TOXICOLOGICAL PROFILE FOR
1,2-DIBROMO-3-CHLOROPROPANE

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

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DISCLAIMER

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

FOREWORD

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

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

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

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

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

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary.

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

Foreword

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

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

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

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1. PUBLIC HEALTH STATEMENT

This Statement was prepared to give you information about 1,2-dibromo-3-chloropropane and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,177 sites on its National Priorities List (NPL) sites. 1,2-Dibromo-3-chloropropane has been found at 8 of these sites. However, we do not know how many of the 1,177 NPL sites have been evaluated for 1,2-dibromo-3-chloropropane. As EPA evaluates more sites, the number of sites at which 1,2-dibromo-3-chloropropane is found may change. This information is important for you because 1,2-dibromo-3-chloropropane may cause harmful health effects and because these sites are potential or actual sources of human exposure to 1,2-dibromo-3-chloropropane.

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

If you are exposed to a hazardous substance such as 1,2-dibromo-3-chloropropane, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

1.1 WHAT IS 1,2-DIBROMO-3-CHLOROPROPANE?

1,2-Dibromo-3-chloropropane is a colorless liquid with a sharp smell. It can be smelled in air at 2 parts chemical in 1 million parts of air. It evaporates about as fast as water does, which is not very quickly. 1,2-Dibromo-3-chloropropane will dissolve in water to a very limited extent. It can be tasted in water when 0.01 mg chemical is present in 1 liter of water. It is a man-made chemical not found naturally in the environment. We do not know exactly how much of it is currently made or used by industry, but it is probably a small amount. Some industries use 1,2-dibromo-3-chloropropane to make a chemical that is used to make materials resistant to burning. Large amounts of 1,2-dibromo-3-chloropropane were used in the past on certain farms to kill pests that were harmful to the crops. Farmers in Hawaii stopped using this chemical in 1985; use in other states stopped in 1979.

1,2-Dibromo-3-chloropropane breaks down slowly in the air. Most of the 1,2-dibromo-3-chloropropane that is released to the air disappears within several months. Most of this chemical that enters surface water evaporates into the air within several days or a week. It does not stick to the soil at the bottom of rivers, lakes, or ponds. We do not expect fish or other seafood from water containing 1,2-dibromo-3-chloropropane to build up large amounts of this chemical in their bodies. Some of what is spilled on or applied to soil moves through the soil into the groundwater, where it may remain for a long time. Some of the 1,2-dibromo-3-chloropropane in soil evaporates from the surface of the soil into the air. Small amounts may stay in the soil for several years. This chemical also breaks down slowly to simpler chemicals in water and soil.

You will find more information in Chapters 3, 4, and 5 on the properties of 1,2-dibromo-3-chloropropane.

1.2 HOW MIGHT I BE EXPOSED TO 1,2-DIBROMO-3-CHLOROPROPANE?

1,2-Dibromo-3-chloropropane is not usually found in the environment (air, water, and soil). Sometimes, however, it is found in the soil and underground water from cropland where it has been used as a pesticide. It has been found in well-water near farms where 1,2-dibromo-3-chloropropane was used. It has been found in food grown on farms that used the chemical and at some hazardous waste sites. Foods today most likely do not contain this chemical.

1,2-Dibromo-3-chloropropane can enter the environment while it is being made or used in industry and research. Because this chemical is not used very much, the releases are probably small. Releases and disposal of 1,2-dibromo-3-chloropropane at waste sites can lead to higher than usual levels in the nearby air, water, and soil.

We do not know exactly what amounts of 1,2-dibromo-3-chloropropane are usually found in the air, surface water, and soil. However, based on the limited usage in the past 5-10 years, we expect that levels where the chemical has not been used or discarded are either low or nonexistent. In areas where the chemical has been used as a soil fumigant, it may still be present in soil and groundwater at low levels.

You can be exposed to 1,2-dibromo-3-chloropropane by drinking water or eating certain foods that may still contain the compound. You might also be exposed to 1,2-dibromo-3-chloropropane by breathing air containing it. Exposure may happen if you live near a hazardous waste site that has released 1,2-dibromochloropropane to the air, water, or soil. Exposure can also occur in the workplace from spills or other accidents or even during routine handling. We do not know how much 1,2-dibromo-3-chloropropane the general public or workers are exposed to or how often they are exposed to it.

However, the limited use of 1,2-dibromo-3-chloropropane in recent years suggests that exposure is minimal and infrequent.

You can find more information in Chapter 5 on how much 1,2-dibromo-3-chloropropane is in the environment and how you can be exposed to it.

1.3 HOW CAN 1,2-DIBROMO-3-CHLOROPROPANE ENTER AND LEAVE MY BODY?

1,2-Dibromo-3-chloropropane can enter your body through the lungs if you breathe air contaminated with it. It can also enter your body if you drink contaminated water or eat contaminated food. It can enter through your skin if it comes into contact with your skin. We do not know exactly how much or how fast 1,2-dibromo-3-chloropropane enters your body through your lungs after breathing it or through your skin after skin contact with it. Studies in animals show- that almost all the 1,2-dibromo-3-chloropropane that they swallowed entered the bloodstream quickly. Inside the body, 1,2-dibromo-3-chloropropane is carried by the blood to many organs and breaks down into other chemicals also called breakdown products. These breakdown products can attach to some chemicals inside the cells of your body and may cause harmful effects in the liver, kidneys, or male reproductive organs. Most of the breakdown products are removed from your body quickly, but they may stay in fatty tissue for a longer period of time. The breakdown products of 1,2-dibromo-3-chloropropane leave the body in urine and in the air you breathe out. Only a small amount leaves in the stool. You can find more information in Chapter 2 on the movement of 1,2-dibromo-3-chloropropane in the body.

1.4 HOW CAN 1,2-DIBROMO-3-CHLOROPROPANE AFFECT MY HEALTH?

Studies of workers in chemical factories that produced 1,2-dibromo-3-chloropropane showed that its main harmful effect is on male reproductive organs. Men exposed to 1,2-dibromo-3-chloropropane in the air may have more girl children than boy children, produce fewer sperm, and eventually become unable to father children. We do not know the exact levels of 1,2-dibromo-3-chloropropane in air that cause these effects. Studies of workers have also suggested that 1,2-dibromo-3-chloropropane may cause headache, nausea, lightheadedness, and weakness. No adverse effect on reproduction was seen in people who drank water contaminated with small amounts (0.004-5.75 parts in a billion parts of water) of 1,2-dibromo-3-chloropropane. Studies in animals show that 1,2-dibromo-3-chloropropane may cause birth defects in the offspring of adult rats exposed to large amounts. However, human exposure to 1,2-dibromo-3-chloropropane that occurred at work or by drinking contaminated water has not been linked with birth defects. Some people have smelled the sharp odor of 1,2-dibromo-3-chloropropane when only small amounts were present, 2 parts in 1 million parts of air (2 ppm).

Some laboratory animals died after they breathed in, received large amounts in their food, or had skin contact with 1,2-dibromo-3-chloropropane. Rats and mice that survived breathing in or eating large amounts of 1,2-dibromo-

3-chloropropane had damaged stomachs, livers, and kidneys. Incoordination and sleepiness were seen in animals that breathed or took large amounts of 1,2-dibromo-3-chloropropane by mouth. Animals that breathed large amounts of this chemical also had damaged brains. In addition, rats and mice that breathed large amounts in 1,2-dibromo-3-chloropropane had damaged air passages and lungs. Some laboratory animals that breathed large amounts of 1,2-dibromo-3-chloropropane had damaged spleens, low blood cell production in the bone marrow, or decreased amounts of blood cells in the blood. Rabbits that had 1,2-dibromo-3-chloropropane placed in contact with their eyes and skin had irritated eyes, cloudy corneas, and damaged skin. Female rats mated with male rats that received low-to-moderate doses of 1,2-dibromo-3-chloropropane in their food for 5 days had miscarriages. Rats and rabbits that breathed in or received low doses of 1,2-dibromo-3-chloropropane in their food for less than 1 year had harmful effects on their reproductive organs. Male offspring of rats that were exposed to 1,2-dibromo-3-chloropropane while they were pregnant also had harmful effects on their reproductive organs. Laboratory animals that were exposed to low-to-moderate amounts of 1,2-dibromo-3-chloropropane through breathing, swallowing, or skin contact for a long time period developed cancer. Cancerous tumors on the inside of the nose were seen after animals breathed 1,2-dibromo-3-chloropropane for long periods. Cancer of the stomach and kidneys was seen after animals were given this chemical by mouth for long periods. Cancer of the stomach and skin was seen after animals had skin contact with this chemical for long periods. The Department of Health and Human Services has determined that 1,2-dibromo-3-chloropropane may reasonably be anticipated to be a carcinogen. The International Agency for Research on Cancer has determined that 1,2-dibromo-3-chloropropane is possibly carcinogenic to humans.

You can find a more complete discussion in Chapter 2 of the effects of 1,2-dibromo-3-chloropropane on health.

1.5 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO 1,2-DIBROMO-3-CHLOROPROPANE?

1,2-Dibromo-3-chloropropane can be measured in exhaled air, blood, and samples of tissues from the body. Samples must be collected shortly after exposure because 1,2-dibromo-3-chloropropane leaves your body rapidly after exposure. If a large exposure has occurred, levels may be detected for longer after exposure than if a small exposure has occurred. The levels of 1,2-dibromo-3-chloropropane cannot be used to predict whether or not you will experience adverse health effects. These tests are probably not available through your doctor's office, but your doctor can refer you to a place where they can be done. Biological changes in the human body have been studied after 1,2-dibromo-3-chloropropane exposure, but they have not been used to tell whether exposure occurred.

Exposure to 1,2-dibromo-3-chloropropane causes lower production of sperm. Therefore, sperm counts and the blood levels of certain hormones

(follicular stimulating hormone, luteinizing hormone) can be checked in exposed men to find out whether harmful effects have occurred. However, these changes have,not been linked with exposure levels of the chemical or lengths of exposure to the chemical. Furthermore, the hormonal changes are not sensitive enough to detect minor changes in sperm counts. See Chapters 2 and 6 for more information about tests for exposure to 1,2-dibromo-3-chloropropane.

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

The Enviromental Protection Agency (EPA) recommends that the amount of 1,2-dibromo-3-chloropropane that is found in underground drinking water be kept to low levels. The highest recommended level is 100 micrograms of 1,2-dibromo-3-chloropropane per liter of water (pg/L). Furthermore, EPA requires that industries report spills of 1 pound or more of 1,2-dibromo-3-chloropropane. EPA banned the use of this chemical as a pesticide in the United States in the early 1980s.

The Occupational Safety and Health Administration (OSHA) recommends that the amount of 1,2-dibromo-3-chloropropane in workplace air be kept to low levels. The highest level allowed in the workplace is 1 part in one billion parts of air (ppb), for an 8-hour workday and a 40-hour workweek.

1.7 WHERE CAN I GET MORE INFORMATION?

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

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

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

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of 1,2-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).

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-l 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 (l-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 lo-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

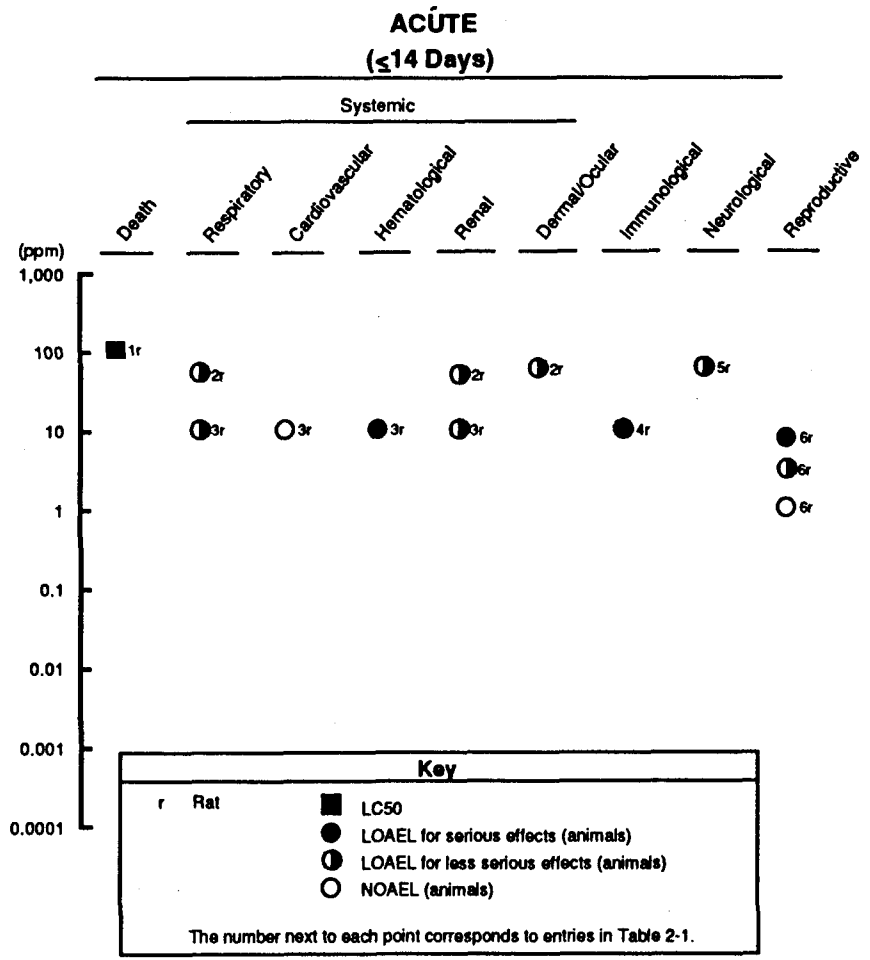


FIGURE 2-1 (Continued)

