Studies, NIOSH. PB83-105080

NIOSH. 1979. NIOSH Current Intelligence Bulletin Reprints. Bulletins 19 through 30 for 1978. Bahlman L.J, ed. Rockville, MD: US Department of Health, Education, and Welfare, Office of Extramural Coordination and Special Projects. DHEW (NIOSH) Publication No. 79-146

*NIOSH. 1981. Current intelligence bulletin 37: Ethylene dibromide (EDB) (revised). Cincinnati, OH: National Institute for Occupational Safety and Health. DHHS/PUB/NIOSH-82-105; NTIS no. PB83-101774, 3, 16.

*NIOSH. 1985. NIOSH pocket Guide to chemicals hazards. Washington, D.C.: US Department of Health and Human Services, National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication No. 85-114

*NIOSH. 1987. NIOSH manual of analytical methods. 3rd ed., 2nd suppl. Cincinnati, OH: US Department of Health and Human Services. NIOSH Publication No. 87-117

Nirmalakhandan NN, Speece RE. 1988. QSAR model for predicting Henry's constant. Environ Sci Tech 22:1349-1357.

*Nitschke KD, Kociba RJ, Keyes DG, et al. 1981. A thirteen week repeated inhalation study of ethylene dibromide in rats. Fundam Appl Toxicol 1:437-442.

NRC. 1980. Ethylene dibromide(l,2-dibromoethane). Drinking Water and Health. Washington, DC: National Research Council, National Academy of Sciences, National Academy Press. 98-100.

*NTP. 1982. Carcinogenesis bioassay of 1,2-dibromoethane (CAS No. 106-93-4) in F344 rats and B6C3F1 mice (inhalation study). National Toxicology Program Technical Report Series. Research Triangle Park, NC: US National Toxicology Program. NTIS no. PB82-181710.

*NTP: 1989. Personal communication. Beth Anderson, National Toxicology Program, Research Triangle Park, NC.

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

8. REFERENCES

Ollis DF. 1985. Contaminant degradation in water: Heterogeneous photocatalysis degrades halogenated hydrocarbon contaminants. Environ Sci Technol 19:480-484.

*Olmstead EV. 1960. Pathological changes in ethylene dibromide poisoning. AMA Archives of Industrial Health 21:45-49, 525-529.

*OSHA. 1974. Occupational Safety and Health Administeration. Code of Federal Regulations. 29 CFR 1910.1000

*OSHA. 1980. Occupational Safety and Health Administeration. Code of Federal Regulations. 29 CFR 1910.20

OSHA. 1987. OSHA Standards. Occupational Safety and Health Administration, 29 CFR 1910.20, 85-92.

Otson R. 1987. Purgeble organics in Great Lakes raw and treated water. Intern J Environ Anal Chem 31:41-53.

*Ott MG, Scharnweber HC, Langner RR. 1980. Mortality experience of 161 employees exposed to ethylene dibromide in two production units. Br J Ind Med 37:163-168.

*Ozawa N, Guengerich FP. 1983. Evidence for formation of an S-[2(N^7-guanyl]ethyl)glutathione adduct in glutathione-mediated binding of the carcinogen 1,2-dibromoethane to DNA. Proc Nat1 Acad Sci USA 80:5266-5270.

*Page BD, Newsome WH, MacDonald SB. 1987. Determination of several halogenated fumigants in cereal products by steam distillation and capillary gas chromatography with electron capture detection. J Assoc Off Anal Chem 70:446-450.

*Page GW. 1981. Comparison of groundwater and surface water for patterns and levels of contamination by toxic substances. Environ Sci Technol 15:1475-1481.

*Parkin DM, Wahrendorf J. 1987. Directory of on-going research in cancer epidemiology. IARC Scientific Publication f/86, Lyon, France: World Health Organization, International Agency for Research on Cancer. p. 384.

*Parrish CF. 1983. Industrial solvents. In: Grayson M, ed. Kirk-Othmer encylopedia of chemical technology. Vol. 23. New York, NY: John Wiley and Sons, 381.

*Patterson DG, Hampton L, Lapeza Cr, et al. 1987. High-resolution gas chromatographic/high-resolution mass spectrometric analysis of human serum on a whole-weight and lipid basis for 2,3,7,8-tetrachlorodibenzo-p-dioxin. Anal Chem 59:2000-2005.

8. REFERENCES

*PDR. 1991. Physicians' Desk Reference. 45th ed. Oradell, NJ: Medical Economics Data, 2358-2359.

*Pellizzari ED, Zweidinger RA, Erickson MD. 1978. Environmental monitoring near industrial sites: Brominated chemicals. Part I. Research Triangle Park, NC: US Environmental Protection Agency, Office of Toxic Substances. EPA 560/6-78-002; Order No. PB-286 484, 325.

Pereira MA, Stoner GD. 1985. Comparison of rat liver foci assay and strain A mouse lung tumor assay to detect carcinogens: A review. Fundam Appl Toxicol 5:688-699.

*Perocco P, Prodi G. 1981. DNA damage by haloalkanes in human lymphocytes cultured in vitro. Cancer Lett 13:213-218.

