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-dibromo-3-chloropropane 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-dibromo-3-chloropropane 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.

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 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

Occupational exposure to 1,2-dibromo-3-chloropropane probably involves both inhalation and dermal exposure. Thus, many of the effects reported in occupational studies in this section may be due, in part, to dermal exposure to l-,2-dibromo-3-chloropropane.

2.2.1.1 Death

No studies were located regarding death in humans after inhalation exposure to 1,2-dibromo-3-chloropropane.

Inhalation LC_{50} values in rats were 103 ppm after 8 hours of exposure, 154 ppm after 4 hours, 232 ppm after 2 hours, and 368 ppm after 1 hour of exposure (Torkelson et al. 1961). No increase in mortality above control levels was observed in Sprague-Dawley rats observed for up to 12 months after 2 weeks of continuous exposure to concentrations up to 10 ppm 1,2-dibromo-3-chloropropane (Saegusa et al. 1982).

Mortality data for intermittent intermediate-duration exposures in animals are conflicting. Increased mortality occurred in Fischer-344 rats exposed to 25 ppm 1,2-dibromo-3-chloropropane for 13 weeks (NTP 1982) and in an unspecified strain of rats exposed to 10 ppm for 10 weeks (Torkelson et al. 1961). The cause of death was not reported; however, renal, respiratory, and/or splenic effects observed under histopathological examination might have contributed to increased mortality. In contrast, no deaths were observed in Sprague-Dawley rats exposed to concentrations up to 10 ppm for 14 weeks (Rao et al. 1983). Increased mortality from pneumonia was observed among male New Zealand rabbits exposed to 10 ppm 1,2-dibromo-3-chloropropane for 8 weeks (Rao et al. 1982), but no deaths were reported in an unspecified strain of rabbits exposed to 12 ppm for 13 weeks (Torkelson et al. 1961). The above-mentioned discrepancies may be due to differences in strain sensitivity to the chemical or to differences in the general health of animals from different animal colonies. Increased mortality was also observed in $B6C3F_1$ mice exposed to 25 ppm for 13 weeks (NTP 1982). No deaths were reported in guinea pigs exposed to 12 ppm 1,2-dibromo-3-chloropropane for 13 weeks (Torkelson et al. 1961).

2. HEALTH EFFECTS

During a chronic-duration exposure experiment, a significant increase in mortality from cancer occurred in both sexes of Fischer 344 rats and in female B6C3Fl mice intermittently exposed to 3 ppm 1,2-dibromo-3-chloropropane. The surviving animals were killed after 76-84 weeks of exposure. However, it should be noted that the survival of male mice was low in all groups, including the control group (NTP 1982).

The LC_{50} values, the highest NOAEL values, and all reliable LOAEL values in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.2 Systemic Effects

The systemic effects of 1,2-dibromo-3-chloropropane following inhalation exposure are discussed below. No studies were located regarding musculoskeletal effects of 1,2-dibromo-3-chloropropane in humans or animals after inhalation exposure. The highest NOAEL values and all reliable LOAEL values for each effect in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Respiratory Effects. No studies were located regarding respiratory effects in humans after inhalation exposure to 1,2-dibromo-3-chloropropane.

Studies in animals demonstrate that 1,2-dibromo-3-chloropropane affects the respiratory system. Pulmonary irritation was reported in rats after an acute (1-7 hours) exposure to 60 ppm or more 1,2-dibromo-3-chloropropane (Torkelson et al. 1961). Bronchial and bronchiolar epithelial cytomegalosis and focal necrosis were observed in rats continuously exposed to 10 ppm for 2 weeks (Saegusa et al. 1982). Pathological changes (emphysema and bronchopneumonia) were seen in lungs of rats exposed to 10 ppm or more 1,2-dibromo-3-chloropropane for 7 hours/day, 5 days/week, for 1o-12 weeks (Torkelson et al. 1961). Cytomegaly and hyperplasia were found in the nasal cavity in rats exposed to 1 ppm and mice exposed to 5 ppm 1,2-dibromo-3-chloropropane for 6 hours/day, 5 days/week, for 13 weeks (NTP 1982; Reznik et al. 1980a). In addition, rats and mice exposed to 25 ppm had more severe respiratory effects, including inflammatory and proliferative changes in the nasal cavity, necrosis of the trachea, and necrosis or metaplasia of the bronchial epithelium. Nonneoplastic changes (hyperplasia) were found in the respiratory system of rats and mice after intermittent chronic-duration exposure to 0.6 ppm or 3 ppm. In addition, neoplasms of the respiratory tract also occurred in both species (NTP 1982) (Section 2.2.1.8).

Cardiovascular Effects. No conclusive evidence was located to indicate that inhalation exposure to 1,2-dibromo-3-chloropropane causes cardiovascular effects in humans. Although higher mortality from arteriosclerotic heart disease was observed in workers in the production of trimethylene chlorobromide where 1,2-dibromo-3-chloropropane was a potential trace

TABLE 2-1. Levels of Significant Exposure to 1,2-Dibromo-3-chloropropane - Inhalation

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	Rat	8 hr				103 (LC50)	Torkelson et al. 1961
Systemic							
2	Rat	1 d 1-7hr/d	Resp Renal Derm/oc		60 (irritation) 50 (kidney scarring) 60 (eye irritation)		Torkelson et al. 1961
3	Rat	2 wk 7d/wk 24hr/d	Resp		10 (bronchial epithelial necrosis)		Saegusa et al. 1982
			Cardio Hemato	10		10 (spleen atrophy)	
			Renal		10 (necrotic cells in proximal tubules)		
Immunological							
4	Rat	2 wk 7d/wk 24hr/d				10 (spleen atrophy)	Saegusa et al. 1982
Neurological							
5	Rat	1 d 1-7hr/d			60 (apathy; ataxia)		Torkelson et al. 1961
Reproductive							
6	Rat	2 wk 7d/wk 24hr/d		1	3 (slight decrease in germ cells, slight atrophy of seminiferous tubules)	8 (necrosis of germ cells, severe atrophy of seminiferous tubules)	Saegusa et al. 1982

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
INTERMEDIATE EXPOSURE							
Death							
7	Rat	10 wk 5d/wk 7hr/d		5		10 (2/15 died)	Torkelson et al. 1961
8	Rat	13 wk 5d/wk 6hr/d		5		25 (5/10 died)	NTP 1982
9	Rabbit	8-14 wk 5d/wk 6hr/d		1.0		10 (4/10 died)	Rao et al. 1982
10	Mouse	13 wk 5d/wk 6hr/d		5		25 (4/20 died)	NTP 1982
Systemic							
11	Rat	14 wk 5d/wk 6hr/d	Cardio Hemato Hepatic Renal Other	10 10 10 10 0.1	1.0 (adrenal cortical necrosis)		Rao et al. 1983
12	Rat	13 wk 5d/wk 6hr/d	Hemato	5	25 (hypocellularity of bone marrow)		NTP 1982
13	Rat	10-12 wk 5d/wk 7hr/d	Resp Hemato Hepatic Renal		12 (increased neutrophiles) 12 (sinusoidal dilation) 12 (cloudy swelling of epithelium)	12 (pneumonia; lung infection)	Torkelson et al. 1961

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
14	Rat	13 wk 5d/wk 6hr/d	Resp		1 (hyperplasia, cytomegaly, squamous metaplasia, loss of cilia in nasal cavity)	25 (metaplasia, necrosis, and hyperplasia in nasal cavity, trachea and bronchial epithelium)	NTP 1982; Reznik et al. 1980a
			Cardio	25			
			Gastro	25			
			Hemato	5	25 (hypocellularity of bone marrow)		
			Hepatic		1 (hydropic changes of hepatocytes)	25 (focal necrosis of liver)	
			Renal			1 (nephrosis)	
			Other	5	25 (adrenal necrosis, body weight loss, body weight gain decreased 100-114%, hair loss)		
15	Rat	10 wk 5d/wk 7hr/d	Resp	5		10 (emphysema)	Torkelson et al. 1961
			Gastro	5	10 (lesions in intestinal mucosa)		
			Hemato	10	20 (depressed white blood count)		
			Hepatic	5	10 (unspecified lesions)		
			Renal	5	10 (unspecified lesions)		
			Derm/oc	10	20 (corneal clouding)		
			Other		5 (body weight gain decreased 24%)		
16	Rabbit	10-12 wk 5d/wk 7hr/d	Other		12 (decreased body weight)		Torkelson et al. 1961

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
17	Rabbit	8-14 wk 53/wk 6hr/d	Cardio	10			Rao et al. 1982
			Hemato	10			
			Hepatic	10			
			Renal	10			
18	Gn Pig	10-12 wk 5d/wk 7hr/d	Hepatic		12 (fatty degeneration)		Torkelson et al. 1961
19	Mouse	13 wk 5d/wk 6hr/d	Resp		1 (cytomegaly, hyper plasia, squamous metaplasia, loss cilia in nasal cavity, hypertrop of occasional cel in bronchiolar ep thelium)	25 (necrosis, proliferation in nasal cavity and bronchiolar epithelium)	NTP 1982; Reznik et al. 1980
			Cardio	25			
			Gastro	25			
			Hepatic	5	25 (hydropic hepatocytes)		
			Renal			25 (nephrosis)	
			Other		1 (body weight gain decreased)		
20	Monkey	10-12 wk 5d/wk 7hr/d	Resp			12 (infection)	Torkelson et al. 1961
			Hemato			12 (severe anemia)	
Immunological							
21	Rat	10-12 wk 5d/wk 7hr/d				12 (lung infection)	Torkelson et al. 1961

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
22	Rabbit	8-14 wk 5d/wk 7hr/d		1.0		10 (pneumonia)	Rao et al. 1982
23	Monkey	10-12 wk 5d/wk 7hr/d				12 (severe infection)	Torkelson et al. 1961
Neurological							
24	Rat	14 wk 5d/wk 6hr/d		1	10 (focal mineralization in the cerebrum)		Rao et al. 1983
25	Rat	13 wk 5d/wk 6hr/d		5		25 (meningo-encephalitis)	NTP 1982
26	Rabbit	8-14 wk 53/wk 6hr/d		10			Rao et al. 1982
Reproductive							
27	Rat	13 wk 5d/wk 6hr/d		5		25 (testicular atrophy)	NTP 1982
28	Rat	10 wk 5d/wk 7hr/d			5 (epithelial changes in testes)	10 (testicular atrophy)	Torkelson et al. 1961
29	Rabbit	8-14 wk 5d/wk 6hr/d		0.1[b]	1.0 (sperm abnormalities; increased serum FSH; reversible decreased spermatogenesis)		Rao et al. 1982
						10 (infertility)	

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
CHRONIC EXPOSURE							
Death							
30	Rat	84-103wk 5d/wk 6hr/d		0.6		3.0 (88/99 died by week 84)	NTP 1982
31	Mouse	76-103wk 5d/wk 6hr/d		0.6		3.0 (43/50 females died by week 74)	NTP 1982
Systemic							
32	Rat	84-103wk 5d/wk 6hr/d	Resp		0.6 (epithelial proliferation in nas cavity)		NTP 1982
			Cardio	3.0			
			Gastro	0.6	3.0 (hyperkeratosis, acanthosis in stomach)		
			Hemato	3.0			
			Hepatic	3.0			
			Renal		0.6 (tubular cell hyperplasia)	3.0 (toxic tubular nephropathy)	
			Derm/oc	3.0			
			Other	0.6	3.0 (weight gain decreased up to 12%-22%)		

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
33	Mouse	76-103wk 5d/wk 6hr/d	Resp		0.6 (hyperplasia in nasal cavity, bronchioles, and alveolar epithelium)		NTP 1982
			Cardio	3.0			
			Gastro		0.6 (hyperplasia in stomach and acanthosis)		
			Hemato	.6		3.0 (splenic atrophy)	
			Hepatic	3.0			
			Renal		0.6 (hyperplasia in urinary bladder, inflammation in kidney)	3.0 (nephrosis)	
			Derm/oc	3.0			
			Other	0.6	3.0 (body weight gain decreased 17%-28%		
Immunological							
34	Mouse	76-103wk 5d/wk 6hr/d		0.6		3.0 (splenic atrophy)	NTP 1982
Neurological							
35	Rat	84-103wk 5d/wk 6hr/d	Other	0.6		3.0 (cerebral necrosis)	NTP 1982
36	Mouse	76-103wk 5d/wk 6h/d		3.0			NTP 1982

TABLE 2-1 (Continued)

Key to figure[a]	Species	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
Cancer							
37	Rat	84-103wk 5d/wk 6hr/d				0.6 (CEL, nasal cavity adenocarcinomas)	NTP 1982
38	Mouse	76-103wk 5d/wk 6hr/d				0.6 (CEL, papillary carcinomas of bronchiole)	NTP 1982

[a]The number corresponds to entries in Figure 2-1.
[b]Used to derive an intermediate inhalation MRL of 0.0002 ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Derm/oc = dermal/ocular; Gastro = gastrointestinal; Gn pig = guinea pig; Hemato = hematological; hr = hour(s); LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

FIGURE 2-1. Levels of Significant Exposure to 1,2-Dibromo-3-chloropropane - Inhalation

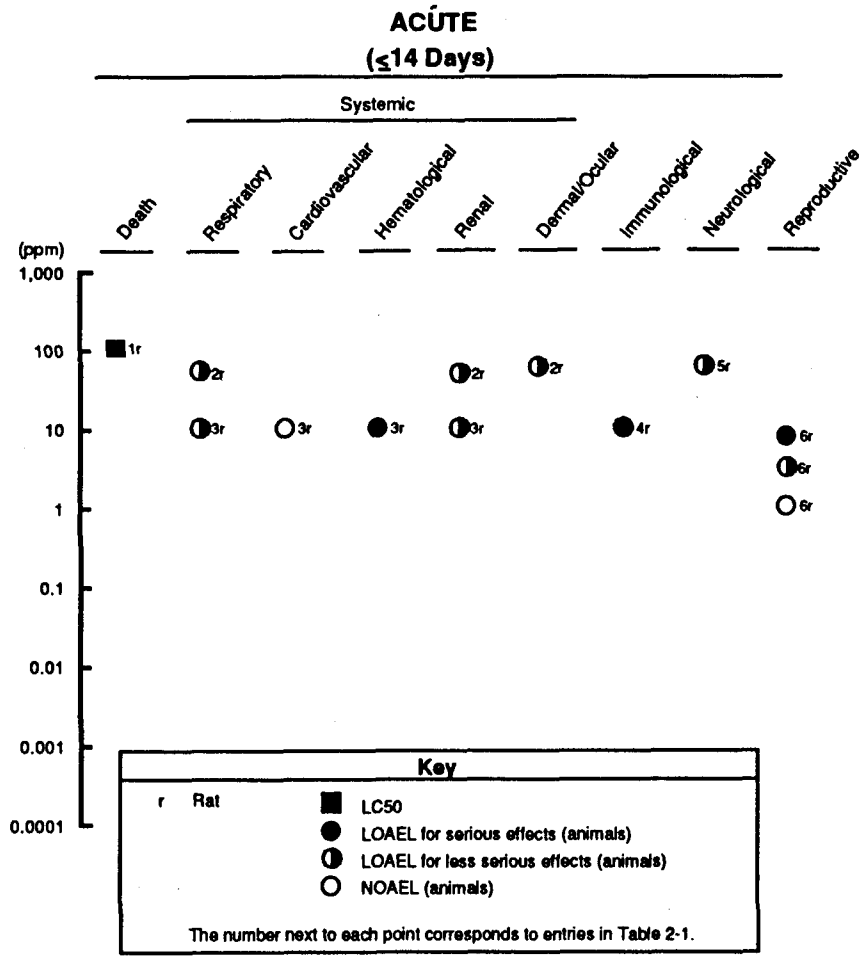


FIGURE 2-1 (Continued)

INTERMEDIATE
(15-364 Days)

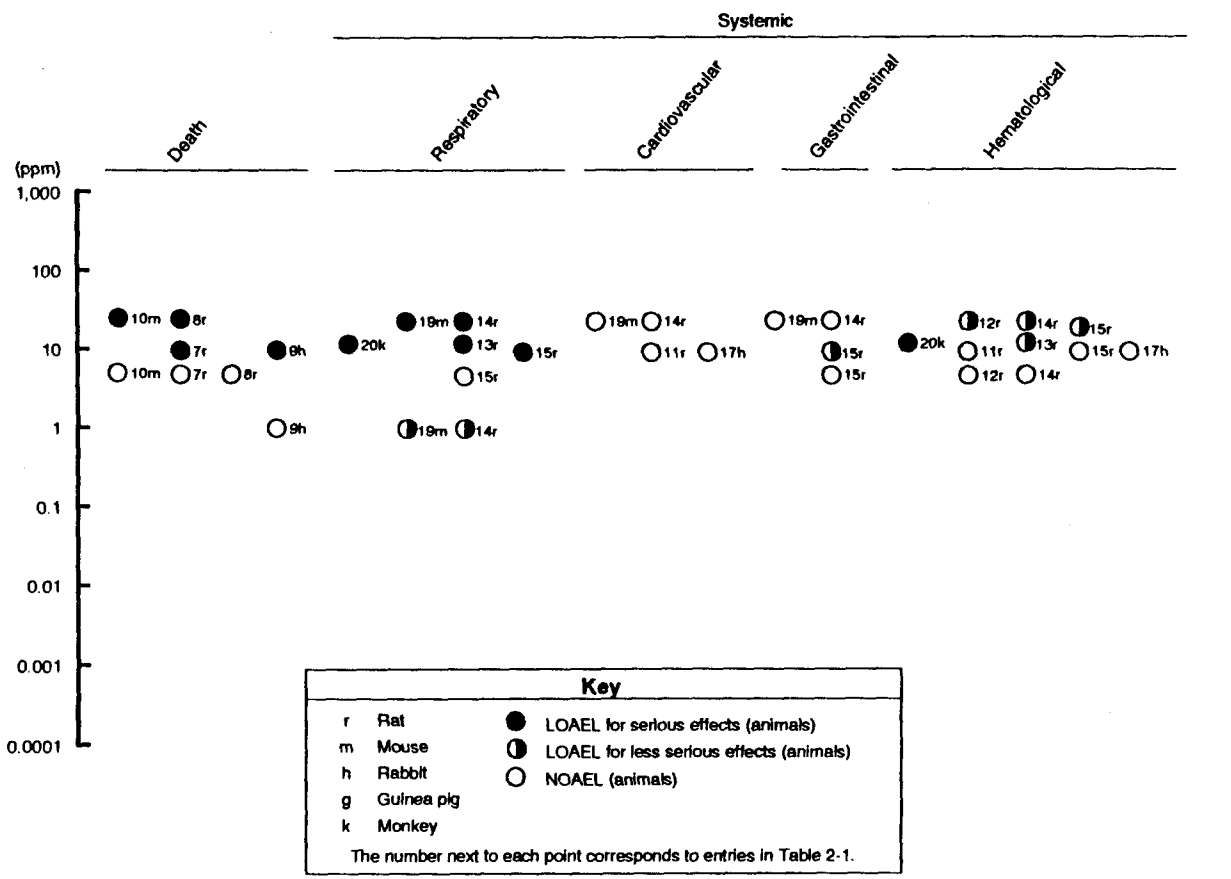


FIGURE 2-1 (Continued)

INTERMEDIATE (Continued)
(15-364 Days)

