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.

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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

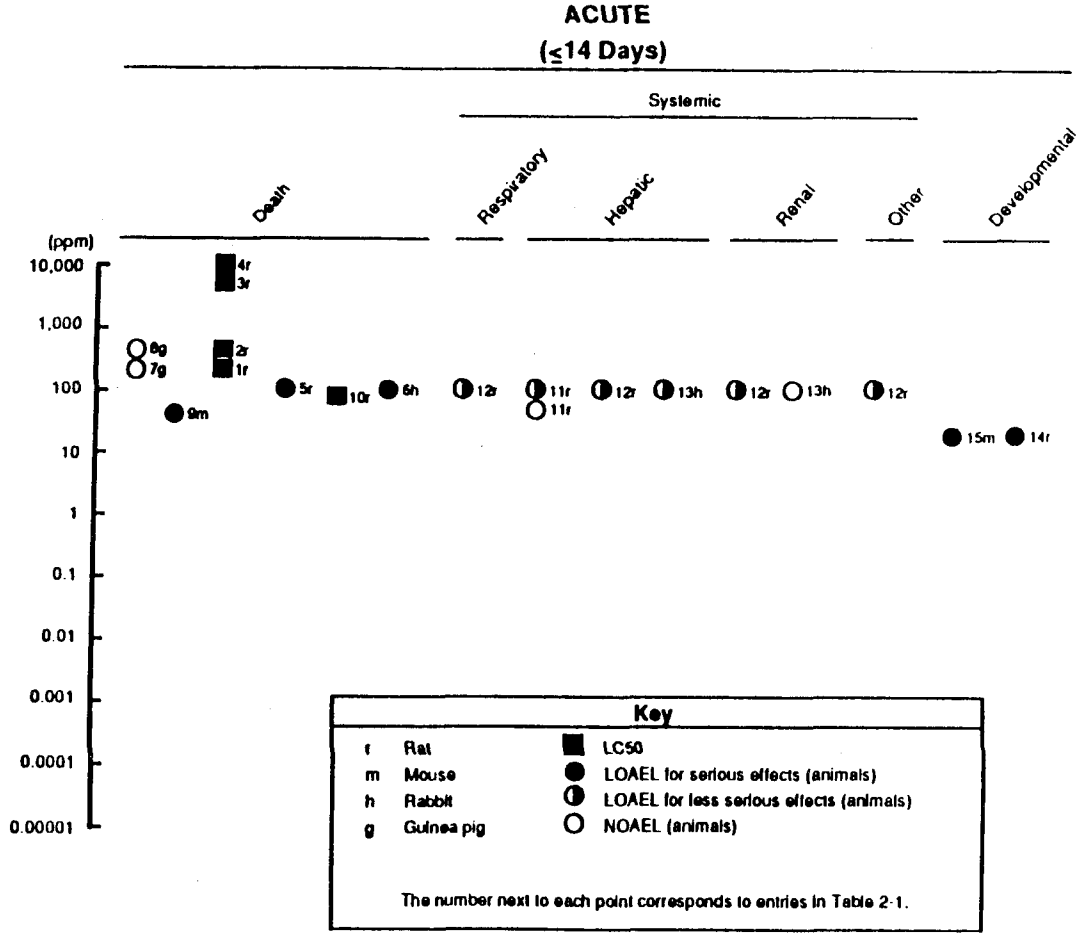


FIGURE 2-1 (Continued)

