DRAFT
TOXICOLOGICAL PROFILE FOR
BROMOFORM AND DIBROMOCHLOROMETHANE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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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.

UPDATE STATEMENT

A Toxicological Profile for bromoform and dibromochloromethane was released in 1990. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
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FOREWORD

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

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

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that 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 are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance 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 that present a significant risk to human health of acute, subacute, and chronic health effects; and

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

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Comments should be sent to:

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The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on October 25, 2001 (66 FR 54014). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); and October 21, 1999 (64 FR 56792). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

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

Julie Louise Gerberding, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6 How Can (Chemical X) Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 3.7 Children's Susceptibility
Section 6.6 Exposures of Children

Other Sections of Interest:

Section 3.8 Biomarkers of Exposure and Effect
Section 3.11 Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-888-42-ATSDR or (404) 498-0110 ***Fax:*** (404) 498-0093
E-mail: atsdric@cdc.gov ***Internet***: http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity*; and numerous chemical-specific case studies.

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

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

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

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

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

Referrals

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

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

A peer review panel was assembled for bromoform and dibromochloromethane. The panel consisted of the following members:

1. Bruce Jarnot, Ph.D., DABT, Senior Toxicologist
   American Petroleum Institute
   Washington DC

2. Kannan Krishnan, Ph.D., Professor
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3. Clint Skinner, Ph.D., Consultant
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These experts collectively have knowledge of bromoform and dibromochloromethane's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

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.

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about bromoform and dibromochloromethane and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Bromoform and dibromochloromethane have been found in at least 141 and 172 of the 1,636 current or former NPL sites, respectively. However, the total number of NPL sites evaluated for this substance is not known. As more sites are evaluated, the sites at which bromoform and dibromochloromethane are found may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

When a substance 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. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to bromoform or dichlorobromomethane, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT ARE BROMOFORM AND DIBROMOCHLOROMETHANE?

Bromoform (also known as tribromomethane) and dibromochloromethane are colorless to yellow, heavy, nonburnable liquids with a sweetish odor. These chemicals are possible contaminants of drinking water that has been chlorinated to kill bacteria and viruses that could cause serious waterborne infectious diseases. Bromoform and dibromochloromethane may form

when chlorine reacts with other naturally occurring substances in water, such as decomposing plant material. Plants in the ocean also produce small amounts of these chemicals.

These chemicals are found mainly in water that originally came from surface sources, such as rivers and lakes. Springs and deep drilled wells usually contain very little of the substances that react with chlorine to form these chemicals; therefore, well and spring water is less likely a source of bromoform and dibromochloromethane than water from a reservoir (artificial lake). The amount of bromoform and dibromochloromethane in drinking water can change considerably from day to day, depending on the source, temperature, amount of plant material in the water, amount of chlorine added, and a variety of other factors.

In the past, bromoform was used by industry to dissolve dirt and grease and to make other chemicals, and it was also used in the early part of this century as a medicine to help children with whooping cough get to sleep. Currently, bromoform is only produced in small amounts for use in laboratories and in geological and electronics testing. Dibromochloromethane was used in the past to make other chemicals such as fire extinguisher fluids, spray can propellants, refrigerator fluid, and pesticides. It is now only used on a small scale in laboratories.

In the environment, bromoform and dibromochloromethane are not found as pure liquids, but instead, they are found either dissolved in water or evaporated into air as a gas. Both bromoform and dibromochloromethane are relatively stable in the air, but reactions with other chemicals in the air cause them to break down slowly (about 50% in 1 or 2 months). Any bromoform and dibromochloromethane in water or soil may also be broken down by bacteria, but the speed of this process is not known.

Further information on the properties, uses, and chemical identity of bromoform and dibromochloromethane in the environment may be found in Chapters 4, 5, and 6.

1.2 WHAT HAPPENS TO BROMOFORM AND DIBROMOCHLOROMETHANE WHEN THEY ENTER THE ENVIRONMENT?

Bromoform and dibromochloromethane enter the environment through the disposal of water that has been disinfected with chlorine or as vapors emitted from chlorinated water. These chemicals are also made naturally by plant-like organisms called algae in the oceans. Some part of bromoform and dibromochloromethane that enters the air is taken out of the air in rain. What is left in the air takes about 1–2 months for half of it to degrade. In water, bromoform and dibromochloromethane are slowly broken down at the water surface where oxygen is available, but break down much faster in deep water and in water that is underground where there is a lot less oxygen. Bromoform and dibromochloromethane are mobile in soils and may seep into groundwater. Bromoform and dibromochloromethane do not appear to concentrate in fish.

1.3 HOW MIGHT I BE EXPOSED TO BROMOFORM AND DIBROMOCHLORO METHANE?

You are most likely to be exposed to bromoform and dibromochloromethane by drinking water that has been treated with chlorine. Usually, the levels in chlorinated drinking water are between 1 and 10 parts of bromoform and dibromochloromethane per billion parts of water (ppb). These are levels that are known to be without health effects. Bromoform and dibromochloromethane have also been detected in chlorinated swimming pools. When you are at a pool, you could be exposed by breathing some bromoform or dibromochloromethane that has evaporated into the air, or by uptake from the water through the skin. Neither dibromochloromethane nor bromoform are likely to be found in food.

If you live near a factory or laboratory that makes or uses dibromochloromethane or bromoform, you might be exposed to dibromochloromethane or bromoform in the air. Currently, bromoform is only used for geological and electronics testing. Dibromochloromethane is used on a small-scale in laboratories. Since neither dibromochloromethane nor bromoform have widespread use in this country, they are usually present in outside air only at very low levels (less than 0.01 ppb). Therefore, exposure to bromoform in the air is a minor route. Another place where you might be exposed is near a chemical waste site where dibromochloromethane or bromoform has been allowed to leak into water or soil. In this case, you could be exposed if you drank the water or,

to a lesser extent, got the soil on your skin. Further information on how you might be exposed to these chemicals is given in Chapter 6.