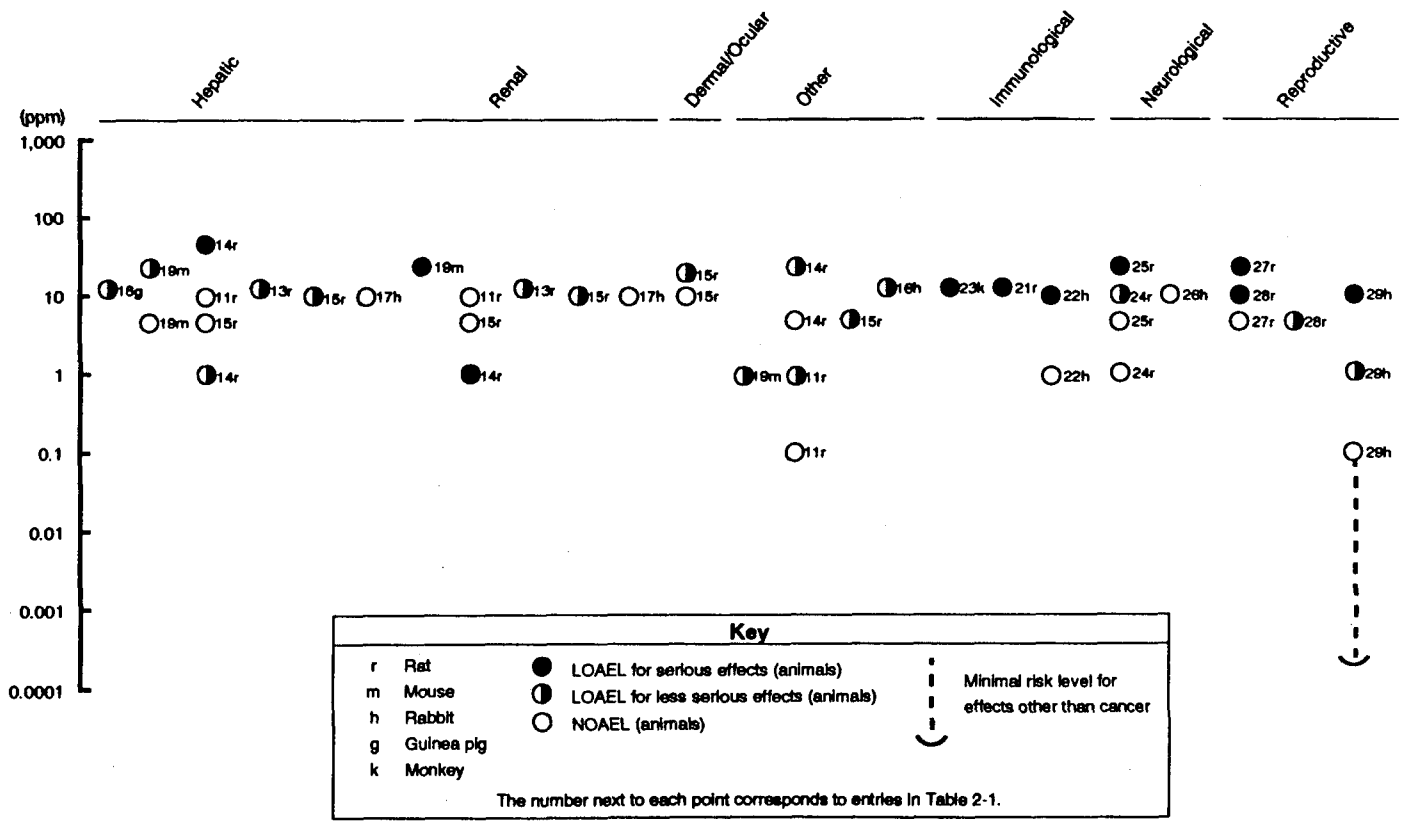
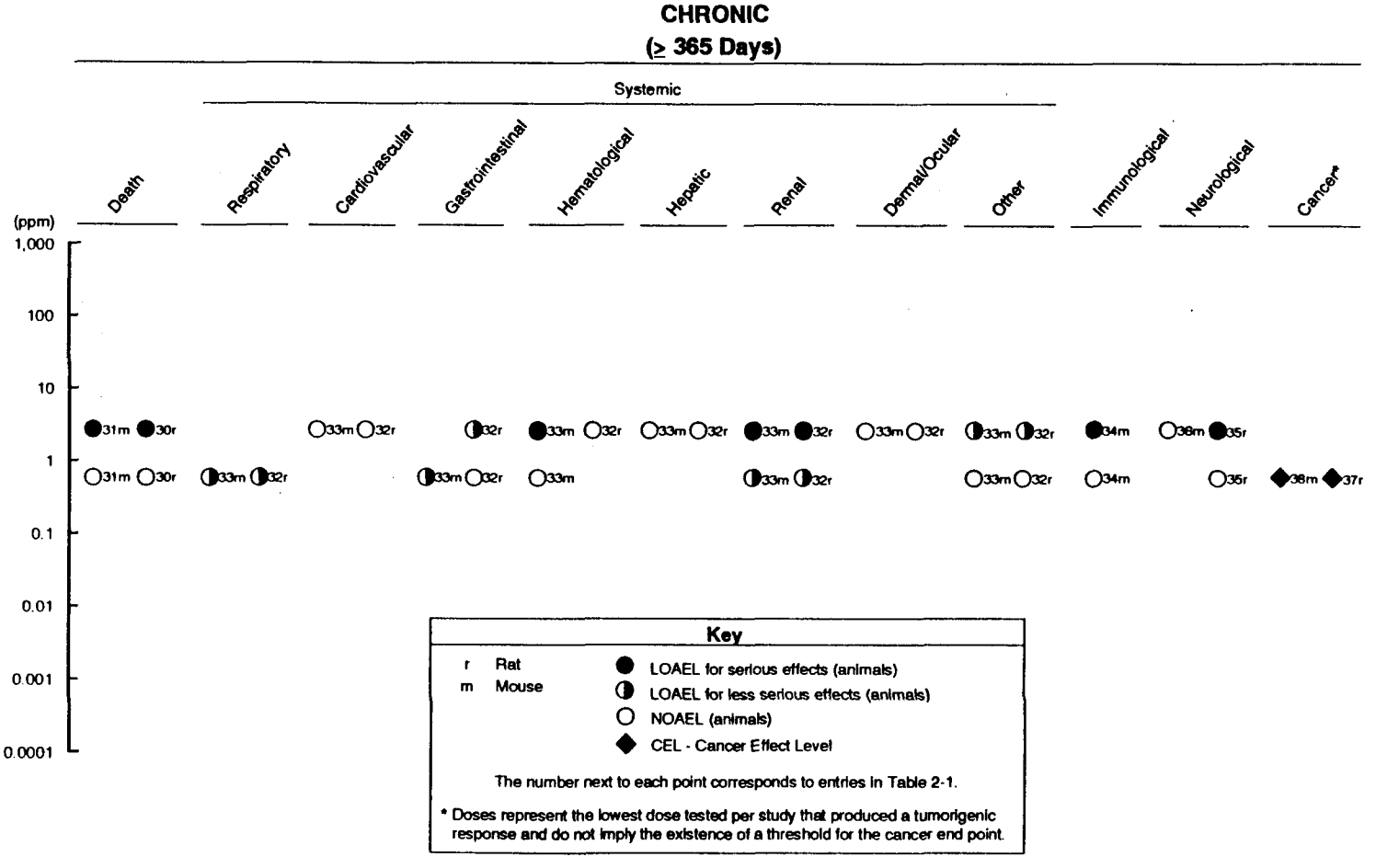


FIGURE 2-1 (Continued)



contaminant (Wong et al. 1984). It is not possible to conclude from this information that 1,2-dibromo-3-chloropropane exposure is associated with heart disease in humans.

The effect of 1,2-dibromo-3-chloropropane on the heart has been tested in a few animal studies. Continuous exposure of rats to 10 ppm 1,2-dibromo-3-chloropropane did not result in cardiac lesions (Saegusa et al. 1982). No histopathological changes were observed in hearts of rats or rabbits following intermittent exposure to 10 ppm or less for 14 weeks (Rao et al. 1982), in rats or mice intermittently exposed to 25 ppm for 13 weeks, or in rats or mice intermittently exposed to 3 ppm or less for up to 103 weeks (NTP 1982).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after inhalation exposure to 1,2-dibromo-3-chloropropane.

Unspecified lesions in the intestinal mucosa were reported in rats after exposure to ≥10ppm 1,2-dibromo-3-chloropropane for 7 hours/day, 5 days/week, for 10 weeks (Torkelson et al. 1961), but no gastrointestinal lesions were reported in rats or mice exposed to 25 ppm or less for 6 hours/day, 5 days/week, for 13 weeks (NTP 1982). In a chronic-duration study, however, epithelial hyperplasia and hyperkeratosis were found in the stomachs of rats exposed to 3.0 ppm and in mice exposed to 0.6 ppm for 6 hours/day, 5 days/week, for 80-107 weeks (NTP 1982).

Hematological Effects. No hematological effects were found in workers at a pesticide factory who were exposed to 1,2-dibromo-3-chloropropane (Whorton et al. 1977). Airborne concentrations, measured by personal airsampling devices at the time of the study, were approximately 0.4 ppm (averaged for an 8-hour day); however, airborne levels prior to the study were not presented.

Splenic atrophy was observed in rats exposed continuously to 10 ppm 1,2-dibromo-3-chloropropane for 2 weeks, but only on the 1st day after the exposure was terminated. No changes were observed after a 16-day recovery period (Saegusa et al. 1982). A significant increase in neutrophil count and a significant decrease in white blood cell count were seen in rats intermittently exposed to 12 or 20 ppm, respectively, for 10-12 weeks (Torkelson et al. 1961); however, concurrent pneumonia in the rats may have influenced this outcome. No hematological changes were found in rats or rabbits intermittently exposed to 10 ppm 1,2-dibromo-3-chloropropane for up to 14 weeks (Rao et al. 1982, 1983; Torkelson et al. 1961). Aplastic anemia and leukopenia were found in two monkeys intermittently exposed to 12 ppm for 10 weeks; this condition was attributed to severe infections, to which the animals were rendered more susceptible by 1,2-dibromo-3-chloropropane exposure (Torkelson et al. 1961). Furthermore, rats intermittently exposed to 25 ppm for 13 weeks had hypocellularity of the bone marrow. No changes in formed

elements of the blood were reported in rats or mice after a chronic intermittent exposure to 3 ppm 1,2-dibromo-3-chloropropane. Splenic atrophy was found in mice but not in rats (NTP 1982).

Hepatic Effects. No studies were located regarding hepatic effects of 1,2-dibromo-3-chloropropane in humans after inhalation exposure.

1,2-Dibromo-3-chloropropane appears to produce minor hepatic effects in animals. No histopathological changes were reported in livers of rabbits or rats after intermittent exposure to 10 ppm 1,2-dibromo-3-chloropropane for 14 weeks (Rao et al. 1982, 1983). Hydropic changes in hepatocytes were observed in rats intermittently exposed to 1 or 5 ppm 1,2-dibromo-3-chloropropane for 13 weeks, while focal necrosis of the liver together with hepatic regenerative changes was seen in the 25-ppm exposure group (NTP 1982). In contrast, hydropic changes in hepatocytes were observed only in the highest (25 ppm) exposure group in mice (NTP 1982). Sinusoidal dilatation and other unspecified lesions were reported in the livers of rats intermittently exposed to 10 or 12 ppm 1,2-dibromo-3-chloropropane for lo-12 weeks (Torkelson et al. 1961). Fatty metamorphosis of livers was found in guinea pigs exposed to 12 ppm for the same duration. There were no statistically significant differences between changes found in the livers of rats or mice chronically exposed to 1,2-dibromo-3-chloropropane concentrations as high as 3 ppm and those found in their matching controls (NTP 1982).

Renal Effects. Urinalysis parameters were within normal limits in workers exposed occupationally to 1,2-dibromo-3-chloropropane (Whorton et al. 1977). The average airborne concentration, measured by personal air-sampling devices at the time of the study, was approximately 0.4 ppm (averaged for an 8-hour day); however, airborne levels prior to the study were not presented. No other studies were located regarding renal effects in humans after inhalation exposure to 1,2-dibromo-3-chloropropane.

The kidney is a target organ of 1,2-dibromo-3-chloropropane in animals. Permanent scarring of the kidneys was observed in rats exposed to 50 ppm or more 1,2-dibromo-3-chloropropane for several hours (Torkelson et al. 1961). Necrotic changes in the proximal tubules were found in rats exposed continuously to 10 ppm 1,2-dibromo-3-chloropropane for 2 weeks (Saegusa et al, 1982).

Nephritis and lesions of the kidneys (cloudy swelling in epithelial cells of the proximal tubules and an increase of interstitial tissue) were observed in rats after intermittent exposure to 12 or 20 ppm 1,2-dibromo-3-chloropropane for 10-12 weeks (Torkelson et al. 1961). Epithelial hyperplasia in tubules and nephrotic changes were found in the 1-ppm exposure group of rats and in the 25-ppm exposure group of mice after 13 weeks (NTP 1982). No renal histopathological changes or changes in urinalysis parameters were detected in rats and rabbits after an intermediate-duration intermittent

exposure to 10 ppm 1,2-dibromo-3-chloropropane (Rao et al. 1982, 1983). The apparent discrepancy in concentrations resulting in renal lesions in rats is possibly attributable to strain differences. NTP (1982) used Fischer 344 rats, while Rao et al. (1983) used Sprague-Dawley rats.

Tubular cell hyperplasia at 0.6 ppm and toxic tubular nephropathy at 3 ppm were found in both rats and mice after intermittent chronic inhalation exposure to 1,2-dibromo-3-chloropropane (NTP 1982).

Dermal/Ocular Effects. No studies were located regarding dermal/ocular effects of 1,2-dibromo-3-chloropropane in humans after inhalation exposure.

At relatively high concentrations, exposure to the vapors of 1,2-dibromo-3-chloropropane causes eye irritation. This is probably due to direct contact of the vapor with the eyes rather than an ocular cytotoxic effect of inhaled vapor. Eye irritation was reported in rats exposed to 60 ppm or more 1,2-dibromo-3-chloropropane for several hours (Torkelson et al. 1961). Clouding of the cornea and lens also occurred in rats during an intermediate-duration exposure to 20 ppm (Torkelson et al. 1961). No histopathological dermal or ocular changes were found in rats or mice after chronic-duration exposure to 3 ppm 1,2-dibromo-3-chloropropane (NTP 1982).

Other Systemic Effects. Adrenal necrosis, body weight loss, and hair loss were reported in Fischer 344 rats after an intermittent 13-week exposure to 25 ppm 1,2-dibromo-3-chloropropane. These effects were not noted after exposure to 5 ppm (NTP 1982). Adrenal cortical necrosis was also seen in female Sprague-Dawley rats after intermittent exposure to 1 ppm (but not 0.1 ppm) for 14 weeks (Rao et al. 1983).

Decreased weight gain was found in mice after intermittent exposure to 1 ppm for 13 weeks. Decreased weight gain was also reported in rats and mice after intermittent chronic exposure to 3 ppm (but not 0.6 ppm) 1,2-dibromo-3-chloropropane (NTP 1982).

2.2.1.3 Immunological Effects

No studies were located regarding immunological effects of 1,2-dibromo-3-chloropropane in humans after inhalation exposure.

Several intermediate-duration studies suggest that 1,2-dibromo-3-chloropropane has immunological effects in animals. Hypocellularity of the bone marrow was observed in rats intermittently exposed to 25 ppm for 13 weeks (NTP 1982). Severe lung infections were found in rabbits (Rao et al 1982), rats, and monkeys (Torkelson et al. 1961) intermittently exposed for up to 14 weeks. The hypocellularity of bone marrow may represent decreased granulopoiesis, and the presence of infection in the exposed animals (but not in control or animals exposed to lower concentrations) suggests that exposure

to 1,2-dibromo-3-chloropropane caused a decreased resistance to disease. The highest NOAEL values and all reliable LOAEL values for immunological effects in each species for the intermediate-duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.4 Neurological Effects

Information regarding neurological effects in humans after inhalation exposure to 1,2-dibromo-3-chloropropane is limited. Subjective neurological symptoms such as headache, nausea, lightheadedness, and weakness were reported by workers occupationally exposed to 1,2-dibromo-3-chloropropane (Whorton et al. 1977). The average airborne concentration, measured by personal airsampling devices at the time of the study, was approximately 0.4 ppm (averaged for an 8-hour day); however, airborne levels prior to the study were not presented.

Neurological effects have been observed in animals exposed to 1,2-dibromo-3-chloropropane by inhalation. Depression of the central nervous system, expressed by apathy, sluggishness, and ataxia, was observed in rats exposed to 60 ppm or more 1,2-dibromo-3-chloropropane for several hours, but complete narcosis was not achieved (Torkelson et al. 1961). Rats intermittently exposed to 10 ppm 1,2-dibromo-3-chloropropane for 14 weeks had focal mineralized deposits in the brain (Rao et al. 1983). In contrast, no histopathological changes were found in the brains of rabbits under the same exposure conditions (Rao et al. 1982). Meningoencephalitis was reported in rats after intermittent intermediate-duration exposure to 25 ppm 1,2-dibromo-3-chloropropane; no such effect was reported in mice (NTP 1982). Cerebral necrosis was observed in rats after an intermittent chronic exposure to 3 ppm 1,2-dibromo-3-chloropropane, but not in mice.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.5 Developmental Effects

No increase in gross congenital malformations and no cytogenetic abnormalities were found in a cohort of 34 children conceived during or after paternal exposure to 1,2-dibromo-3-chloropropane, as compared with the control group that was conceived before the exposure (Goldsmith et al. 1984; Potashnik and Abeliovich 1985; Potashnik and Phillip 1988). Exposure levels were not specified in these reports.

No studies were located regarding developmental effects of 1,2-dibromo-3-chloropropane in animals after inhalation exposure.

2.2.1.6 Reproductive Effects

The toxicity of 1,2-dibromo-3-chloropropane to the human male reproductive system has been assessed in cohorts of occupationally exposed factory workers (Cortes-Gallegos et al. 1980; Egnatz et al. 1980; Lipshultz et al. 1980; Potashnik et al. 1978; Scharnweber 1979; Whorton et al. 1977, 1979) and in cohorts of farmers or pesticide applicators (Glass et al. 1979; Sandifer et al. 1979; Takahashi et al. 1981). An epidemiological approach to the assessment of occupationally linked sperm count reduction was considered in some reports (Milby and Whorton 1980; Levine et al. 1981). Follow-up studies were performed in some of the original cohorts (Eaton et al. 1986; Lantz et al. 1981; Olsen et al. 1990; Potashnik 1983; Potashnik and Yanai-Inbar 1987; Schenker et al. 1988). Changes in sperm counts ranging from oligospermia (deficient or low sperm levels) to azoospermia (absences of sperm) were found among exposed workers. Histopathological changes observed after testicular biopsy revealed atrophy of the seminiferous epithelium (Biava et al. 1978; Potashnik et al. 1978) or tubular hyalinization with sparsity of germ cells; in some tubules, only Sertoli cells persisted (Lantz et al. 1981). Histopathological changes in testes were associated with elevated plasma levels of luteinizing hormone (IX) (Cortes-Gallegos et al. 1980) and follicle stimulating hormone (FSH) (Eaton et al. 1986; Lantz et al. 1981; Potashnik et al. 1978). Furthermore, decreased testicular size tended to be associated with lower sperm counts (Egnatz et al. 1980; Lantz et al. 1981; Olsen et al. 1990). In individuals whose sperm counts returned to normal, testicular atrophy was also found to be reversible (Olsen et al. 1990).

Those men who showed decreased spermatogenesis with normal FSH levels showed greater recovery of spermatogenesis during an 8-year postexposure recovery period than men whose FSH and/or LH levels were elevated throughout the 8-year period (Potashnik 1983; Potashnik and Yanai-Inbar 1987). The results suggest that 1,2-dibromo-3-chloropropane-induced sterility can persist for at least 8 years (Eaton et al. 1986; Potashnik 1983).

A standardized fertility ratio for the period when workers were exposed was depressed compared with the period prior to exposure (Levine et al. 1981).

The changes in sperm count appear to be associated with workplace airborne concentrations of less than 1 ppm of 1,2-dibromo-3-chloropropane (Whorton et al. 1977, 1979). A correlation was found between the severity of testicular effects and the length of exposure calculated either in years (Whorton et al. 1979) or in hours of direct 1,2-dibromo-3-chloropropane exposure (Potashnik et al. 1978). Lack of spermatogenesis recovery was found to be job (e.g., exposure) and possibly, age related (Olsen et al. 1990). In contrast, cross-sectional (Coye et al. 1983) and longitudinal (Coye et al. 1990) studies in pineapple workers who were exposed to lower levels of 1,2-dibromo-3-chloropropane (around 1 ppb) did not find any effects on sperm counts. The exposure levels were not clearly defined in any of the human studies. This was because either the historical data regarding workplace

levels were lacking or, in the case of pineapple workers, exposure levels were so low that they were undetectable in some samples. Furthermore, most human studies were conducted in small cohorts with a low participation of exposed individuals.