*Peterson LA, Harris TM, Guengerich FP. 1988. Evidence for an episulfonium ion intermediate in the formation of S-(2-N^7-guanyl)ethyl)glutathione in DNA. J Am Chem Sot 110:3284-3291.

*Pflesser G. 1938. [Skin-damaging effect of ethylene dibromide, a constituent of the liquid from remote water gauges]. Archiv fuer Gewerbepathologie und Gewerbehygiene 8:591-600. (German).

*Pignatello JJ. 1986. Ethylene dibromide mineralization in soils under aerobic conditions. Appl Environ Microbial 51:588-592.

*Pignatello JJ. 1987. Microbial degradation of 1,2-dibromoethane in shallow aquifer materials. J Environ Qua1 16:307-312.

*Plotnick HB, Conner WL. 1976. Tissue distribution of 14C-labeled ethylene dibromide in the guinea pig. Pharmacology 13:251-258.

*Plotnick HB, Weigel WW, Richards DE, et al. 1979. The effect of dietary disulfiram upon the tissue distribution and excretion of ^{14}C-1,2-dibromoerhane in the rat. Res Commun Chem Pathol Pharmacol 26:535-543.

Pohl L, Gillette J. 1984-1985. Determination of toxic pathways of metabolism by deuterium substitution. Drug Metab Rev 15:1335-1351.

*Pranoto-Soetardhi LA, Rijk MAH, DeKruijf N, et al. 1986. Automatic headspace sampling for determination of ethylene dibromide residues in cereals. Int J Environ Anal Chem 25:151-159.

*Principe P, Dogliotti E, Bignami M, et al. 1981. Mutagenicity of chemicals of industrial and agricultural relevance in Salmonella, Streptomyces and Aspergillus. J Sci Food Agric 32:826-832.

8. REFERENCES

*Prodi G, Arfellini F, Colacci A, et al. 1986. Interaction of halocompounds with nucleic acids. Toxicol Pathol 14:444.

Quillardet P, De Bellecombe C, Hofnung M. 1985. The SOS chromotest, a calorimetric bacterial assay for genotoxins: Validation study with 83 compounds. Mutat Res 147:79-95.

Ramsey JC, Park CN, Ott MG, et al. 1979. Carcinogenic risk assessment: Ethylene dibromide. Toxicol Appl Pharmacol 47:411-414.

Rannug U. 1980. Genotoxic effects of 1,2-dibromoethane and 1,2-dichloroethane. Mutat Res 76:269-295.

Rannug U, Beije B. 1979. The mutagenic effect of 1,2-dichloroethane on Salmonella typhimurium. Part II. Activation by the isolated perfused rat liver. Chem-Biol Interact 24:265-286.

Rannug U, Sundvall A, Ramel C. 1978. The mutagenic effect of 1,2-dichloroethane on Salmonella typhimurium. Part I. Activation through conjugation with glutathion in vitro. Chem Biol Interact 20:1-16.

*Rasmussen RA, Khalil MAK. 1984. Gaseous bromine in the arctic and arctic haze. Geophys Res Lett 11:433-436.

Ratcliffe JM, Schrader SM, Turner TW, et al. 1986. The use of new field methods of semen analysis in the study of occupational hazards to reproduction: The example of ethylene dibromide. The Changing Nature of Work and Workforces, Proceedings of the Third Joint US-Finnish Science Symposium, Frankfort, Kentucky October 22-24,1986. Cincinnati, OH: National Institute for Occupational Safety and Health (NIOSH), 103-106.

*Ratcliffe JM, Schrader SM, Steenland K, et al. 1987. Semen quality in papaya workers with long term exposure to ethylene dibromide. Br J Ind Med 44:317-326.

*Rathbun RE, Tai DY. 1986. Gas-film coefficients for the volatilization of ethylene dibromide from water. Environ Sci Technol 20:949-952.

Rathbun RE, Tai DY. 1987. Volatilization of ethylene dibromide from water. Environ Sci Technol 21:248-252.

Reed NR, Narloch BA, Olsen HE, et al. 1987. Health risk assessment of 1,2-dibromoethane (EDB) in California drinking water. Gov Rep Announce Index. Davis, CA: California Public Health Foundation. Order No. PB88-169701, 168.

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

8. REFERENCES

Rinkus SJ, Legator MS. 1985. Fluorometric assay using high-pressure liquid chromatography for the microsomal metabolism of certain substituted aliphatics to 1 N-6 ethenoadenine-forming metabolites. Anal Biochem 150:379-393.

*Rogers RD, McFarlane JC. 1981. Sorption of carbon tetrachloride, ethylene dibromide, and trichloroethylene on soil and clay. Environ Monit Assess 1:155-162.

Rosenberg MJ, Feldblum PJ, Marshall EG. 1987. Occupational influences on reproduction: A review of recent literature. J Occup Med 29:584-591.

*Rosenkranz HS. 1977. Mutagenicity of halogenated alkanes and their derivatives. Environ Health Perspect 21:79-84.

Rowe VK, Hollingsworth RL, McCollister DD. 1954. Pesticide toxicity: Toxicity study of a grain fumigant (Dowfume EB-5). J Agric Food Chem 2:1318-1323.