1.4 HOW CAN BROMOFORM AND DIBROMOCHLOROMETHANE ENTER AND LEAVE MY BODY?

Studies in animals or humans indicate that both bromoform and dibromochloromethane can easily enter your body after you drink them in water or breathe them in air. They can also enter your body after you get them on your skin (for example, by washing or showering in water containing these chemicals). After bromoform and dibromochloromethane enter your body, they are broken down to other compounds. These compounds, as well as bromoform and dibromochloromethane, are removed from the body by being breathed out through the lungs. These chemicals leave the body fairly rapidly and completely. Of the amount that enters the body, 50–90% leaves the body in 8 hours, so bromoform and dibromochloromethane do not tend to build up in the body. Further information on how bromoform and dibromochloromethane enter and leave your body is given in Chapter 3.

1.5 HOW CAN BROMOFORM AND DIBROMOCHLOROMETHANE AFFECT MY HEALTH?

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

The effects of bromoform and dibromochloromethane on your health depend on how much you take into your body. In general, the more you take in, the greater the chance that an effect will occur. Studies in animals or humans indicate that the main effect of eating or breathing large amounts of these chemicals (for example, swallowing 1–4 drops of liquid bromoform, which is a much greater amount than that usually found in a glass of drinking water) is a slowing down of normal brain activities. The amount of dibromochloromethane taken by mouth that would affect humans is not known, but is probably about the same as for bromoform. Sleepiness or sedation occurs quickly after the chemicals enter your body. In humans, the usual result is only sleepiness, which tends to go away within a day. At higher amounts, or in extreme cases, a person may become unconsciousness or die.

Studies in animals indicate that exposure to high doses of bromoform or dibromochloromethane may also lead to injury to the liver and the kidneys within a short period of time. Exposure to low levels of bromoform or dibromochloromethane do not appear to seriously affect the brain, liver, or kidneys, but studies in animals indicate that long-term intake of either bromoform or dibromochloromethane can cause cancer. Although no cases of cancer in humans can be definitely attributed to these chemicals, this is an effect of special concern, since many people are exposed to low levels of bromoform and dibromochloromethane in chlorinated drinking water.

Studies in animals also suggest that neither bromoform nor dibromochloromethane has a high risk of affecting the chance of becoming pregnant or harming an unborn baby.

Further information on how bromoform and dibromochloromethane can affect the health of humans and animals is presented in Chapter 3.

1.6 HOW CAN BROMOFORM AND DIBROMOCHLOROMETHANE AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans.

In the early 1900s, bromoform was given to children suffering from whooping cough, and several deaths resulted when children accidentally took overdoses. Children appeared drowsy, then lifeless, just before dying.

There are no studies in humans or laboratory animals that have examined whether the effects of bromoform dibromochloromethane change with age. Based on current knowledge of how the body functions, and what is known about what happens to these chemicals in the bodies of animals, there is no indication that children will be affected to a greater degree than adults.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO BROMOFORM AND DIBROMOCHLOROMETHANE?

If your doctor finds that you have been exposed to significant amounts of bromoform and/or dibromochloromethane, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate.

The risk of consuming bromoform or dibromochloromethane in chlorinated public drinking water varies with season, water temperature, water chemistry, disinfection method, and other factors. However, the health risks, associated with drinking non-disinfected water when there is evidence of pathogenic contamination (i.e., bacteria, viruses, etc.), are much greater than the risk of exposure to bromoform or dibromochloromethane.

There are water treatment methods that people can use in their homes (point-of-use filtration) to reduce exposure to bromoform and dibromochloromethane from chlorinated tap water. These include potential do-it-yourself methods such as connecting solid carbon block filters to your faucet and shower taps. Homeowners may discuss other home water treatment methods, including filtering, aeration or boiling, distillation, and/or activated charcoal, with a professional plumber or water well contractor. While bromoform is no longer used as a medicine, keeping children away from or supervising children with chemicals brought into the home, will reduce the potential for accidental exposures. The risk of exposure to bromoform and dibromochloromethane may be reduced by minimizing contact with water expected to have a higher levels of these chemicals, such as swimming pool water. When taking a bath or

showering in water in which dibromochloromethane and/or bromoform is present, greater amounts of these chemicals evaporate into the air at hotter temperatures and during longer time periods. Opening the windows in bathrooms, and taking quick baths or showers may reduce the amount of chemical vapor that is inhaled or absorbed through the skin.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO BROMOFORM AND DIBROMOCHLOROMETHANE?

If you are exposed to bromoform or dibromochloromethane, measurable levels of the chemicals can sometimes be detected in samples of your blood, breath, or fat. However, there is not enough information at present to use the results of such tests to estimate the level of exposure or to predict the nature or the severity of any health effects that might result. Since special equipment is needed, these tests are not routinely performed in doctors' offices. Because bromoform and dibromochloromethane are eliminated from the body fairly quickly, these special laboratory tests are only effective in detecting recent exposures (within 1 or 2 days). Further information on how bromoform and dibromochloromethane can be measured in exposed humans is presented in Chapters 3 and 7.

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

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals; then they are adjusted to help protect

people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for bromoform include the following:

OSHA has set a legally enforceable limit of 0.5 ppm for bromoform in workroom air to protect workers during an 8-hour shift over a 40-hour work week.

EPA recommends that drinking water levels for bromoform should not be more than 0.7 parts per million (ppm) for bromoform and 0.7 ppm for dibromochloromethane.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below.