Effects on the male reproductive system have also been found in animals. Atrophy of seminiferous tubules was found in rats continuously exposed to 3 or 8 ppm 1,2-dibromo-3-chloropropane for 2 weeks; no changes were found after exposure to 1 ppm (Saegusa et al. 1982).

Testicular atrophy was observed in rats intermittently exposed to 10 ppm 1,2-dibromo-3-chloropropane for 10 weeks (Torkelson et al. 1961). At 5 ppm, epithelial changes in the testes were observed. Testicular atrophy with hypospermatogenesis was also observed in rats intermittently exposed to 25 ppm 1,2-dibromo-3-chloropropane for 13 weeks; no changes were reported after 5 ppm exposure to 5 ppm (NTP 1982). Testicular atrophy and ovarian cysts, probably follicular in origin, were found in rats intermittently exposed to 10 ppm for 14 weeks (Rao et al. 1983). Dominant lethality was observed when the exposed males were mated with unexposed females but returned to normal after the recovery period. No changes in fertility were found in exposed females. No reproductive effects were seen in either sex after 1 ppm exposure. Increased serum FSH levels together with testicular atrophy were seen in rabbits intermittently exposed to 1 and 10 ppm 1,2-dibromo-3-chloropropane for 8-14 weeks (Rao et al. 1982). The changes after exposure to 1 ppm were reversible. No evidence of gonadotoxicity was found in rabbits exposed to 0.1 ppm. Based on this value, an intermediate inhalation MRL of 0.0002 ppm was calculated as described in the footnote in Table 2-1. Rabbit data were used to calculate the MRL value because this species appears to be more sensitive to the reproductive effects of 1,2-dibromo-3-chloropropane than rats.

The highest NOAEL values and all reliable LOAEL values for reproductive effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.7 Genotoxic Effects

A predominance of the female sex among the offspring of male workers occupationally exposed to 1,2-dibromo-3-chloropropane was reported in one epidemiological study. In the cohort studied, 52.9% male infants were born during the pre-exposure period, while 35.2% males were born during the exposure. When the group with paternal azoospermia and oligospermia was evaluated separately, the percentage of newborn boys was only 16.6. The change in sex ratio indicates the lower fertility potential of sperm bearing the Y-chromosome (Goldsmith et al. 1984; Potashnik et al. 1984).

Dominant lethality was observed after an intermediate-duration exposure of male rats to 10 ppm 1,2-dibromo-3-chloropropane, but it was reversed after

a recovery period (Rao et al. 1983). This implies that male fertility, and in particular, spermatids, may be affected.

Other genotoxicity studies are discussed in Section 2.4.

2.2.1.8 Cancer

In an epidemiological study of workers exposed to 1,2-dibromo-3-chloropropane, no increase in the incidence of mortality from cancer of the lungs, stomach, liver, kidney, testes, or skin was found. The workers were exposed to airborne concentrations lower than 1 ppm 1,2-dibromo-3-chloropropane during the 2 years preceding the study, but the exposure levels in previous years were not known (Hearn et al. 1984).

When rats were exposed by inhalation (6 hours/day, 5 days/week, for 84-103 weeks) to 0.6 or 3 ppm 1,2-dibromo-3-chloropropane, multiple-site tumors developed. The most common were carcinomas and squamous cell carcinomas of the nasal cavity (squamous cell papilloma, adenocarcinoma, and adenomatous polyps also observed) and squamous cell papillomas of the tongue in both sexes; fibroadenomas of the mammary gland and adenomas of the adrenal cortex in females; and trichoadenomas of the skin and mesotheliomas of the tunica vaginalis in males. Adenomas, squamous cell carcinomas, and carcinomas of the respiratory tract also developed in mice after intermittent chronicduration exposure to 0.6 or 3 ppm 1,2-dibromo-3-chloropropane (NTP 1982). The cancer effect level is recorded in Table 2-l and plotted in Figure 2-l.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death in humans after oral exposure to 1,2-dibromo-3-chloropropane.

After a single dose of 400 mg/kg 1,2-dibromo-3-chloropropane, all treated rats died within 24 hours. These rats were given a known lethal dose in order to study the relationship between 1,2-dibromo-3-chloropropane-induced hepatotoxicity and death (Kato et al. 1980). Reported LD_{50} values for male rats were 170 and 300 mg/kg (results from two independent laboratories) (Torkelson et al. 1961). For female mice, LD_{50} values were reported to be 340 (Moody et al. 1984), 260, and 410 mg/kg (Torkelson et al. 1961); the latter two values were results from two independent laboratories. Oral LD_{50} values for rabbits and guinea pigs were 180 and 210 mg/kg, respectively (Torkelson et al. 1961). A 14-day LD_{50} of 205 mg/kg/day was determined in male and female mice by probit analysis (Reel et al. 1984).

Increased mortality was observed in female rats dosed 5 days/week by gavage with 1,2-dibromo-3-chloropropane at 40 mg/kg/day and in mice at 251 mg/kg/day for 6 weeks. No deaths were reported in rats at 25 mg/kg/day or

in mice at 160 mg/kg/day (NC1 1978). Increased mortality in rats was also found at an equivalent dose of 67.5 mg/kg/day 1,2-dibromo-3-chloropropane that was administered in the diet for 90 days (Torkelson et al. 1961). The cause of death was not reported in intermediate-duration studies. In a chronic study, mortality due to cancer was increased after treatment with 15 mg/kg/day in rats and 110 mg/kg/day in mice (NC1 1978). The survival of rats was also decreased because of cancer after dietary exposure to 1,2-dibromo-3-chloropropane at a dose of 3 mg/kg/day for 104 weeks (Hazleton 1977, 1978a), while no increase in mortality was found in mice that ingested 4.6 mg/kg/day for 78 weeks (Hazleton 1978b).

The LD_{50} values, the highest NOAEL values, and all reliable LOAEL values in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

The systemic effects of 1,2-dibromo-3-chloropropane after oral exposure are described below. The highest NOAEL values and all reliable LOAEL values for each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to 1,2-dibromo-3-chloropropane. Pulmonary metastases occurred in rats chronically exposed by gavage with 15 or 29 mg/kg 1,2-dibromo-3-chloropropane and in mice gavaged with 110-219 mg/kg (NC1 1978). No treatment-related respiratory effects were found in rats exposed to 1,2-dibromo-3-chloropropane in the diet at a dose of 3 mg/kg/day for 104 weeks (Hazleton 1977, 1978a) or in mice that ingested 4.6 mg/kg/day in the diet for 78 weeks (Hazleton 1978b).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after oral exposure to 1,2-dibromo-3-chloropropane.

No histopathological changes were found in the hearts of rats or mice that were gavaged daily with doses as high as 29 or 219 mg/kg 1,2-dibromo-3-chloropropane, respectively, for 47-78 weeks (NC1 1978). Similarly, no changes were observed in the hearts of rats that received 3 mg/kg/day in the diet for 104 weeks (Hazleton 1977, 1978a).

Gastrointestinal Effects. No correlation was observed between gastric cancer incidence in humans and the contamination of drinking water with 1,2-dibromo-3-chloropropane (Wong et al. 1989) (also discussed in Section 2.2.2.8).

TABLE 2-2. Levels of Significant Exposure to 1,2-Dibromo-3-chloropropane - Oral

Key to figure[a]	Species	Route	Exposure duration/ frequency	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				340 (LD50)	Moody et al. 1984
2	Rat	(G)	1 d 1x/d				170-300 (LD50)	Torkelson et al. 1961
3	Rabbit	(G)	1 d 1x/d				180 (LD50)	Torkelson et al. 1961
4	Gn Pig	(G)	1 d 1x/d				210 (LD50)	Torkelson et al. 1961
5	Mouse	(G)	1 d 1x/d				260-410 (LD50)	Torkelson et al. 1961
6	Mouse	(GO)	14 d 1x/d		65		130 (2 out of 8 died) 205 (LD50)	Reel et al. 1984
Systemic								
7	Rat	(GO)	2 wk 5d/wk	Gastro	15	29 (cell proliferation, hyperkeratosis)		Ghanayem et al. 1986
8	Rat	(GO)	1 d 1x/d	Renal			200 (renal insufficiency)	Russell 1989
9	Rat	(G)	1 d 1x/d	Hepatic Renal			400 (focal necrosis of livers) 400 (tubular degeneration)	Kato et al. 1980
Neurological								
10	Mouse	(GO)	14 d 1x/d		65		130 (ataxia)	Reel et al. 1984

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
Developmental								
11	Rat	(GO)	10 d Gd6-15 1x/d		25		50 (embryotic lethality)	Ruddick and Newsome 1979
Reproductive								
12	Rat	(GO)	5 d 1x/d				10 (increased post-implantation loss	Teramoto et al. 1980
13	Mouse	(GO)	5 d 1x/d		150			Teramoto et al. 1980
INTERMEDIATE EXPOSURE								
Death								
14	Rat	(GO)	6 wk 5d/wk 1x/d		25		40 (death; number of deaths not reported)	NCI 1978
15	Rat	(F)	90 d		22.5		67.5 (6 out of 28 died)	Torkelson et al. 1961
16	Mouse	(GO)	6 wk 5d/wk 1x/d		160		251 (2 out of 10 died)	NCI 1978
Systemic								
17	Rat	(W)	64 d ad lib	Hepatic	9.7			Heindel et al. 1989
				Renal	3.3	5.4 (increased turnover of proximal tubular cells)		
				Other	5.4	9.7 (decreased body weight gain)		

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
18	Rat	(W)	60 d	Cardio	19.43			Johnston et al. 1986
				Gastro	19.43			
				Hepatic	19.43			
				Renal	19.43			
				Other	2.96	19.43 (decreased body weight gain)		
19	Rat	(G)	6 wk 1x/d	Gastro		70 (necrosis)		Rakhmatullayev 1969
				Hemato		70 (depressed erythrocytes, leukocytes)		
				Hepatic			70 (necrosis, cirrhosis)	
				Renal		70 (necrosis, regeneration)		
20	Rat	(F)	90 d	Gastro		67.5 (intestinal edema)		Torkelson et al. 1961
				Hepatic	67.5			
				Renal	67.5			
				Other	2.5	7.5 (decreased weight gain)		
21	Rabbit	(W)	10 wk 5d/wk	Other	15			Foote et al. 1986b
22	Mouse	(GO)	6 wk 5d/wk 1x/d	Other	631			NCI 1978
Neurological								
23	Rat	(W)	60 d		19.43			Johnston et al. 1986
24	Rat	(F)	90 d		22.5	67.5 (decreased activity)		Torkelson et al. 1961
Developmental								
25	Rat	(W)	60 d		2.96	19.43 (decreased pup weight)		Johnston et al. 1986

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
Reproductive								
26	Rat	(GO)	77 d 1x/d		7.5		15 (testicular degeneration)	Amann and Berndtson 1986
27	Rat	(W)	64 d ad lib		9.7			Heindel et al. 1989
28	Rat	(W)	60 d		19.45			Johnston et al. 1986
29	Rabbit	(W)	10 wk 5d/wk			1.88[b] (abnormal sperm morphology; decreased spermatogenesis)	15.0 (testicular atrophy and increased serum FSH levels)	Foote et al. 1986a, 1986b
30	Mouse	(GO)	128 d 1x/d				25 (reduced number of litters)	Reel et al. 1984
CHRONIC EXPOSURE								
Death								
31	Rat	(GO)	64-78 wk 5d/wk 1x/d				15 (at week 73: survival in males 40%, in females 17%, and in vehicle controls 73% and 79% respectively)	NCI 1978
32	Rat	(F)	104 wk 7d/wk		1.0		3.0 (at week 104: survival in males 38%, in females 40%, and in vehicle controls 62%)	Hazleton 1977, 1978a

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
33	Mouse	(GO)	47-60 wk 5d/wk 1x/d				110 (at week 58: survival in males 16%, in females 18%, and in vehicle controls 90%)	NCI 1978
34	Mouse	(F)	78 wk 7d/wk		4.6			Hazleton 1978b
Systemic								
35	Rat	(F)	104 wk 7d/wk	Resp	3.0			Hazleton 1977, 1978a
				Cardio	3.0			
				Gastro	0.3	1.0 (acanthosis, hyperkeratosis)		
				Hemato	3.0			
				Musc/skel	3.0			
				Hepatic		0.3 (peliosis hepatitis)		
				Renal	1.0	3.0 (epithelial hyperplasia)		
				Derm/oc	3.0			
				Other	1.0	3.0 (decreased body weight)		
36	Rat	(GO)	64-78 wk 5d/wk 1x/d	Resp			15 (pulmonary metastases)	NCI 1978
				Cardio	29			
				Gastro		15 (hyperkeratosis, acanthosis)		
				Hemato	29			
				Musc/skel	29			
				Hepatic	29			
				Renal			15 (nephrosis)	
				Derm/oc	29			
				Other		15 (weight gain decrease)		

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
37	Mouse	(F)	78 wk 7d/wk	Resp	4.6			Hazleton 1978b
				Gastro		4.6 (acanthosis, hyperkeratosis)		
				Hemato	4.6			
				Hepatic	4.6			
				Renal	4.6			
				Other	4.6			
38	Mouse	(GO)	47-60 wk 5d/wk 1x/d	Resp			110 (pulmonary metastases)	NCI 1978
				Cardio	219			
				Gastro	219			
				Hemato	219			
				Musc/skel	219			
				Hepatic	219			
				Renal			110 (toxic nephropathy)	
				Derm/oc	219			
				Other	219			
Immunological								
39	Rat	(F)	104 wk 7d/wk		3.0			Hazleton 1977, 1978a
Neurological								
40	Rat	(F)	104 wk 7d/wk		3.0			Hazleton 1977, 1978b
41	Rat	(GO)	64-78 wk 5d/wk 1x/d		29			NCI 1978
42	Mouse	(GO)	47-60 wk 5d/wk 1x/d		219			NCI 1978

TABLE 2-2 (Continued)

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference
Reproductive								
43	Rat	(GO)	64-78 wk 5d/wk 1x/d				15 (testicular atrophy)	NCI 1978
44	Rat	(F)	104 wk 7d/wk		3.0			Hazleton 1977, 1978a
45	Mouse	(GO)	47-60 wk 5d/wk 1x/d		219			NCI 1978
Cancer								
46	Rat	(GO)	64-78 wk 5d/wk 1x/d				15 (CEL, stomach carcinomas, mammary carcinomas)	NCI 1978
47	Rat	(F)	104 wk 7d/wk				3.0 (liver, kidney, stomach tumors)	Hazleton 1977, 1978a
48	Mouse	(F)	78 wk 7d/wk				4.6 (stomach tumors)	Hazleton 1978b
49	Mouse	(GO)	47-60 wk 5d/wk 1x/d				110 (CEL, stomach carcinoma)	NCI 1978

[a]The number corresponds to entries in Figure 2-2.
[b]Used to derive an intermediate oral Minimal Risk Level (MRL) of 0.002 mg/kg/day; dose divided by an uncertainty factor of 1000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

ad lib. = ad libitum; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Derm/oc = dermal/ocular; (f) = feed; FSH = follicle stimulating hormone; (G) = gavage - not specified; Gastro = gastrointestinal; Gd = gestation day; Gn pig = guinea pig; (GO) = gavage - oil; Hemato = hematological; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; (W) = water; wk = week(s); x = time(s)

FIGURE 2-2. Levels of Significant Exposure to 1,2-Dibromo-3-chloropropane - Oral

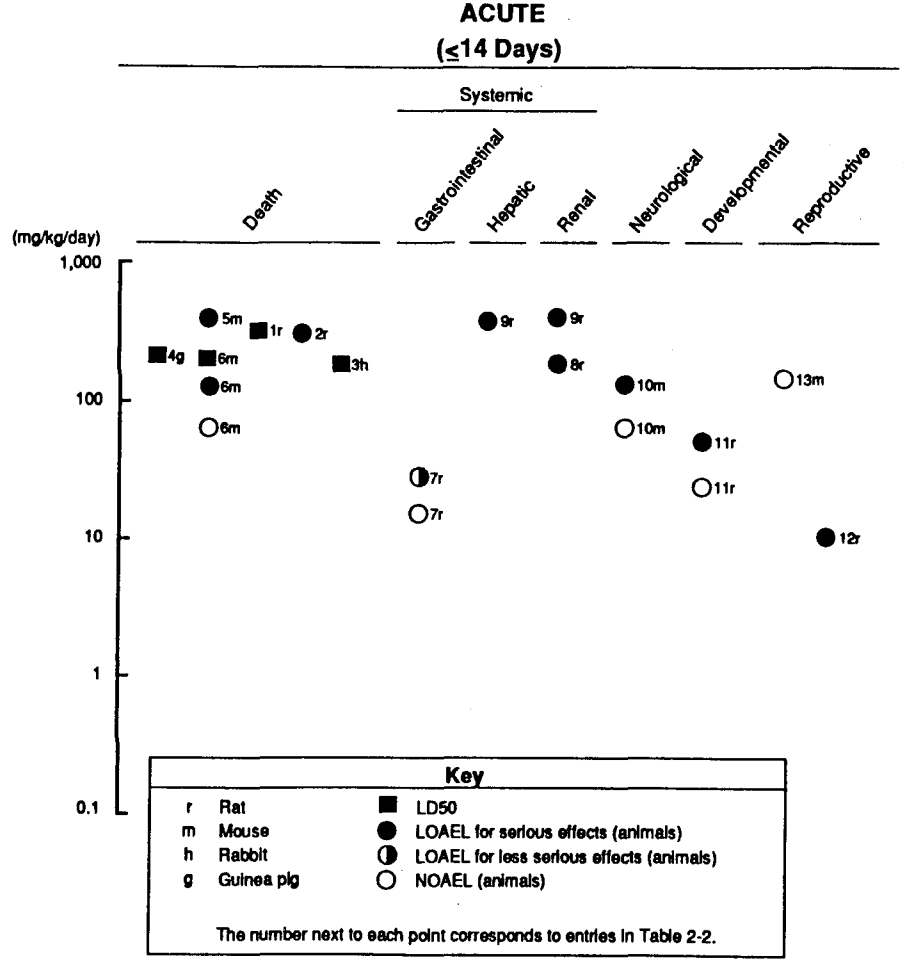


FIGURE 2-2 (Continued)