*Rowe VK, Spencer HC, McCollister DD, et al. 1952. Toxicity of ethylene dibromide determined on experimental animals. Industrial Hygiene and Occupational Medicine 6:158-173.

*Rumsey DW, Tanita RK. 1978. An industry-wide industrial hygiene study of ethylene dibromide. Cincinnati, Ohio: National Institute for Occupational Safety and Health. DHEW/PUB/NIOSH-79/112; Order No. PB-297773, 65.

*Rush GF, Smith JH, Newton JF, et al. 1984. Chemically-induced nephrotoxicity: Role of metabolic activation. CRC Critical reviews in toxicology 13:99-160.

*Rydell, CD. 1990. Written communication (March 27) to Barry L. Johnson. Agency for Toxic Substances and Disease Registry, regarding North Dakota Air Contaminant Limits. North Dakota State Department of Health and Consolidated Laboratories, Bismarck, ND.

*Santodonato J, Bosch S, Meylan W, et al. 1985. Monograph on human exposure to chemicals in the workplace: Ethylene dibromide (EDB). Center for Chemical Hazard Assessment. Syracuse, New York: Syracuse Research Corporation. SRC TR 84-622, p. 2-2

*Saraswat PK, Kandara M, Dhurva AK, et al. 1986. Poisoning by ethylene dibromide-Six cases: A clinicopathological and' toxicological study. Indian J Med Sci 40:121-123.

*Sawhney BL, Pignatello JJ, Steinberg SM. 1988. Determination of 1,2-dibromoethane (EDB) in field soils: Implications for volatile organic compounds. J Environ Qua1 17:149-152.

8. REFERENCES

*Sax I, ed. 1989. Dangerous Properties of Industrial Materials. 6 ed. New York, NY: Van Nostrand Reinhold Company.

*Schlinke JC. 1969. Toxicologic effects of five soil nematocides in cattle and sheep. J Am Vet Med Assoc 155:1364-1366.

Schoenberg JB, Stemhagen A, Mason TJ, et al. 1987. Occupation and lung-cancer risk among New Jersey white males. J Nat1 Cancer Inst 79:13-21.

Schrader SM, Ratcliffe JM, Turner TW, et al. 1987. The use of new field methods of semen analysis in the study of occupational hazards to reproduction: The example of ethylene dibromide. J Occup Med 29:963-966.

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

Scott BR, Sparrow AJ, Schwemmer SS, et al. 1978. Plant metabolic activation of 1,2-dibromoethane (EDB) to a mutagen of greater potency. Mutat Res 49:203-212.

*Scott DR, Dunn WJ III, Emery SL. 1987. Classification and identification of hazardous organic compounds in ambient air by pattern recognition of mass spectral data. Environ Sci Technol 21:891-897.

*Scudamore KA. 1985. Gas chromatographic determination of chloroform, carbon tetrachloride, ethylene dibromide and trichloroethylene in cereal grains after distillation. IARC Sci Pub1 68:361-367.

Shah JJ, Heyerdahl EK. 1988. National ambient volatile organic compounds (VOCs) database update. US Environmental Protection Agency. Research Triangle Park, NC: US Environmental Protection Agency, Atmospheric Sciences Research Laboratory. EPA 6OO/S3-88-010, l-11.

*Shiau SY, Huff RA, Wells BC, et al. 1980. Mutagenicity and DNA-damaging activity for several pesticides tested with Bacillus subtilis mutants. Mutat Res 71:169-179.

Shih TW, Hill DL. 1981. Metabolic activation of 1,2-dibromoethane by glutathione transferase and by microsomal mixed function oxidase: Further evidence for formation of two reactive metabolites. Res Commun Chem Pathol Pharmacol 33:449-461.

Shikiya J, Tsou G, Kowalski J, et al. 1984. Ambient monitoring of selected halogenated hydrocarbons and benzene in the California South Coast air basin. Proc APCA Annu Meet 1:21.

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

8. REFERENCES

*Short RD, Minor JL, Winston HM, et al. 1978. Inhalation of ethylene dibromide during gestation by rats and mice. Toxicol Applied Pharmacol 46:173-182.

Short RD, Minor JL, Ferguson B, et al. 1976. The developmental toxicity of ethylene dibromide inhaled by rats and mice during organogenesis. US Environmental Protection Agency. Washington, D.C.: US Environmental Protection Agency. EPA-560/6-76-018 NTIS no. PB-256659, 11.

Short RD, Minor JL, Winston JM, et al. 1977. Task IV. Developmental toxicity of ethylene dibromide inhaled by rats and mice during organogenesis. Toxicity studies of selected chemicals. Washington, D.C. : US Environmental Protection Agency, Office of Toxic Substances. EPA-560/6-77-028. NTIS no. PB-273 267, l-15 117-127.

*Short RD, Winston JM, Hong CB, et al. 1979. Effects of ethylene dibromide on reproduction in male and female rats. Toxicol Appl Pharmacol 49:97-105.