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles CD-ROM by calling the information and technical assistance toll-free number at 1-888-42ATSDR (1-888-422-8737), by email at atsdric@cdc.gov, or by writing at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE
Mailstop E-29
Atlanta, GA 30333
Fax: 1-404-498-0093

For-profit organizations may request a copy of final profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO BROMOFORM AND DIBROMOCHLOROMETHANE IN THE UNITED STATES

Bromoform ($CHBr_3$; CAS Number 75-25-2), also known as tribromomethane, and dibromochloromethane ($CHClBr_2$; CAS Number 124-48-1) belong to a group of chemicals referred to as trihalomethanes; the other two chemicals in this group are chloroform and dichlorobromomethane. Trihalomethanes are formed when raw source water is disinfected by chlorination. In the United States, over 280 million people are served by public water systems that apply chlorine or some of its compounds as disinfectants to water in order to provide protection against microbial contaminants that otherwise might cause serious water-borne diseases. While these chlorine-containing disinfectants are effective in controlling many microorganisms, they react with natural organic or carbon-containing matter in the water to form disinfection byproducts, undesirable chemicals inadvertently produced when disinfectants react with plant material in the source water. Therefore, the principal source of human exposure to bromoform and dibromochloromethane is water supplied to homes, work, and public places that has been disinfected by chlorination. Bromoform and dibromochloromethane concentrations in public supply or tap water are in the low microgram/L range. Dibromochloromethane is often found more frequently than bromoform in samples from chlorinated water systems.

In the past, it was thought that most of the human exposure to bromoform and dibromochloromethane occurred through consumption of chlorinated drinking water. However, because of their physical properties (see Henry's law constants in Chapter 4), some bromoform and dibromochloromethane volatilize into the air from normal household use of water containing these chemicals; and recent models for residential exposure predict that exposure by the inhalation and dermal routes may be significant. Dermal exposure is expected from showering or bathing. Total administered doses of bromoform or dibromochloromethane for low microgram/L residential tap water concentrations are predicted to be on the order of 10^{-4} mg/kg/day.

2.2 SUMMARY OF HEALTH EFFECTS

The general population is primarily exposed to bromoform and dibromochloromethane via tap water, and the primary routes of exposure are inhalation (from volatilized compounds) and ingestion. However, showering and bathing can also result in inhalation and dermal exposure. Bromoform and

dibromochloromethane are readily absorbed from the gastrointestinal tract and are likely absorbed from the respiratory tract and skin. They are rapidly distributed throughout the body. In the liver, bromoform and dibromochloromethane are metabolized by cytochrome P-450 mixed function oxidase system to a highly reactive metabolite, which is ultimately metabolized to carbon dioxide or carbon monoxide.

Studies in animals, combined with limited observations in humans, indicate that the principal adverse health effects associated with oral exposure to bromoform or dibromochloromethane are central nervous system depression, liver damage, and kidney damage. The very limited data on the toxicity of inhaled bromoform suggest that the central nervous system, liver, and kidney would also be the primary targets of toxicity. Although no dermal data were located, it is likely that similar adverse health effect would occur from dermal exposure. Based on the no-observed-adverse-effect level (NOAEL) and lowest-observed-adverse-effect level (LOAEL) values identified in animal studies, the liver appears to be the most sensitive target. Two types of liver effects have been observed in laboratory animals. At the lower adverse effect levels, lipidosis is found; lipidosis is an accumulation of lipids in the hepatocytes resulting in cellular vacuolization and swelling. At higher doses, hepatocellular necrosis is observed. It is not known if these effects represent a continuum of liver damage or are due to separate modes of action. Kidney effects are typically observed at higher doses than hepatic effects. Tubular cell degeneration and nephrosis are the most commonly reported effects in laboratory animals. Central nervous system depression, as evidenced by lethargy, ataxia, and shallow breathing, are typically observed at very high, often lethal, doses. High-dose exposure is also associated with decreases in body weight gain. There are limited data on the immunotoxicity of bromoform and dibromochloromethane; only one study assessed immune function. Impaired humoral and cell-mediated (only observed with dibromochloromethane) immunity were observed in mice administered bromoform or dibromochloromethane via gavage for 14 days. For bromoform, the immune and liver effects occurred at the same dose level; for dibromochloromethane, the immune effects occurred at a lower dose than the liver effects.

The available data on the potential of bromoform and dibromochloromethane to induce reproductive and/or developmental effects are inconclusive. Human data primarily come from epidemiological studies of pregnancy outcomes in women exposed to trihalomethanes in drinking water. These studies involved mixed exposures to the trihalomethane compounds (chloroform, dichlorobromomethane, bromoform, and dibromochloromethane), and many did not analyze for possible risks associated with bromoform or dibromochloromethane water concentrations. These data are inadequate for establishing a causal relationship between trihalomethane exposure and reproductive and/or developmental toxicity. The animal data suggest that exposure to bromoform or dibromochloromethane does not cause histological

damage to reproductive organs or impair reproductive function; although high- dose exposure may result in reduced fertility. The available developmental toxicity data suggest that bromoform and dibromochloromethane may be toxic to the developing fetus, but these data are inadequate to establish firm conclusions.

The carcinogenicity of bromoform and dibromochloromethane has been assessed in both humans and laboratory animals. The human data consist of studies of trihalomethane exposure via tap water. As with the reproductive and developmental toxicity studies, these data are inconclusive and do not establish causal relationships. Carcinogenic effects have been observed in animals exposed to bromoform and dibromochloromethane. Chronic oral exposure to bromoform resulted in increases in the occurrence of intestinal tumors in female rats. Dibromochloromethane induced liver tumors in male and female mice (1985). The International Agency for Research on Cancer (IARC) concluded that there were inadequate human data and limited animal data and assigned bromoform and dibromochloromethane to weight of evidence category 3, not classifiable as to carcinogenicity in humans. EPA classified bromoform as a probable human carcinogen, group B2 and dibromochloromethane as a possible human carcinogen, group C.

The primary targets of bromoform and dibromochloromethane toxicity— liver, kidney, and central nervous system—are discussed in greater detail below. The reader is referred to Section 3.2, Discussion of Health Effects by Route of Exposure, for additional information on other health effects.

Liver Effects. Acute, intermediate-, and chronic-duration studies in laboratory animals provide strong evidence that the liver is the critical target of bromoform and dibromochloromethane toxicity. There are very limited human data on the toxicity of these two compounds; data for other trihalomethanes, particularly chloroform, suggest that the liver will also be a target of toxicity in humans.