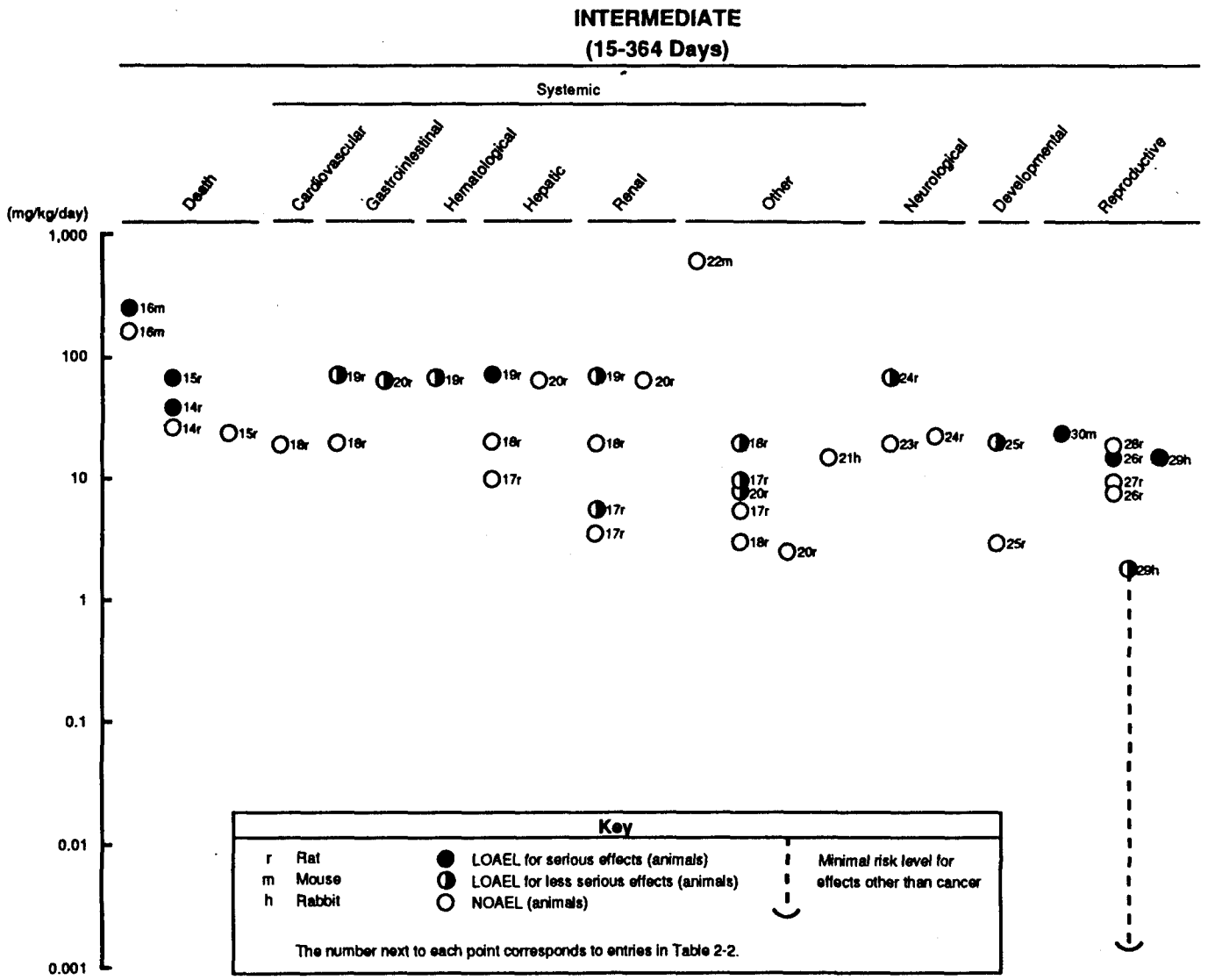
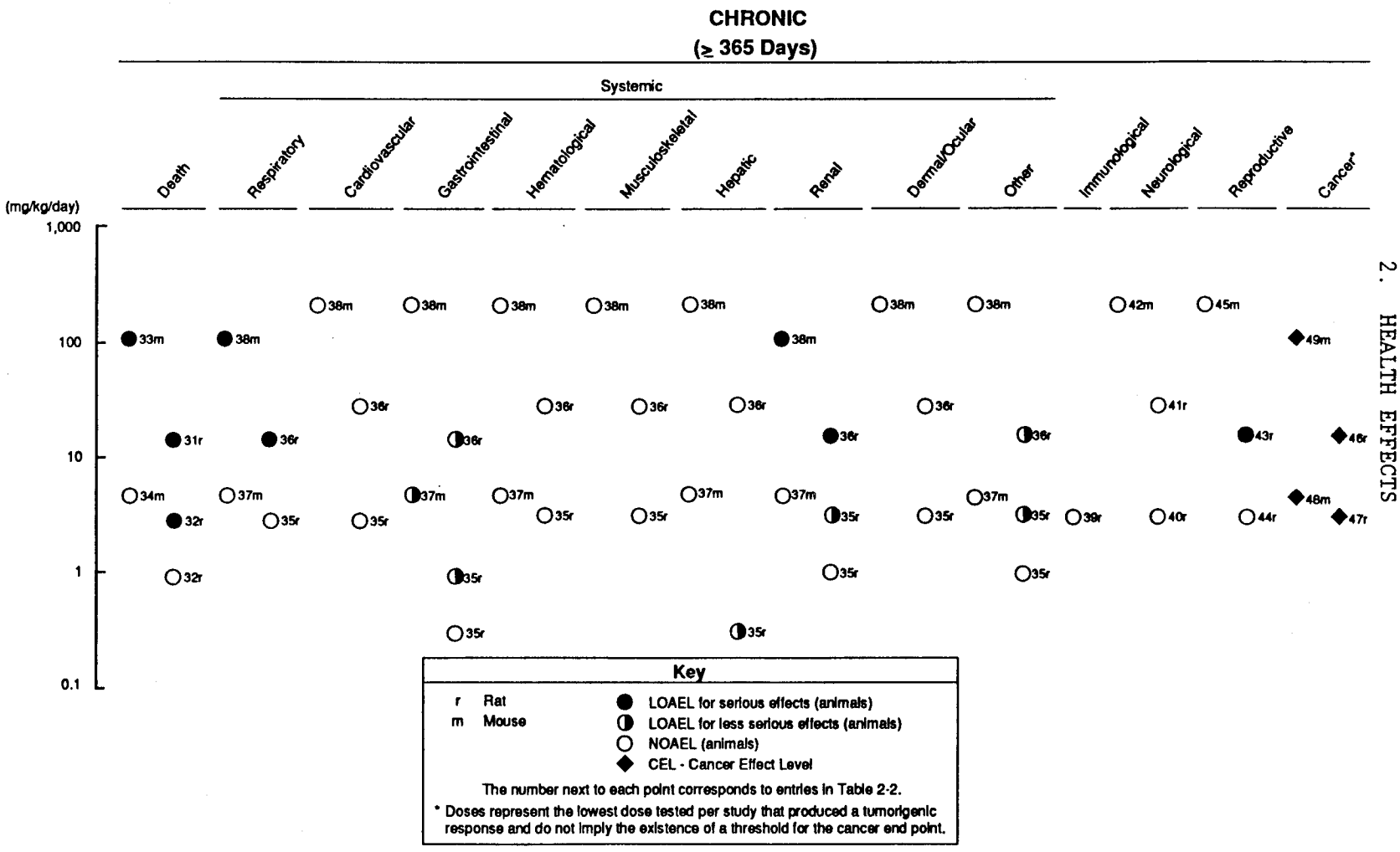


FIGURE 2-2 (Continued)



Gastrointestinal effects have been observed in rats treated orally with 1,2-dibromo-3-chloropropane for acute, intermediate, and chronic durations. Cell proliferation and hyperkeratosis of the forestomach were observed in rats after 2 weeks of treatment with 29 mg/kg/day 1,2-dibromo-3-chloropropane by gavage; no changes were detected after treatment with 15 mg/kg/day (Ghanayem et al. 1986). No histopathological changes were found in the gastrointestinal tracts of rats that were maintained for 60 days on drinking water that contained 1,2-dibromo-3-chloropropane equivalent to a dose of 19.43 mg/kg/day (Johnston et al. 1986). Intestinal edema was reported in rats that were fed diets containing an equivalent dose of 67.5 mg/kg/day 1,2-dibromo-3-chloropropane for 90 days (Torkelson et al. 1961); necrosis of the gastric mucosa was observed in rats treated by gavage with 70 mg/kg for 6 weeks (Rakhmatullayev 1969). Acanthosis and hyperkeratosis of the stomach were reported as nonneoplastic gastrointestinal lesions in rats after chronic treatment with 15 mg/kg/day by gavage (NC1 1978). However, a high incidence of gastric cancer occurred in treated animals (see discussion of Cancer in Section 2.2.2.8). Similar findings were also observed in rats chronically exposed to doses as low as 1 mg/kg/day (Hazleton 1977, 1978a) and in mice chronically exposed to 4.6 mg/kg/day 1,2-dibromo-3-chloropropane in their diet (Hazleton 1978b).

Hematological Effects. Investigators who analyzed the frequency of leukemia in a population in Fresno County, California, where the drinking water supply was contaminated with 1,2-dibromo-3-chloropropane, found no increase in leukemia incidence (Wong et al. 1989). Levels in the drinking water ranged from 0.004 to 5.75 ppb during 1978-1982.

Limited information suggests that 1,2-dibromo-3-chloropropane induces adverse hematological effects in rats after high-level oral exposure. Decreased hemoglobin concentration and erythrocyte and leukocyte counts were reported in rats after gavage with 70 mg/kg/day for 6 weeks (Rakhmatullayev 1969). Decreased reticulocytes and leukocytes were reported at doses as low as 0.5 mg/kg/day after 8 months of exposure of rats to 1,2-dibromo-3-chloropropane (Rakhmatullaev 1971). At 5 mg/kg/day hemoglobin and red blood cell count were also decreased. However, interpretation of this study is limited because data supporting these conclusions was not presented. No hematological changes were found in rats or mice after a chronic exposure to 29 or 219 mg/kg/day, respectively (NCI 1978). Furthermore, no hematological effects were reported in rats (Hazleton 1977, 1978a) or mice (Hazleton 1978b) chronically exposed to 3 or 4.6 mg/kg/day 1,2-dibromo-3-chloropropane, respectively, in the diet.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to 1,2-dibromo-3-chloropropane.

No histopathological changes in skeletal muscle were found in rats chronically exposed to 29 mg/kg/day 1,2-dibromo-3-chloropropane or in mice exposed to 219 mg/kg/day (NC1 1978). Similarly, no changes were observed in rats chronically exposed to 3 mg/kg/day 1,2-dibromo-3-chloropropane (Hazleton 1977, 1978a).

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to 1,2-dibromo-3-chloropropane.

Degeneration and focal necrosis of centrilobular hepatocytes were observed in rats that died within 24 hours after a single gavage dose of 400 mg/kg 1,2-dibromo-3-chloropropane (Kato et al. 1980). The rats in this study were deliberately given a lethal dose so that the relationship between hepatotoxicity and death could be studied. Mild periportal hepatocellular swelling and increased cytoplasmic basophilia were noted in male rats following gavage with 40 mg/kg/day 1,2-dibromo-3-chloropropane for 4 days (Kluwe 1981). This study is limited because only one dose was tested. No histopathological changes were found in livers of rats after intermediateduration oral exposure to drinking water that delivered 19.45 mg/kg/day 1,2-dibromo-3-chloropropane (Johnston et al. 1986), or to diets that delivered 67.5 mg/kg/day (Torkelson et al. 1961). Also, there were no effects on enzyme markers for hepatic toxicity (serum glutamic-oxaloacetic transaminase [SGOT], serum glutamic-pyruvic transaminase [SGPT], sorbitan dehydrogenase) in male rats that were exposed to 0.4-9.7 mg/kg/day 1,2-dibromo-3-chloropropane in drinking water for 64 days (ad libitum) (Heindel et al. 1989). In contrast, necrosis and cirrhosis were found in livers of rats treated by gavage with 70 mg/kg/day for 6 weeks (Rakhmatullayev 1969). Hepatic toxicity was reported to have been manifested as increased prothrombin time, decreased urea, and increased coproporphyrin in the urine of rats after gavage with 0.5 mg/kg/day 1,2-dibromo-3-chloropropane for 8 months in a poorly documented study by Rakhmatullaev (1971). The absence of liver effects in the rats that were administered a similar dose in the diet may reflect the different modes of administration, that is, diet versus bolus, and the resulting differences in absorption kinetics. No statistically significant changes were reported in livers of rats or mice chronically gavaged with doses as high as 29 or 219 mg/kg/day, respectively (NC1 1978). In contrast, a dose-related increased incidence of poliosis hepatitis was found in rats that ingested 0.3 mg/kg/day or more 1,2-dibromo-3-chloropropane for 104 weeks (Hazleton 1977, 1978a). No such changes were reported in matching controls. No hepatic changes were reported in mice exposed chronically to 4.6 mg/kg/day 1,2-dibromo-3-chloropropane (Hazleton 1978b).

Renal Effects. No studies were located regarding renal effects in humans after oral exposure to 1,2-dibromo-3-chloropropane.

The kidney is a target organ of 1,2-dibromo-3-chloropropane in experimental animals. Renal effects have been observed in studies of acute,

intermediate, and chronic durations. Degeneration of renal tubules was found in rats that died after treatment with a single dose of 400 mg/kg 1,2-dibromo-3-chloropropane (Kato et al. 1980). Acute renal insufficiency with tubular necrosis was reported in rats after a single dose of 200 mg/kg 1,2-dibromo-3-chloropropane (Russell 1989). The insufficiency reversed with time, but focal glomerulosclerosis persisted 28 weeks postexposure. Increased blood urea nitrogen levels, decreased urine specific gravity, increased kidney weight to brain weight ratio, proximal kidney tubule necrosis, and increased basophilia were noted in male rats following gavage with 40 mg/kg/day 1,2-dibromo-3-chloropropane for 4 days (Kluwe 1981). This study is limited because only one dose was tested.

While no histopathological changes were found in kidneys of rats after intermediate-duration ingestion of as much as 19.45 mg/kg/day 1,2-dibromo-3-chloropropane in drinking water (Johnston et al. 1986) or 67.5 mg/kg/day 1,2-dibromo-3-chloropropane in the diet (Torkelson et al. 1961), necrosis and signs of regeneration were found in rats after gavage treatment with 70 mg/kg/day for 6 weeks (Rakhmatullayev 1969). The difference in response between rats treated by gavage and rats exposed in the diet to an equivalent dose is probably a function of the dosing regimen mode and consequent differences in absorption kinetics. There was no effect on blood urea nitrogen levels, but there was a slight increase in the number of cells in the proximal convoluted tubules was noted at doses of 5.4-9.7 mg/kg/day 1,2-dibromo-3-chloropropane given in drinking water for 64 days (Heindel et al. 1989). Although the increased number of cells was not significant, this effect may be an indication of increased turnover of proximal tubular cells. Toxic nephropathy was observed in rats and mice chronically exposed by gavage with doses as low as 15 or 110 mg/kg/day, respectively (NC1 1978). Tubular epithelial hyperplasia and megalocytosis were found in the kidneys of rats chronically treated with 3 mg/kg/day 1,2-dibromo-3-chloropropane in the diet, while no changes were reported in rats exposed to 1 mg/kg/day (Hazleton 1977, 1978a). In contrast, no renal effects were found in mice chronically treated with 4.6 mg/kg/day (Hazleton 1978b).

Dermal/Ocular Effects. No studies were located regarding dermal/ocular effects in humans after oral exposure to 1,2-dibromo-3-chloropropane.

No histopathological changes were found in the skin or eyes of rats or mice chronically gavaged with as much as 29 or 219 mg/kg/day 1,2-dibromo-3-chloropropane, respectively (NC1 1978). Similarly, no changes were found in rats chronically exposed to 3 mg/kg/day by ingestion (Hazleton 1977, 1978a).

Other Systemic Effects. Depressed growth occurred when rats were given 1,2-dibromo-3-chloropropane in drinking water at 19.43 mg/kg/day for 60 days (Johnston et al. 1986) or 9.7 mg/kg/day for 64 days (Heindel et al. 1989), in the diet at 7.5 mg/kg/day -for 90 days (Torkelson et al. 1961), or by gavage at 3.75 mg/kg/day for 77 days (Amann and Berndtson 1986) or 15 mg/kg/day for

64-78 weeks (NC1 1978). Although no effect on body weight was seen in rabbits given 15 mg/kg/day 1,2-dibromo-3-chloropropane by gavage for 10 weeks (Foote et al. 1986b), or in mice given up to 631 mg/kg/day by gavage for 6 weeks (NC1 1978) or up to 219 mg/kg/day by gavage for 47-60 weeks (Hazleton 1978b; NC1 1978), decreased body weight gain was a consistent finding in rats. Decreased body weight gain was observed in male rats exposed to 3 mg/kg/day for 104 weeks but not in rats exposed to 1 mg/kg/day (Hazleton 1977, 1978a). The reduced body weight gain after dietary or drinking water exposure to 1,2-dibromo-3-chloropropane was probably the result of decreased food or water consumption due to taste aversion.

2.2.2.3 Immunological Effects

No studies were located regarding immunological effects in humans after oral exposure to 1,2-dibromo-3-chloropropane.

An impaired ability of neutrophils to phagocytize bacteria was reported following gavage administration of 0.05 mg/kg/day of 1,2-dibromo-3-chloropropane to rats for 8 months in a poorly documented study by Rakhmatullaev (1971). However, no abnormalities were observed after histological evaluation of bone marrow, mesenteric lymph nodes, or spleens from rats chronically given 3 mg/kg/day 1,2-dibromo-3-chloropropane in their diet (Hazleton 1977, 1978a). This value is recorded as the NOAEL level for immunological effects after oral exposure in Table 2-2 and plotted in Figure 2-2.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to 1,2-dibromo-3-chloropropane.

Lethargy, ptosis, ataxia, and convulsions were among the signs in mice that died after administration of 130 mg/kg/day 1,2-dibromo-3-chloropropane for 2 weeks (Reel et al. 1984). Decreased activity was observed in rats during dietary exposure to 67.5 mg/kg/day 1,2-dibromo-3-chloropropane for 90 days (Torkelson et al. 1961). Impaired acquisition of conditioned reflexes by rats receiving gavage doses of 1,2-dibromo-3-chloropropane as low as 0.05 mg/kg/day for 8 months was reported (Rakhmatullaev 1971). However, no data were presented to support this conclusion. Histological examination of brain and spinal cord tissues in other studies failed to reveal any structural lesions (Hazleton 1977, 1978a; Johnston et al. 1986; NC1 1978).

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Tab,le 2-2 and plotted in Figure 2-2.

2.2.2.5 Developmental Effects

No correlation between low birth weights or birth defects and 1,2-dibromo-3-chloropropane contamination of drinking water was found in a population exposed in Fresno County, California, during 1978-1982 (Whorton et al. 1989). Potential exposure concentrations of 1,2-dibromo-3-chloropropane in the water system ranged from 1~10-~to 1.6x10m4mg/kg/day.

Developmental effects of 1,2-dibromo-3-chloropropane in animals have been seen only in the presence of maternal toxicity. No teratogenicity was observed in rats after dams were treated with doses up to 50 mg/kg/day 1,2-dibromo-3-chloropropane during gestation, but an increase in embryonic lethality occurred in the highest dose group (Ruddick and Newsome 1979). Maternal toxicity was manifested as severely decreased body weight gain. A statistically significant decrease in average litter weight was found after parental treatment for 60 days with 19.45 mg/kg/day 1,2-dibromo-3-chloropropane in drinking water (Johnston et al. 1986). The dams had decreased bc weight gain during pregnancy.

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

2.2.2.6 Reproductive Effects

No change in birth ratios was found in a population of Fresno County, California, during the years 1978-1982 when the drinking water system was contaminated with 1,2-dibromo-3-chloropropane at concentrations ranging from 0.004 to 5.75 ppb (Wong et al. 1988).

1,2-Dibromo-3-chloropropane is a reproductive toxicant in male rats and rabbits. Increased postimplantation loss, as a result of genetic damage to sperm, was observed in rats after males were treated for 15 days with 10 mg/kg/day and mated to nonexposed females (Teramoto et al. 1980). The peak incidence was observed after mating during weeks 4-5 postexposure, which suggests that the spermatids were the most likely target. In contrast, no increase in postimplantation loss was observed in mice after the treatment of males with 150 mg/kg/day for 5 days.

Histological examination revealed destruction of the architecture of the seminiferous tubules, severe degenerative changes and sloughing into the tubular lumen of the epididymis, and lowered sperm density in male rats following gavage with 40 mg/kg/day 1,2-dibromo-3-chloropropane for 4 days (Kluwe 1981). This study is limited because only one dose was tested. There was no significant change in testes weight, relative to body weight and no there were no effects on sperm count; levels of LH, FSH, or testicular testosterone in serum; histopathology of the seminiferous tubules; or spermatozoa1 development in male rats that were exposed to 0.4-9.7 mg/kg/day

1,2-dibromo-3-chloropropane in drinking water for 64 days (ad libitum) (Heindel et al. 1989). Histological evaluation of the testes from rats gavaged with 15 mg/kg/day 1,2-dibromo-3-chloropropane for 77 days revealed a reduced ratio of leptotene spermatocytes to Sertoli cells and reduced diameter of seminiferous tubules; this is evidence of reduced production of sperm. There was an increased incidence of dead embryos when the exposed males were allowed to mate with unexposed females during the last days of exposure (Amann and Berndtson 1986). Testicular necrosis was observed in rats after gavage dosing with 70 mg/kg/day for 6 weeks (Rakhmatullayev 1969). Decreased generative function (possibly referring to spermatogenesis or fertility) was reported at doses as low as 0.05 mg/kg/day in rats given gavage doses of 1,2-dibromo-3-chloropropane for 8 months (Rakhmatullaev 1971). At 0.5 mg/kg/day, pathomorphology (unspecified) and decreased fertility were observed, and at the highest dose tested, 5 mg/kg/day, decreased sperm motility and complete infertility were observed. This study is limited in that no data were presented to support these conclusions. No changes in fertility, gestation, or survival, however, were observed in rats when both males and females consumed up to 19.45 mg/kg/day 1,2-dibromo-3-chloropropane in drinking water for 60 days and were then allowed to mate (Johnston et al. 1986).