INTERMEDIATE
(15-364 Days)

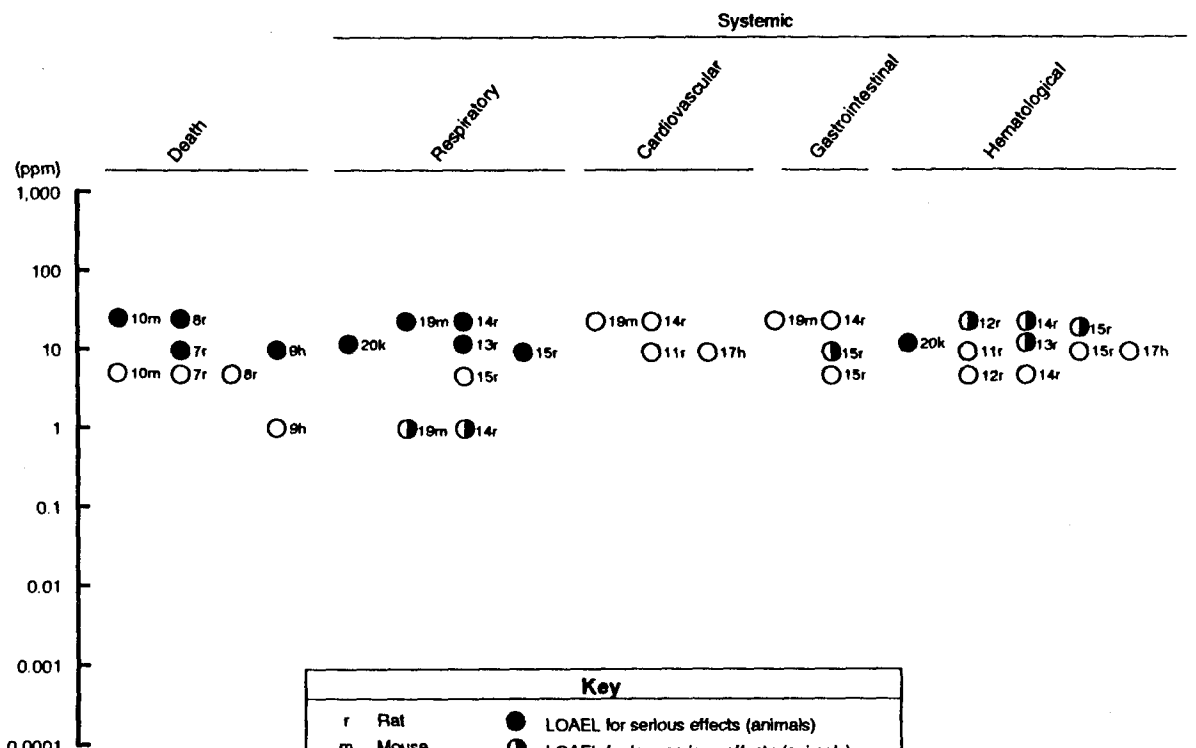


FIGURE 2-1 (Continued)

INTERMEDIATE (Continued)
(15-364 Days)

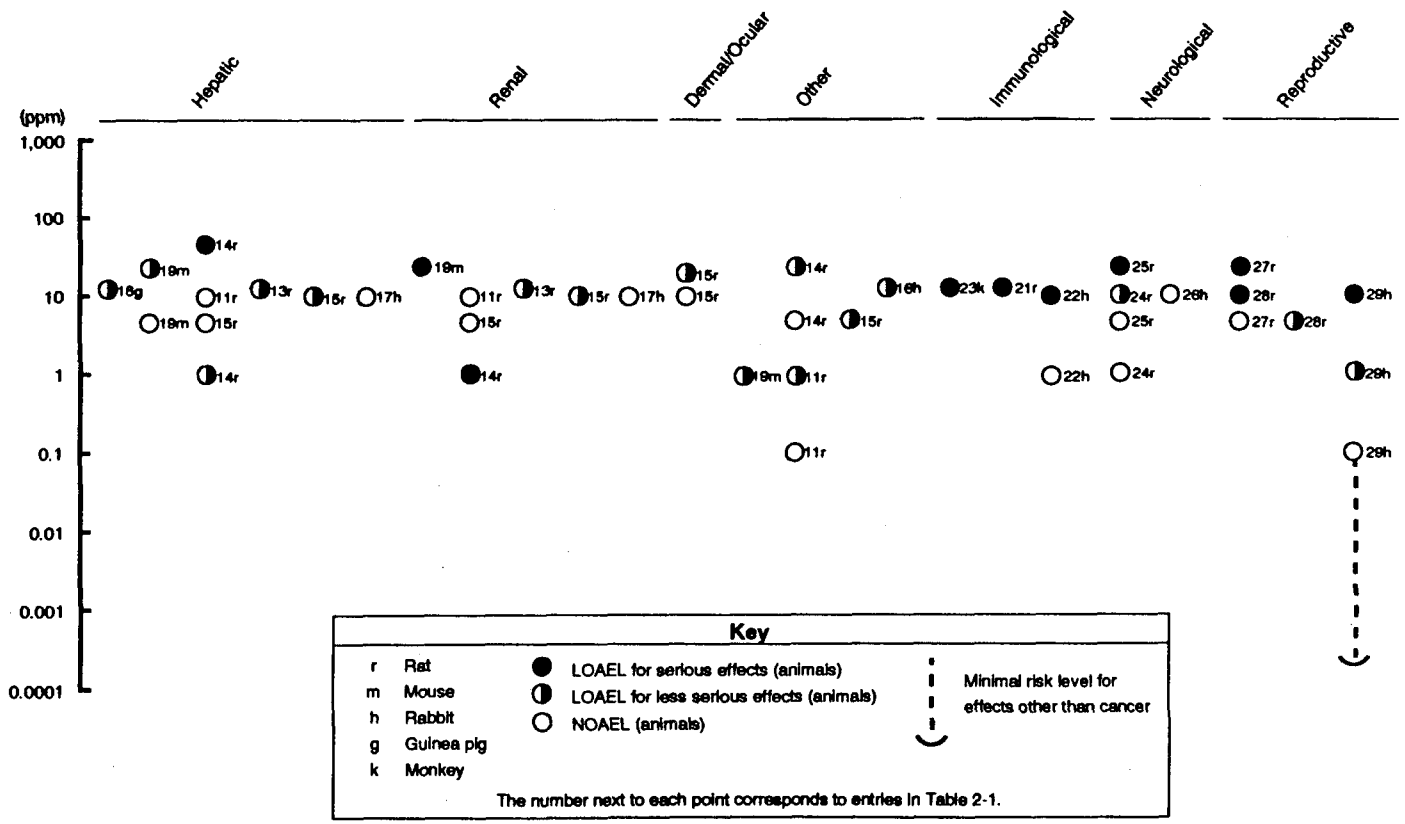
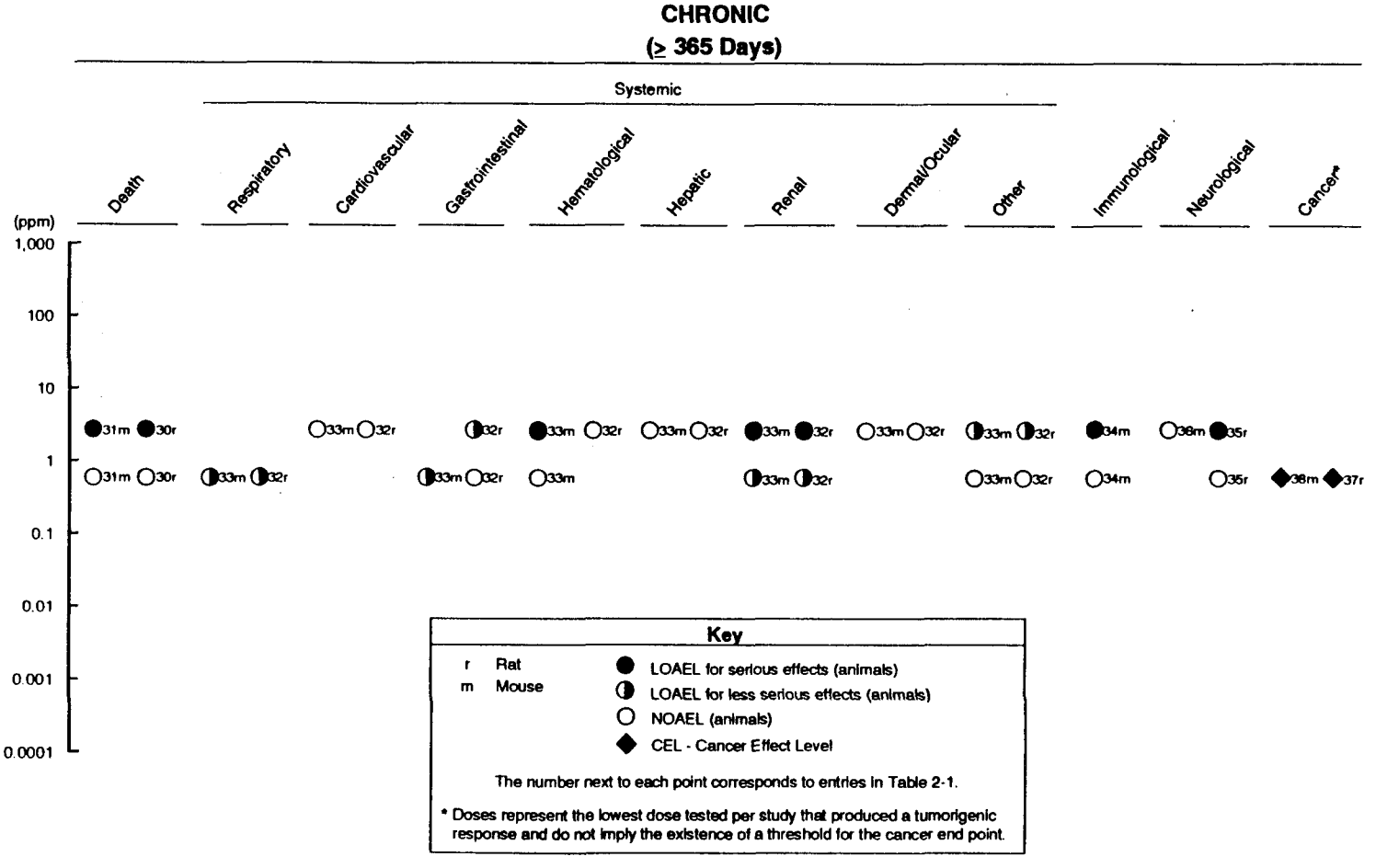


FIGURE 2-1 (Continued)



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

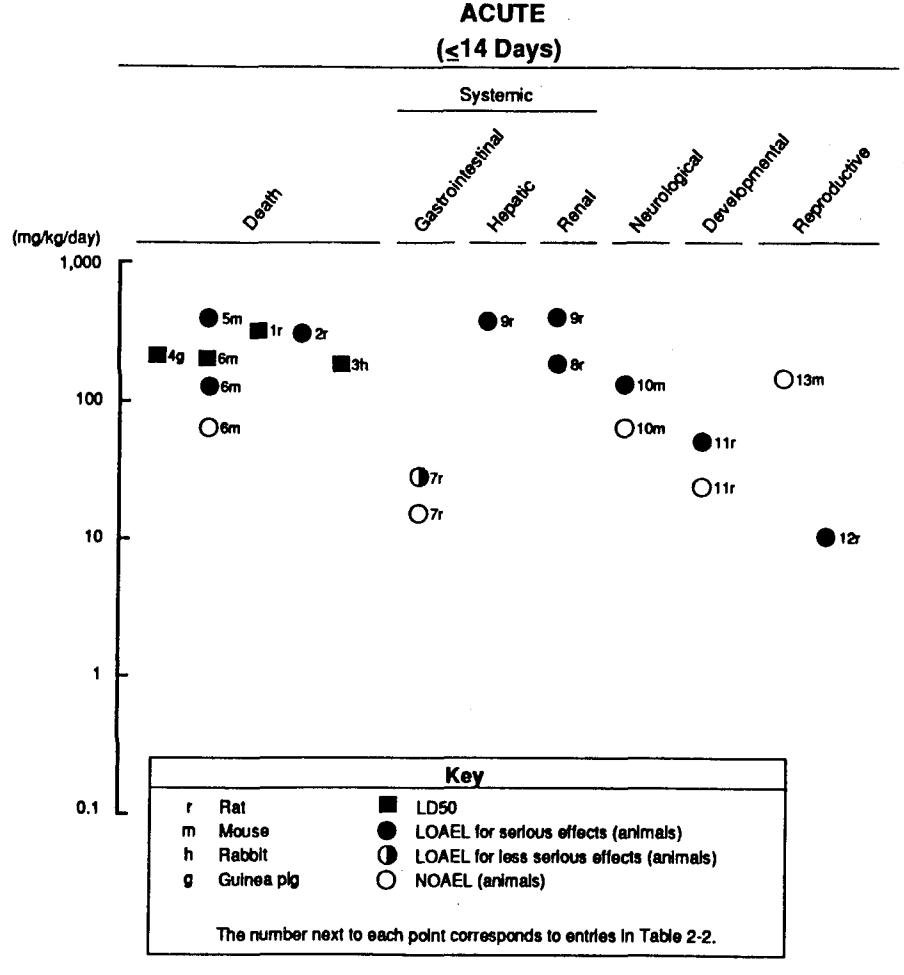


FIGURE 2-2 (Continued)