There is strong evidence that the hepatotoxicity of bromoform and dibromochloromethane is due to their metabolism to reactive intermediates and highly reactive trihalomethyl free radicals. At lower doses, the hepatotoxicity of bromoform and dibromochloromethane is characterized by fatty infiltration, cellular vacuolization and swelling, and increases in liver weight. Consistent with the accumulation of lipids is the observed decrease in serum triglyceride levels and alterations in serum cholesterol levels. At higher doses, focal centrolobular necrosis and increases in SGOT and SGPT levels have been observed. For bromoform, the lowest-observed-adverse–effect level is 50 mg/kg (5 days/week; 36 mg/kg/day) for fatty changes observed in rats administered via gavage bromoform in corn oil for 13 weeks. Necrosis was

observed in rats receiving gavage doses of 200 mg/kg (143 mg/kg/day), 5 days/week for 2 years, but not after 13 weeks of dosing. For dibromochloromethane, the lowest-observed-adverse-effect level is 40 mg/kg (5 days/week; 28 mg/kg/day) for fatty liver changes in rats receiving gavage doses of dibromochloromethane in corn oil for 2 years. Necrosis was observed at 173.3 mg/kg/day in rats exposed via the diet for 1 month.

Species and possibly sex differences in the hepatotoxicity of bromoform and dibromochloromethane have been identified. Rats appear to be more sensitive than mice to the liver effects. Under similar exposures scenarios, respective NOAEL and LOAEL values of 25 and 50 mg/kg (5 days/week) for fatty changes were identified in rats exposed to bromoform for 13 weeks; the NOAEL and LOAEL values in mice were 100 and 200 mg/kg (5 days/week), respectively. For dibromochloromethane, the NOAEL and LOAEL values for fatty changes following a 13-week gavage exposure (5 days/week) were 30 and 60 mg/kg for rats and 125 and 250 mg/kg for mice.

Kidney Effects. Renal effects have not been consistently found in studies of laboratory animals, particularly in the case of bromoform exposure. One study reported renal effects (mesangial nephrosis) in mice exposed to 145 mg/kg/day bromoform via gavage for 14 days; a NOAEL of 37 mg/kg/day was also identified in this study. Comprehensive intermediate- and chronic-duration studies in rats and mice did not find significant renal effects at doses as high as 400 mg/kg (5 days/week; 286 mg/kg/day). In contrast, exposure to dibromochloromethane resulted in mesangial hyperplasia in mice exposed to ≥37 mg/kg/day via gavage for 14 days and toxic nephropathy in rats and mice exposed to 250 mg/kg (179 mg/kg/day) for 13 weeks and in mice receiving gavage doses of 100 mg/kg (71 mg/kg/day) for 2 years.

Central Nervous System Depression. In children, oral doses of around 60 mg/kg/day of bromoform typically produced only mild sleepiness, while doses of 150 mg/kg sometimes produced stupor or deep narcosis, usually accompanied by depressed respiration and erratic heartbeat. The onset of sedation after ingestion is rapid, reportedly minutes in children and about an hour in mice. In intermediate and chronic oral studies in animals, doses of bromoform ≥100 mg/kg (5 days/week; 71 mg/kg/day) caused lethargy. Airborne concentrations of bromoform leading to central nervous system depression in humans are not known, but brief exposures of laboratory animals to high concentrations (7,000 ppm) leads to deep sedation within minutes. Central nervous system effects were also observed in laboratory animals at a concentration of 240 ppm in a short-term, repeated dose study. These depressant

effects on the nervous system appear to be fully reversible both in animals and humans, but it is difficult to rule out the possibility of subtle, but enduring, neurological changes following narcotizing doses.

2.3 MINIMAL RISK LEVELS (MRLs)

The details regarding calculations of the MRLs for bromoform and dibromochloromethane are described in Appendix A.

Inhalation MRLs

MRLs for acute- (≤14 days), intermediate- (15–364 days), and chronic-duration (≥364 days) inhalation exposure to bromoform or dibromochloromethane have not been derived because quantitative data were not available to determine NOAELs or LOAELs.

Information on the toxicity of bromoform or dibromochloromethane in humans following inhalation exposure was not available. Brief summaries of adverse effects in laboratory animals following inhalation exposure to bromoform, reported in abstract form, do not provide sufficient basis for MRL derivation. No studies were located regarding effects of dibromochloromethane in animals exposed via inhalation. Therefore, inhalation MRLs were not derived for either bromoform or dibromochloromethane.

Oral MRLs

Bromoform

- An MRL of 0.7 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to bromoform.

A number of animal studies have examined the acute toxicity of bromoform. The threshold for liver effects appears to be between 50 and 125 mg/kg/day. Increases in absolute and relative liver weights were observed in mice exposed to 125 mg/kg/day bromoform in emulphor in water for 14 days (Munson et al. 1982). Centrilobular pallor, considered to be indicative of hepatocellular degeneration, was observed at 145 mg/kg/day in mice receiving gavage doses of bromoform in corn oil for 14 days (Condie et al. 1983). Hepatocellular vacuolization and/or swelling was observed at 200 mg/kg (9 days/11 days) and higher (Coffin et al. 2000). Other effects observed in acute-duration animal studies include

mesangial nephrosis in mice exposed to 145 mg/kg/day via gavage for 14 days (Condie et al. 1983), impaired humoral immune function at 125 mg/kg/day in mice exposed via gavage for 14 days (Munson et al. 1982), central nervous system depression, as evidenced by lethargy, labored and shallow breathing, and ataxia in rats and mice at ≥600 mg/kg/day for 1–14 days (Balster and Borzelleca 1982; Bowman et al. 1978; NTP 1989a), and developmental effects (increases in the occurrence of skeletal anomalies) in the offspring of rats exposed to 200 mg/kg/day on gestational days 6–15 (Ruddick et al. 1983).