Dose-related adverse reproductive effects were reported in rabbits given 1,2-dibromo-3-chloropropane in drinking water for 10 weeks (Foote et al. 1986a, 1986b). Abnormalities in sperm morphology were observed after treatment with 1.88 mg/kg/day or more in the drinking water for 10 weeks (Foote et al. 1986b). Testicular atrophy occurred after exposure to 15 mg/kg/day. Increases in serum FSH levels, which are indicative of impaired spermatogenesis, were detected after exposure to 7.50 or 15.0 mg/kg/day but were significant only at the higher dose. Serum levels of LH and testosterone were not affected at any dose. Fertility was not affected when the exposed males were allowed to mate during the last week of the exposure. Decreased spermatogenesis was also noted in rabbits following exposure to 1.88-15.0 mg/kg/day 1,2-dibromo-3-chloropropane in drinking water (Foote et al. 1986a). The high dose also induced testicular atrophy in this study. A NOAEL of 0.94 mg/kg/day was not derived from this study because the data suggest that decreased spermatogenesis may occur at this dose.

Reproductive toxicity expressed as a reduction of number of litters was also observed after male and female mice were treated with 25 mg/kg/day 1,2-dibromo-3-chloropropane for 128 days (Reel et al. 1984). Complete azoospermia without recovery developed in monkeys within 45 days of 1,2-dibromo-3-chloropropane treatment. The initial concentration of 650 ppm in drinking water was gradually reduced to 10 ppm over 27 days (Overstreet et al. 1988).

Statistically significant increased incidences of testicular atrophy were observed in rats chronically gavaged with 15 or 29 mg/kg/day as compared with control groups. In contrast, no increase in testicular atrophy was found in chronically dosed mice (NC1 1978). Furthermore, no testicular changes were

found in rats (Hazleton 1977, 1978a) or mice (Hazleton 1978b) chronically exposed to 3 or 4.6 mg/kg/day 1,2-dibromo-3-chloropropane in the diet, respectively.

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

2.2.2.7 Genotoxic Effect&

No effects on sex ratios of human newborns were found in Fresno County, California (1978-1982), where the drinking water was contaminated with 1,2-dibromo-3-chloropropane (Whorton et al. 1989).

An increased incidence of dominant lethality was observed in rats after 5 days of paternal treatment with 10 mg/kg/day 1,2-dibromo-3-chloropropane. In contrast, no induction of dominant lethality was observed in mice after the treatment of males with 150 mg/kg/day for 5 days (Teramoto et al. 1980).

Other genotoxicity studies are discussed in Section 2.4.

2.2.2.8 Cancer

An environmental epidemiological study did not find any correlation between mortality rates for gastric cancer and leukemia and 1,2-dibromo-3-chloropropane drinking water contamination in Fresno County, California, during the years 1960-1983 (Wong et al. 1989). Similarly, case-control analysis of gastric cancer and leukemia incidences revealed no correlations with exposure.

Increased carcinogenicity has been observed in animals that have chronically ingested 1,2-dibromo-3-chloropropane. Multiple-site carcinomas were found in rats chronically treated with 1,2-dibromo-3-chloropropane by gavage (NC1 1978). An increased incidence of carcinomas, squamous cell carcinomas, and papillomas of the forestomach was observed in rats of both sexes treated with 15 or 29 mg/kg/day 1,2-dibromo-3-chloropropane. Hemangiomas were detected in the spleens of both sexes treated with the lower dose, while mammary adenocarcinomas were found in both groups of females. Squamous cell carcinomas of the stomach were observed in mice chronically administered 114 mg/kg/day (males) or 110 mg/kg/day (females) 1,2-dibromo-3-chloropropane by gavage (NC1 1978). Increased incidences of squamous cell carcinoma of the forestomach, hepatocellular carcinoma, and adenoma and/or carcinoma of the kidneys were observed in rats that ingested 3 mg/kg/day 1,2-dibromo-3-chloropropane for 104 weeks in their diet (Hazleton 1977, 1978a). Squamous cell papillomas and carcinomas also developed in the stomachs of mice chronically exposed to 4.6 mg/kg/day (Hazleton 1978b). Metastatic lesions of these tumors were observed in livers, kidneys, and other viscera. The cancer effect levels are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.3 Dermal Exposure

Dermal exposure of humans to 1,2-dibromo-3-chloropropane can occur in occupational settings. It is often difficult to clearly separate dermal from inhalation exposures in many studies. Thus, many of the findings from occupational studies described in Section 2.2.1 regarding inhalation exposure are repeated here.

2.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to 1,2-dibromo-3-chloropropane.

The local effects after application of 1,2-dibromo-3-chloropropane on the skin of rabbits increased in severity over time from erythema to extensive necrosis. The LD_{50} in rabbits after 1,2-dibromo-3-chloropropane application to shaven skin for 24 hours under a rubber sleeve was 1,400 mg/kg (Torkelson et al. 1961). This LD_{50} level is recorded in Table 2-3.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, gastrointestinal, musculoskeletal, or hepatic effects in humans or animals after dermal exposure to 1,2-dibromo-3-chloropropane.

Cardiovascular Effects. No conclusive evidence was located to indicate that dermal exposure to 1,2-dibromo-3-chloropropane causes cardiovascular effects in humans. Higher mortality from arteriosclerotic heart disease was observed in workers who may have had skin contact with 1,2-dibromo-3-chloropropane during the production of trimethylene chlorobromide (1,2-dibromo-3-chloropropane is a potential trace contaminant of trimethylene chlorobromide) (Wong et al. 1984). However, it is not possible to conclude from this information that dermal 1,2-dibromo-3-chloropropane exposure is associated with heart disease in humans.

No studies were located regarding cardiovascular effects of 1,2-dibromo-3-chloropropane in animals after dermal exposure.

Hematological Effects. No hematological effects were found in workers at a pesticide factory who may have had skin contact with 1,2-dibromo-3-chloropropane (Whorton et al. 1977). Estimates of dermal exposure were not presented.

No studies were located regarding hematological effects of 1,2-dibromo-3-chloropropane in animals after dermal exposure.

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

Key to figure[a]	Species	Route	Exposure duration/ frequency	System	NOAEL	LOAEL (effect) Less serious	LOAEL (effect) Serious	Reference
ACUTE EXPOSURE								
Death								
	Rabbit						1400 (LD50) mg/kg	Torkelson et al. 1961
Systemic								
	Rabbit		1 d 1x/d	Derm/oc		1% (eye irritation) sol.		Torkelson et al. 1961
	Rabbit		1 d 1x/d	Derm/oc		0.5 (slight erythema) mL		Torkelson et al. 1961
INTERMEDIATE EXPOSURE								
Systemic								
	Rabbit		20 d 1x/d	Derm/oc		0.5 (crustiness of mL skin)		Torkelson et al. 1961
CHRONIC EXPOSURE								
Cancer								
	Mouse		63-85 wk 3d/wk 1x/d				11.7[a] (CEL, stomach mg/ carcinomas) appl/ mouse	Van Duuren et al. 1979

[a]Cumulative dose based on exposure to 390 mg/kg, 3 days/week up to 85 weeks.

CEL = cancer effect level; d = day(s); Derm/oc = dermal/ocular; LD_{50} = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; sol = solution; wk = week(s); x = time(s)

Renal Effects. Urinalysis parameters were within normal limits in workers who may have had skin contact with 1,2-dibromo-3-chloropropane during its production (Whorton et al. 1977). Estimates of dermal exposure were not presented in this study. No other studies were located regarding renal effects in humans after dermal exposure to 1,2-dibromo-3-chloropropane.

No studies were located regarding renal effects of 1,2-dibromo-3-chloropropane in animals after dermal exposure.

Dermal/Ocular Effects. No studies were located regarding dermal/ocular effects of 1,2-dibromo-3-chloropropane in humans after dermal exposure.

The local effects after application of 0.5 mL 1,2-dibromo-3-chloropropane on the skin of rabbits increased in severity over time from erythema after 1 day of treatment to extensive necrosis of the dermis and subcutaneous tissue after 20 days of treatment. Application of a 1% solution of 1,2-dibromo-3-chloropropane in propylene glycol to the eyes of rabbits caused irritation of the conjunctiva and iris (Torkelson et al. 1961). The LOAEL values for dermal/ocular effects in rabbits in each duration category are recorded in Table 2-3.

No studies were located regarding the following health effects in humans or animals after dermal exposure to 1,2-dibromo-3-chloropropane:

2.2.3.3 Immunological Effects
2.2.3.4 Neurological Effects
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 cancer in humans after dermal exposure to 1,2-dibromo-3-chloropropane.

Benign lung papillomas and stomach carcinomas and papillomas were found in mice after dermal application of 390 mg/kg, 3 days/week for up to 85 weeks (11.7 mg/mouse/day) (Van Dureen et al. 1979). 1,2-Dibromo-3-chloropropane was also active as a skin-tumor initiator in a two-stage carcinogenicity assay. Phorbol myristate acetate was used as a promoter. The median survival time for mice was 342-468 days. The cancer effect level is recorded in Table 2-3.

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

No studies were located regarding absorption by humans or animals after inhalation exposure to 1,2-dibromo-3-chloropropane. Evidence that 1,2-dibromo-3-chloropropane can be absorbed by this route of exposure is provided by toxicity studies (Section 2.2.1).

2.3.1.2 Oral Exposure

No studies were located regarding absorption by'humans after oral exposure to 1,2-dibromo-3-chloropropane.

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

2.3.1.3 Dermal Exposure

No studies were located regarding absorption in humans or animals after dermal exposure to 1,2-dibromo-3-chloropropane. Evidence that 1,2-dibromo-3-chloropropane can be absorbed by this route of exposure is provided by the observation that death occurred following a 24-hour dermal exposure to this chemical (Torkelson et al. 1961).

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were located regarding distribution in humans or animals after inhalation exposure to 1,2-dibromo-3-chloropropane.

2.3.2.2 Oral Exposure

No studies were located regarding distribution in humans after oral exposure to 1,2-dibromo-3-chloropropane.

Following absorption in rats, 1,2-dibromo-3-chloropropane, which was administered by corn oil gavage for 10 consecutive days to pregnant rats, was rapidly and widely distributed to tissues and tended to remain longest in fat (Ruddick and Newsome 1979). The concentration of 1,2-dibromo-3-chloropropane in pooled fetuses and in spleens, brains, hearts, kidneys, and livers of dams was highest within 3 hours of the exposure to the last dose of 1,2-dibromo-3-chloropropane. The peak level in fat occurred after 6 hours, and 1,2-dibromo-3-chloropropane was still detectable after 24 hours. The elimination of unchanged 1,2-dibromo-3-chloropropane from other tissues was much faster. The detection in tissues of pooled fetuses provides evidence that 1,2-dibromo-3-chloropropane crossed the placenta.

In rats administered ^{14}C-1,2-dibromo-3-chloropropane in corn oil by gavage , unchanged 1,2-dibromo-3-chloropropane accumulated only in the adipose tissues, while the unextractable metabolites were found in kidneys and livers (Kato et al. 1979a). The unextractable metabolites were detected in most tissues, possibly as reactive metabolites bound to tissue macromolecules. The highest level of radioactivity was found in livers and kidneys (Kato et al. 1980) 6 and 20 hours postexposure. These are the organs where histopathological changes were apparent (Section 2.2.2.2).

2.3.2.3 Dermal Exposure

No studies were located regarding distribution in humans or animals after dermal exposure to 1,2-dibromo-3-chloropropane.

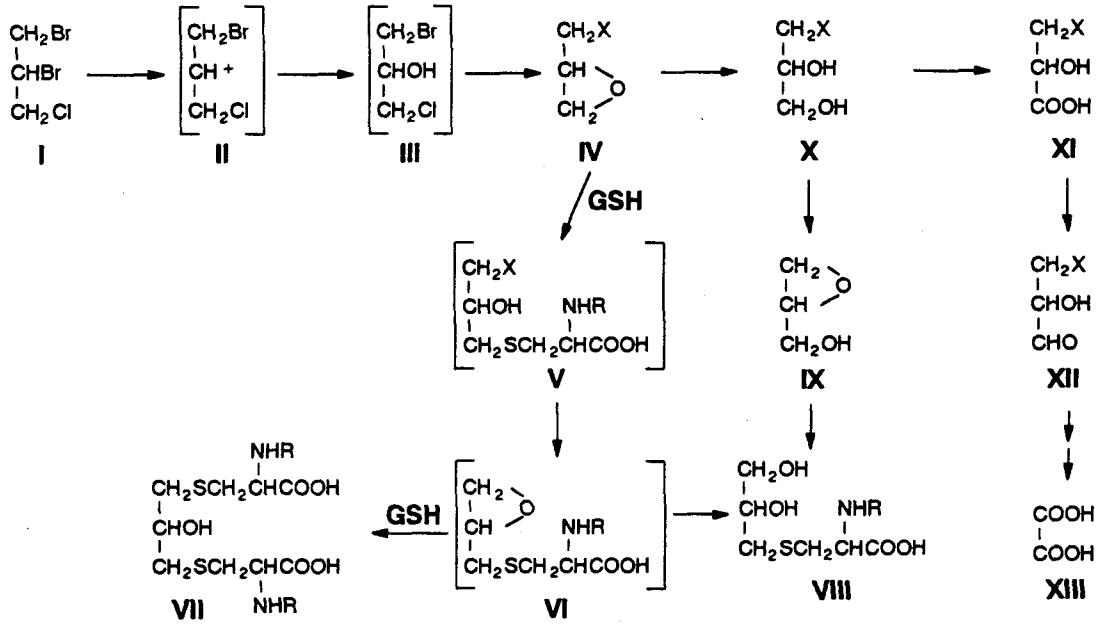
2.3.3 Metabolism

No studies were located regarding metabolism of 1,2-dibromo-3-chloropropane in humans.

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

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

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



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

***Adapted from Jones et al. 1979**

GSH levels were depleted in the liver and kidney, but not in the testes, after intraperitoneal administration of 1,2-dibromo-3-chloropropane in rats (Lag et al. 1989a). Since both testes and kidneys are target organs of 1,2-dibromo-3-chloropropane toxicity, a correlation between GSH depletion in these tissues and induced organ toxicity is lacking. Furthermore, there was no preferential accumulation of 1,2-dibromo-3-chloropropane metabolites in testes in another study (Shemi et al. 1987). Studies of the mechanism of 1,2-dibromo-3-chloropropane induced testicular toxicity suggest that in the testes, conjugation with glutathione with subsequent metabolism to a reactive metabolite represents a toxifying mechanism (Kluwe 1983; Omichinski et al. 1988a, 1988b).

The interspecies differences in 1,2-dibromo-3-chloropropane gonadotoxicity are probably due to interspecies differences in metabolism within the testicular cells to convert 1,2-dibromo-3-chloropropane to more reactive forms. After a single intraperitoneal injection of 1,2-dibromo-3-chloropropane, atrophy of seminiferous epithelium was more severe in rats and guinea pigs than in hamsters and mice. Furthermore, testicular deoxyribonucleic acid (DNA) damage was observed only in rats and guinea pigs (Lag et al. 1989a). These findings suggest that rats and guinea pigs are sensitive to 1,2-dibromo-3-chloropropane because their testicular cells more readily activate 1,2-dibromo-3-chloropropane to a DNA-damaging intermediate(s). Species differences in metabolism were also found in in vitro experiments with tissues from rats and mice. Rats metabolized 1,2-dibromo-3-chloropropane in liver, kidney, testes, and stomach preparations much faster than mice, as measured by GSH-dependent debromination in cytosolic fractions (MacFarland et al. 1984).

2.3.4 Excretion

2.3.4.1 Inhalation Exposure

No studies were located regarding the excretion in humans or animals following inhalation exposure to 1,2-dibromo-3-chloropropane.

2.3.4.2 Oral Exposure

No studies were located regarding excretion in humans following oral exposure to 1,2-dibromo-3-chloropropane.

Excretion after administration of radioactively labeled 1,2-dibromo-3-chloropropane in rats occurred via several routes, including exhalation and biliary and urinary elimination. Radioactivity was primarily expired as carbon dioxide; only a trace of unchanged 1,2-dibromo-3-chloropropane was detected. Mercapturic acids were detected in the urine; biliary excretion accounted for approximately 23% of the administered dose (Kato et al. 1979a). Within 3 days of gavage administration of radioactively labeled 1,2-dibromo-3-chloropropane to rats, 55% of the radioactivity was found in the urine, 18%

in the feces, and 19.5% in the exhaled air as carbon dioxide. Less than 1% was exhaled as unchanged 1,2-dibromo-3-chloropropane (Gingell et al. 198717).

2.3.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals after dermal exposure to 1,2-dibromo-3-chloropropane.

2.4 RELEVANCE TO PUBLIC HEALTH

Information regarding health effects of 1,2-dibromo-3-chloropropane in humans and animals is available for the inhalation and oral routes of exposure. Inhalation is the main route of exposure to 1,2-dibromo-3-chloropropane in occupational settings, while oral exposure most often results from ingestion of contaminated drinking water. Until 1977, 1,2-dibromo-3-chloropropane was used in the United States as a nematocide (Section 4.3).

Epidemiological studies have indicated that the testes are the main targets of 1,2-dibromo-3-chloropropane toxicity following occupational exposures. Decreased spermatogenesis, atrophy of the seminiferous epithelium with azoospermia, and possible sex ratio differences in offspring were observed in exposed workers. Studies indicate that the testicular damage can be permanent. Other effects reported by exposed workers include headache, nausea, lightheadedness, and weakness. No reproductive or carcinogenic effects were detected in a population exposed to concentrations of 1,2-dibromo-3-chloropropane ranging from 0.004 ppb to 5.75 ppb in drinking water (Wong et al. 1988, 1989).

In animals, effects after inhalation and oral exposures include increased mortality, fetotoxicity, hepatic and renal lesions, gonadal atrophy, and cancer. Respiratory lesions and carcinomas of the respiratory tract were observed after inhalation exposure, while gastrointestinal lesions and stomach carcinomas were seen after oral exposure. In addition, anemia, central nervous system depression, and brain lesions were observed in animals after inhalation exposures.

After dermal exposure, 1,2-dibromo-3-chloropropane was reported to cause ocular and dermal irritation and stomach cancer in experimental animals.

Studies in humans did not provide sufficient data regarding exposure levels and their correlation with observed effects. Therefore, animal studies were used for the derivation of MRLs.

Sufficient information was not available on the health effects of 1,2-dibromo-3-chloropropane to derive an MRL for acute-duration inhalation exposure. In one study, reproductive effects were noted in rats following acute inhalation exposure to 1,2-dibromo-3-chloropropane (Saegusa et al. 1982). Although this is the most sensitive end point for 1,2-dibromo-

3-chloropropane toxicity, the data are only available for rats. Reproductive toxicity data are needed for acute inhalation exposures in rabbits and humans since these appears to be more sensitive species than the rat for such effects.