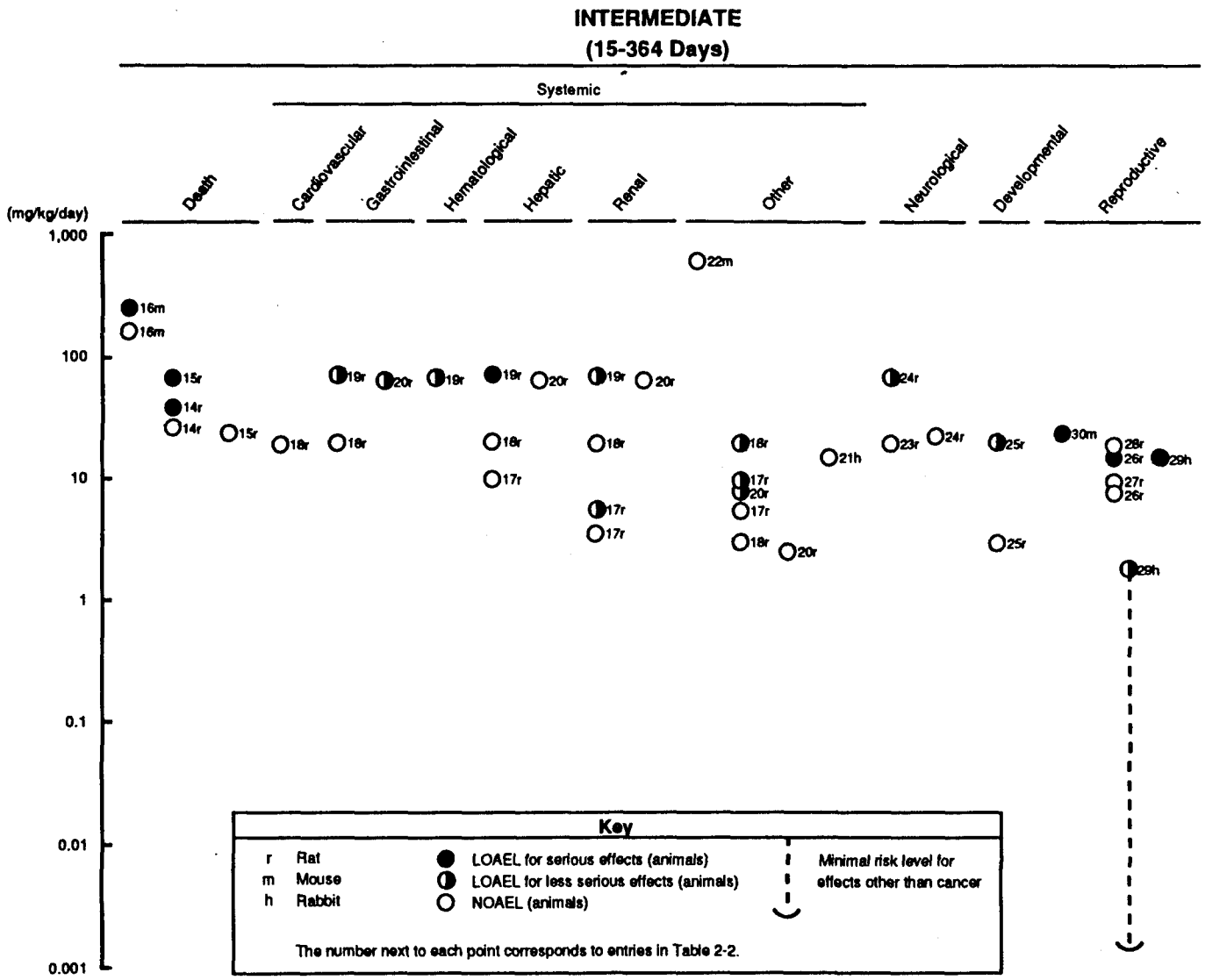
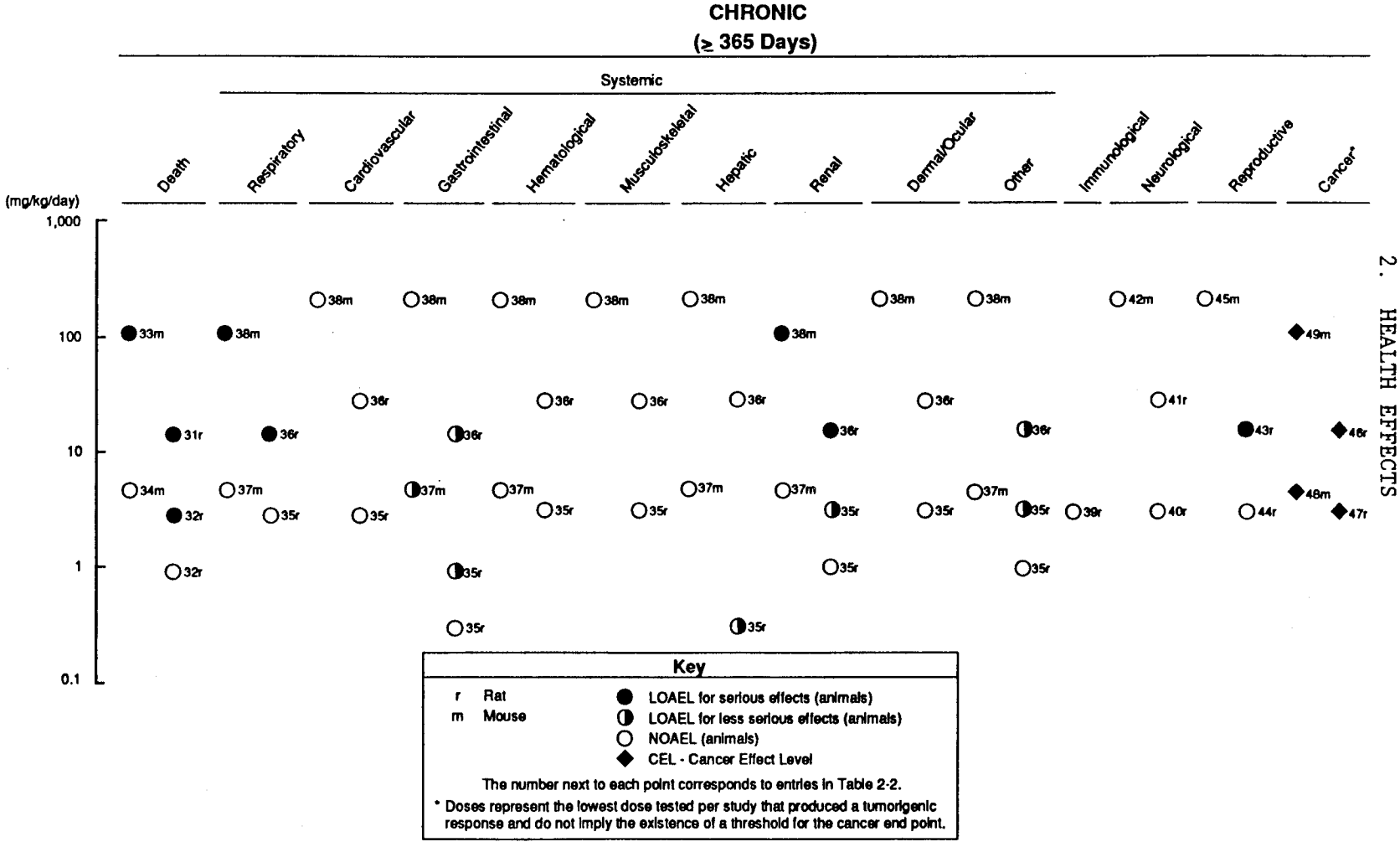


FIGURE 2-2 (Continued)



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.

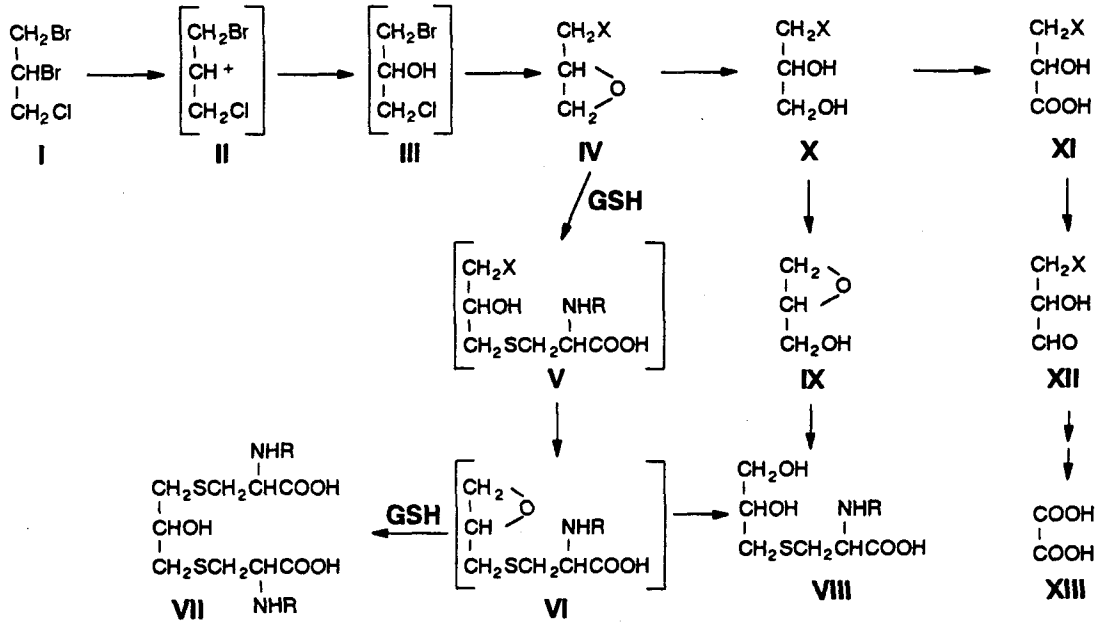
2.3.3 Metabolism

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 intermediat-eduration 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:				
WP2h_{uv}r	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.

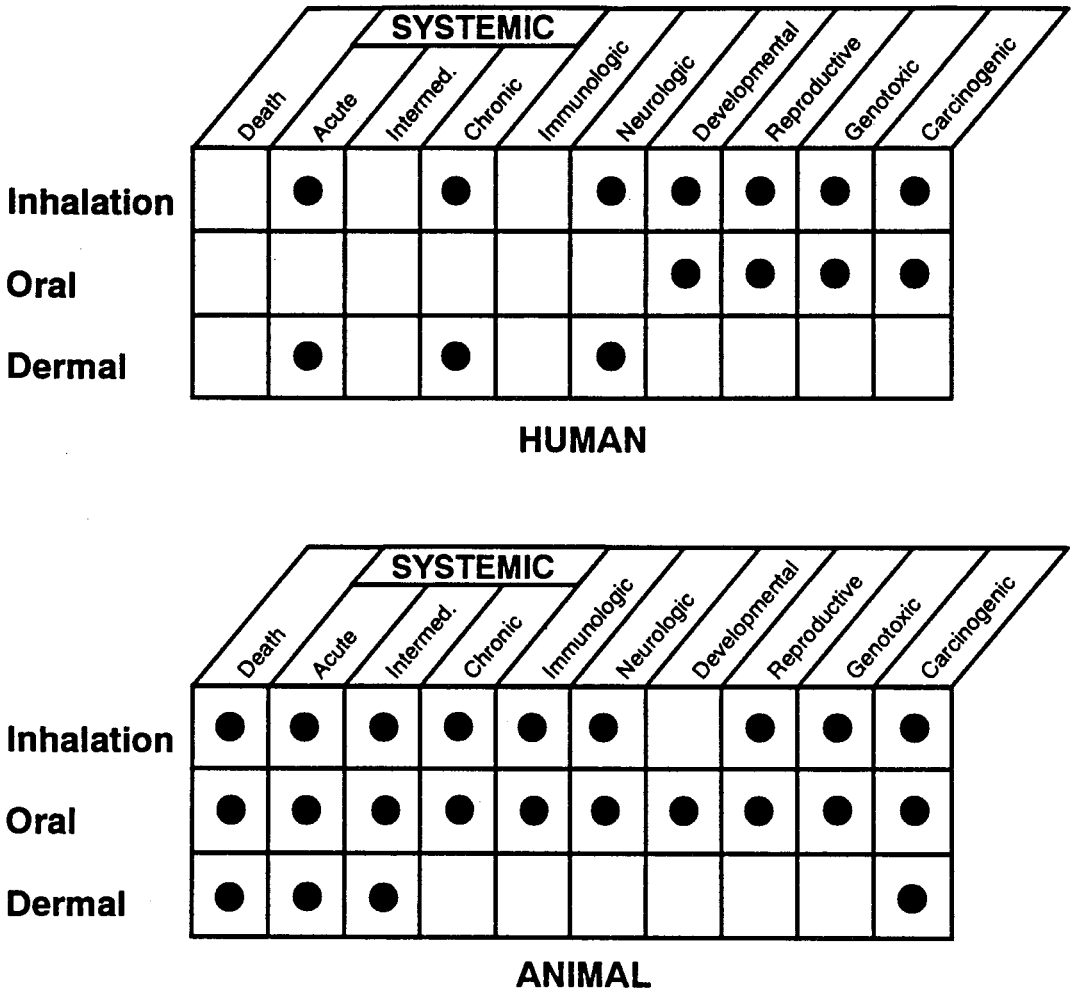
2.9.1 Existing Information on Health Effects of 1,2-Dibromo-3-chloropropane