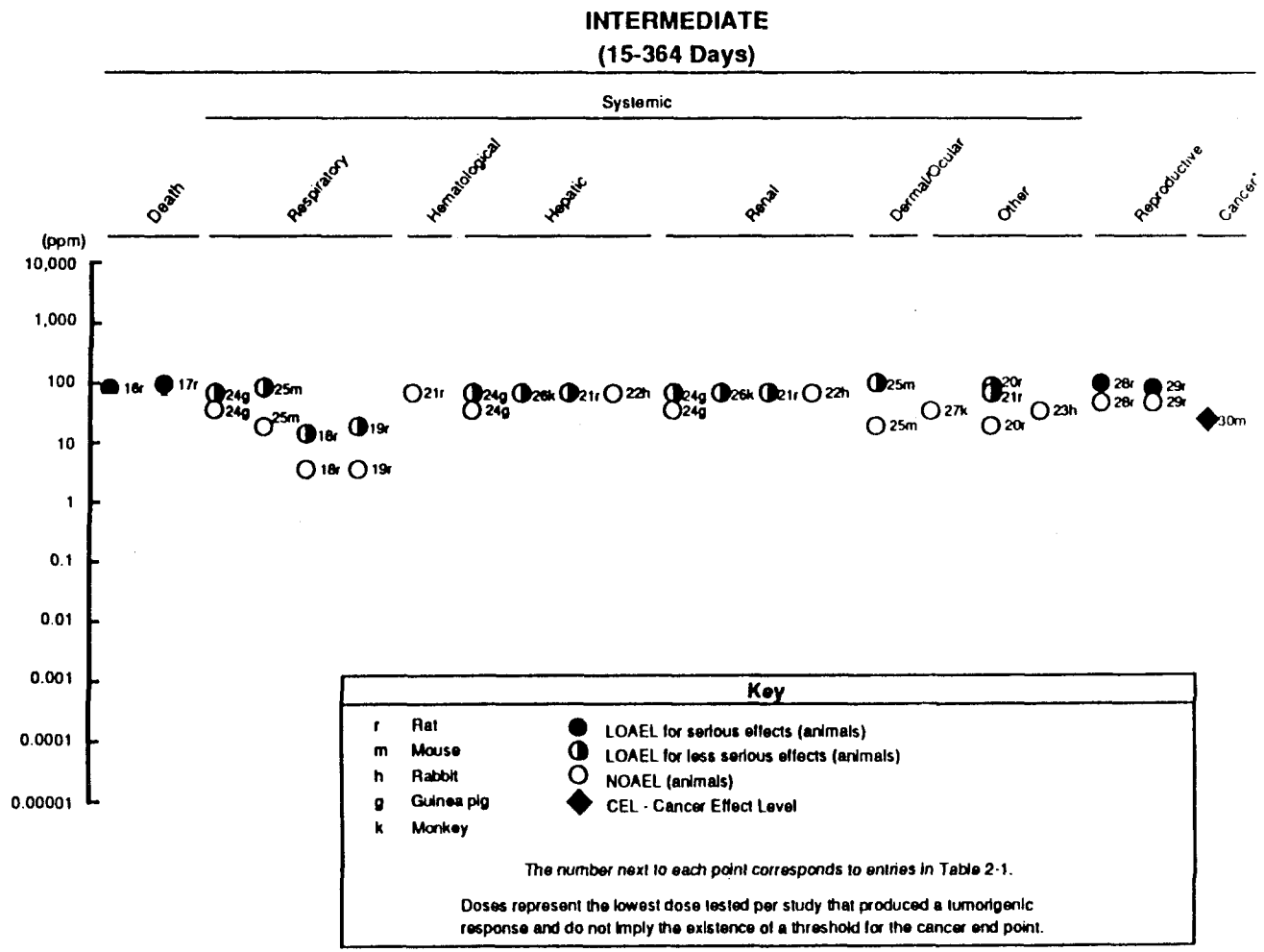
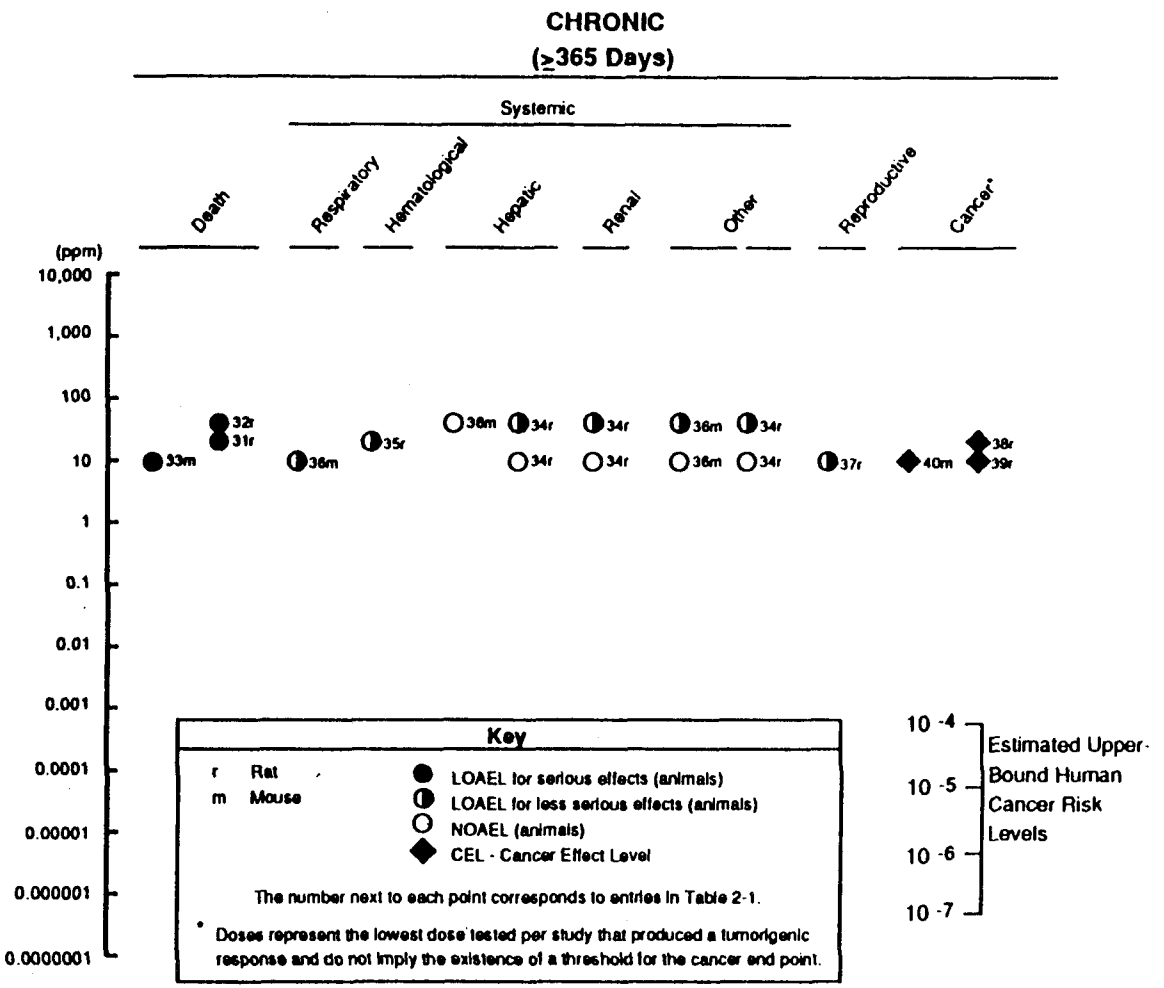