An intermediate-duration inhalation MRL of 0.0002 ppm was derived from a NOAEL value of 0.1 ppm for changes in spermatogenesis and testicular atrophy in rabbits (Rao et al. 1982). The ratio of the blood/gas partition coefficients was assumed to be 1. The dose was adjusted for intermittent exposure by multiplying the NOAEL by 6/24 to correct for less than a full day of exposure and by 5/7 to correct for less than a full week of exposure. The result was then divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). The lowest human equivalent concentration from the available intermediate-duration inhalation studies and the most sensitive (reproductive) end point were used. Intermediate-duration exposure to 1 ppm induced, decreased spermatogenesis, sperm abnormalities, and testicular atrophy (Rao et al. 1982); and infertility occurred at 10 ppm (Rao et al. 1982). Testicular atrophy was also noted at 10 or 25 ppm in rats (NTP 1982; Torkelson et al. 1961) Other effects included nephrosis at 1 ppm in rats (NTP 1982), decreased weight gain at 1 ppm in mice, and bronchial hyperplasia at 5 ppm in mice (NTP 1982).

Information regarding effects following chronic inhalation exposure to 1,2-dibromo-3-chloropropane was limited to carcinogenicity studies in rats and mice (NTP 1982). The data were not suitable for the MRL development because no NOAEL value for the most sensitive (reproductive) system was available from the studies. Considering a NOAEL or a LOAEL value from any other end points would result in a chronic-duration inhalation MRL higher than the intermediate-duration inhalation MRL. In addition, systemic effects occurred in various organs of rats and mice at the same exposure levels that tumors were observed in these organs.

Several studies provided information on LD50 values and systemic effects following acute oral exposure to 1,2-dibromo-3-chloropropane. However, no acute oral MRL was derived for 1,2-dibromo-3-chloropropane because dominant lethality was observed at the lowest dose tested (10 mg/kg/day) (Teramoto et al. 1980) from all available studies.

An intermediate-duration oral MRL was derived from information for reproductive effects noted in rabbits (Foote et al. 1986a, 1986b). Decreased spermatogenesis and abnormal sperm morphology were observed in rabbits at the end of a 10-week exposure to concentrations of 1,2-dibromo-3-chloropropane as low as 1.88 mg/kg/day (Foote et al. 1986a, 1986b). These effects increased with dose. At the highest dose tested, 15 mg/kg/day, testicular atrophy and increased serum FSH levels were observed. No NOAEL was identified in this study. An intermediate-duration oral MRL of 0.002 mg/kg/day was derived from the LOAEL value of 1.88 mg/kg/day for effects on spermatogenesis and sperm morphology (Foote 1986a, 1986b). The MRL value was obtained by dividing the

LOAEL by an uncertainty factor of 1000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability). Intermediate-duration oral exposure to 1,2-dibromochloropropane has also been reported to result in testicular degeneration in rats at 15 mg/kg/day (Amann and Berndtaon 1986), testicular necrosis in rats at 70 mg/kg/day (Rakhmatullayev 1969); reduced litters in mice at 25 mg/kg/day (Reel et al. 1984), and azoospermia in monkeys (Overstreet et al. 1988). Adverse reproductive effects in rats were also reported after intermediate-duration exposure to 0.05 mg/kg/day of 1,2-dibromo-3-chloropropane (Rakhmatullaev 1971). However, the effects were poorly described and very few study details were given. Therefore, this value was not used to derive an MRL.

Toxicity information from chronic oral exposure to 1,2-dibromo-3-chloropropane cannot be used to derive an MRL because reproductive toxicity, which may be the most sensitive end point, was tested at levels that also induced cancer or death. Systemic toxicity data in rats cannot be used for MRL derivation because the statistical significance of the effects was not reported for the available LOAEL values (Hazleton 1977, 1978a). Additional data are needed to determine whether hepatic toxicity, which was noted at the lowest LOAEL of 0.3 mg/kg/day (Hazleton 1977, 1978a), is the primary end point following chronic oral exposure.

Death. No studies were located regarding death in humans after exposure to 1,2-dibromo-3-chloropropane. Mortality was induced in experimental animals by all routes of exposure and corresponding LC_{50} and LD_{50} values were derived (Moody et al. 1984; Torkelson et al. 1961). Increased mortality was also observed in rats and mice after intermediate- and chronic-duration oral exposure (Hazleton 1977, 1978b; NC1 1978) and chronic-duration inhalation exposure (NTP 1982). The risk of shortened lifespan may be of concern for people who are exposed to substantial amounts over extended periods of time.

Systemic Effects

Respiratory Effects. No studies were located regarding respiratory effects in humans after exposure to 1,2-dibromo-3-chloropropane by any route. 1,2-Dibromo-3-chloropropane-induced toxicity in the respiratory tract (inflammatory and proliferative changes in the nasal cavity, necrosis of the trachea and bronchial epithelium, nasal cavity carcinomas) was observed in animals after inhalation exposure (NTP 1982), but not after oral exposure (NC1 1978). Irritation of the upper respiratory tract of the rat occurred after acute high-level exposure (Torkelson et al. 1961). Histopathological changes such as epithelial cytomegaly and focal necrosis occurred after more prolonged exposure (Saegusa et al. 1982). Inflammatory and proliferative changes were seen in the nasal cavity, trachea, and bronchial epithelium of rats and mice in an intermediate-duration study with exposures up to 25 ppm 1,2-dibromo-3-chloropropane for 90 days (NTP 1982). Rats exposed to 10 and 20 ppm 1,2-dibromo-3-chloropropane for 10 weeks had emphysema and bronchopneumonia

(Torkelson et al. 1961). However, infection from stress-induced lowered immunity cannot be ruled out in the case of the rodents. Chronic exposure of rats and mice resulted in tumors of the respiratory tracts. Epithelial hyperplasia was listed among nonneoplastic effects (NTP 1982). The animal studies show a correlation between the severity of induced respiratory changes and exposure concentrations and durations, and suggest the potential of respiratory effects in people exposed by inhalation to 1,2-dibromo-3-chloropropane.

Cardiovascular Effects. The only epidemiological data available cannot provide definitive conclusions regarding cardiovascular effects in humans (Wong et al. 1984). No histopathological changes were associated with the cardiovascular system in experimental animals by any exposure route (Hazleton 1977, 1978a; NC1 1978; NTP 1982; Rao et al. 1982). Based on the possible association in occupationally exposed humans, a potential for increased incidence of cardiovascular disease in humans exposed to 1,2-dibromo-3-chloropropane in the environment or at hazardous waste sites may exist.

Gastrointestinal Effects. No studies were located regarding nonneoplastic gastrointestinal effects in humans after exposure to 1,2-dibromo-3-chloropropane by any route. One study examined the correlation between ingestion of drinking water containing 0.004-5.75 ppb 1,2-dibromochloropropane and gastric cancer and found no correlation (Wong et a1.1989). Gastrointestinal effects occurred in experimental animals mainly after oral exposure to 1,2-dibromo-3-chloropropane. Cell proliferation and hyperkeratosis were observed in stomachs of rats after acute-duration exposure (Ghanayem et al. 1986). Changes varied from edema to necrosis after intermediate-duration exposure (Rakhmatullajev 1969; Torkelson et al. 1961). Acanthosis and hyperkeratosis of the stomach were seen in rats after chronic exposure; however, after chronic exposure, the most significant effect was stomach cancer in both rats and mice (Hazleton 1977, 1978a, 1978b; NC1 1978). Therefore, people who are orally exposed to substantial amounts of 1,2-dibromo-3-chloropropane (i.e., by ingestion of heavily contaminated drinking water) may experience adverse gastrointestinal effects.

Hematological Effects. No studies were located regarding hematological effects in humans after exposure to 1,2-dibromo-3-chloropropane by the oral route. No hematological effects were found in workers exposed to 1,2-dibromo-3-chloropropane (Whorton et al. 1977). A marked decrease in the white blood cell count was reported in monkeys after an intermediate duration inhalation exposure to 1,2-dibromo-3-chloropropane (Torkelson et al. 1961). Splenic atrophy was observed in rats after an acute inhalation exposure (Saegusa et al. 1982) and in mice after a chronic inhalation exposure (NTP 1982). Rats exposed by inhalation developed hypocellularity of the bone marrow (NTP 1982). These findings may indicate a hematological effect of 1,2-dibromo-3-chloropropane exposure. However, no hematological changes were observed in several other inhalation experiments in rats, mice, guinea pigs, or rabbits (NTP 1982; Rao et al. 1982, 1983; Torkelson et al. 1961). No changes were

found after oral exposure. The possibility that 1,2-dibromo-3-chloropropane could cause hematological effects in humans cannot be ruled out.

Hepatic Effects. No studies were located regarding hepatic effects in humans after exposure to 1,2-dibromo-3-chloropropane by any route. Hydropic hepatocytes and focal necrosis were found in rats and mice after intermediateduration inhalation exposure. No changes were found after chronic exposure of either species to lower concentrations (NTP 1982). Focal centrilobular necrosis and hydropic hepatocytes (Kato et al. 1980) and hepatocellular swelling and increased cytoplasmic basophilia (Kluwe 1981) were also reported in rats after acute oral exposure. Poliosis hepatitis was observed in rats after chronic oral exposure (Hazleton 1977, 1978a). The hepatic toxicity of 1,2-dibromo-3-chloropropane was supported by results in rats treated with 1,2-dibromo-3-chloropropane by injection. Dose-related changes that ranged from hepatocellular swelling to necrosis were observed (Kluwe 1981; Kluwe et al. 1985; Saegusa 1986, 1987). There were no differences in the incidence or severity of hepatocytic effects in rats regardless of whether exposure was conducted by oral gavage, intraperitoneal injection, or subcutaneous injection (Kluwe 1981).

The mechanism of 1,2-dibromo-3-chloropropane-induced hepatic toxicity has been investigated in several studies. The role of microsomal metabolism was demonstrated by the enhancement of macromolecular binding after pretreatment of rats with phenobarbital (Kato et al. 1980). However, pretreatment of rats with phenobarbital was shown to reduce 1,2-dibromo-3-chloropropane-induced hepatic toxicity (Kluwe 1983). Thus, the role of the microsomal system in the hepatic toxicity induced by 1,2-dibromo-3-chloropropane or its metabolites is not clear. An *in vitro* study demonstrated DNA damage and a depletion of hepatocellular GSH after liver cells were exposed to 1,2-dibromo-3-chloropropane (Holme et al. 1989). The initial metabolism of 1,2-dibromo-3-chloropropane to reactive epoxide metabolites that bind to DNA and other macromolecules may be responsible for the hepatotoxicity.

The demonstration of hepatic effects in animals indicates that 1,2-dibromo-3-chloropropane has the potential to cause liver injury in humans.

Renal Effects. No studies were located regarding renal effects in humans after exposure to 1,2-dibromo-3-chloropropane by the oral route. No renal effects were detected from the urinalysis of workers exposed to 1,2-dibromo-3-chloropropane (Whorton et al. 1977). Renal toxicity of 1,2-dibromo-3-chloropropane in animals, however, was apparent after inhalation and oral exposures, as well as after injection of experimental animals. Necrotic changes in the proximal tubules were reported after an acute inhalation exposure (Saegusa et al. 1982), while nephritis and nephrosis were observed after intermediate-duration (NTP 1982; Torkelson et al. 1961) and chronic exposures (NTP 1982). Similarly, acute renal insufficiency and/or tubular necrosis were reported after an acute oral exposure (Kato et al. 1980;

Kluwe 1981; Russell 1989). Renal function recovered, but focal glomerulosclerosis persisted (Russell 1989). Increased turnover of proximal tubular cells was noted in rats following intermediate exposure (Heindel et al. 1989). Tubular epithelial changes were observed in the kidneys of rats after chronic oral exposure (Hazleton 1977, 1978a). Furthermore, increased incidence of renal carcinomas occurred in these exposed rats. Acute tubular necrosis was also observed in rats that were injected with 1,2-dibromo-3-chloropropane (Kluwe 1981; Kluwe et al. 1985; Saegusa 1986, 1987). There were no differences in the incidence or severity of kidney tubular necrosis in rats regardless of whether exposure was conducted by oral gavage, intraperitoneal injection, or subcutaneous injection (Kluwe 1981).

A recent study in rats indicates that renal DNA damage correlates with renal necrosis after injection of 1,2-dibromo-3-chloropropane (Omichinski et al. 1987). The.involvement of oxidative metabolism in producing the nephrotoxic effect seems to be unlikely because deuteration of the parent compound did not decrease the DNA damaging effect. (Deuterium substitution can often decrease the extent of a compound's toxicity that is due to a reactive metabolite formed by oxidation of the carbon-hydrogen bond because of the high activation energy required to break the carbon-deuterium bond.) An accumulation of 1,2-dibromo-3-chloropropane metabolites in the kidneys was observed together with the depletion of renal GSH concentrations after an oral exposure of rats (Kato et al. 1980); however, the results of experiments with modulators of NPS conjugate formation indicated that this mechanism is not rate-limiting in 1,2-dibromo-3-chloropropane-induced nephrotoxicity (Omichinski et al. 1987). Experiments with methylated analogs of 1,2-dibromo-3-chloropropane suggested the importance of a dibromo-ethyl group to the toxic effects. Although the mechanism is not clear, the demonstration of renal effects in rats and mice in several studies suggests the potential for renal effects in humans who are substantially exposed to 1,2-dibromo-3-chloropropane.

Dermal/Ocular Effects. Eye irritation and clouding of the cornea and lens were observed in rats after an inhalation exposure to high concentrations of 1,2-dibromo-3-chloropropane (Torkelson et al. 1961). Changes varying from erythema to necrosis were seen in rabbits after dermal application. 1,2-Dibromo-3-chloropropane that was applied to the skin caused death in exposed animals, indicating that it was dermally absorbed. It is evident that 1,2-dibromo-3-chloropropane can be absorbed through the skin of humans. There is, therefore, a potential for systemic and local effects to occur following 1,2-dibromo-3-chloropropane contact with the skin.

Immunological Effects. No data were located regarding immunological effects of 1,2-dibromo-3-chloropropane in humans after inhalation exposure. No histopathological changes were observed in bone marrow, lymph nodes, or spleen of rats after chronic oral exposure (Hazleton 1977, 1978a). However, reversible atrophy and depletion of lymphocytes in the thymus, spleen, and

lymphatic nodules were reported in rats after a single subcutaneous injection of 1,2-dibromo-3-chloropropane (Saegusa 1986). In addition, hypocellularity of bone marrow was observed in rats exposed by inhalation (NTP 1982). Severe respiratory infections were found in rats (Torkelson et al. 1961) and monkeys and rabbits (Rao et al. 1982) that were exposed to 1,2-dibromo-3-chloropropane; control animals did not have infections. These findings suggest that 1,2-dibromo-3-chloropropane may have caused a decreased resistance to infection. The possibility of immunological effects in humans exposed to 1,2-dibromo-3-chloropropane cannot be ruled out.

Neurological Effects. No studies were located regarding neurological effects in humans after exposure to 1,2-dibromo-3-chloropropane by the oral route. Subjective symptoms (nausea, headache, and weakness) were reported by workers exposed occupationally to 1,2-dibromo-3-chloropropane (Whorton et al. 1977). Inhalation is the primary route of exposure in industrial settings, although dermal exposure is also likely. Neurological effects of 1,2-dibromo-3-chloropropane have been described after inhalation and oral exposures of experimental animals. Depression of the central nervous system was reported in rats after an acute inhalation exposure, but without complete narcosis (Torkelson et al. 1961). Histopathological changes found in the brains of exposed animals include focal mineralization, meningoencephalitis and cerebral necrosis. The severity increased with increasing exposure (NTP 1982; Rao et al. 1983). No histopathological changes in brains of rats or mice were reported after oral treatment with 1,2-dibromo-3-chloropropane (Hazleton 1977, 1978a; Johnston et al. 1986; NCI 1978); however, depression of the central nervous system was observed after oral treatment with high doses (Rakhmatullaev 1969; Reel et al. 1984). The findings in animals suggest a potential for neurological effects in humans who are exposed to very large amounts of 1,2-dibromo-3-chloropropane.

Developmental Effects. No developmental effects were found among the offspring of workers occupationally exposed to 1,2-dibromo-3-chloropropane (Goldsmith et al. 1984; Potashnik and Abeliovich 1985; Potashnik and Phillip 1988). Negative results were also obtained after examining the offspring of a population in Fresno County, California, who were exposed to drinking water contaminated with 1,2-dibromo-3-chloropropane (Whorton et al. 1989).

No teratogenicity was observed in the offspring of rats after oral exposure of the dams to 1,2-dibromo-3-chloropropane during gestation (Ruddick and Newsome 1979), or after exposure of both parents to drinking water that contained 1,2-dibromo-3-chloropropane (Johnston et al. 1986). Effects on pup weight and litter size were attributed to maternal toxicity manifested as decreased body weight gain. Testicular degeneration was observed in male rats postexposure in utero when their dams had been injected with 1,2-dibromo-3-chloropropane during gestation (Warren et al. 1988). Although 1,2-dibromo-3-chloropropane does not appear to cause developmental effects in animals at

doses that are not toxic to the dams, developmental effects after inhalation or oral exposure in humans cannot be ruled out.

Reproductive Effects. 1,2-Dibromo-3-chloropropane toxicity to the human male reproductive system was demonstrated in numerous studies. 1,2-Dibromo-3-chloropropane-induced changes were found in cohorts of workers exposed in factories that produced this nematocide (Potashnik et al. 1978; Whorton et al. 1979) and in 1,2-dibromo-3-chloropropane applicators and farmers exposed to 1,2-dibromo-3-chloropropane (Glass et al. 1979; Sandifer et al. 1979). The actual levels of exposure were not established in most studies, but the testicular toxicity can apparently occur upon inhalation of concentrations in air of less than 1 ppm (Whorton et al. 1977). When the cohorts were divided according to their length of exposure either by years (Whorton et al. 1979) or by hours when they were directly involved in 1,2-dibromo-3-chloropropane production (Potashnik et al. 1978), a correlation was found between the length of exposure and the severity of changes. Exposure to levels of about 1 ppb 1,2-dibromo-3-chloropropane did not cause any effects in pineapple workers in Hawaii (Coye et al. 1983, 1990). Azoospermia or oligospermia found by analysis of sperm counts was a reflection of the measure of damage demonstrated in histopathological examinations at biopsy (Lantz et al. 1981; Potashnik et al. 1978). Depletion of germ cells in seminiferous tubules with intact Sertoli cells was seen in most cases of azoospermia. Azoospermia was accompanied with an increase in plasma FSH levels (Eaton et al. 1986; Lantz et al. 1981). The hormonal changes were more'pronounced in unrecovered workers after a nonexposure period (Potashnik and Yanai-Inbar 1987). The FSH assay alone, however, was not sensitive enough to detect oligospermia (Whorton et al. 1979). A depressed fertility rate resulted as a direct consequence of testicular changes in these workers who were exposed to 1,2-dibromo-3-chloropropane.

Oral exposure to 1,2-dibromo-3-chloropropane through contaminated drinking water occurred in Fresno County, California (Wong et al. 1988); however, the concentrations of 1,2-dibromo-3-chloropropane in the water were low (0.004-5.75 ppb), and no changes in birth rates were detectable.

1,2-Dibromo-3-chloropropane-induced testicular toxicity has been demonstrated in several animal studies. Atrophy of the seminiferous tubules was reported in rats after acute- or intermediate-duration inhalation exposures (NTP 1982; Rao et al. 1983; Saegusa et al. 1982). Similar changes were also found in exposed rabbits, together with an increase of plasma FSH levels (Rao et al. 1982). Testicular damage was reversible in rabbits (Rao et al. 1982), and humans (Olson et al. 1990). In addition, dominant lethality recorded in rats was reversed after a recovery period (Rao et al. 1983). Following oral exposures, the induction of dominant lethality was also observed after in rats (Amann and Berndtson 1986; Teramoto et al. 1980) but not in mice (Teramoto et al. 1980). Dominant lethality was not induced in mice after intraperitoneal injections of 1,2-dibromo-3-chloropropane (Generoso

et al. 1985). Histopathological changes found in testes of rats and/or rabbits after oral exposure to 1,2-dibromo-3-chloropropane were similar to those found after inhalation exposure (Amann and Berndtson 1986; Foote et al. 1986b; Kluwe 1981). The changes were dose-related and accompanied by elevated FSH levels in rabbits (Foote et al. 1986b). Impaired spermatogenesis was also noted in rabbits under identical exposure conditions (Foote et al. 1986a). No changes in fertility were recorded in these rabbits (Foote et al. 1986b). There were no differences in the incidence or severity of testicular effects in rats regardless of whether exposure was conducted by oral gavage, intraperitoneal injection, or subcutaneous injection (Kluwe 1981).