*Simmonds PG. 1984. Analysis of trace halocarbons in natural waters by simplified purge and cytotrap method. J Chromatogr 289:117-127.

Singh G, Rigney CF, Gilbert WS. 1979. Ethylene dibromide and inorganic bromide residues in oranges after fumigation and storage. Aust J Exp Agric Anim Husb 19:377-381.

Singh G, Rippon LE, Gilbert WS, et al. 1976. Inorganic bromide residue in bananas, bell capsicums (sweet peppers), cherries and apples following fumigation with ethylene dibromide and methyl bromide. Aust J Exp Agric Anim Husb 16:780-784.

*Singh HB, Salas T.J, Shigeishi H. 1981. Atmospheric measurements of selected hazardous organic chemicals. Research Triangle Park, NC: US Environmental Protection Agency, Environmental Sciences Research. EPA 6OO/S3-81-032, l-7.

*Sipes IG, Gandolfi AJ. 1986b. Chapter 4: Biotransformation of toxicants. In: Klaassen CD, Admur MO, Doull J, ed. Casarett and Doull's Toxicology: The Basic Science of Poisons. 3rd ed. New York, NY: Macmillan Publishing Company, 64-98.

*Sipes IG, Wiersma DA, Armstrong DJ. 1986a. The role of glutathione in the toxicity of xenobiotic compounds: Metabolic activation of 1,2-dibromoethane by glutathione. Adv Exp Med Biol 197:457-467.

Sittig M, ed. 1979. 1,2-Dibromoethane. Hazardous and Toxic Effects of Industrial Chemicals. NJ: Noyes Data Corp, 163-166.

*Smith RF, Goldman L. 1983. Behavioral effects of prenatal exposure to ethylene dibromide. Neurobehav Toxicol Teratol 5:579-585.

8. REFERENCES

Snelson A, Butler R, Jarke F. 1978. Study of removal processes for halogenated air pollutants. Research Triangle Park, NC: US Environmental Protection Agency, Environmental Sciences Research Lab. EPA-600/3-78-058

Stampfer JF. 1982. Respirator canister evaluation for nine selected organic vapors. Am Ind Hyg Assoc J 43:319-328.

*State of Wisconsin Department of Natural Resources. 1988a. Wisconsin Administrative Code. Control of hazardous pollutants. Chapter NR 445. Register No. 393.

*State of Wisconsin Department of Natural Resources. 1988b. Wisconsin Administrative Code. Groundwater quality. Chapter NR 140. Register No. 394.

*State of Vermont Agency of Natural Resources. 1988. Chapter 12. Ground water protection rule and strategy. Vermont: State of Vermont, Agency of Natural Resources, Department of Environmental Conservation. 099/1100/GW2, 28.

*Steenland K, Carrano A, Clapp D, et al. 1985. Cytogenetic studies in humans after short-term exposure to ethylene dibromide. J Occup Med 27:729-732.

*Steenland K, Carrano A, Ratcliffe J, et al. 1986. A cytogenetic study of papaya workers exposed to ethylene dibromide. Mutat Res 170:151-160.

*Steinberg SM, Pignatello JJ, Sawhney BL. 1987. Persistence of 1,2-dibromoethane in soils: Entrapment in intraparticle micropores. Environ Sci Technol 21:1201-1208.

*Stenger VA. 1978. Bromine Compounds. In: 3rd, ed. Kirk-Othmer Encyclopedia of Chemical Technology. Vol. 4, New York, NY: Wiley-Interscience, 243-263.

*Stinson SF, Reznik G, Ward JM. 1981. Characteristics of proliferative lesions in the nasal cavities of mice following chronic inhalation of 1,2-dibromoethane. Cancer Lett 12:121-129.

*Stolzenberg SJ, Hine CH. 1980. Mutagenicity of 2- and 3-carbon halogenated compounds in the Salmonella/mammalian-microsome test. Environ Mutagen 2:59-66.

Stoner GD, Conran PB, Greisiger EA, et al. 1986. Comparison of two routes of chemical administration on the lung adenoma response in Strain A/J mice. Toxicol Appl Pharmacol 82:19-31.

*Storer RD, Conolly RB. 1983. Comparative in vivo genotoxicity and acute hepatotoxicity of three 1,2-dihaloethanes. Carcinogenesis 4:1491-1494.

8. REFERENCES

*Stott WT, McKenna MJ. 1984. The comparative absorption and excretion of chemical vapors by the upper, lower, and intact respiratory tract of rats. Fundam Appl Toxicol 4:594-602.

*Stutz DR, Janusz SJ. 1988. Hazardous Materials Injuries. Beltsville, MD: Bradford Communications Corp., 300-301.

Sullivan FM, Barlow SM. 1985. The relevance for man of animal data on reproductive toxicity of industrial chemicals. Prevention of Physical and Mental Congenital Defects, Part B: Epidemiology, Early Detection and Therapy, and Environmental Factors. Alan R. Liss, Inc.

Sundheimer DW, White R, Sipes IG, et al. 1981. Nucleic acid alkylation and production of DNA strand breaks by ethylene dibromide in isolated rat hepatocytes. Fed Proc Fed Am Sot Exp Biol 40:688.