The Condie et al. (1983) study, which identified a NOAEL of 72 mg/kg/day and LOAEL of 145 mg/kg/day for centrilobular pallor, was selected as the basis of the acute-duration oral MRL for bromoform. This study was selected because it identified a highest NOAEL for the most sensitive target, the liver. Although several effects have been reported at 100–200 mg/kg/day, the liver was selected as the critical target because adverse liver effects are consistently observed in animals following acute-, intermediate-, and chronic-duration exposure. The NOAEL of 72 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) to yield an acute-duration oral MRL of 0.7 mg/kg/day

- An MRL of 0.2 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to bromoform.

The oral toxicity database in animals provides strong evidence that the liver is the most sensitive target of bromoform toxicity. Several intermediate-duration studies have reported liver effects, typically at the lowest-observed-adverse-effect level. At lower doses, fatty changes, characterized as hepatocellular vacuolization and swelling, were observed in rats and mice. Focal necrosis was observed at higher oral doses. The lowest LOAEL for liver effects identified in an intermediate-duration study is 50 mg/kg in rats receiving gavage doses of bromoform in corn oil 5 days/week for 13 weeks (NTP 1989a); this study identified a NOAEL of 25 mg/kg. The intermediate-duration oral MRL of 0.2 mg/kg/day for bromoform was derived by applying an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) to the duration-adjusted NOAEL of 18 mg/kg/day.

- An MRL of 0.2 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to bromoform.

Three studies have examined the chronic toxicity of bromoform in animals. Rat and mouse studies conducted by NTP (1985) are comprehensive studies that found fatty liver changes (hepatocellular vacuolization) at the lowest dose tested, 100 mg/kg (5 days/week; 71 mg/kg/day). The third study (Tobe et al. 1982) identified a similar LOAEL (140 mg/kg/day) in rats exposed to bromoform in the diet for

2 years; a NOAEL of 35 mg/kg/day was also identified. At 140 mg/kg/day, yellowing of the liver and increased absolute and relative liver weights were observed. The NTP (1985) rat study was selected as the basis of the chronic-duration oral MRL for bromoform. Even though the Tobe et al. (1982) study identified a NOAEL for liver effects, this study was not selected as the critical study because no histological examination of the liver was conducted and the results were poorly reported. The duration-adjusted LOAEL of 71 mg/kg/day was divided by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for animal to human extrapolation, and 10 for human variability) resulting in an MRL of 0.07 mg/kg/day.

Dibromochloromethane

- An MRL of 0.1 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to dibromochloromethane.

The available data on the oral toxicity of dibromochloromethane in animals strongly suggest that the liver is the most sensitive target of toxicity. In most studies, liver effects are observed at lower doses than kidney effects (the next most sensitive end point). The study of Condie et al. (1983) was selected as the basis for the acute-duration oral MRL for dibromochloromethane because it showed dose-related incidences of liver and kidney lesions and identified the lowest LOAEL for liver effects among the available studies. A LOAEL of 37 mg/kg/day, the lowest dose tested, was identified for liver damage (hepatocellular vacuolization) in mice administered dibromochloromethane in corn oil for 14 consecutive days. A reliable NOAEL for liver or kidney effects could not be determined from the available acute data. Applying an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) to the LOAEL of 37 mg/kg/day yields an acute-duration oral MRL of 0.1 mg/kg/day for dibromochloromethane.

No data were located regarding the toxicity of dibromochloromethane following intermediate-duration oral exposure in humans. A number of intermediate-duration studies of rats and mice were located. The liver was identified as the most sensitive target. Hepatocellular vacuolization was observed at 43 mg/kg/day (60 mg/kg, 5 days/week) and higher (Aida et al. 1992; Daniel et al. 1990; NTP 1985); the highest NOAEL for liver effects is 21 mg/kg/day (30 mg/kg, 5 days/week) (NTP 1985). At higher doses (≥100 mg/kg/day), proximal tubular degeneration and nephropathy were observed (Daniel et al. 1990; NTP 1985). Several animal studies also reported neurological effects: decreases in brain weight and decreases in operant behavior at ≥100 mg/kg/day (Balster and Borzelleca 1982; Daniel et al. 1990).

Borzelleca and Carchman (1982) found decreases in fertility at high dibromomochloromethane doses (685 mg/kg/day).

Derivation of an intermediate-duration oral MRL for dibromochloromethane based on the NTP (1985) rat study, which identified NOAEL and LOAEL values of 21 and 43 mg/kg/day, was considered. However, the resultant MRL would be higher than the acute-duration oral MRL.

- An MRL of 0.09 mg/kg/day has been derived for chronic-duration oral exposure (365 days or less) to dibromochloromethane.

Studies of dibromochloromethane consistently indicate that the liver is a target tissue. The NTP (1985) study, in which rats received gavage doses of 0, 40, or 80 mg/kg of dibromochloromethane in corn oil, 5 days/week, for 104 weeks, was selected as the basis for the chronic-duration oral MRL. This study (NTP 1985) was selected because it showed dose-related incidences of microscopic hepatic lesions and also identified the lowest LOAEL of 40 mg/kg (duration-adjusted LOAEL of 28 mg/kg/day) for hepatic effects in chronic studies (NTP 1985; Tobe et al. 1982) of dibromochloromethane toxicity. A chronic-duration oral MRL of 0.03 mg/kg/day was derived by applying an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) to the LOAEL of 28 mg/kg/day.

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of bromoform and dibromochloromethane. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), 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. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is

considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others 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 (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of bromoform or dibromochloromethane are indicated in Tables 3-1 and 3-2 and Figures 3-1 and 3-2.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for bromoform and dibromochloromethane. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), 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.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

No studies were located regarding health effects of bromoform or dibromochloromethane in humans following inhalation exposure. In animals, there are limited data from several older studies on the effects of inhalation exposure to bromoform; no studies were located regarding effects of dibromochloromethane.

3.2.1.1 Death

Inhalation of very high concentrations (56,000 or 84,000 ppm) of bromoform vapor for 1 hour has been reported to cause death in dogs (Merzbach 1928). The chief symptoms noted were initial excitation followed by deep sedation. This indicates that central nervous system depression is probably the chief cause of death in such acute exposures. Because only two animals were used (one animal per dose) and only high doses were administered, these data do not provide a reliable estimate of the minimum lethal concentration in dogs or other animal species.