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.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

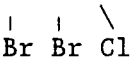
Data pertaining to the chemical identity of 1,2-dibromo-3-chloropropane are listed in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of 1,2-dibromo-3-chloropropane are presented in Table 3-2.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of 1,2-Dibromo-3-chloropropane

Characteristic	Information	Reference
Chemical name	1,2-Dibromo-3-chloropropane	CAS 1989
Synonyms	DBCP; BBC12	CAS 1989
Trade names	Nemagon; Nemafume; Fumazone; Fumagon; Nemabrom; Nemazon; OS 1897; and others	OHM/TADS 1989
Chemical formula	$C_3H_5Br_2Cl$	CAS 1989
Chemical structure		CAS 1989
Identification numbers:		
CAS registry	96-12-8	CAS 1989
NIOSH RTECS	TX8750000	HSDB 1989
EPA hazardous waste	U066	HSDB 1989
OHM/TADS	7216513	OHM/TADS 1989
DOT/UN/NA/IMCO shipping	UN 2872	HSDB 1989
HSDB	1629	HSDB 1989
NCI	C00500	HSDB 1989

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

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

Property	Information	Reference
Molecular weight	236.36	Windholz 1983
Color	Colorless (when pure); amber to dark brown, yellow (technical grade)	Sax and Lewis 1987; Verschueren 1983; NIOSH 1985
Physical state	Liquid	Windholz 1983
Melting point	6°C	Stenger 1978
Boiling point	196°C	Windholz 1983
Density at 14°C	2.093 g/cm^3	Windholz 1983
Odor	Pungent	Windholz 1983
Odor threshold:		
Water	No data	
Air	0.0965 mg/m^3	Ruth 1986
Solubility:		
Water at 20°C	1,230 mg/L	Munnecke and VanGundy 1979
Organic solvents	Miscible with methanol, ethanol, isopropyl alcohol, hydrocarbons, halogenated hydrocarbons, and oils	IARC 1979; Windholz 1983
Partition coefficients:		
Log K_{ow}	2.26 (estimated)	EPA 1988a
Log K_{oc}	2.17; 2.11	Sabljic 1984; Wilson et al. 1981
Bioconcentration factor	11.2[a]	Bysshe 1982
Vapor pressure at 20°C	0.58 mmHg	Munnecke and VanGundy 1979
Henry's law constant:		
at 20°C	1.47×10^{-4} atm-m^3/mol[b]	Thomas 1982
Autoignition temperature	No data	
Flashpoint:		
Open cup	76.6°C (170°F)	Sax and Lewis 1987
Flammability limits	No data	

TABLE 3-2 (Continued)

Property	Information	Reference
Conversion factors:		
ppm (v/v) to mg/m^3 in air (20°C)	1 ppm (v/v) x 9.67 = mg/m3	
mg/m^3 to ppm (v/v) in air (20°C)	1 mg/m^3 x 0.103 = ppm (v/v)	
Explosive limits	No data	

[a]Calculated from water solubility using equation 5-3 in Lyman et al. 1982
[b]Calculated from vapor pressure and water solubility using equation 15-8 in Lyman et al. 1982

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

1,2-Dibromo-3-chloropropane was first produced commercially in the United States in 1955 (IARC 1979). In 1969, U.S. production was 8.58 million pounds (IARC 1979). Estimates of annual production during 1974-1975 ranged from 18 to 20 million pounds (IARC 1979; NTP 1985). 1,2-Dibromo-3-chloropropane is no longer commercially manufactured in the United States (Hawley 1981; Sax and Lewis 1987). R.W. Greeff & Co., Inc., in Old Greenwich, Connecticut, is listed as a current supplier of 1,2-dibromo-3-chloropropane for domestic research purposes (OPD 1989). It is not known whether this supplier produces 1,2-dibromo-3-chloropropane in the United States or imports the chemical. Two companies were listed as producers of 1,2-dibromo-3-chloropropane in 1977 (EPA 1989b). The production volume of Columbia Organic Chemicals Co., in Columbia, South Carolina, was listed as less than 1,000 pounds. No production volume was listed for the other producer, Velsicol Chemical Corp., in El Dorado, Arkansas. As 1,2-dibromo-3-chloropropane is no longer used as a fumigant and nematocide in the United States, it is likely that its current production volume in the United States, if any, is very low.

4.2 IMPORT/EXPORT

No quantitative data concerning the recent import or export of 1,2-dibromo-3-chloropropane in the United States were found. Ameribrom Inc., in New York, New York, was listed as an importer of 1,2-dibromo-3-chloropropane in 1977; no import volume was listed (EPA 1989b). Because R.W. Greeff 6 Co., Inc., is listed as a current supplier of 1,2-dibromo-3-chloropropane (OPD 1989), it may be an importer of the chemical. It is unlikely that significant amounts of the chemical are imported into the United States since its former major uses as a soil fumigant and nematocide are no longer permitted in the United States (EPA 1977, 1979, 1985b, 1985c). No significant exports are expected since it has been reported that 1,2-dibromo-3-chloropropane is no longer made in the United States (Hawley 1981; Sax and Lewis 1987).

4.3 USE

1,2-Dibromo-3-chloropropane is used as an intermediate in the synthesis of organic chemicals, such as the brominated flame retardant tris[(2,3-dibromopropyl)phosphate] (Verschueren 1983). Until 1977, 1,2-dibromo-3-chloropropane was extensively used as a soil fumigant and nematocide on over 40 different crops in the United States (Anonymous 1988). The chemical was used to protect field crops, vegetables, fruits and nuts, nursery and greenhouse crops, and turf from pests (NTP 1985). From 1977 to 1979, EPA suspended registration of products containing 1,2-dibromo-3-chloropropane except for use on pineapples in Hawaii (Anonymous 1988; EPA 1977, 1979). In 1985, EPA issued an intent to cancel all registrations for 1,2-dibromo-3-chloropropane-containing pesticide products, including use on pineapples.

Subsequently, the use of existing stocks of 1,2-dibromo-3-chloropropane on pineapples was prohibited (EPA 1985b, 1985c).

Prior to the cancellation of pesticide uses, 1,2-dibromo-3-chloropropane was used extensively; 9.8 million pounds of 1,2-dibromo-3-chloropropane were applied in 1974 (NTP 1985). In California, 831,000 pounds of the chemical were applied, mainly on grapes and tomatoes, during 1977 (NTP 1985). The volume of 1,2-dibromo-3-chloropropane applied to pineapple fields in Hawaii between 1979 and 1985 was probably high, since during much of that time, the chemical was the preferred fumigant for use on pineapple fields (Albrecht 1987).

4.4 DISPOSAL

1,2-Dibromo-3-chloropropane has been identified as a hazardous waste by EPA, and the disposal of this compound is regulated under the federal Resource Conservation and Recovery Act (RCRA) (EPA 1988b, 1988c). Specific information regarding federal regulations on the land disposal of 1,2-dibromo-3-chloropropane is provided in the Code of Federal Regulations (EPA 1988c). No acceptable chemical decontamination is known for 1,2-dibromo-3-chloropropane (HSDB 1989). Dilution of the chemical with a flammable solvent is necessary for incineration to be effective, and the products must be passed through scrubbers to remove the hydrogen bromide and hydrogen chloride that is produced (HSDB 1989).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

There are no known natural sources of 1,2-dibromo-3-chloropropane (IARC 1979). Although data on releases of 1,2-dibromo-3-chloropropane to the atmosphere, water, and soil are lacking, current releases of the chemical to the environment that result from the production and use of the chemical are probably low because the chemical is used only as an intermediate in organic synthesis and for research purposes. Relatively minor releases to the environment may still occur from contaminated soil, groundwater, and surface water. This is especially true at or near agricultural areas where 1,2-dibromo-3-chloropropane had been extensively used in the past or where a chemical spill occurred, and from hazardous waste sites where improper disposal techniques were used.

1,2-Dibromo-3-chloropropane in soil is subject both to leaching into groundwater and to volatilization to the atmosphere from near-surface soil, as has been observed in field soil studies. Small amounts of 1,2-dibromo-3-chloropropane may be absorbed through the soil roots and translocated to other plant parts. 1,2-Dibromo-3-chloropropane that is present in water is expected to volatilize to the atmosphere. 1,2-Dibromo-3-chloropropane is not expected to adsorb significantly to sediment or suspended organic matter in water, bioconcentrate in fish and other aquatic organisms, or to biomagnify from lower to higher trophic levels of the food chain. The primary degradation process for 1,2-dibromo-3-chloropropane in the atmosphere is estimated to occur via gas-phase reaction with photochemically produced hydroxyl radicals. Degradation of 1,2-dibromo-3-chloropropane in natural waters and soil is a slow process. 1,2-Dibromo-3-chloropropane may be susceptible to slow biodegradation in soil and natural waters based on the observation of biologically mediated dehalogenation in certain soils. 1,2-Dibromo-3-chloropropane residues that do not leach or volatilize appear to be very persistent in soil based upon monitoring data. Laboratory experiments using anoxic biofilm columns showed that biodegradation of 1,2-dibromo-3-chloropropane in groundwater may occur under anaerobic conditions.

The general population may be infrequently exposed to very small amounts of 1,2-dibromo-3-chloropropane through the ingestion of contaminated drinking water and food. Since 1,2-dibromo-3-chloropropane is no longer used as a fumigant and nematocide in the United States and since such use in the past was limited to certain agricultural areas, widespread exposure of the general public or of workers to 1,2-dibromo-3-chloropropane is not likely. Even in the agricultural areas, exposure is probably minor.

EPA has identified 1,177 National Priorities list (NPL) sites. 1,2-Dibromo-3-chloropropane has been found at 8 of the sites evaluated for the presence of this chemical (View 1990). However, we do not know how many of the 1,177 sites have been evaluated for this chemical. As more sites are

evaluated by the EPA, the number may change. The frequency of these sites within the United States can be seen in Figure 5-1. The Contract Laboratory Program (CLP) Statistical Database did not list 1,2-dibromo-3-chloropropane among the compounds that are most commonly found at NPL waste sites in groundwater, surface water, or soil (CLPSD 1989).