A high incidence of testicular atrophy was observed in rats (but not in mice) after chronic gavage dosing with 1,2-dibromo-3-chloropropane (NC1 1978); however, no effects were found in rats after administration of lower doses (Hazleton 1977, Hazleton 1978a). No statistically different changes from the ' controls were seen in reproductive organs of rats or mice after chronic inhalation exposure (NTP 1982). Interspecies differences have been shown between rats and rabbits; rabbits were found to be more susceptible to male reproductive effects (Rao et al. 1982, 1983). The interspecies differences for testicular effects induced in rats or mice were also apparent after parenteral exposure. While testicular changes were found in rats after 1,2-dibromo-3-chloropropane injections (Ahmad et al. 1988; Kluwe et al. 1985; Lui and Wysocki 1987; Warren et al. 1984), no changes were observed in mice (Oakberg and Cummings 1984).

The difference in susceptibility between immature and adult rats was also investigated (Kluwe et al. 1985; Lui and Wysocki 1987). Sexually mature male rats seemed to be less susceptible to 1,2-dibromo-3-chloropropane-induced testicular toxicity. Changes that were induced in neonates or *in utero* were carried on to adulthood (Kluwe et al. 1985; Warren et al. 1988). These results are in contrast with a report that found degenerative testicular changes in the adult group of rats and not in the immature group (Saegusa 1987).

The mechanism of 1,2-dibromo-3-chloropropane testicular toxicity has been investigated in several studies *in vitro*. The inhibition of sperm carbohydrate metabolism, probably at the step of nicotinamide adenine dinucleotide (NADH) dehydrogenase activity in the mitochondrial electron transport chain, was suggested to be the cause of the toxicity (Bartoov et al. 1987; Greenwell et al. 1987). Alternatively, well-conducted toxicokinetic studies have indicated that the severity of testicular necrosis is directly related to DNA damage (Omichinski et al. 1988a, 1988b; Soderlund et al. 1988). Metabolism via a cytochrome P-450-dependent pathway is probably not involved in the DNA-damaging effects because the use of deuterated analogs of the parent compound, which interfere with cytochrome P-450 metabolism, did not decrease the amount of the damage. Investigators have suggested that the testicular genotoxicity of 1,2-dibromo-3-chloropropane may involve conjugation with glutathione, with subsequent formation of a reactive episulphonium ion

that can cause.direct alkylation of target molecules. If so, in contrast to the apparent detoxifying role of glutathione conjugation in the liver, conjugation,with glutathione in the testes may be a toxifying mechanism.

1,2-Dibromo-3-chloropropane-induced toxicity to the female reproductive system is not so obvious. No histological changes were found in female reproductive organs after an intermediate- or chronic-duration inhalation exposure (NTP 1982) or chronic oral exposure in rats or mice (NC1 1978). Ovarian cysts were recorded in rats exposed to 10 ppm 1,2-dibromo-3-chloropropane for 14 weeks; fertility, however, was not affected (Rao et al. 1983). No changes in fertility were found in female rats exposed to 1,2-dibromo-3-chloropropane in drinking water (Johnston et al. 1986). In contrast, only 60% of treated females became pregnant after mating when the proestrus rats were given a single injection of 1,2-dibromo-3-chloropropane so that cells in the first meiotic division could be targeted (Shaked et al. 1988). No effect on dominant lethality or fertility was observed in female mice after a single intraperitoneal injection of 1,2-dibromo-3-chloropropane (Generoso et al. 1985).

Evidence that the male reproductive system is a target of 1,2-dibromo-3-chloropropane in humans and some laboratory animals is overwhelming. Recovery is possible, but with higher doses and/or longer exposure, the changes may become permanent.

Genotoxic Effects. 1,2-Dibromo-3-chloropropane has been tested for genotoxicity in a number of in vivo and in vitro studies (Tables 2-4 and 2-5).

The mutagenic potential of 1,2-dibromo-3-chloropropane was demonstrated in humans by the evidence of a change in sex ratio among the offspring of exposed workers (Potashnik et al. 1984). In contrast, no alterations in sex ratios of newborns were found in Fresno County (1978-1982), California, where the drinking water Kas contaminated with 1,2-dibromo-3-chloropropane (Whorton et al. 1989). However, total exposure via drinking water was probably much lower than that experienced by occupationally exposed workers.

Increased dominant lethality was reported in rats after inhalation (Rao et al. 1983) and oral exposures to 1,2-dibromo-3-chloropropane (Teramoto et al. 1980). In contrast, no dominant lethal effect was observed in mice treated either orally for 5 days (Teramoto et al. 1980) or intraperitoneally or subcutaneously with a single injection of 1,2-dibromo-3-chloropropane (Generoso et al. 1985). Positive results were obtained in mice in the spot test (Sasaki et al. 1986) but not in the specific-locus gene mutation test (Russell et al. 1986).

Positive results were found in the reverse mutation assay in Salmonella typhimurium TA1535, TAlOO, and TA98 with metabolic activation but not without

TABLE 2-4. Genotoxicity of 1,2-Dibromo-3-chloropropane *In Vivo*

Species (test system)	End point	Results	Reference
Mouse	Dominant lethal	-	Teramoto et al. 1980
Rat	Dominant lethal	+	Teramoto et al. 1980
Mouse	Dominant lethal	-	Generoso et al. 1985
Mouse	Spot test	+	Sasaki et al. 1986
Mouse	Specific-locus gene mutations	-	Russell et al. 1986
Mouse (prepubertal)	UDS	+	Lee and Suzuki 1979
Mouse (adult)	UDS	-	Lee and Suzuki 1979
Rat	UDS	+	Bentley and Working 1988
Drosophila melanogaster	Recessive lethal	-	Kale and Baum 1982a
	Recessive lethal	+	Kale and Baum 1982a
	Recessive lethal	+	Zimmering 1983
	Recessive lethal	+	Inoue et al. 1982
	Heritable translocations	+	Zimmering 1983
		-	Kale and Baum 1982a
	Genetic crossing over	+	Kale and Baum 1982a
	Chromosome loss	+	Zimmering 1983

+ = positive result; - = negative result; DNA = deoxyribonucleic acid; UDS = unscheduled DNA synthesis

TABLE 2-5. Genotoxicity of 1,2-Dibromo-3-chloropropane In Vitro

Species (test system)	End point	Results: With activation	Results: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium:				
TA1535	Reverse mutation	+	+	Moriya et al. 1983
TA100	Reverse mutation	+	+	Moriya et al. 1983
TA1537	Reverse mutation	No data	-	Moriya et al. 1983
TA1538	Reverse mutation	No data	-	Moriya et al. 1983
TA98	Reverse mutation	+	+	Moriya et al. 1983
TA1535	Reverse mutation	+	-	Biles et al. 1978
TA100	Reverse mutation	+	-	Stolzenberg and Hine 1979
TA98	Reverse mutation	+	-	Stolzenberg and Hine 1979
TA1535	Reverse mutation	+	-	Ratpan and Plaumann 1988
TA100	Reverse mutation	+	-	Ratpan and Plaumann 1988
Escherichia coli:				
WP2hυr	Reverse mutation	No data	+	Moriya et al. 1983
Eukaryotic organisms:				
Chinese hamster cells, V79	Sister chromatid exchange	No data	+	Tezuka et al. 1980
Chinese hamster cells, V79	Polyploid test	No data	-	Tezuka et al. 1980
Chinese hamster ovary cells	Sister chromatid exchange	+	+	Loveday et al. 1989
Chinese hamster ovary cells	Chromosome aberration	+	+	Loveday et al. 1989

+ = positive result
- = negative result

activation (Ratpan and Plauman 1988; Stolzenberg and Hine 1979). Purified 1,2-dibromo-3-chloropropane was considered a potent indirect mutagen.

In in vitro studies with eukaryotic systems, 1,2-dibromo-3-chloropropane induced an increased incidence of sister chromatid exchanges in Chinese hamster V79 cells (Tezuka et al. 1980) and in sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells (Loveday et al. 1989).

1,2-Dibromo-3-chloropropane was mutagenic in the recessive lethal assay in Drosophila melanogaster (Inoue et al. 1982; Zimmering 1983). In contrast, the increased lethality was observed only when male flies were treated as embryos (Kale and Baum 1982b). A positive response was also obtained in the induction of genetic crossing-over (Kale and Baum 1982b), chromosome loss (Zimmering 1983), and heritable translocations (Zimmering 1983).

1,2-Dibromo-3-chloropropane induced unscheduled DNA synthesis in the premeiotic germ cells after a single injection to prepubertal mice (Lee and Suzuki 1979). Unscheduled DNA synthesis was also induced in spermatocytes in adult rats (Bentley and Working 1988).

The aforementioned results demonstrate that 1,2-dibromo-3-chloropropane is a potent genetic toxicant. Microbial assays showed that it is capable of inducing gene mutations, and mammalian assays showed that it can cause chromosomal mutations in both somatic and germinal cells. The demonstrated potential for a genotoxic effect in humans is supported by results from a variety of experimental systems.

Cancer. Information regarding carcinogenicity of 1,2-dibromo-3-chloropropane in humans is sparse. Only two epidemiological studies regarding cancer risk were located. One did not report any increased incidence of cancer among exposed workers (Hearn et al. 1984). The other study found no correlation between the risk of gastric cancer in a population residing in an area where drinking water was contaminated with 1,2-dibromo-3-chloropropane (Wong et al. 1989).

There is conclusive evidence of the carcinogenicity of 1,2-dibromo-3-chloropropane in experimental animals. Rats that were exposed to 1,2-dibromo-3-chloropropane by inhalation for 84-103 weeks developed multiplesite neoplasms (NTP 1982). Adenomas and carcinomas of the respiratory tract and tongue in both sexes, fibroadenomas of the mammary gland and adenomas of the adrenal cortex in females, and trichoadenomas of the skin and mesotheliomas of the tunica vaginalis in males were observed in the exposed animals. In contrast, the development of neoplasms was restricted only to the respiratory tract in mice exposed to the same concentrations for 76-103 weeks (NTP 1982). When administered chronically by gavage, 1,2-dibromo-3-chloropropane induced squamous cell carcinomas of the forestomach in rats and mice of both sexes and carcinomas of the mammary gland in female rats (NC1 1978).

When administered chronically in the diet, 1,2-dibromo-3-chloropropane induced squamous cell carcinomas of the forestomach in rats and mice and adenomas and/or carcinomas of the kidneys in rats (Hazleton 1977, 1978a, 1978b). Systemic papillomas and carcinomas developed in the lungs and stomachs of mice after dermal application of 1,2-dibromo-3-chloropropane (Van Duuren et al. 1979). Thus, 1,2-dibromo-3-chloropropane induced cancer, not only at the initial site of contact (respiratory tract or stomach), but also in distant organs. It is possible that metabolites play a significant role in the carcinogenicity of 1,2-dibromo-3-chloropropane.

Based on the evidence in animals, 1,2-dibromo-3-chloropropane is reasonably anticipated to be carcinogenic in humans who are exposed to sufficient doses for long enough periods.

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-dibromo-3-chloropropane 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 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-dibromo-3-chloropropane 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-Dibromo-3-chloropropane

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

Toxicokinetic studies performed in animals after acute exposures to 1,2-dibromo-3-chloropropane indicate that this chemical preferentially partitions to fat; however, upon termination of exposure the accumulated chemical is rapidly lost from this tissue (Kato et al. 1979a; Ruddick and Newsom 1979). Over 80% of adipose tissue 1,2-dibromo-3-chloropropane is lost by 24 hours postexposure. 1,2-Dibromo-3-chloropropane was lost from other tissues more rapidly. Thus, determination of tissue levels of 1,2-dibromo-3-chloropropane must be made shortly after exposure. 1,2-Dibromo-3-chloropropane may be found in exhaled air, but less than 1% of an administered dose was found in exhaled air during the first 24 hours after dosing. At least 20 metabolites were detected in the urine of rats following ingestion of radioactively labeled 1,2-dibromo-3-chloropropane (Gingell et al. 1987b). However, it is not known if these metabolites occur in human urine following exposure to 1,2-dibromo-3-chloropropane by inhalation, oral, or dermal exposures. Also, the detection of these metabolites may not be specific for 1,2-dibromo-3-chloropropane exposures.

The induction of microsomal enzymes, particularly aryl hydrocarbon hydroxylase and epoxide hydrolase, was observed in tissues of rats that were exposed to 1,2-dibromo-3-chloropropane (Suzuki and Lee 1981). However, microsomal enzyme induction may be caused by over 300 drugs, pesticides, and industrial chemicals. Therefore, changes in microsomal enzyme activity does not specifically indicate exposure to 1,2-dibromo-3-chloropropane. Increased concentrations of serum creatinine, urea nitrogen, glutamic pyruvic transaminase, and sorbitol dehydrogenase were detected in exposed rats (Kluwe 1983). These changes are not, however, specific for 1,2-dibromo-3-chloropropane exposure. Increased concentrations of serum creatinine and urea nitrogen are indicative of kidney damage and may be raised by an chemical exhibiting renal toxicity. Likewise, increased concentrations of serum glutamic pyruvic transaminase are indicative of liver damage and may be raised by any chemical resulting in hepatocellular damage.

The possible effect of 1,2-dibromo-3-chloropropane metabolites on heme synthesis and breakdown was investigated in rats (Moody et al. 1984; Tofilon et al. 1980). Decreased incorporation of radioactively labeled aminolevulinic acid into liver protein and extracted heme was observed in 1,2-dibromo-3-chloropropane-exposed rats (Moody et al. 1984). Furthermore, heme catalase activity was also decreased, while increased heme oxygenase activity and increased liver concentrations of uroporphyrin and coproporphyrin were detected. The mechanism of this effect is unknown. Similarly, heme concentrations were depressed in testicular microsomal fractions after oral exposure of rats to 1,2-dibromo-3-chloropropane (Tofilon et al. 1980); however, 1,2-dibromo-3-chloropropane administration did not alter testicular heme oxygenase activity, indicative of a possible difference in the mechanism of organ injury. The reason for the 1,2-dibromo-3-chloropropane-induced changes in heme turnover, and its relationship to a lesion in the testes, needs to be further investigated, The application as a biomarker of exposure would involve a biopsy to obtain the liver or testicular tissue. Use of changes in heme synthesis as a biomarker is limited because the test would not be specific for 1,2-dibromo-3-chloropropane.

Although inorganic bromide could be found in the serum of 1,2-dibromo-3-chloropropane-exposed animals, its measurement was not useful in demonstrating excessive exposure (Torkelson et al. 1961). Furthermore, elevated inorganic bromide levels may result from occupational exposure to methyl bromide or ingestion of inorganic bromides as sleep aids.

Further information on distribution and excretion of 1,2-dibromo-3-chloropropane and its metabolites in animal tissues can be located in Section 2.3.2.

2.5.2 Biomarkers Used to Characterize Effects Caused by 1,2-Dibromo-3-chloropropane

The only consistently observed effects in humans exposed to 1,2-dibromo-3-chloropropane are testicular. An attempt has been made to identify early subtle changes caused by 1,2-dibromo-3-chloropropane in the male reproductive system. For this purpose, the measuring of FSH plasma levels in exposed workers was proposed; however, the elevation of FSH correlates with more serious testicular changes and azoospermia and is not sensitive enough to detect oligospermia (Whorton et al. 1979). Foote et al. (1986a, 1986b) suggest several tests that may be used to identify testicular effects and/or abnormalities in spermatogenic function in males. These include decreases in testis weight, FSH concentration in blood, seminiferous tubular diameter, and enumeration of germ cells per Sertoli cell or per tubular Stage I cross section. The authors concluded that the most sensitive indicator would be germ cell counts; changes in seminiferous tubule diameter would also be a sensitive indicator. Sperm count analysis is a reliable method for detecting 1,2-dibromo-3-chloropropane-induced reproductive toxicity. The other methods

suggested by Foote et al. have not been tested for their reliability in humans.

2.6 INTERACTIONS WITH OTHER CHEMICALS

No studies were located regarding interaction of 1,2-dibromo-3-chloropropane with other chemicals. Workers who are occupationally exposed to 1,2-dibromo-3-chloropropane in chemical factories are also exposed to other chemicals. In addition, technical 1,2-dibromo-3-chloropropane contains a trace of epichlorohydrin, which is a known carcinogen (Kawabata 1981; Laskin et al. 1980) and testicular toxicant (Cooper et al. 1974; Hahn 1970) in animals. In contrast, reproductive effects were not found in workers occupationally exposed to epichlorohydrin (Milby et al. 1981). However, interpretation of this study was confounded by only partial participation of the exposed cohort, by the lack of a matched control from the geographic area, and the lack of exposure data. In conclusion, whether epichlorohydrin or other chemicals have synergistic systemic, reproductive, or carcinogenic effects in humans is not known.

2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

1,2-Dibromo-3-chloropropane toxicity to the reproductive system is pronounced in males. Persons suffering from asthma or chronic respiratory disease might be vulnerable to the respiratory irritant effects of 1,2-dibromo-3-chloropropane. Persons with impaired liver and kidney function may also be more susceptible to the toxic effects of 1,2-dibromo-3-chloropropane because these organs are involved in the detoxification and excretion of this chemical.

2.8 MITIGATION OF TOXICOLOGICAL EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to 1,2-dibromo-3-chloropropane. 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-dibromo-3-chloropropane. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

No specific data were located regarding the mitigation of effects of 1,2-dibromo-3-chloropropane once it has entered the bloodstream and no specific antidotes are known. Therefore, steps should be taken to minimize exposure to this chemical, and in the event that exposure has taken place, to limit absorption into the bloodstream. To minimize occupational exposure, chemical protective clothing, gloves, face shields, and goggles should be provided for workers (NIOSH 1988). In addition, exposure levels should be maintained below permissible exposure limits. In situations where exposure levels may exceed these limits, respirators may also be required. Absorption

by persons who have been exposed to elevated levels of 1,2-dibromo-3-chloropropane may be limited by removing the exposed individual from the contaminated area and by removing contaminated clothing (Bronstein and Currance 1988; NIOSH 1988; Stutz and Janusz 1988). Exposed skin should be washed with soapy water and contaminated eyes flushed with water. Proparacaine hydrochloride (0.5% solution) can be used to facilitate eye irrigation (Bronstein and Currance 1988). Water or milk should be ingested following oral exposure (Bronstein and Currance 1988; Stutz and Janusz 1988). Activated charcoal should be given orally to adsorb the chemical. Emetics should not be used (Bronstein and Currance 1988). Oxygen may be administered and ventilation assistance provided as needed and standard procedures may be used for the treatment of cardiac arrhythmias and pulmonary edema (Bronstein and Currance 1988; Stutz and Janusz 1988).

Studies on the microsomal metabolism of 1,2-dibromo-3-chloropropane showed that the chemical is converted to its epoxy derivatives that can be further hydrolyzed or debrominated (Jones et al. 1979) (Jones et al. 1979; Kale and Baum 1982a; Kato et al. 1979b). Some of the intermediate or end metabolites (α-chlorohydrin, epichlorohydrin, oxalic acid, and a bromide ion) may be responsible for observed toxic effects. The active metabolites are able to bind covalently with nucleophilic sites of macromolecules, such as DNA and protein. In vitro binding to liver protein was found to be enzymedependent as demonstrated by alteration of the reaction with metabolic modifiers (Kato et al. 1979b). The addition of nicotinamide adenine dinucleotide phosphate (NADPH) to the system stimulated the binding, while the addition of sesamex, an inhibitor of microsomal oxidation, inhibited the binding (Kato et al. 1979b). Conversely, pretreatment of mice with polybrominated biphenyls (PBB), inducers of microsomal enzymes, protected the animals from 1,2-dibromo-3-chloropropane toxicity, perhaps by shifting the metabolic pathway in favor of metabolites that do not bind to macromolecules (Kluwe et al. 1981).