3.2.1.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, endocrine, dermal, ocular, or body weight effects in animals or humans following inhalation exposure to bromoform or dibromochloromethane.

Hepatic Effects. Two studies (Dykan 1962, 1964; published in Russia and available only as the English abstract) indicate that inhalation exposure of animals to high concentrations of bromoform leads to hepatic injury. Exposure of rats to 240 ppm of bromoform for 10 days resulted in dystrophic and vascular changes in the liver, with altered hepatic metabolism (Dykan 1964). Longer-term exposure (2 months) to concentrations of 24 ppm also led to hepatic changes (decreased blood clotting and impaired glycogenesis) (Dykan 1962). No significant alterations were observed after exposure to 4.8 ppm (Dykan 1964). These changes appear to resemble the changes produced after oral exposure to bromoform

(see Section 3.2.2.2), indicating that bromoform produces similar systemic effects by either route of exposure.

Renal Effects. Similar to the hepatic effects, exposure to 240 ppm bromoform for 10 days resulted in dystrophic and vascular changes in the kidney with altered renal filtration (Dykan 1964). Longer-term exposure (2 months) to concentrations of 24 ppm also led to renal injury (proteinuria and decreased creatinine clearance) (Dykan 1962). A concentration of 4.8 ppm was estimated to be without significant effects on the kidney (Dykan 1964). These changes appear to resemble the changes produced after oral exposure to bromoform (see Section 3.2.2.2).

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans or animals after inhalation exposure to bromoform or dibromochloromethane.

3.2.1.4 Neurological Effects

Inhalation exposure to high levels (29,000 ppm or above) of bromoform has been observed to lead to rapid and profound depression of the central nervous system in dogs (Graham 1915; Merzbach 1928). This is presumably due to a nonspecific anesthetic effect similar to that produced by various other volatile halocarbons. Obvious clinical signs included deep relaxation and sedation (Merzbach 1928). Clinical signs of nervous system depression appeared quickly (within minutes), and tended to disappear within a day after exposure ceased (Graham 1915).

No studies were located regarding the following effects in humans or animals after inhalation exposure to bromoform or dibromochloromethane:

3.2.1.5 Reproductive Effects

3.2.1.6 Developmental Effects

3.2.1.7 Cancer

3.2.2 Oral Exposure

Most information on the health effects of bromoform and dibromochloromethane comes from studies in animals (rats and mice) exposed by the oral route. For bromoform, there are some observations in humans stemming from the past use of bromoform as a sedative, but no studies were located on the effect of dibromochloromethane in humans. Summaries of studies that provide reliable quantitative toxicity data are presented in Table 3-l and Figure 3-l for bromoform and in Table 3-2 and Figure 3-2 for dibromochloromethane. The main conclusions from these studies are discussed below.

3.2.2.1 Death

Bromoform. In the early part of this century, bromoform was often given as a sedative to children suffering from whooping cough, and several deaths due to accidental overdoses have been described (Dwelle 1903; Kobert 1906; Roth 1904 as cited in von Oettingen 1955). The principal clinical signs in fatal cases were those of severe central nervous system depression (unconsciousness, stupor, and loss of reflexes), and death was generally the result of respiratory failure (von Oettingen 1955). If death could be averted, recovery was generally complete within several days (Benson et al. 1907; Burton-Fanning 1901; Kobert 1906). The dose needed to cause death in children is not known with certainty, but both Dwelle (1903) and Roth (1904) estimated that a dose of about 5 g had been fatal. For a 10–20-kg child, this corresponds to a dose of around 250–500 mg/kg.

In animal studies, estimates of the acute oral LD_{50} for bromoform typically range between 707 and 1,550 mg/kg (Bowman et al. 1978; Chu et al. 1982a; NTP 1989a). There does not appear to be much difference in the doses that cause death across species or between sexes. The LD_{50} values for a 1-day exposure to bromoform ranged from 933 to 1,388 mg/kg in rats (Chu et al. 1980; NTP 1989a) and from 707 to 1,550 mg/kg in mice (Bowman et al. 1978; NTP 1989a). LD_{50} values ranged from 1,072 to 1,550 for females and from 707 to 1,388 for males exposed to bromoform for 1 day (Bowman et al. 1978; Chu et al. 1980, 1982a; NTP 1989a). Acute, repeated oral exposure to 600 mg/kg/day resulted in 100% mortality in rats (NTP 1989a). However, only 2/10 mice died from exposure to 800 mg/kg/day (NTP 1989a). No deaths were observed in rats and mice administered 200 or 400 mg/kg (5 days/week) via gavage for 90 days (NTP 1989a). However, significant reductions in survival were observed in rats administered 200 mg/kg via gavage (5 days/week) for 2 years (NTP 1989a).

Table 3-1 Levels of Significant Exposure to Bromoform - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Human	1 d				445 F (single child died due to overdose)	Dwelle 1903
2	Rat (Sprague-Dawley)	1 day (GO)				1147 F (LD50)	Chu et al 1982a
3	Rat (Sprague-Dawley)	(G)				1388 M (LD50) 1147 F[b] (LD50)	Chu et al. 1980
4	Rat (Fischer- 344)	1 d (GO)				933 (LD50)	NTP 1989a
5	Rat (Fischer- 344)	14 d 1x/d (GO)				600 (100% mortality)	NTP 1989a
6	Mouse (ICR)	1 d (GW)				1400 M[b] (LD50) 1550 F (LD50)	Bowman et al 1978
7	Mouse (B6C3F1)	1 d (GO)				707 M[b] (LD50) 1072 F (LD50)	NTP 1989a
Systemic							
8	Rat (Fischer- 344)	14 d 1x/d (GO)	Endocr	600	800 (enlarged thyroid gland)		NTP 1989a
			Bd Wt	200 M	400 M (14% decreased body weight gain)		