5.2 RELEASES TO THE ENVIRONMENT

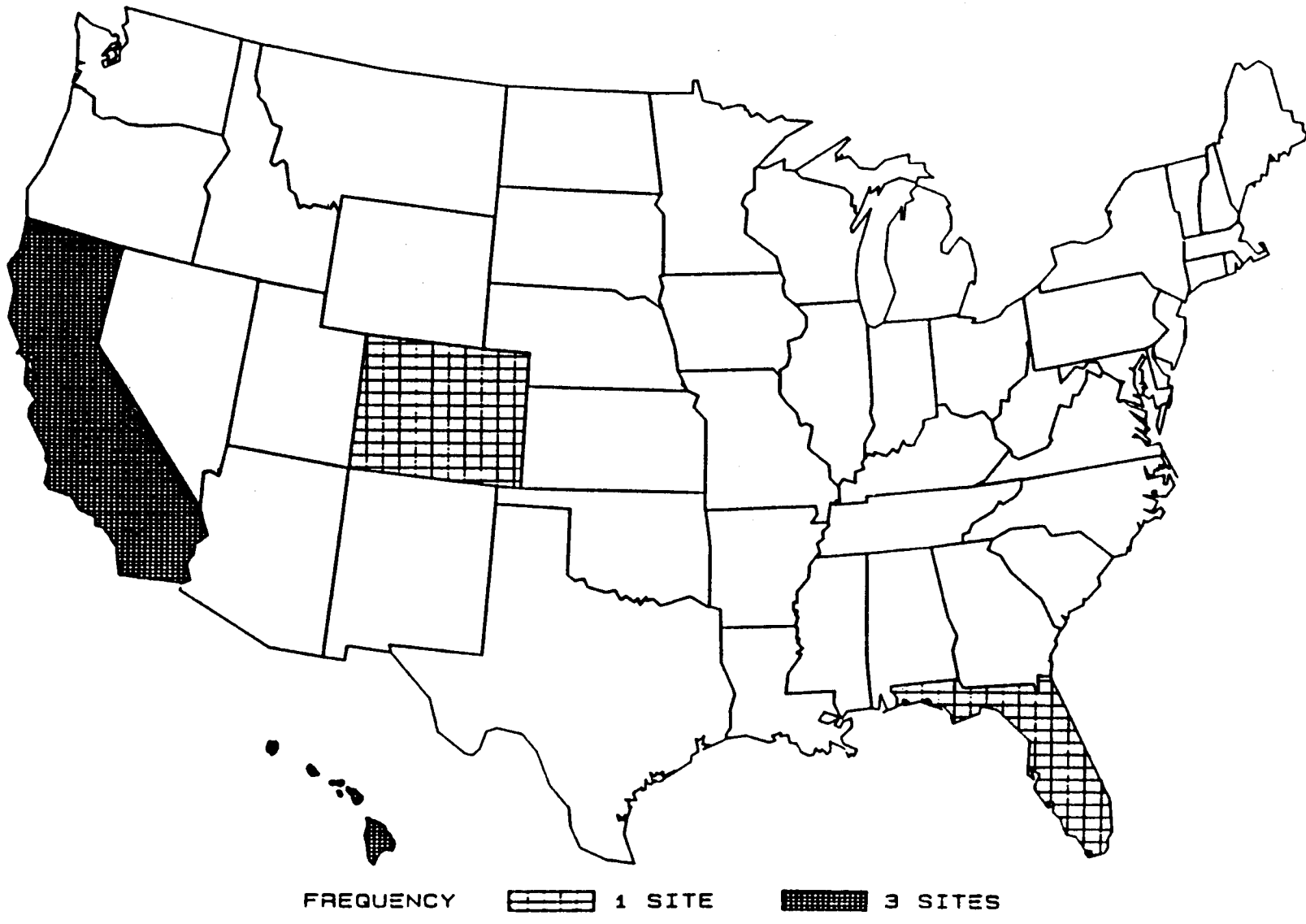
5.2.1 Air

Data on releases of 1,2-dibromo-3-chloropropane to the atmosphere are lacking. Significant releases to the atmosphere probably occurred in the past due to the extensive manufacture and use of the chemical as a soil fumigant on a wide variety of crops in the United States (Section 5.3.1) (Albrecht and Chenchin 1985; Hodges and Lear 1974; NTP 1985; Peoples et al. 1980). However, current releases of 1,2-dibromo-3-chloropropane to the atmosphere that result from the production and use of the chemical are probably very low because the chemical is used only as an intermediate in organic synthesis and for research purposes. Use of 1,2-dibromo-3-chloropropane as a soil fumigant, the only major purpose for which the chemical had been used in the past, is no longer permitted in the United States (Anonymous 1988; EPA 1977, 1979, 1985b). Releases to the atmosphere may continue to occur from soils that were treated with 1,2-dibromo-3-chloropropane in the past and that still contain residues in the soil. Further releases, may result from the use of well water and other water sources that were contaminated with the chemical due to leaching through soil. However, no data were found that would permit the estimation of the amount that is currently being released to the ambient atmosphere. Additional potential sources of release to the atmosphere include identified and unidentified hazardous waste sites that contain 1,2-dibromo-3-chloropropane either in surface water or in near-surface soil.

5.2.2 Water

Data on release of 1,2-dibromo-3-chloropropane to water are lacking. Significant releases to water may have occurred in the past due to the extensive manufacture and use of the chemical as a soil fumigant on a wide variety of crops in the United States (Section 5.3.1), but current releases are probably very low because the chemical is now used only as an intermediate in organic synthesis and for research purposes. Its use as a soil fumigant, the only major purpose for which the chemical was used in the past, is no longer permitted in the United States (Section 4.3). The potential pathways for release to surface waters include runoff from spill and hazardous waste sites where improper disposal techniques were used, runoff from farmland that was irrigated with contaminated well water or other water, and direct release during manufacture and use as an intermediate for organic synthesis and research. Releases to groundwater may occur via leaching of residues in

FIGURE 5-1. FREQUENCY OF NPL SITES WITH DIBROMOCHLOROPROPANE CONTAMINATION *



* Derived from View 1989

agricultural soils that were treated with 1,2-dibromo-3-chloropropane in the past, and via leaching through soils at hazardous waste and spill sites that contain the chemical.

The CLP Statistical Database (CLPSD) did not list 1,2-dibromo-3-chloropropane among the compounds most commonly found in groundwater or surface water at NPL waste sites (CLPSD 1989).

5.2.3 Soil

Data on current release of 1,2-dibromo-3-chloropropane to soils are lacking probably because few, if any, releases to soil are currently occurring. Significant releases to soil occurred in the past as a result of its extensive use as a soil fumigant on a wide variety of crops in the United States (Section 5.3.1). Current releases are probably very low because the chemical is used only as an intermediate in organic synthesis and for research purposes. Its use as a soil fumigant, the only major purpose for which the chemical was used in the past, is no longer permitted in the United States (Section 4.3). Potential pathways for release to soil include disposal at hazardous waste sites with improper disposal techniques, spills, and irrigation with contaminated well water or other water. The CLPSD did not list 1,2-dibromo-3-chloropropane among the compounds most commonly found in soil at NPL waste sites (CLPSD 1989).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

1,2-Dibromo-3-chloropropane in soil is subject both to leaching into groundwater and to volatilization from near-surface soil. The experimental K,,s of approximately 149 in Lincoln fine sand (Wilson et al. 1981) and 128 in an unspecified soil (Sabljic 1984) indicate that 1,2-dibromo-3-chloropropane is highly mobile in soil (Swann et al. 1983). Data from field and laboratory experiments confirm that 1,2-dibromo-3-chloropropane has a strong potential to leach through soil to groundwater (Bomberger et al. 1983; Carter et al. 1984; Hodges and Lear 1974; Kloos 1983; Oki and Giambelluca 1987; Wilson et al. 1981). The rate and extent that 1,2-dibromo-3-chloropropane leaches through agricultural soil depend upon various factors that include the water-holding capacity of the soil (which is related to the size of the air spaces in the soil), the amount of organic matter in the soil, the amount of water applied, and the method of 1,2-dibromo-3-chloropropane application (Hodges and Lear 1974).

In a study using primarily clay, silt, and sandy soils, mobility was lowest in the clay soil, which had a higher content of organic matter than both sandy and silt soil and a lower amount of air space between particles of soil than was found in the silt soil (Hodges and Lear 1974). Mobility was highest in the sandy soil, which had the largest spaces between soil particles

(and therefore the fastest rate of water movement) and the lowest amount of organic matter (Hodges and Lear 1974). Application of 1,2-dibromo-3-chloropropane by either injection or application in irrigation water (flood application) led to extensive and rapid penetration of the fumigant. Application of 1,2-dibromo-3-chloropropane by injection led to greater penetration in the clay and silt soils, compared to its flood application, because it was retained near the soil surface in the latter case and was subsequently lost to the atmosphere (Hodges and Lear 1974). An illustration of the volatilization behavior of 1,2-dibromo-3-chloropropane from soil was obtained in a study of a pineapple field that was treated with 4 gallons per acre of the chemical injected to a depth of 12 inches (Albrecht and Chenchin 1985). 1,2-Dibromo-3-chloropropane concentration in the air at ground level and at 42 inches above the ground reached peaks after 2 days (approximately 0.4 and 8 ppb, respectively), dropped off to non-detectable levels after 3 days, peaked after 6 days following a 6-mm rainfall on days 5-6 (approximately 1.2 and 0.5 ppb at ground level and 42 inches, respectively), and dropped off but remained at measurable levels for the remainder of the 30-day experiment (Albrecht and Chenchin 1985). These data support results obtained in modeling studies that predict that volatilization of 1,2-dibromo-3-chloropropane from near-surface soil is important (Bomberger et al. 1983; Jury et al. 1987). Estimated volatilization half-lives for 1,2-dibromo-3-chloropropane that was evenly distributed in the top 10 cm of soil varied between 0.6 days in dry soil with very low soil organic content to 26.2 days in wet soil with relatively high soil organic content (Bomberger et al. 1983). The use of plastic coverings over 1,2-dibromo-3-chloropropane treated fields retards volatilization loss from soil.

Small amounts of 1,2-dibromo-3-chloropropane may be absorbed through the roots of plants growing in 1,2-dibromo-3-chloropropane contaminated soil and may be translocated to other parts of the plants (see Section 5.4.4.) (Carter and Riley 1982; Newsome et al. 1977). 1,2-Dibromo-3-chloropropane was found in peaches and in the roots and tops of carrots and radishes that were grown in 1,2-dibromo-3-chloropropane treated soil. The generally lower amounts of the chemical found in the foliage than in the roots of the carrot and radish plants may have resulted from translocation from the roots or from absorption of 1,2-dibromo-3-chloropropane that had volatilized from the soil to the air (Newsome et al. 1977). The possibility of absorption of volatilized 1,2-dibromo-3-chloropropane by the peaches appears to be a less likely explanation than translocation because the 1,2-dibromo-3-chloropropane was applied to the fields in the fall, months before the spring harvest of the peaches (Carter and Riley 1984).

In the atmosphere, 1,2-dibromo-3-chloropropane is expected to exist predominantly in the vapor phase based upon its vapor pressure (Table 3-2) (Eisenreich et al. 1981; Munnecke and VanGundy 1979). Because significant amounts of 1,2-dibromo-3-chloropropane are not likely to be present in the particulate phase, dry deposition to the earth's surface is not a significant removal process. Based upon its high water solubility (Table 3-2), the small

amounts of 1,2-dibromo-3-chloropropane that are present in air may be removed by wet deposition; however, much of the 1,2-dibromo-3-chloropropane removed from the atmosphere by washout is likely to reenter the atmosphere by volatilization. No experimental or predictive data were located in the literature regarding the transport of 1,2-dibromo-3-chloropropane in the atmosphere; however, the expected half-life of 36 days (Section 5.3.2.1) indicates that it could be transported long distances in the atmosphere.

1,2-Dibromo-3-chloropropane that is present in water 'is expected to volatilize rapidly to the atmosphere. Using the Henry's law constant, a halflife of 13.5 hours was calculated for evaporation from a model river l-m deep, flowing at 1 m/second, with a wind velocity of 3 m/second, and neglecting adsorption to sediment (Thomas 1982). A volatilization half-life of 8 days from a model pond can be estimated using a three-compartment EXAMS model (EPA 1985d). 1,2-Dibromo-3-chloropropane is not expected to adsorb significantly to sediment and suspended organic matter based upon a K_{OC} ranging between 128 and 149 (Sabljic 1984; Wilson et al. 1981). It is not expected to bioconcentrate in fish and other aquatic organisms based upon an estimated bioconcentration factor (BCF) of 11.2 (calculated from water solubility; Table 3-2) (Bysshe 1982; Munnecke and VanGundy 1979). No data were located that would indicate a potential for 1,2-dibromo-3-chloropropane to biomagnify from lower to higher trophic states of aquatic or terrestrial food chains.

5.3.2 Transformation and Degradation

5.3.2.1 Air

The primary degradation process for 1,2-dibromo-3-chloropropane in the atmosphere is likely to be a vapor-phase reaction with photochemically produced hydroxyl radicals. The experimental rate constant for this process is 4.4×10^{-13} cm^3/molecule-set (Tuazon et al. 1986). This corresponds to a half-life of 36 days at an estimated atmospheric concentration of 5~10~ hydroxyl radicals/cm^3. Direct photolysis of 1,2-dibromo-3-chloropropane is not expected to occur in the atmosphere since the chemical lacks a chromophore that absorbs light at environmentally significant wavelengths (greater than 290 nm) (Silverstein et al. 1974).

5.3.2.2 Water

Degradation of 1,2-dibromo-3-chloropropane in natural waters is a slow process. It volatilizes from surface waters before significant degradation can occur. Hydrolysis of 1,2-dibromo-3-chloropropane in natural waters is unlikely to be an important removal process. The base hydrolysis rate constant at 25°C of 20.6 hr^{-1} M^{-1} was extrapolated from data obtained at 40° 100°C (Burlinson et al. 1982). This rate constant corresponds to half-lives for hydrolysis of 38 years and 140 days at pH 7 and 9, respectively. Direct photolysis of 1,2-dibromo-3-chloropropane is not likely to occur in environmental waters since the chemical lacks a chromophore that absorbs light

at environmentally significant wavelengths (greater than 290 nm) (Silverstein et al. 1974).

No studies were located regarding the biodegradation of 1,2-dibromo-3-chloropropane in natural waters. 1,2-Dibromo-3-chloropropane may be susceptible to slow biodegradation in natural waters based upon the observation of biologically mediated dehalogenation in certain soils amended with a nutrient (Castro and Belser 1968). In experiments using anoxic biofilm columns that were designed to resemble groundwater environments, 1,2-dibromo-3-chloropropane was susceptible to biodegradation under conditions of methanagenesis, denitrification, and sulfate respiration (Bouwer and Wright 1988). Although data from these experiments cannot be used to predict what type of aquifer is likely to support biodegradation or the rate of biodegradation to be expected, they indicate that some biodegradation of 1,2-dibromo-3-chloropropane in groundwater may occur under anaerobic conditions.

5.3.2.3 Soil

1,2-Dibromo-3-chloropropane is subject to biodehalogenation in soilwater suspensions (aerobic/anaerobic conditions not specified) in the presence of an added nutrient (Castro and Belser 1968). Biodegradation did not occur in the absence of the added glycerol nutrient or in suspensions of sterilized soil. Approximately 75% of the soil samples that were tested affected dehalogenation of 1,2-dibromo-3-chloropropane. The highest rate of dehalogenation was 20% in 1 week at pH 8, which was measured by the rate of bromide ion formation. The maximum observed yield of bromide from 1,2-dibromo-3-chloropropane was 63% of the theoretical yield in 4 weeks under unspecified conditions. The data from these experiments suggest that 1,2-dibromo-3-chloropropane may be susceptible to biodegradation in soil under certain conditions; however, it is not possible to predict the soils that will biodegrade the chemical or what the rate of biodegradation might be (Castro and Belser 1968). In another study, it appears that no degradation of 1,2-dibromo-3-chloropropane was observed in soil columns within 25 days under aerobic conditions (Wilson et al. 1981). Based upon aqueous hydrolysis data, chemical hydrolysis is not expected to be significant except in very alkaline soils.