FIGURE 2-1 (Continued)



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.

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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.

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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.

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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

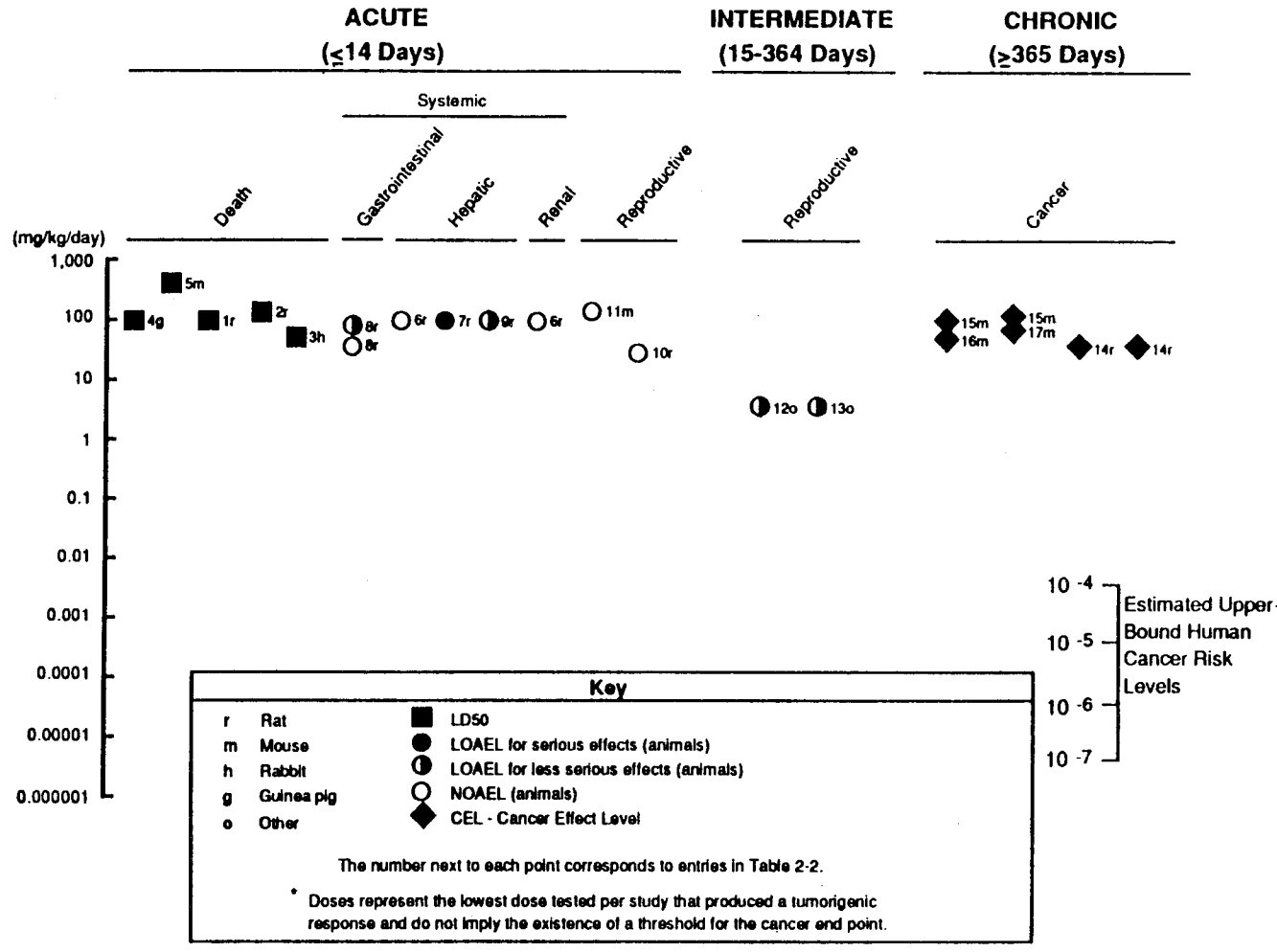
TABLE 2-2 (Continued)