*Sundheimer DW, White RD, Brendel K, et al. 1982. The bioactivation of 1,2-dibromoethane in rat hepatocytes: covalent binding to nucleic acids. Carcinogenesis 3:1129-1133.

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

*Tamura S, Sugiyama T, Minami Y, et al. 1986. Analysis of debromination of 1,2-dibromoethane by cytochrome P-450-linked hydroxylation systems as observed by bromide electrode. J Biochem 99:163-171.

*Tan EL, Hsie AW. 1981. Mutagenicity and cytotoxicity of haloethanes as studied in the CHO/HGPRT system. Mutat Res 90:183-191.

Tennant RW, Margolin BH, Shelby MD, et al. 1987. Prediction of chemical carcinogenicity in rodents from in vitro genetic toxicity assays. Science 236:933-941.

*Ter Haar G. 1980. An investigation of possible sterility and health effects from exposure to ethylene dibromide. In: Ames B, Infante P, and Reitz R, eds. Cold Spring Harbor, NY: Banbury report. Vol. 5. Cold Spring Harbor Laboratory, 167-188.

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

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

8. REFERENCES

Tokoro R, Osteryoung J. 1982. [Study of the reduction mechanism of 1,2-dibromothane by reverse pulse polarography]. An Sim Bras Eletroquim Eletroanal 1:307-316. (Spanish)

*Tomasi A, Albano E, Dianzani MU, et al. 1983. Metabolic activation of 1,2-dibromoethane to a free radical intermediate by rat liver microsomes and isolated hepatocytes. FEBS Lett 160:191-194.

*Tomasi A, Albano E, Bini A, etal. 1984. Free radical intermediates under hypoxic conditions in the metabolism of halogenated carcinogens. Toxicol Pathol 12:240-246.

*TRI87. 1989. Toxic Release Inventory Database. National Library of Medicine, Bethesda, MD.

Tsani-Bazaca E, McIntyre AE, Lester JN, et al. 1981. Concentrations and correlations of 1,2 dibromoethane 1,2-dichloroethane, benzene, and toluene in vehicle exhaust and ambient air. Environ Technol Lett 2:303-316.

*Tucker JD, Xu J, Stewart J, et al. 1984. Detection of sister-chromatid exchanges in human peripheral lymphocytes induced by ethylene dibromide vapor. Mutat Res 138:93-98.

*Turner D, Barry PSI. 1979. An epidemiological study of workers in plants manufacturing ethylene dibromide. Arh hig rada toksikol 30 (suppl):621-626.

*USDA. 1988. Department of Agriculture. Federal Register 53:16538-16539.
Vamvakas S, Elfarra AA, Dekant W, et al. 1988. Mutagenicity of amino-acid and glutathion S-conjugates in the ames test. Mutat Res 206:83-90.

*Van Bladeren PJ. 1983. Metabolic activation of xenobiotics: Ethylene dibromide and structural analogs. J Am Co11 Toxicol 2(3):73-83.

*Van Bladeren PJ, Breimer DD, Rotteveel-Smijs GMT, et al. 1980. The role of glutathione conjugation in the mutagenicity of 1,2-dibromoethane. Biochem Pharmacol 29:2975-2982.

*Van Bladeren PJ, Breimer DD, Van Huijgevoort JA, et al, 1981. The metabolic formation of N-acetyl-S-2-hydroxyethyl-L-cysteine from tetradeutero-1,2-dibromoethane. Relative importance of oxidation and glutathione conjugation in vivo. Biochem Pharmacol 30:2499-2502.

*Van Bladeren PJ, Breimer DD, Rotteveel-Smijs GM, et al. 1982. The activating role of glutathione in the mutagenicity of 1,2-dibromoethane. Adv Exp Med Biol 136:809-820.

8. REFERENCES

*Van Duuren BL, Goldschmidt BM, Loewengart G, et al. 1979. Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. J Nat1 Cancer Inst 63:1433-1439.

*Van Duuren BL, Seidman I, Melchionne S, et al. 1985. Carcinogenicity bioassays of bromoacetaldehyde and bromoethanol--potential metabolites of dibromoethane. Teratogenesis Carcinog Mutagen 5:393-403.

*Van Duuren BL, Melchionne S, Seidman I, et al. 1986. Chronic bioassays of chlorinated humic acids in B6C3Fl mice. Environ Health Perspect 69:109-117.

*Van Iersel AAJ, Vanholsteijn I, Blaauboer BJ. 1988. Effects of 1,2-dibromoethane on isolated hepatocytes: Functional alterations and induction of lipid-peroxidation. Xenobiotica 18:675-683.

*Van Rillaer WG, Beernaert H. 1985. Determination of residual ethylene dibromide in cereals by glass capillary gas chromatography. Z Lebensm Unters Forsch 180:284-288.

Venkateswarlu P, Manjubhashni AB, Kumari SR, et al. 1987. Volumetric behavior of an alcohol with 1,2-dibromoethane. Phys Chem Liq 16:225-230.

*View Database. 1989. Agency for Toxic Substances and Disease Registry (ATSDR), Office of External Affairs, Exposure and Disease Registry Branch, Atlanta, GA. September 25, 1989.