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Table 3-1 Levels of Significant Exposure to Bromoform - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
9	Rat	1 d (G)	Hepatic	1440			Plaa and Hewitt 1982a
10	Rat (Fischer- 344)	7 d (GW)	Endocr	190 M	380 M (decreased serum testosterone)		Potter et al 1996
			Bd Wt	380 M			
11	Mouse (B6C3F1)	9 doses in 11 days (GO)	Hepatic		200 F (hepatocellular ballooning and proliferation)		Coffin et al 2000
12	Mouse (B6C3F1)	11 days (W)	Hepatic		300 F (hepatocellular ballooning)		Coffin et al 2000
13	Mouse (CD-1)	14 d 1x/d (GO)	Hepatic	72 M[c]	145 M (centrilobular pallor)		Condie et al 1983
			Renal	72 M	145 M (mesangial nephrosis)		
			Bd Wt	289 M			
14	Mouse (CD-1)	14 d 1x/d (GW)	Hepatic	50 M	125 M (increased absolute and relative liver weights)		Munson et al 1982
15	Mouse (B6C3F1)	14 d 1x/d (GO)	Gastro	200 M	400 M (stomach nodules)		NTP 1989a

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Table 3-1 Levels of Significant Exposure to Bromoform - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Immuno/ Lymphoret						
16	Mouse (CD-1)	14 d 1x/d (GW)		50 M	125 M (impaired humoral immune function)		Munson et al 1982
	Neurological						
17	Rat (Fischer- 344)	14 d 1x/d (GO)		400		600 (lethargy, labored and swallowing breathing, ataxia)	NTP 1989a
18	Rat (Fischer- 344)	1 d (GO)		500		1000 (shallow breathing)	NTP 1989a
19	Mouse (ICR)	14 days daily (GW)		9.7 M			Balster and Borzelleca 1982 Bromoform
20	Mouse (ICR)	1 d (GW)			431 M (ED50 for impaired motor performance)		Balster and Borzelleca 1982
21	Mouse (ICR)	1 d (GW)				1000 (ataxia, sedation, anesthesia)	Bowman et al 1978
22	Mouse (B6C3F1)	14 d 1x/d (GO)		400		600 (lethargy and ataxia)	NTP 1989a
	Developmental						
23	Rat (Sprague-Dawley)	9 d Gd 6-15 (GO)		100		200 (skeletal anom.)	Ruddick et al 1983

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Table 3-1 Levels of Significant Exposure to Bromoform - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	INTERMEDIATE EXPOSURE						
	Systemic						
24	Rat (Wistar)	30 d (F)	Hepatic		56.4 F (hepatocellular vacuolization and swelling)		Aida et al 1992
			Bd Wt	187.2 M		617.9 M (24% decreased body weight)	
25	Rat (Sprague-Dawley)	28 d (W)	Hemato	14 M			Chu et al 1982a
			Hepatic	14 M			
			Renal	14 M			
			Bd Wt	14 M			
26	Rat (Fischer- 344)	13 wk 5d/wk (GO)	Resp	200			NTP 1989a
			Cardio	200			
			Gastro	200			
			Hepatic	25 M[d]	50 M (hepatocellular vacuolization)		
			Renal	200			
			Endocr	200			
			Dermal	200			
			Bd Wt	200			

Table 3-1 Levels of Significant Exposure to Bromoform - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
27	Mouse (B6C3F1)	3 wk 5 d/wk (GO)	Hepatic	200 F	500 F (hepatocyte hydropic degeneration; increased SGPT and sorbitol dehydrogenase)		Melnick et al 1998
			Bd Wt	500 F			
28	Mouse (B6C3F1)	13 wk 5d/wk (GO)	Resp	400			NTP 1989a
			Cardio	400			
			Hepatic	100 M	200 M (minimal to moderate heptocellular vacuoles)		
			Renal	400			
			Endocr	400			
			Dermal	400			
			Bd Wt	400			
29	Mouse (Swiss)	102 d 1x/d (GO)	Resp	200			NTP 1989b
			Hepatic		200 (hepatocullular vacuoles)		
			Renal	200			
			Endocr	200			
	Neurological						
30	Rat (Fischer- 344)	13 wk 5d/wk (GO)		50 M	100 M (lethargy)		NTP 1989a

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Table 3-1 Levels of Significant Exposure to Bromoform - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
31	Mouse (ICR)	90 d 1x/d (GW)		0.9 M	9.2 M (decreased exploratory activity)		Balster and Borzelleca 1982 Bromoform
32	Mouse (ICR)	60 d 1x/d (GW)			100 M (decreased response rate in operant behavior test)		Balster and Borzelleca 1982 Bromoform
33	Mouse (ICR)	30d 1x/d (GW)		100 M			Balster and Borzelleca 1982
	Reproductive						
34	Rat (Fischer- 344)	13 wk 5d/wk (GO)		200			NTP 1989a
35	Mouse (B6C3F1)	13 wk 5d/wk (GO)		400			NTP 1989a
36	Mouse (Swiss)	105 d 1x/d (GO)		200			NTP 1989b
	CHRONIC EXPOSURE						
	Death						
37	Rat (Fischer- 344)	103 wk 5d/wk (GO)				200 M (decreased survival)	NTP 1989a

Table 3-1 Levels of Significant Exposure to Bromoform - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Systemic						
38	Rat (Fischer- 344)	103 wk 5d/wk (GO)	Cardio	200			NTP 1989a
			Gastro	100 M	200 M (forestomach ulcer)		
			Hemato	100 F	200 F (spleen pigmentation)		
			Hepatic		100[e] (hepatocellular vacuolization)		
			Renal	200			
			Endocr		100 M (pituitary gland hyperplasia)		
			Dermal	200			
			Bd Wt	100	200 (>10% decrease in body weight gain)		
39	Rat (Wistar)	2 year (F)	Hepatic	35 F	140 F (yellowing of liver; increased absolute and relative liver weight)		Tobe et al 1982
			Bd Wt	90 M		590 M (40% decrease in body weight gain)	