Based upon monitoring data obtained years after the last known application, 1,2-dibromo-3-chloropropane residues that do not leach or

volatilize appear to be very persistent in soil. For example, 1,2-dibromo-3-chloropropane residues as high as 0.5 μg/kg were found in the soil at a site 6-7 years following the last known application (Nelson et al. 1981).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

Few data concerning the detection of 1,2-dibromo-3-chloropropane in the atmosphere were found. Ambient air surrounding bromine industry chemical plants in the vicinity of two cities in Arkansas were analyzed for the presence of 1,2-dibromo-3-chloropropane in 1976 and 1977 (Pellizzari et al. 1978). In the vicinity of Magnolia, Arkansas, the maximum concentration of the chemical found in air surrounding a Dow Chemical Company plant was 6,653 ng/m^3. The maximum concentration in the El Dorado, Arkansas, area was 187 ng/m^3 at the Velsicol Chemical Corporation (Pellizzari et al. 1978). In a study that reported data collected primarily between 1970 and 1980, the median concentration of 1,2-dibromo-3-chloropropane was 1.8 ng/m^3 in ambient air near source-dominated areas; no data were listed for rural, remote, urban, or suburban areas (Brodzinsky and Singh 1982). This study is not comprehensive since it involved only scattered sampling of bromine industry chemical plants in one state. Furthermore, the data are old and were taken when the chemical was still being manufactured and widely used as a soil fumigant. Current releases to the atmosphere from manufacturing or research-use point sources are not likely to be significant since only limited amounts are presumed to be made and used (Sections 4.3 and 5.2.1). Significant concentrations of the chemical are probably not present in the ambient atmosphere at this time; therefore, the background level estimated for ambient air is expected to be less than'the detection limit. Exceptions may include air near hazardous waste sites where 1,2-dibromo-3-chloropropane has been disposed, although no data were found concerning atmospheric concentrations at these sites.

5.4.2 Water

Data concerning levels of 1,2-dibromo-3-chloropropane in water are lacking, and those available are neither current nor comprehensive (Table 5-l). The data in Table 5-l indicate that contamination of municipal drinking water supplies was not widespread in the past. Where contamination was found, the concentrations had been less than 10 μg/L; however, concentrations as high as 95 and 137 μg/L have been reported in water from drinking water wells in California and Arizona, respectively, although no information was provided on possible sources of contamination (Burmaster 1982). In a study of water from drinking water wells in the Fresno area of California's Central Valley conducted between 1979 and 1983, the tested wells generally had seasonal concentration patterns ranging from a low in winter to highs in spring/summer months. The 1,2-dibromo-3-chloropropane concentration also changed with daily use patterns ranging from highs at the start of pumping with lower concentrations as pumping continued (Kloos 1983). In a

TABLE 5-1. Levels of 1,2-Dibromo-3-chloropropane in Potable Water

Location	Date of sampling	Number of samples	Number positive samples	Concentration (µg/L) Range[a]	Concentration (µg/L) Mean[a]	Reference
Municipal water supplies						
United States	1981–82	466	1	5.5	Not applicable	Westrick et al. 1984
Mainly rural California	1979	61	14	0.1–9.5	1.4	Peoples et al. 1980
Riverside & Stanislas Counties, California	1979	3	3	0.1	0.1	Kutz and Carey 1986
South Carolina - DBCP nonuse area[b]	1979–80	3	1	0.05	Not applicable	Carter and Riley 1981
South Carolina -high DBCP use area[b]	1979–80	8	4	0.008–0.05	No data	Carter and Riley 1981
Drinking water wells						
South Carolina - DBCP nonuse area[b]	1979–80	8	3	0.008–0.05	Not applicable	Carter and Riley 1981
South Carolina -high DBCP use area[b]	1979–80	49	29	0.008–>1.0[c]	No data	Carter and Riley 1981
Madera, Stanislaus, & San Joaquin Co., California	1979	7	7	0.1–10.8	3.2	Kutz and Carey 1986
Well water and groundwater in areas with agricultural or undefined uses						
California	1979–84	8,190	2,522	No data[d]	No data	Cohen 1986
Fresno County, California	1979–83	9,000–10,000	1,500[e]	0.001–32[f]	No data	Kloos 1983
Mainly rural California	1979	262	90	0.1–39.2	No data	Peoples et al. 1980
Hawaii pineapple growing regions	1980–83	No data	No data	0.002–11	No data	Oki and Giambelluca 1987
United States[g]	No data	No data	No data	0.02–20[h]	No data	Cohen et al. 1986
San Joaquin Valley, California	April 1980	4 sites	3 sites	0.54–12	4.6	Nelson et al. 1981

[a]Based upon positive values; if one value is listed, it is a maximum.
[b]Areas of no 1,2-dibromo-3-chloropropane use (nonuse) and widespread use (high use), respectively.
[c]13 of 49 sites contained greater than the background level of 0.05 µg/L, and 5 contained greater than 1.0 µg/L.
[d]1,455 wells contained greater than 1.0 µg/L 1,2-dibromo-3-chloropropane.
[e]Approximate numbers
[f]850 wells contained greater than 1.0 µg/L 1,2-dibromo-3-chloropropane.
[g]Five U.S. states: Arizona, California, Hawaii, Maryland, South Carolina
[h]Typical positive values

DBCP = 1,2-dibromo-3-chloropropane

study of various waters in South Carolina sampled between 1979 and 1980, concentrations of 1,2-dibromo-3-chloropropane in water from one of three municipal water supplies ranged from 0.008 μg/L (detection limit) to 0.05 μg/L in an area where 1,2-dibromo-3-chloropropane was not known to have been used (Carter and Riley 1981).

Few data concerning the detection of 1,2-dibromo-3-chloropropane in surface water were found. In a study of South Carolina surface waters that were sampled between 1979 and 1980, concentrations of 1,2-dibromo-3-chloropropane ranged from not detected (detection limit = 0.008 μg/L) to 0.05 μg/L in areas where 1,2-dibromo-3-chloropropane usage rates ranged from non-use to scattered use (Carter and Riley 1981). In high-use areas, 18 of 48 sites had concentrations exceeding the background level of 0.05 μg/L; concentrations as high as 0.35 μg/L were detected (Carter and Riley 1981). 1,2-Dibromo-3-chloropropane was identified, but not quantified, in surface water at a bromine industry chemical plant in the vicinity of Magnolia, Arkansas, which was sampled in 1977 (Pellizzari et al. 1978).

These data, combined with the knowledge that use of 1,2-dibromo-3-chloropropane as a soil fumigant has not been permitted in the United States for several years, suggest that widespread exposure to the chemical in drinking water is not likely. The estimated background level for groundwater in areas where the chemical has not been used or disposed of in the past and in surface water is less than the detection limit. In areas where it was used as a soil fumigant, background levels of 0.001-0.008 μg/L can be expected depending on the amount used and environmental conditions.

5.4.3 Soil

Few data concerning the detection of 1,2-dibromo-3-chloropropane in soil were found. In a study conducted in 1980, 1,2-dibromo-3-chloropropane was analyzed in soils and subsoils from fields at four sites that were known to have been treated with 1,2-dibromo-3-chloropropane (the last application was 3-6 years prior to sampling) and where groundwater contamination with the chemical had been identified (Nelson et al. 1981). The concentrations in the soil and subsoils ranged from not detected (detection limit not stated) to 9 μg/kg (dry weight basis); higher levels were generally found in clay and silt layers (Nelson et al. 1981). In 32 fields that had received 1,2-dibromo-3-chloropropane treatments 2-4 years prior to sampling, the surface of the topsoil contained approximately 2-5 μg/kg of the chemical (Peoples et al. 1980).

In another study, soil samples taken from two South Carolina peach orchards with similar histories of 1,2-dibromo-3-chloropropane usage contained mostly undetectable levels (detection limit 0.025 μg/kg), but up to less than 0.1 and less than 0.5 μg/kg of the chemical was found in soil from the two orchards (Carter et al. 1984). Soil profile samples indicated that the residues were usually found in the upper 90 cm (Carter et al. 1984). Higher

levels of contamination in the groundwater at the first site were explained by a spill in which a formulation containing 1,2-dibromo-3-chloropropane had leaked from a rusting barrel (30 m from the well) leading to concentrations as high as 7.844 μg/kg in the adjacent soil (Carter et al. 1984).

These data, combined with the knowledge that use of 1,2-dibromo-3-chloropropane as a soil fumigant has not been permitted in the United States for several years, suggest that widespread exposure to the chemical due to contamination of soil is unlikely. The estimated background level for ambient soil in areas where the chemical has not been used is less than the detection limit. In areas where it was used as a soil fumigant or disposed, background levels of up to 0.5 μg/kg can probably be expected.

5.4.4 Other Environmental Media

Few data concerning levels of 1,2-dibromo-3-chloropropane in other environmental media were found. 1,2-Dibromo-3-chloropropane was tentatively identified, not quantified, in sediment at a bromine industry chemical plant in the vicinity of Magnolia, Arkansas, which was sampled in 1977 (Pellizzari et al. 1978).

Peaches grown in soil treated by injection into the soil of 51.4 and 137.5 L/hectare of a fumigant formulation containing 1.45 kg/L of 1,2-dibromo-3-chloropropane (peaches harvested between 183 and 217 days following treatment) contained 0.13 and 0.72 ppb 1,2-dibromo-3-chloropropane (Carter and Riley 1984). No residues were found in peaches grown in nonfumigated soil or in soil treated at or below the recommended treatment rate of 46.8 L/treated hectare (Carter and Riley 1984). In another study, Carter and Riley (1982) found levels as high as 24.7 ppb in peaches that were treated 114 days prior to harvest (application rate not reported). Carrots grown in soil that was treated with 12.26 pounds/acre of 1,2-dibromo-3-chloropropane by injection to a depth of 7 inches contained up to 1.50 ppm 3 weeks after treatment, and the residues persisted for 16 weeks when fumigation was at seeding (Newsome et al. 1977). Most of the residues were contained in the pulp of the carrots and two-thirds of the residues in unpeeled carrots disappeared when the carrots were boiled for 5 minutes. The maximum concentration found in radishes from treated fields (application rate of 12.26 pounds/acre of 1,2-dibromo-3-chloropropane) was 0.194 ppm (Newsome et al. 1977).

1,2-Dibromo-3-chloropropane was found at concentrations between 15 and 25 ppb in a commercial sample of sodium humate that was apparently imported from Germany (Gabbita 1986). It was not known whether the soil from which the humate was extracted was itself contaminated with the chemical.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population may be exposed to 1,2-dibromo-3-chloropropane through the ingestion of contaminated drinking water and food. Contaminated drinking water is most likely to be derived from contaminated groundwater sources at or near locations where 1,2-dibromo-3-chloropropane had been used as a soil fumigant. Not only are these areas limited in number and size, but the use of 1,2-dibromo-3-chloropropane as a soil fumigant has been banned for some time; therefore, although no current and comprehensive data were found to calculate an estimate of general population exposure to 1,2-dibromo-3-chloropropane from drinking water, the estimate is expected to be minimal based upon older data concerning the presence of 1,2-dibromo-3-chloropropane in drinking water and groundwater in the United States (Section 5.4.2). Since use of 1,2-dibromo-3-chloropropane has been prohibited for several years, it seems unlikely that foods recently harvested would contain 1,2-dibromo-3-chloropropane: Foods grown in fields that were irrigated with water derived from groundwater contaminated with 1,2-dibromo-3-chloropropane may contain small amounts of 1,2-dibromo-3-chloropropane based upon detection of the chemical in certain foods (Carter and Riley 1982, 1984; Newsome et al. 1977). Although data are lacking, inhalation is not expected to contribute significantly to general population exposure to 1,2-dibromo-3-chloropropane.

Due to the lack of recent comprehensive monitoring data, the average daily intake of 1,2-dibromo-3-chloropropane and the relative significance of each source of exposure cannot be determined. Since releases of 1,2-dibromo-3-chloropropane to the environment are generally limited to areas where it was used as a soil fumigant, a use which has been banned by the EPA in 1985, widespread exposure to the chemical is not likely.

The National Occupational Hazard Survey (NOHS) conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1972 and 1974 statistically estimated that 9,682 workers were exposed to 1,2-dibromo-3-chloropropane in the workplace in 1972 (RTECS 1984). The NOHS database does not contain information on the frequency, concentration, or duration of exposure of workers to any of the chemicals therein. The survey provides only an estimate of the number of workers potentially exposed to chemicals in the workplace; furthermore, the NOHS data are no longer valid to predict current numbers of workers exposed to 1,2-dibromo-3-chloropropane in the United States since the use of 1,2-dibromo-3-chloropropane as a soil fumigant (by far its major use in the past) has been banned in the United States, and since it is presumed that only relatively small amounts are produced for research purposes, and for use as an intermediate in chemical synthesis. 1;2-Dibromo-3-chloropropane was not listed by the National Occupational Exposure Survey (NOES) conducted by NIOSH (NIOSH 1989).

5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The highest levels of exposure may occur with workers who manufacture or use the compound for research or as a chemical intermediate in synthesis.