In the liver, conjugation of the reactive metabolites with GSH may represent a detoxifying mechanism. The liver was the major site of GSH conjugation with 1,2-dibromo-3-chloropropane metabolites in vivo (Kluwe et al. 1982), and the depletion of GSH correlated with observed toxicity in the liver. That conjugation of intermediate metabolites with GSH is a detoxifying mechanism was further demonstrated in rats (Kluwe et al. 1982). Pretreatment of rats with diethyl maleate, a GSH depletor, increased the renal and hepatic toxicity of the subsequent 1,2-dibromo-3-chloropropane dose.

In contrast, studies in animals indicated that conjugation with GSH is not a detoxifying mechanism in the testes, but rather a toxifying mechanism (Kluwe 1983; Lag et al. 1989a; Omichinski et al. 1988a, 1988b). 1,2-Dibromo-3-chloropropane exposure causes a depletion of seminiferous epithelial germ cells in humans (Biava et al. 1978) and in animals (Lag et al. 1989a). The results of genotoxicity studies indicated that 1,2-dibromo-3-chloropropane metabolites interact with the DNA of spermatogenic cells (Lee and Suzuki

1979). The difference between the mechanism of toxicity in the liver and in the testes precludes the clinical use of agents that would alter the conjugation of metabolites with GSH. Agents that would deplete GSH could protect against harmful effects of 1,2-dibromo-3-chloropropane in the testes but would increase the toxicity in the liver. Agents that would prevent the binding to germ cell DNA would decrease the toxicity in the testes.

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-dibromo-3-chloropropane 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-dibromo-3-chloropropane.

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.

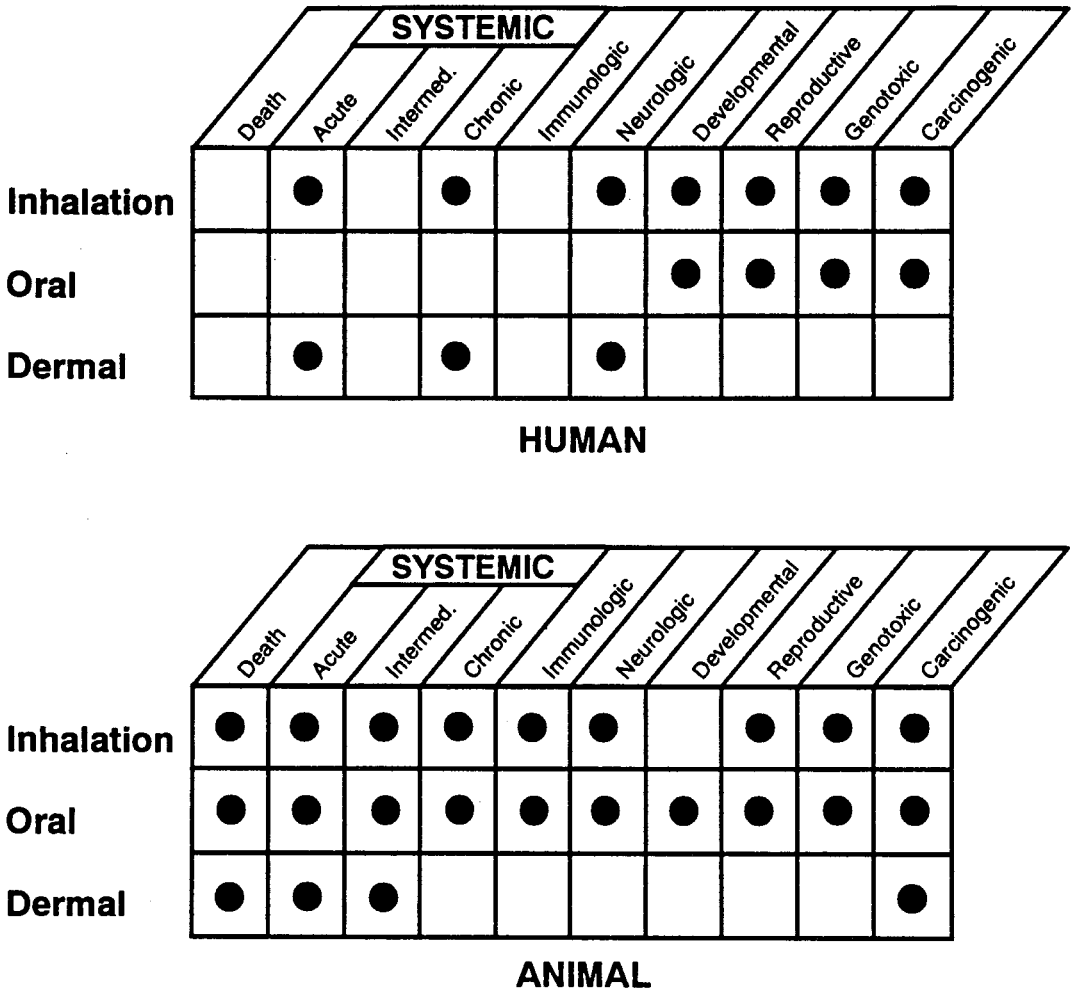
2.9.1 Existing Information on Health Effects of 1,2-Dibromo-3-chloropropane

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1,2-dibromo-3-chloropropane are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of 1,2-dibromo-3-chloropropane. 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.

As seen from Figure 2-4, information regarding chronic systemic effects (cardiovascular, hematological, and renal), neurologic, developmental and reproductive effects, genotoxicity, and cancer exists for inhalation exposure of humans to 1,2-dibromo-3-chloropropane. Human data regarding developmental, reproductive, and genotoxic effects, and cancer were located for oral exposure. No information was located regarding solely dermal exposure of humans to 1,2-dibromo-3-chloropropane, although dermal exposure may have contributed to the effects observed in studies of occupational exposures.

Studies in animals regarding death, systemic effects, neurologic effects, developmental effects, reproductive effects, genotoxicity, and cancer

FIGURE 2-4. Existing Information on Health Effects of 1,2-Dibromo-3-chloropropane



were located for inhalation exposure. Oral studies provide information about death, systemic, neurologic, developmental, and reproductive effects, genotoxicity, and cancer. Information about death, effects on the skin and eyes, and cancer for dermal exposure to 1,2-dibromo-3-chloropropane in animals is available.

2.9.2 Data Needs

Acute-Duration Exposure. Reliable data regarding human acute toxicity following exposure by any route were not located. Systemic effects observed in animals exposed to 1,2-dibromo-3-chloropropane were either route specific or nonspecific. Data were sufficient to identify target organs and systems in animals. Respiratory tract irritation and toxicity were observed after inhalation exposure (Saegusa et al. 1982; Torkelson et al. 1961), gastrointestinal toxicity was reported after oral exposure (Ghanayem et al. 1986), and dermal irritation was reported after dermal exposure (Torkelson et al. 1961). Hepatic and renal toxicity were observed after both inhalation and oral exposures (Kato et al. 1980; Russell 1989; Torkelson et al. 1961). Reproductive system toxicity was also reported after acute inhalation and oral exposures (Saegusa et al. 1982; Teramoto et al. 1980). Pharmacokinetic data are not sufficient to identify additional target organs following dermal exposure. Since hepatic, renal, and reproductive toxicity seem to be common effects of oral and inhalation exposure, and dermal lethality data suggest that absorption occurs by the dermal route, further studies on dermal exposure investigating the target organs might be useful. Dominant lethality was observed in the lowest dose tested in available studies (Teramoto et al. 1980); therefore, an acute oral MRL could not be derived. Reproductive toxicity of 1,2-dibromo-3-chloropropane in humans exposed occupationally for intermediate durations suggests the possibility of similar effects for acuteduration exposure. Furthermore, there are populations living near hazardous waste sites that might be exposed to 1,2-dibromo-3-chloropropane in soil or water through dermal contact, ingestion, or inhalation for brief periods of time.

Intermediate-Duration Exposure. The results obtained from workers who were exposed for intermediate durations show that 1,2-dibromo-3-chloropropane is toxic to the male reproductive system (Potashnik et al. 1978, 1984; Whorton et al. 1979). Data were sufficient to identify the male reproductive system and other organs and systems as targets in animals. Respiratory tract irritation and toxicity were observed in mice and rats after inhalation exposure (NTP 1982). Hepatic and renal toxicity were observed after inhalation and oral exposures of rats and mice in several studies (NTP 1982; Rakhmatullayev 1969; Torkelson et al. 1961). Testicular changes were also found in various species after both routes of exposure. MRLs were derived from the most sensitive end point (reproductive) for inhalation (Rao et al. 1982) and oral (Foote et al. 1986a, 1986b) exposures. The only information located regarding toxicity via dermal exposure of intermediate duration was

crustiness of the skin of rabbits. An investigation of internal effects of intermediate-duration dermal exposure may identify target organs similar to those of oral and inhalation exposures. Because people who work with 1,2-dibromo-3-chloropropane or people living near hazardous waste sites may have skin contact with soil or water contaminated with 1,2-dibromo-3-chloropropane for intermediate durations, information about 1,2-dibromo-3-chloropropane toxicity by the dermal route is important.

Chronic-Duration Exposure and Cancer. The evidence of reproductive toxicity of 1,2-dibromo-3-chloropropane in humans after inhalation exposure is substantial. One study regarding reproductive effects after oral exposure in humans was located (Wong et al. 1988). Exposure to contaminated drinking water probably represented not only oral exposure, but dermal and inhalation exposure as well. Chronic oral and inhalation studies have been conducted in rats and mice, and extensive histological examinations have identified the target organs: respiratory after inhalation (NTP 1982); gastrointestinal, hepatic, renal, and reproductive after oral exposure (Hazleton 1977, 1978a; NC1 1978). No studies were located regarding 1,2-dibromo-3-chloropropane toxicity after chronic dermal exposure. Although chronic inhalation NOAEL and LOAEL values are available for most target organs and systems, a chronic inhalation MRL was not derived because a reproductive NOAEL for chronic exposure is not available, and a MRL derived for any other non-cancer end point might not reflect adequate protection against reproductive effects. The lowest available LOAEL cannot be used to derive an MRL because it does not protect against reproductive effects and the data have not been verified as statistically significant for the observed effects. Information regarding the internal effects of chronic dermal exposure may identify target organs and thresholds of dermal exposure in animals. This information is important because populations living near waste sites for long periods of time might be continuously exposed dermally to 1,2-dibromo-3-chloropropane in contaminated media.

Well-conducted chronic inhalation, oral, and dermal exposure studies provide evidence that 1,2-dibromo-3-chloropropane is carcinogenic in animals (NC1 1978; NTP 1982; Van Duuren et al. 1979). This is supported by the genotoxicity studies on prokaryotic and eukaryotic organisms. On the basis of these data, IARC (1979) and EPA (1985a) concluded that there is sufficient evidence for the carcinogenicity of 1,2-dibromo-3-chloropropane in animals. EPA has classified 1,2-dibromo-3-chloropropane as a probable human carcinogen. Further epidemiological studies of exposed workers would be useful to determine the possible risk in humans.

Genotoxicity. A 1,2-dibromo-3-chloropropane-induced genotoxic effect was reported in humans after occupational exposure. A higher incidence of newborn girls than boys was observed among offspring of exposed men (Goldsmith et al. 1984; Potashnik et al. 1984). In animals, dominant lethal effects were induced after both inhalation and oral exposures in rats (but not in mice)

(Rao et al. 1983; Teramoto et al. 1980). 1,2-Dibromo-3-chloropropane has been tested in a number of studies in Drosophila melanogaster (Inoue et al. 1982; Kale and Baum 1982a; Zimmering 1983). The induction of recessive lethals. genetic crossing-over, chromosome loss, and heritable translocations were observed. 1,2-Dibromo-3-chloropropane was also mutagenic in a battery of in vitro tests in prokaryotic systems and in eukaryotic systems (Biles et al. 1978; Loveday et al. 1989; Moriya et al. 1983; Ratpan and Plauman 1988; Tezuka et al. 1980). These data sufficiently characterize the genotoxic properties of 1,2-dibromo-3-chloropropane, but further information about genotoxic effects of 1,2-dibromo-3-chloropropane in humans would be useful. Cytogenetic analysis of peripheral lymphocytes and sperm examination of exposed workers and correlation of obtained results with exposure concentrations would be helpful.

Reproductive Toxicity. The evidence that 1,2-dibromo-3-chloropropane is toxic to male reproductive organs in workers who were exposed primarily by inhalation is extensive (Eaton et al. 1986; Egnatz et al. 1980; Glass et al. 1979; Goldsmith et al. 1984; Lantz et al. 1981; NIOSH 1979; Potashnik et al. 1978, 1984; Whorton et al. 1977, 1979). The only information on reproductive effects in low-dose orally exposed humans is that no changes in birth rates were observed in populations that were exposed to 1,2-dibromo-3-chloropropanecontaminated water (Wong et al. 1988). This route of exposure was not studied in the human population sufficiently, and it might be important for populations near the waste sites. Therefore, more studies regarding reproductive ef.fects in humans after oral exposure from contaminated water would be useful. The testicular toxicity of 1,2-dibromo-3-chloropropane after inhalation and oral exposure was demonstrated in rats, but not in mice. AMRL for intermediate-duration inhalation (Rao et al. 1982) exposure was derived from a NOAEL for reproductive effects in the rabbit. More information for reproductive effects from all routes of exposure and different exposure durations, and on interspecies differences would be useful. No data were located about reproductive toxicity of 1,2-dibromo-3-chloropropane after dermal exposure, but skin contact with soil near hazardous waste sites, or with contaminated water supplies may occur. Mostly negative results were obtained for reproductive effects in experimental animals after inhalation and oral exposure of females; however, ovarian cysts were reported in rats after inhalation exposure (Rao et al. 1983). More data about 1,2-dibromo-3-chloropropane toxicity to the female reproductive system would be useful. More data about 1,2-dibromo-3-chloropropane reproductive toxicity in human males might be helpful to correlate exposure levels with effects.

Developmental Toxicity. No developmental effects were observed among workers who were exposed to 1,2-dibromo-3-chloropropane, but the cohort was not big enough to give reliable information (Potashnik and Abeliovich 1985; Potashnik and Phillip 1988). Negative results were obtained after examination of the offspring in a population exposed to 1,2-dibromo-3-chloropropane through drinking water (Whorton et al. 1989). Reduced litter weight and size

were found in rats at doses that caused maternal toxicity (Johnston et al. 1986; Ruddick and Newsome 1979). No information about developmental toxicity after dermal exposure is available. More data on developmental toxicity in experimental animals would be useful to identify possible risks for humans.

Immunotoxicity. No data were located regarding immunological effects of 1,2-dibromo-3-chloropropane in humans after inhalation, oral, or dermal exposure of any duration. Results of animal studies suggest that bone marrow may be a target (NTP 1982). The apparent greater susceptibility of 1,2-dibromo-3-chloropropane-exposed animals to pulmonary infections also suggests a possible immunologic effect. A battery of immune function tests has not been performed in humans or in animals, but would provide valuable information to confirm or refute the suggestive evidence. Studies regarding skin sensitization with 1,2-dibromo-3-chloropropane have not been performed.

Neurotoxicity. Workers exposed to 1,2-dibromo-3-chloropropane occupationally reported subjective neurological symptoms (Whorton et al. 1977). Depression of the central nervous system was observed in rats after acute inhalation (Torkelson et al. 1961) and oral (Reel et al. 1984; Torkelson et al. 1961) exposure. Histopathological changes in brains were detected after intermediate and chronic inhalation exposures in animals (NTP 1982; Rao et al. 1983). In contrast, no histopathological changes were found after oral exposure in the same duration categories (Johnston et al. 1986; NC1 1978). No data were located regarding neurotoxicity of 1,2-dibromo-3-chloropropane after dermal exposure in animals. Additional neurological and neurobehavioral tests in experimental animals would help to identify possible subtle neurological effects and the exposures associated with them.

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

Other epidemiologic studies dealt with 1,2-dibromo-3-chloropropane toxicity on the reproductive system after occupational exposure (Eaton et al. 1986; Egnatz et al. 1980; Glass et al. 1979; Goldsmith et al. 1984; Lantz et al. 1981; NIOSH 1979; Potashnik et al. 1978, 1984; Whorton et al. 1979) or exposure to contaminated drinking water (Wong et al. 1988). 1,2-Dibromo-3-chloropropane-induced toxicity to the human male reproductive system was well established in several cross-sectional studies. Reliable dosimetry data on the exposed population and its correlation with early signs of mild oligospermia would be useful. Follow-up studies of exposed workers would be

of value to further determine the reversibility of testicular effects. The determination of 1,2-dibromo-3-chloropropane toxicity to the female reproductive system would be valuable. More data about the reproductive outcome in exposed populations and the possibility of spontaneous abortions after exposure would be useful. The inhalation and dermal routes of exposure are important for occupationally exposed individuals; inhalation, oral, and dermal exposure might be of concern to populations living near hazardous waste sites as 1,2-dibromo-3-chloropropane might get into soil and then contaminate the source of water used for bathing or drinking.

Biomarkers of Exposure and Effect. No biomarkers of exposure were identified for 1,2-dibromo-3-chloropropane. Several studies indicated that 1,2-dibromo-3-chloropropane induced DNA damage and changes in the activity of microsomal enzymes (Kluwe 1983; Suzuki and Lee 1981); however, these changes are not.specific for 1,2-dibromo-3-chloropropane exposure and cannot be used as biomarkers. Further studies regarding possible biochemical changes after 1,2-dibromo-3-chloropropane exposure would be useful. The identification of 1,2-dibromo-3-chloropropane metabolites in the urine and their correlation with levels of exposure would also be useful.

Elevated levels of FSH were found in men exposed to 1,2-dibromo-3-chloropropane (Whorton et al. 1979); however, this elevation does not usually occur after a short-term exposure. It is associated with severe testicular degeneration and azoospermia in exposed men. It might occur after prolonged exposure or even after a nonexposure period following exposure in unrecovered men. This assay, however, cannot be correlated with the early signs of testicular toxicity. Further studies for developing specific early biomarkers of disease would be useful. Identification of biochemical changes in sperm would be particularly useful because sampling would involve methods that are already used to monitor occupational exposure.

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

excretion of 1,2-dibromo-3-chloropropane and its metabolites in exposed humans with known exposure would be useful for future monitoring purposes.

Comparative Toxicokinetics. The differences between reproductive toxicity in mice and rats were demonstrated in several studies. Similar differences were observed in toxicokinetics between rats and hamsters (with high testicular toxicity) and mice and guinea pigs (with low testicular toxicity) (Lag et al. 1989a; MacFarland et al. 1984). Also, rabbits were found to be more susceptible to reproductive effects than rats (Rao et al. 1982, 1983). The fact that reproductive toxicity of 1,2-dibromo-3-chloropropane was also observed in humans might suggest that rabbits, and possibly rats, could serve as a model for 1,2-dibromo-3-chloropropane toxicity. Further investigation of toxicokinetics in different species and the comparison of detected metabolites with those detected in humans would be useful.

Mitigation of Toxicological Effects. No specific information was located regarding mitigation of effects in 1,2-dibromo-3-chloropropane. The characteristic effects of 1,2-dibromo-3-chloropropane-induced toxicity are known, and nonspecific treatments for intoxicated persons have been recommended (Bronstein and Currance 1988; NIOSH 1988; Stutz and Janusz 1988). The mechanism of toxicity involves microsomal metabolism of 1,2-dibromo-3-chloropropane to reactive intermediates that are capable of binding to biological macromolecules such as DNA and protein. Conjugation of reactive metabolites with GSH acts as a detoxifying mechanism in the liver (Kato et al. 1979b; Kluwe et al. 1982). In contrast, conjugation with GSH increases the toxicity in the testes (Kluwe 1983). Agents that deplete GSH might, therefore, decrease testicular toxicity but might also increase liver toxicity. Therefore, the development of specific agents that prevent liver and testicular toxicity by obstructing the binding of active metabolites to DNA would be useful.

2.9.3 On-going Studies

No on-going studies were located regarding 1,2-dibromo-3-chloropropane toxicity or toxicokinetics.