Vineis P, Thomas T, Hayes RB, et al. 1988. Proportion of lung cancers in males, due to occupation, in different areas of the USA. Int J Cancer 42:851-856.

Vogel EW, Zijlstra JA. 1987. Mechanistic and methodological aspects of chemically-induced somatic mutation and recombination in Drosophila melanogaster. Mutat Res 182:243-264.

*Vogel E, Chandler JL, R. 1974. Mutagenicity testing of cyclamate and some pesticides in Drosophila melanogaster. Experientia 30:621-623.

*Vogel TM, Reinhard M. 1986. Reaction products and rates of disappearances of simple bromoalkanes, 1,2-dibromopropane, and 1,2-dibromoethane in water. Environ Sci Technol 20:992-997.

Wallace LA, Pellizzari E, Hartwell T, et al. 1984. Personal exposure to volatile organic compounds. I. Direct measurements in breathing-zone air, drinking water, food, and exhaled breath. Environ Res 35:293-319.

8. REFERENCES

*Wallace L, Zweidinger R, Erickson M, Cooper S, et al. 1982. Monitoring individual exposure. Measurements of volatile organic compounds in breathing-zone air, drinking water, and exhaled breath. Environ Int 8:269-282.

Watanabe PG, Young JD, Schlachter MM, et al. 1978. Fate of inhaled ethylene dibromide in rats. Toxicol Appl Pharmacol 45:224.

*Weiss G, ed. 1986. Hazardous Substances Data Book. 2 ed. Park Ridge, NJ: Noyes Data Corporation,

White RD. 1982. Chemical induction of genetic injury: The bioactivation of 1,2-dibromoethane. Diss Abstr Int 43:696-698.

White RD, Sipes IG, Gandolfi AJ, et al. 1980. Determination of ethylene bromide induced DNA injury by alkaline elution. Fed Proc Fed Am Sot Exp Biol 39:1022.

*White RD, Gandolfi AJ, Bowden GT, et al. 1983. Deuterium isotope effect on the metabolism and toxicity of 1,2-dibromoethane. Toxicol Appl Pharmacol 69:170-178.

*Wiersma DA, Sipes IG. 1983. Metabolism of 1,2-dibromoethane by cytosol of rat liver, forestomach, and glandular stomach [Abstract]. Tox Lett 18 (Suppl 1):155.

*Williams GM, Laspia MF, Dunkel VC. 1982. Reliability of the hepatocyte primary culture/DNA repair test in testing of coded carcinogens and noncarcinogens. Mutat Res 97:359-370.

*Williams WM, Holden PW, Parsons DW, et al. 1988. Pesticides in Groundwater Data Base: 1988 Interim Report. Washington, D.C.: US Environmental Protection Agency. NTIS no. PB89 164230.

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

Winston JM, Hong CB, Lee CC, et al. 1979. Effect of 3- or 6-month inhalation of 1,2-dibromoethane in rats treated with disulfiram [Abstract]. Toxicol Appl Pharmacol 48:A25.

*Wang LC, Winston JM, Hong CB, et al. 1982. Carcinogenicity and toxicity of 1,2-dibromoethane in the rat. Toxicol Appl Pharmacol 63:155-165.

*Wang 0, Utidjian MD, Karten VS. 1979. Retrospective evaluation of reproductive performance of workers exposed to ethylene dibromide (EDB). J Occup Med 21:98-102.

8. REFERENCES

Working PK, Smith-Oliver T, Butterworth BE. 1985. Glutathione dependent induction of unscheduled DNA synthesis by ethylene dibromide in rat spermatocytes and hepatocytes. J Cell Bio. Vol. 101, 462A.

*Working PK, Smith-Oliver T, White RD, et al. 1986. Induction of DNA repair in rat spermatocytes and hepatocytes by 1,2-dibromoethane: The role of glutathione conjugation. Carcinogenesis 7:467-472.

*Wyrobek AJ. 1984. Identifying agents that damage human spermatogenesis: Abnormalities in sperm concentration and morphology. Monitoring human exposure to carcinogenic and mutagenic agents. Lyon, France: International Agency for Research on Cancer, Scientific Publication No. 59. 387-402.

Zijlstra JA, Vogel EW. 1988. The ratio of induced recessive lethals to ring-x loss has prognostic value in terms of functionally of chemical mutagenesis in Drosophila melanogaster. Mutat Res 201:27-38.

*Zoetemelk CEM, Mohn GR, Van DerGen A, et al. 1987. 1,2-Dibromo compounds: Their mutagenicity in Salmonella strains differing in glutathione content and their alkylating potential. Biochem Pharmacol 36:1829-1835.

Zweidinger R, Erickson M, Cooper S, et al. 1982. Direct measurement of volatile organic compounds in breathing-zone air, drinking water, breath, blood, and urine. Washington, DC: US Environmental Protection Agency. EPA 600/4-82-015.

9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

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 a 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.

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.

Cancer Effect Level (CEL) -- The lowest dose of 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.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

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.