Populations with potentially higher exposure than normal for the general population include those in areas that obtain drinking water from contaminated groundwater sources. These areas are generally at or near agricultural regions where 1,2-dibromo-3-chloropropane had been used as a soil fumigant, and include, for example, the San Joaquin Valley in California (Kloos 1983), the pineapple-growing regions of Hawaii (Oki and Giambelluca 1987), and the peach-growing regions of South Carolina (Carter and Riley 1981). Drinking water derived from contaminated groundwater at or near hazardous waste sites that contain 1,2-dibromo-3-chloropropane might contain the chemical and contribute to exposure. Inhalation of contaminated air may contribute significantly to overall exposure of the general public, especially for populations living at or near hazardous waste dumps where 1,2-dibromo-3-chloropropane has been found. Most, if not all, of these exposures are expected to be rare and at relatively low levels.

5.7 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) ta 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 NTP, is required to assure the initiation of a program of research designed to determine the 3 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.

5.7.1 Data Needs

Physical and Chemical Properties. Physical and chemical property data are essential for estimating the transport and partitioning of a chemical in the environment. Most of the essential physical and chemical properties needed to estimate the environmental fate and transport of 1,2-dibromo-3-chloropropane are available (Table 3-2) (IARC 1979; Munnecke and VanGundy 1979; Ruth 1986; Sabljic 1984; Sax and Lewis 1987; Stenger 1978; Thomas 1982; Wilson et al. 1981; Windholz 1983). No experimental values are available for

the log octanol/water partition coefficient (log K_{OW}) and BCF. Since an estimated log K_{OW} was used to estimate the K_{OC} and BCF, the availability of an experimentally determined log K_{OW} would lead to less uncertainty in those estimated properties. While the techniques used for these estimations are reasonably accurate (Bysshe 1982; EPA 1988a), having the experimentally determined values would eliminate uncertainty concerning the reliability of these data.

Production, Import/Export, Use, and Disposal. Data regarding the production methods for 1,2-dibromo-3-chloropropane are available (Windholz 1983); however, data regarding current production volumes, release, and use patterns are lacking. Current levels of production, release, and use are considered relatively low due to the banning of the chemical's major use as a soil fumigant. Use, release, and disposal data can be useful for determining areas where environmental exposure to 1,2-dibromo-3-chloropropane may be high. Based upon relatively outdated data, significant concentrations are expected to be found mainly in the groundwater and drinking water derived from the groundwater at or near areas where 1,2-dibromo-3-chloropropane was used extensively as a soil fumigant (Burmaster 1982; Carter and Riley 1981; Cohen 1986; Kloos 1983; Kutz and Carey 1986; Nelson et al. 1981; Oki and Giambelluca 1987; Peoples et al. 1980; Westrick et al. 1984). Only general data are available on the methods of disposal of 1,2-dibromo-3-chloropropane (HSDB 1989). Specific disposal information would be useful for determining the effectiveness of the disposal methods. Regulations are available pertaining to the restrictions upon the land disposal of 1,2-dibromo-3-chloropropane.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxic Release Inventory (TRI), which contains this information for 1987, became available in May of 1989. This database will be updated yearly and should provide a list of industrial production facilities and emissions. Information specifically for 1,2-dibromo-3-chloropropane is dependent upon the current status of the TRI.

Environmental Fate. The ultimate environmental fate of 1,2-dibromo-3-chloropropane remains unclear due to a lack of experimental data. It is known, however, that the chemical has a tendency to partition into groundwater and into the atmosphere (Hodges and Lear 1974; Sabljic 1984; Wilson et al. 1981). It does not bind strongly to sediment or soil, but leaches rapidly through soil. It is subject to volatilization from surface water and near surface soil (Albrecht and Chenchin 1985; Bomberger et al. 1983; Thomas 1982). It degrades in the atmosphere via reaction with hydroxyl radicals (Tuazon et al. 1986). The chemical is not expected to significantly photolyze directly or to hydrolyze in water, but it is not known whether it biodegrades in water. It may biodegrade in certain soils provided adequate nutrients are available (Castro and Belser 1968). Residues of 1,2-dibromo-3-chloropropane evaporate

from near-surface soil and could leach through soil to groundwater. Experimental data regarding the processes that determine the fate and transport of 1,2-dibromo-3-chloropropane in air and soil are unavailable. Nothing definite is known about the biodegradability of the compound in soil or natural waters. Monitoring data obtained years after the last known applications of 1,2-dibromo-3-chloropropane indicate that small residues of the chemical are persistent in soil and groundwater (Carter and Riley 1981). Experimental data concerning biodegradation in soil would aid in assessing the ultimate environmental fate of 1,2-dibromo-3-chloropropane. This, in turn, would aid in understanding the levels that may be found in the environment and the observed or predicted levels of human exposure.

Bioavailability from Environmental Media. Studies have shown that 1,2-dibromo-3-chloropropane is absorbed through the gastrointestinal tract (Kato et al. 1979a) (Section 2.3.1), indicating that it may be absorbed through the ingestion of contaminated water and food. This suggests that exposure to 1,2-dibromo-3-chloropropane may occur as the result of ingestion of soil by children playing in hazardous waste sites. Thus, monitoring data on the actual number of children who eat soil while playing at toxic waste sites are needed. No data were found concerning absorption through the lungs or through dermal contact. Knowledge of the bioavailability through the various exposure routes is essential in assessing the potential body burdens that may occur as a result of exposure to known environmental concentrations.

Food Chain Bioaccumulation. Experimental data regarding the bioconcentration of 1,2-dibromo-3-chloropropane in plants, aquatic organisms, and animals were not located in the literature. However, based on an estimated BCF of 11.2, it is not expected to bioconcentrate in fish and other aquatic organisms (Bysshe 1982; Munnecke and VanGundy 1979); thus biomagnification in aquatic food chains is unlikely. Additional information on bioconcentration in plants and animals and biomagnification in terrestrial food chains would be helpful in assessing the potential for exposure of terrestrial animals at higher trophic levels.

Exposure Levels in Environmental Media. The data concerning the detection of 1,2-dibromo-3-chloropropane in the environment are so limited and outdated that estimation of human intake is not possible (Brodzinski and Singh 1982; Burmaster 1982; Carter and Riley 1981; Cohen 1986; Kloos 1983; Pellizzari et al. 1978; Peoples et al. 1980; Westrick et al. 1984). Current and comprehensive monitoring data, especially in areas where the chemical has been used in the past and is being used at the present time, would be helpful to estimate human intake. This may pertain to food survey analyses since it is difficult to ascertain whether the surveys to date tested for the presence of 1,2-dibromo-3-chloropropane.

Exposure Levels in Humans. No monitoring data were found indicating that 1,2-dibromo-3-chloropropane has been found in human tissues or blood.

The only biological monitoring studies that were found analyzed human breath samples for the presence of 1,2-dibromo-3-chloropropane (Pellizzari et al. 1978). 1,2-Dibromo-3-chloropropane was not found in any of the samples tested. Data concerning the level of 1,2-dibromo-3-chloropropane in human tissue samples would be helpful in assessing the extent of human exposure to the chemical and in estimating its body burden.

Exposure Registries. No exposure registries for 1,2-dibromo-3-chloropropane were located. This compound is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The compound will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this compound. Determination of the number of workers who are exposed to this compound may be included in the information since occupational exposure may be the major area of exposure.

5.7.2 On-going Studies

As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environmental Health Laboratory Sciences Division of the Center for Environmental Health and Injury Control, Centers for Disease Control, will be analyzing human blood samples for 1,2-dibromo-3-chloropropane and other volatile organic compounds. These data will indicate the frequency of occurrence and background levels of these compounds in the general population.

Remedial investigations and feasibility studies conducted at the eight NPL sites known to be contaminated with 1,2-dibromo-3-chloropropane will add to the available database on exposure levels in environmental media, exposure levels in humans, and exposure registries and will increase current knowledge regarding the transport and transformation of 1,2-dibromo-3-chloropropane in the environment.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring 1,2-dibromo-3-chloropropane in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify 1,2-dibromo-3-chloropropane. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect 1,2-dibromo-3-chloropropane in environmental samples are the methods approved by federal agencies such as EPA. Additionally, analytical methods are included that refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

6.1 BIOLOGICAL MATERIALS

Methods for analyzing 1,2-dibromo-3-chloropropane in biological samples are presented in Table 6-1. All of the methods listed utilize gas chromatography (GC) with various detectors. For most of the methods, detection limit and recovery data are not provided. No studies that reported the analysis of 1,2-dibromo-3-chloropropane in urine were located in the literature. With suitable modifications, the methods used for the determination of this chemical in water samples may be applicable for its determination in urine samples (Section 6.2).

6.2 ENVIRONMENTAL SAMPLES

Methods for analyzing 1,2-dibromo-3-chloropropane in environmental samples are presented in Table 6-2. As with the methods for the analysis of biological samples, all of the listed methods for the analysis of environmental samples utilize GC with various detection methods. The preconcentration/pretreatment methods use either adsorption onto a sorbent column for air samples, purge-and-trap methods for environmental water, soil, and solid samples, or simple extraction for food samples. The detection systems used, which include halogen-specific detection (e.g., Hall electrolytic conductivity detector), electron capture detector (ECD), and mass spectrometry (MS), generally provide excellent detection limits. An advantage of halogen-specific detectors is that they are not only very sensitive but also are specific to halogen compounds. The mass spectrometer, on the other hand, provides additional confirmation of a compound's identity through its ion fragment patterns. High-resolution gas chromatography (HRGC) with capillary columns provides better resolution for volatile compounds than packed columns. In this method, desorbed compounds are cryogenically trapped onto the head of the capillary column.

TABLE 6-1. Analytical Methods for Determining 1,2-Dibromo-3-chloropropane in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Exhaled air	Exhaled air collected by valved Teflon® Spirometer mouthpieces into Teflon® bag; contents of bag sorbed in Tenax® and thermally desorbed	Cryofocusing HRGC-MS	No data	77%-96%	Wallace et al. 1986
Exhaled air	Sorb into Tenax® column; thermally desorb	GC-MS	No data	No data	Pellizzari et al. 1985a
Blood	Pass inert gas over warmed sample; adsorb in Tenax® cartridges; thermally desorb	GC-MS	Approximately 3 ng/mL (10 mL sample)	No data	Pellizzari et al. 1985b
Rat blood	Extract with toluene	GC-ECD	No data	92.6%-102.4% (mean 96.7%)	Kastl et al. 1981
Tissues	Sample suspended in water; warmed and pass inert gas; adsorb in Tenax® cartidges; thermally desorb	GC-MS	Approximately 6 ng/g for 5g tissue	No data	Pellizzari et al. 1985b

ECD = electron capture detector; GC = gas chromatography; HRGC = high resolution gas chromatography; MS = mass spectrometry

TABLE 6-2. Analytical Methods for Determining 1,2-Dibromo-3-chloropropane in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Adsorb in Tenax® column; thermally desorb	Cryofocusing HRGC-MS	No data	77%-96%	Wallace et al. 1986
Air	Adsorb onto activated charcoal; desorb with hexane	GC-ECD	No data	90%	Fredrickson et al. 1985
Air	Adsorb onto Chromosorb II®; desorb with toluene	GC-ECD	0.02 ppb	>90% for 0.07-20 ppm	Mann et al. 1980
Air	Adsorb onto coconut charcoal; desorb with bezene, methanol-benzene, or methanol-toluene	GC-ECD	No data	87.7%-93.9%	Albrecht et al. 1986
Finished drinking/ raw source water/ groundwater	Extract with hexane	GC-HECD	0.01 µg/L	94%-105% at 2.0 µg/L	EPA 1986a (EPA Method 504)
Finished drinking/ raw source water	Purge and trap in Tenax®/ silica/charcoal; thermally desorb	Subambient programmable HRGC-MS	1.8 µg/L	No data	EPA 1986a (EPA method 524.1)
Finished drinking/ raw source water	Purge and trap in Tenax®/ silica/charcoal; thermally desorb	Cryofocusing (wide or narrow bore) HRGC-MS	0.26 µg/L[a]	83% at 0.5-10 µg/L[a]	EPA 1986a
			0.50 µg/L[b]	92% at 0.5 µg/L[b]	EPA 1986a (EPA method 524.2)
Drinking water	Purge and trap in Tenax®/ silica/charcoal; thermally desorb	GC-HECD and PID in series	3.0 µg/L	86%	Ho 1989
Liquid and solid waste, groundwater, soil, and sludge	Soil and viscous samples dispersed in water or methanol/water; purge and trap in Tenax®/silica/charcoal and thermally desorb	GC-HECD	No data	No data	EPA 1986b; Garman et al. 1987 (EPA method 5030 and 8010)
Food	Extract composited, table-ready food with isooctane or acetone-isooctane	GC-ECD/HECD	5 ng/g (ECD); 95 ng/g (HECD)	45%-102%	Daft 1988, 1989

TABLE 6-2 (Continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Citrus fruit (lemon, orange, grapefruit)	Sample blended with water; distilled into cyclohexane in essential oil apparatus; cleanup on Florisil column; injected into GC	GC-ECD	No data	96.5%-97.1% at 0.01 ppm	Tonogai et al. 1986

[a]Wide bore capillary column
[b]Narrow bore capillary column

ECD = electron capture detector; GC = gas chromotography; HECD = Hall electron capture detector; HRGC = high resolution gas chromatography; MS = mass spectrometry; PID = photoionization detector

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of 1,2-dibromo-3-chloropropane is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1,2-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.