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

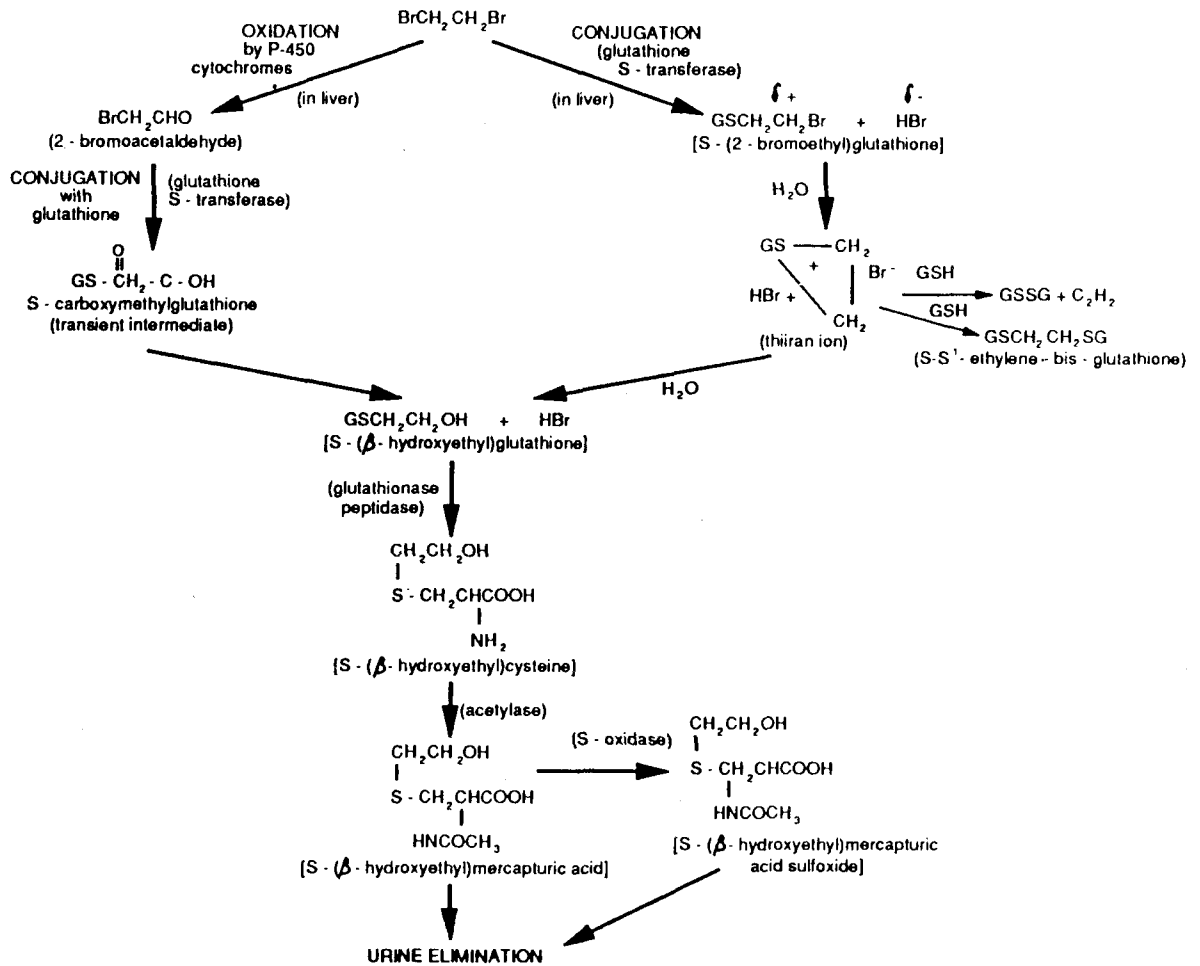
[a]Source: Edwards et al. 1970
[b]Intraperitoneal injection of 40 mg/kg body weight