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 insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

EPA Health Advisory -- An estimate of acceptable drinking water levels for a chemical substance 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.

9. GLOSSARY

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

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

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

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 which 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 is expected to have caused death in humans or animals.

Lethal Dose $_{(50)}$ (LD_{50}) -- The dose of a chemical which 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 dose 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.

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

Minimal Risk Level -- An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

9. GLOSSARY

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of 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.** Effects may be produced at this dose, but 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.

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

q_1* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The ql* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and pg/m^3 for air).

Reference Dose (RFD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 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 chemical. 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.

9. GLOSSARY

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

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) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD 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 LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in nontechnical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or substance release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the substance.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects by duration of exposure and endpoint and to illustrate graphically levels of exposure associated with those effects. All entries in these tables and figures represent studies that 'provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed- Adverse-Effect Levels (LOAELS) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate differences in response by species, Minimal Risk Levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. 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. The legends presented below demonstrate the application of these tables and figures. A representative example of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-l

(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. 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 Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes.

(2). Exposure Duration Three exposure periods: acute (14 days or less); intermediate (15 to 364 days); and chronic (365 days or more) are presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported.

(3). Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table.

(4). Key to Figure 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 18 has been used to define a NOAEL and a Less Serious LOAEL (also see the two "181:" data points in Figure 2-l).

(5). Species The test species, whether animal or human, are identified in this column.

(6). Exposure Frenquency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to [substance x] via inhalation for 13 weeks, 5 days per week, for 6 hours per day.

(7). System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated in this study.

(8). NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MKL of 0.005 ppm (see footnote “c”).

(9). LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the Lowest exposure level used in the study that caused a harmful 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 end point used to

quantify the adverse effect accompanies the LOAEL. The "Less Serious" respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.

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

(11). CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiological studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses which did not cause a measurable increase in cancer.

(12). Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "c" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See LSE Figure 2-1

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

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

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

(15). Levels of Exposure Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported 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). NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates a NOAEL for the test species (rat). The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17). CEL Key number 38r is one of three studies for which Cancer Effect Levels (CELs) were derived. The diamond symbol refers to a CEL for the test species (rat). The number 38 corresponds to the entry in the LSE table.

(18). Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1^*).

(19). Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

TABLE 2-1. Levels of Significant Exposure to [Chemical x] - Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
INTERMEDIATE EXPOSURE							
Systemic							
18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer							
38	Rat	18 mo 5d/wk 7hr/d				20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5d/wk 6hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79-103 wk 5d/wk 6hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