6.3.1 Data Needs

Methods for Determining Biomarkers of Exposure and Effect. No biomarker that can be associated quantitatively with exposure to 1,2-dibromo-3-chloropropane has been identified (Moody et al. 1984; Suzuki and Lee 1981; Tofilon et al. 1980) (Section 2.5). If a biomarker in a human tissue or fluid were available, and a correlation between the level of the biomarker and exposure existed, it could be used as an indication of the levels and extent of exposure to this chemical. If exposure to bromine compounds is limited to 1,2-dibromo-3-chloropropane, serum bromide can be used as an indication of exposure (Torkelson et al. 1961). There are accurate techniques available for this analysis.

No biomarker of effect that can be associated quantitatively and directly attributed to 1,2-dibromo-3-chloropropane exposure has been identified (Whorton et al. 1979) (Section 2.5). If biomarkers of effect were available, and a correlation existed between the level or intensity of the biomarker of effect and the level of exposure, it could be used as an indication of the levels and extent of exposure to this chemical.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods for the determination of 1,2-dibromo-3-chloropropane in environmental media are generally available (Albrecht et al. 1986; Daft 1988, 1989; EPA 1986a, 1986b; Fredrickson et al. 1985; Garman et al. 1987; Ho 1989; Kastl et al. 1981; Mann et al. 1980; Pellizzari et al. 1985a, 1985b; Tonogai et al. 1986; Wallace et al. 1986). Groundwater contaminated by leached 1,2-dibromo-3-chloropropane and air contaminated by volatilization of 1,2-dibromo-3-chloropropane from soil are the media of most concern for

potential human exposure. The precision, accuracy, reliability, and specificity of the methods for environmental waters are well documented and well suited for the determination of low levels of 1,2-dibromo-3-chloropropane and levels at which health effects occur; however, these data are lacking for the soil methods.

6.3.2 On-going Studies

The Environmental Health Laboratory Sciences Division of the Center for Environmental Health and Injury Control, Centers for Disease Control, is developing methods for the analysis of 1,2-dibromo-3-chloropropane and other volatile organic compounds in blood. These methods use purge-and-trap methodology and magnetic sector mass spectrometry which give detection limits in the low parts per trillion (ppt) range.

No other on-going studies were located.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines pertinent to human exposure to 1,2-dibromo-3-chloropropane are summarized in Table 7-1.

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to 1,2-Dibromo-3-chloropropane

Agency	Description	Information	References
INTERNATIONAL			
IARC	Carcinogenic classification	Group 2B[a]	IARC 1979, 1987
NATIONAL			
Regulations:			
a. Air:			
OSHA	PEL	1 ppb	OSHA 1988 (29 CFR 1910.1044)
b. Water:			
EPA	PQL	100 µg/L	EPA 1987a (40 CFR 264 and 270)
c. Other:			
EPA	Reportable quantity (ruled)	1 pound (0.454 kg)	EPA 1985e (40 CFR 117 and 302)
Guidelines:			
a. Air:			
NIOSH	Occupational carcinogen	Lowest feasible concentration	NIOSH 1990
b. Water:			
EPA ODW	1-day Health Advisory:		
	Child	0.2 mg/day	EPA 1985a
	Adult	1.4 mg/day	EPA 1985a
	10-day Health Advisory:		
	Child	0.05 mg/day	EPA 1987b
c. Other:			
EPA	RfC	2.0×10^{-4} mg/m^3	IRIS 1991
EPA	Carcinogenic classification	Pending	IRIS 1991
NTP	Carcinogenic classification	Positive	NTP 1991
STATE			
Regulations and Guidelines:			
a. Air:	Acceptable ambient air concentrations		
Connecticut		0.05 µg/m^3 per 8 hours	EPA 1988c; NATICH 1988
Nevada		0.00	EPA 1988c; NATICH 1988
Pennsylvania		0.10 ppb	EPA 1988c; NATICH 1988
Kentucky		5.1×10^{-7} pounds per 1 hour	State of Kentucky 1986

TABLE 7-1 (Continued)

Agency	Description	Information	References
STATE (Cont.)			
b. Water:	Acceptable ambient water concentrations		
Arizona		0.025 µg/L	FSTRAC 1988
California		1.00 µg/L	FSTRAC 1988
Minnesota		0.25 µg/L	FSTRAC 1988
Wisconsin		0.50 µg/L	FSTRAC 1988

[a]Group 2B = Possible human carcinogen.

EPA = Environmental Protection Agency
IARC = International Agency for Research on Cancer
NIOSH = National Institute for Occupational Safety and Health
NTP = National Toxicology Program
ODW = Office of Drinking Water
OSHA = Occupational Safety and Health Administration
PEL = permissible exposure limit
RfC = reference concentration
PQL = permissible quantity limit

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9. GLOSSARY

Acute Exposure -- Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

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

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

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

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

Carcinogen -- A chemical capable of inducing cancer.

Ceiling Value -- A concentration of a substance that should not be exceeded, even instantaneously.
Chronic Exposure -- Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

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

Embryotoxicity and Fetotoxicity -- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

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

9. GLOSSARY

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

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

Immunologic Toxicity -- The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

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

In Vivo -- Occurring within the living organism.

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

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

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

Lethal Dose$_{(50)}$ (LD50) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

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

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

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

Minimal Risk Level -- An estimate of daily human exposure to a chemical that is likely to be without an appreciable risk of deleterious effects (noncancerous) over a specified duration of exposure.

9. GLOSSARY

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

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

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

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an 8-hour shift.

q_1* -- The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Reference Dose (RfD) -- An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 lb or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

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

9. GLOSSARY

Short-Term Exposure Limit (STEL) -- The maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily TLV-TWA may not be exceeded.

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

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

Threshold Limit Value (TLV) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) -- A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in nontechnical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or substance release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the substance.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects by duration of exposure and endpoint and to illustrate graphically levels of exposure associated with those effects. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELS), Lowest-Observed- Adverse-Effect Levels (LOAELs) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate differences in response by species, Minimal Risk Levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text.

The legends presented below demonstrate the application of these tables and figures. A representative example of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exist,

three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-i) and oral (LSE Figure 2-2) routes.

2) Exposure Duration Three exposure periods: acute (14 days or less); intermediate (15 to 364 days); and chronic (365 days or more) are presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported.

3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table.

4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to define a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in Figure 2-l).

5) Species The test species, whether animal or human, are identified in this column.

6) Exposure Freouencv/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to [substance x] via inhalation for 13 weeks, 5 days per week, for 6 hours per day.

7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated in this study.

8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote IIc").

9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest exposure level used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to

quantify the adverse effect accompanies the LOAEL. The "Less Serious" respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.

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

11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiological studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses which did not cause a measurable increase in cancer.

12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "c" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See LSE Figure 2-1

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

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

14) Health Effect These are the categories of health effects for which reliable quantitative data exist. The same health effects appear in the LSE table.

15) Levels of ExDosure Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported on the log scale "y" axis. Inhalation exposure is reported in mg/m3 or ppm and oral exposure is reported in mg/kg/day.

16) NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates a NOAEL for the test species (rat). The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

17) CEL Key number 38r is one of three studies for which Cancer Effect Levels (CELs) were derived. The diamond symbol refers to a CEL for the test species (rat). The number 38 corresponds to the entry in the LSE table.

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18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

1 → **TABLE 2-1. Levels of Significant Exposure to [Chemical x] - Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
3 → Systemic	5 ↓	6 ↓	7 ↓	8 ↓	9 ↓		10 ↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer					11 ↓		
38	Rat	18 mo 5d/wk 7hr/d				20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5d/wk 6hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79-103 wk 5d/wk 6hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

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

12 → [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

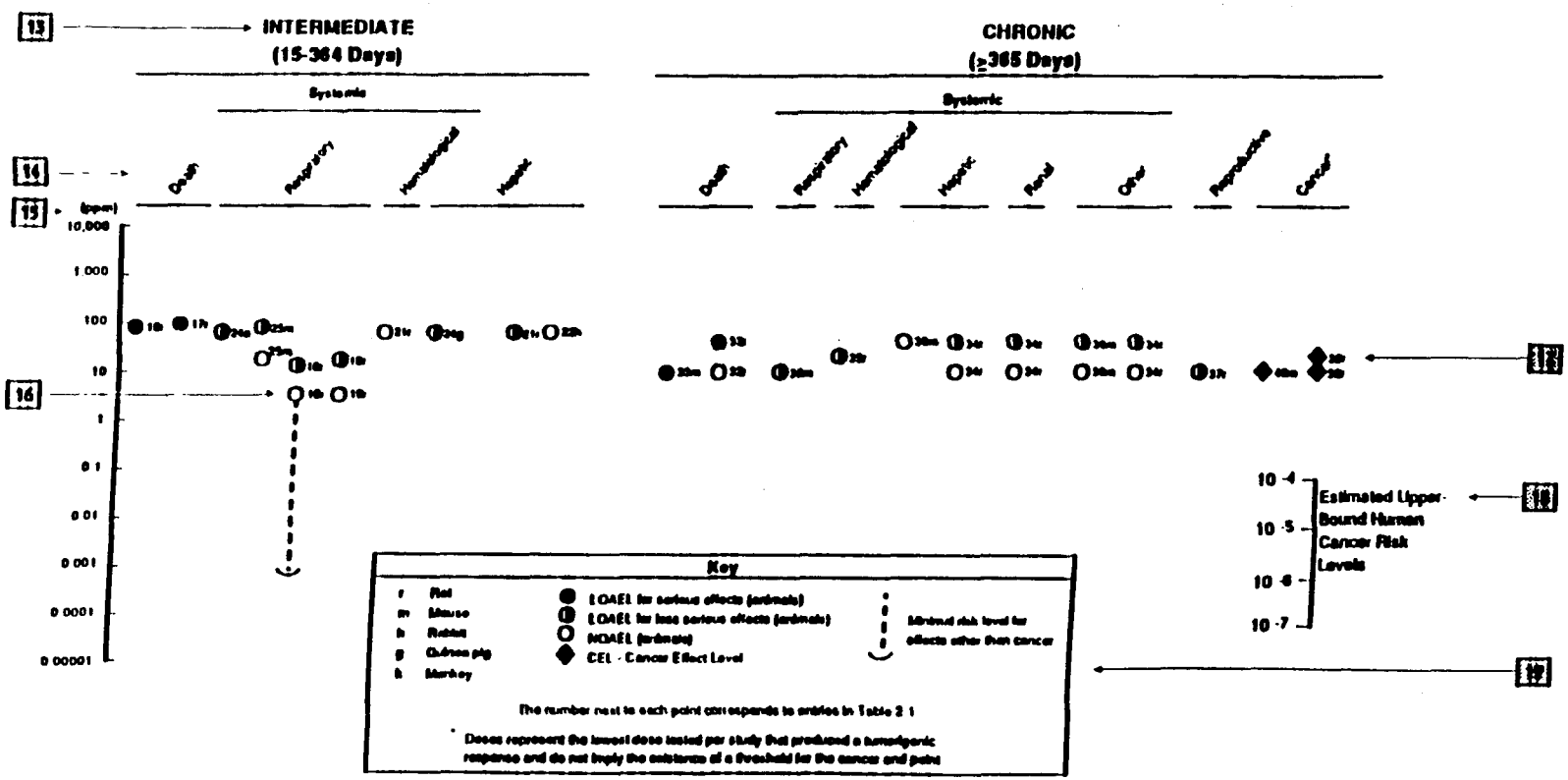

FIGURE 2-1. Levels of Significant Exposure to [Chemical X]-Inhalation

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Chapter 2 (Section 2.4)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicological, epidemiological, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

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

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

The section discusses health effects by end point. Human data are presented first, then animal data. Both are organized by route of exposure (inhalation, oral, and dermal) and by duration (acute, intermediate, and chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existingtoxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. MRLs for noncancer end points if derived, and the end points from which they were derived are indicated and discussed in the appropriate section(s).

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Identification of Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute, - intermediate, - chronic). These MRLs are not meant to support regulatory action, but to aquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

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MRL users should be familiar with the toxicological information on which the number is based. Section 2.4, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.6, "Interactions with Other Chemicals" and 2.7, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology used by the Environmental Protection Agency (EPA) (Barnes and Dourson, 1988; EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the end point which, in its best judgement, represents the most sensitive humanhealth effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continous exposure (i.e., 7 days/week). If the information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor (UF) of 10 is employed. MRLs are not derived from Serious LOAELs. Additional uncertainty factors of 10 each are used for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the adjusted inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX B

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACIGH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
f_1	first generation
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
HPLC	high performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
Kg	kilogram
K_{OC}	octanol-soil partition coefficient
K_{OW}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{LO}	lethal concentration low
LC_{50}	lethal concentration 50 percent kill
LD_{LO}	lethal dose low
LD_{50}	lethal dose 50 percent kill
LOAEL	lowest-observed-adverse-effect level

LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeters
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectroscopy
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
nm	nanometer
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportional mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short-term exposure limit
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxic Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
WHO	World Health Organization
>	greater than
≥	greater than or equal to
=	equal to

<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram

APPENDIX C

PEER REVIEW

A peer review panel was assembled for 1,2-dibromo-3-chloropropane. The panel consisted of the following members: Dr. James Bruckner, University of Georgia, Athens, Georgia; Dr. Fumio Matsumura, University of California, Davis, California; Dr. Donald Morgan, University of Iowa Medical School, Iowa City, Iowa; Dr. Jay Silkworth, New York State Department of Health, Albany, New York; Dr David Strayer, University of Texas, Houston, Texas. These experts collectively have knowledge of 1,2-dibromo-3-chloropropane's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in the Comprehensive Environmental Response, Compensation, and Liability Act of 1986, Section 104.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.
The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.