TABLE 2-6. Percentage of Administered ^{14}C in Selected Tissues and Body Fluids of Male Guinea Pigs at Various Time Intervals Follbwing 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.

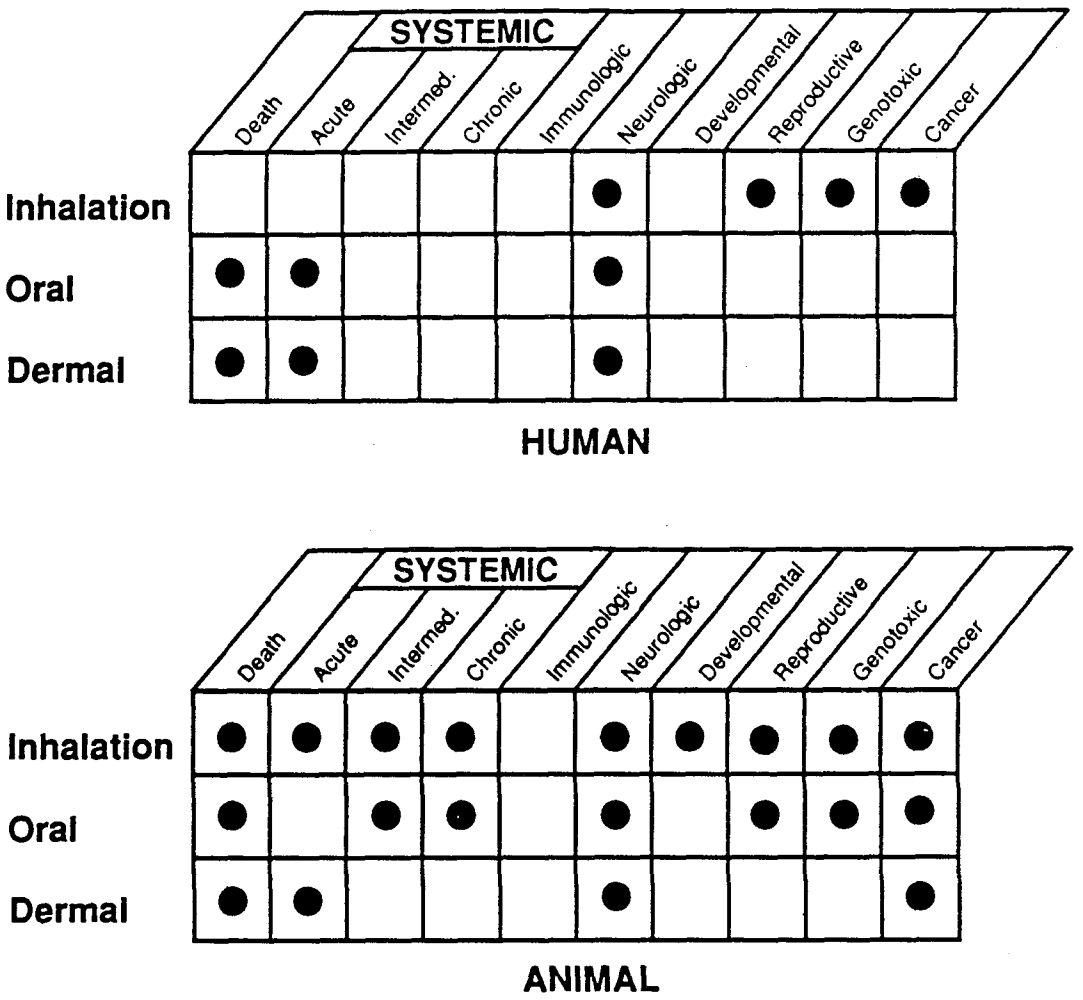
2.9.1 Existing Information on Health Effects of 1,2-Dibromoethane

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.