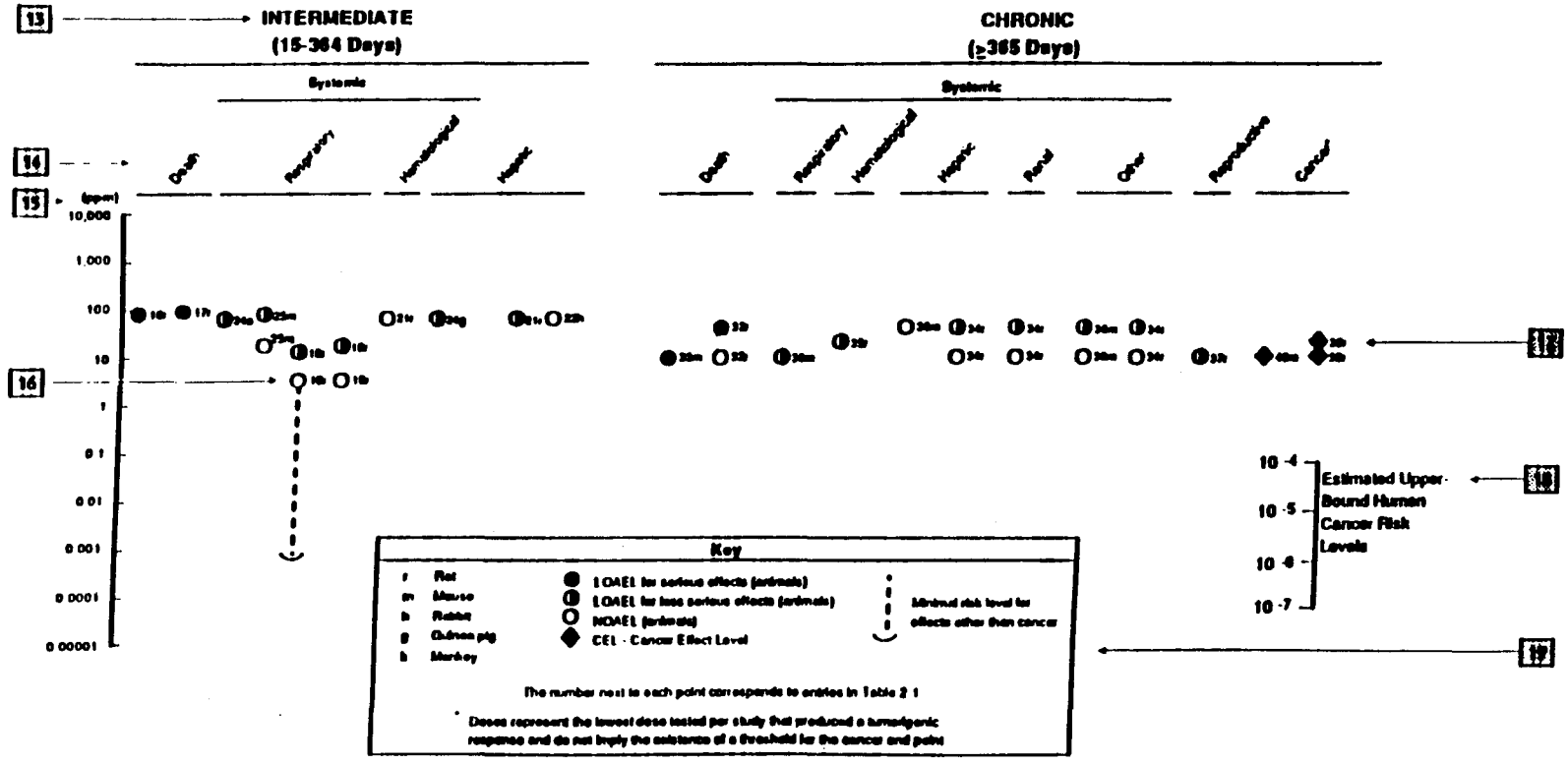


FIGURE 2-1. Levels of Significant Exposure to [Chemical X]-Inhalation

APPENDIX A

Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicological, epidemiological, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points 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?

The section discusses health effects by end point. Human data are presented first, then animal data. Both are organized by route of exposure (inhalation, oral, and dermal) and by duration (acute, intermediate, and chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. MRLs for noncancer end points if derived, and the end points from which they were derived are indicated and discussed in the appropriate section(s).

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Identification of Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute, -intermediate, - chronic). These MRLs are not meant to support regulatory action, but to aquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water, MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

APPENDIX A

MRL users should be familiar with the toxicological information on which the number is based. Section 2.4, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.6, "Interactions with Other Chemicals" and 2.7, "Populations that are Unusually Susceptible" 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 used by the Environmental Protection Agency (EPA) (Barnes and Dourson, 1988; EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the end point which, in its best judgement, represents the most sensitive humanhealth 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 effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continous exposure (i.e., 7 days/week). If the information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor (UF) of 10 is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of 10 each are used 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 adjusted 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 LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability
CFR	Act
CLP	Code of Federal Regulations
cm	Contract Laboratory Program
CNS	centimeter
DHEW	central nervous system
DHHS	Department of Health, Education, and Welfare
DOL	Department of Health and Human Services
ECG	Department of Labor
EEG	electrocardiogram
EPA	electroencephalogram
EKG	Environmental Protection Agency
FAO	see ECG
FEMA	Food and Agricultural Organization of the United
FIFRA	Nations
f_1	Federal Emergency Management Agency
fpw	Federal Insecticide, Fungicide, and Rodenticide Act
ft	first generation
FR	feet per minute
g	foot
GC	Federal Register
HPLC	gram
hr	gas chromatography
IDLH	high performance liquid chromatography
IARC	hour
ILO	Immediately Dangerous to Life and Health
In	International Agency for Research on Cancer
Kd	International Labor Organization
kg	inch
Koc	adsorption ratio
Kow	kilogram
L	octanol-soil partition coefficient
LC	octanol-water partition coefficient
LC_{Lo}	liter
LC_{50}	liquid chromatography
LD_{Lo}	lethal concentration low
LD_{50}	lethal concentration 50 percent kill
	lethal dose low
American	lethal dose 50 percent kill

APPENDIX B

LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeters
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	minimal risk level
MS	mass spectroscopy
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
nm	nanometer
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportional mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short-term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxic Release Inventory
TWA	time-weighted average
U.S.	United States

APPENDIX B

UF	uncertainty factor
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
δ	delta
γ	micron
μm	microgram
μg	

APPENDIX C

PEER REVIEW

A peer review panel was assembled for 1,2-dibromoethane. The panel consisted of the following members: Dr. Donald Hill, Southern Research Institute, Birmingham, Alabama; Dr. Herbert Rosenkrantz, Professor and Chairman of Department of Environmental Health Sciences, Case Western Reserve University, Cleveland, Ohio; and Dr. John Egle, Jr., Associate Professor of Pharmacology, Medical College of Virginia, Richmond, Virginia. These experts collectively have knowledge of 1,2-dibromoethane's physical and chemical properties,
toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(i)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

A second peer review panel was assembled to review mitigation of effects (Section 2.8) for 1,2-dibromoethane. The panel consisted of the following members: Dr. Brent Burton, Medical Director, Oregon Poison Center, Oregon Health Sciences University, Portland, Oregon; Dr. Alan Hall, Private Consulting and Medical Translating Services, Evergreen, Colorado; and Dr. Alan Woolf, Director of Clinical Pharmacology, and Toxicology, Massachusetts Poison Control System, The Children's Hospital, Boston, Massachusetts. All reviewers were selected under the same conditions mentioned above.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

☆U.S. Government Printing Offce: 1992- 636-281