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Table 3-1 Levels of Significant Exposure to Bromoform - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
40	Mouse (B6C3F1)	103 wk 5d/wk (GO)	Resp	100 M			NTP 1989a
			Cardio	100 M			
			Gastro	50 M	100 M (hyperplasia in glandular stomach)		
			Musc/skel	100 M			
			Hepatic		100 F (hepatocellular vacuolization)		
			Renal	100 M			
			Endocr	100 F	200 F (follicular cell hyperplasia in thyroid)		
			Dermal	100 M			
			Bd Wt	100 M			
	Neurological						
41	Rat (Fischer- 344)	103 wk 5d/wk (GO)			100 (lethargy)		NTP 1989a
	Reproductive						
42	Rat (Fischer- 344)	103 wk 5d/wk (GO)		100 M[b] 200 F	200 M (squamous metaplasia in prostate)		NTP 1989a
43	Mouse (B6C3F1)	103 wk 5d/wk (GO)		100 M[b] 200 F			NTP 1989a

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Table 3-1 Levels of Significant Exposure to Bromoform - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Cancer						
44	Rat (Fischer- 344)	103 wk 5d/wk (GO)				200 F (CEL: adenomatous polyps and adenocarcinoma in large intestine)	NTP 1989a

a The number corresponds to entries in Figure 3-1.

b Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

c Used to derive an acute-duration oral MRL of 0.7 mg/kg/day; dose divided by an uncertainty factory of 100 (10 for extrapolation from animals to humans and 10 for human variability).

d Used to derive an intermediate-duration oral MRL of 0.2 mg/kg/day; 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).

e Used to derive a chronic-duration oral MRL of 0.2 mg/kg/day; dose adjusted for intermittent exposure and divided by an uncertainty factory of 300 (3 for extrapolation from a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

d = day(s); F = female; (F) = food; (G) = gavage; Gastro = gastrointestinal; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; (W) = water; wk = week(s); x = time(s)

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Figure 3-1. Levels of Significant Exposure to Bromoform - Oral

Acute (≤14 days)

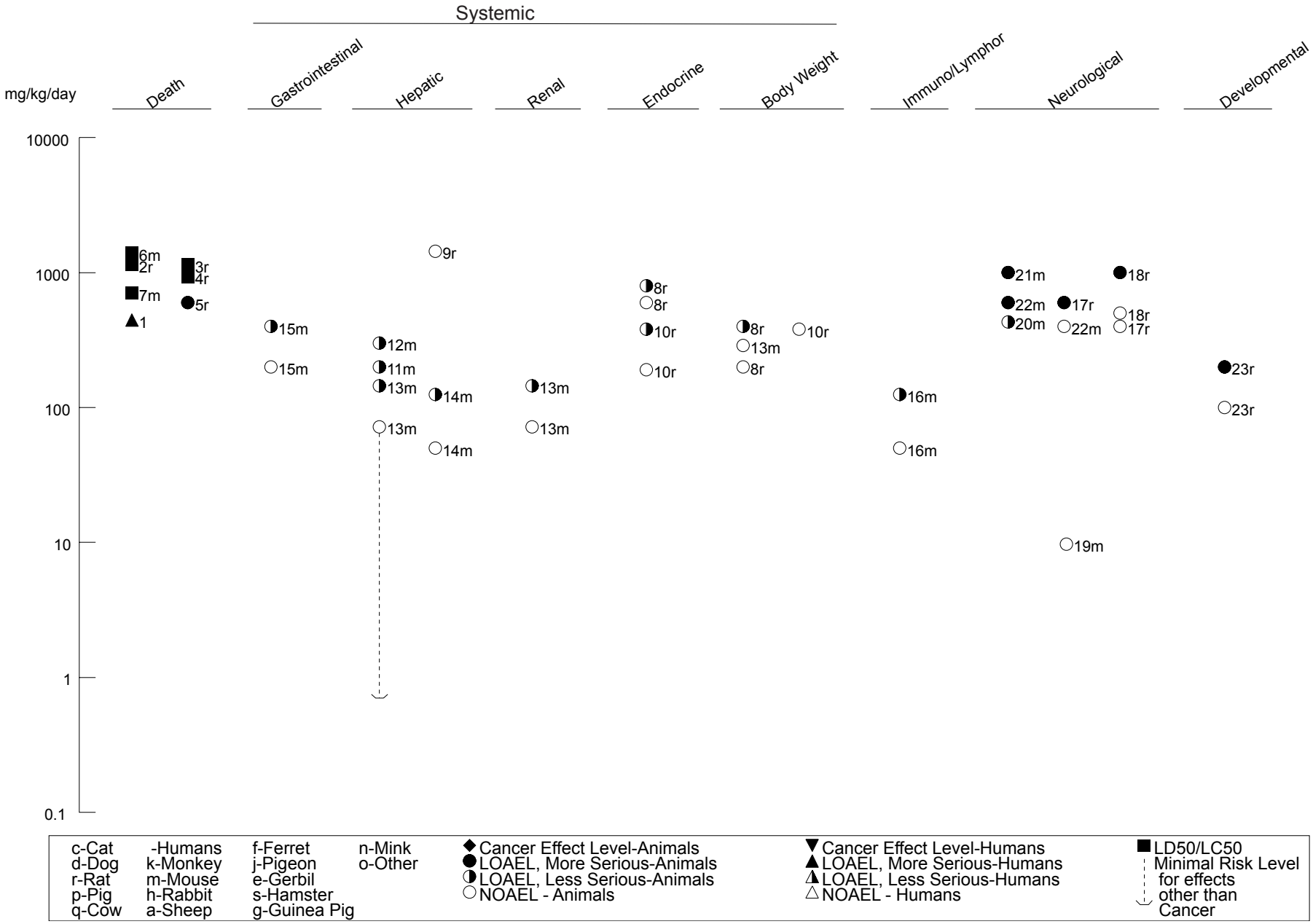

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Figure 3-1. Levels of Significant Exposure to Bromoform - Oral (*Continued*)

Intermediate (15-364 days)

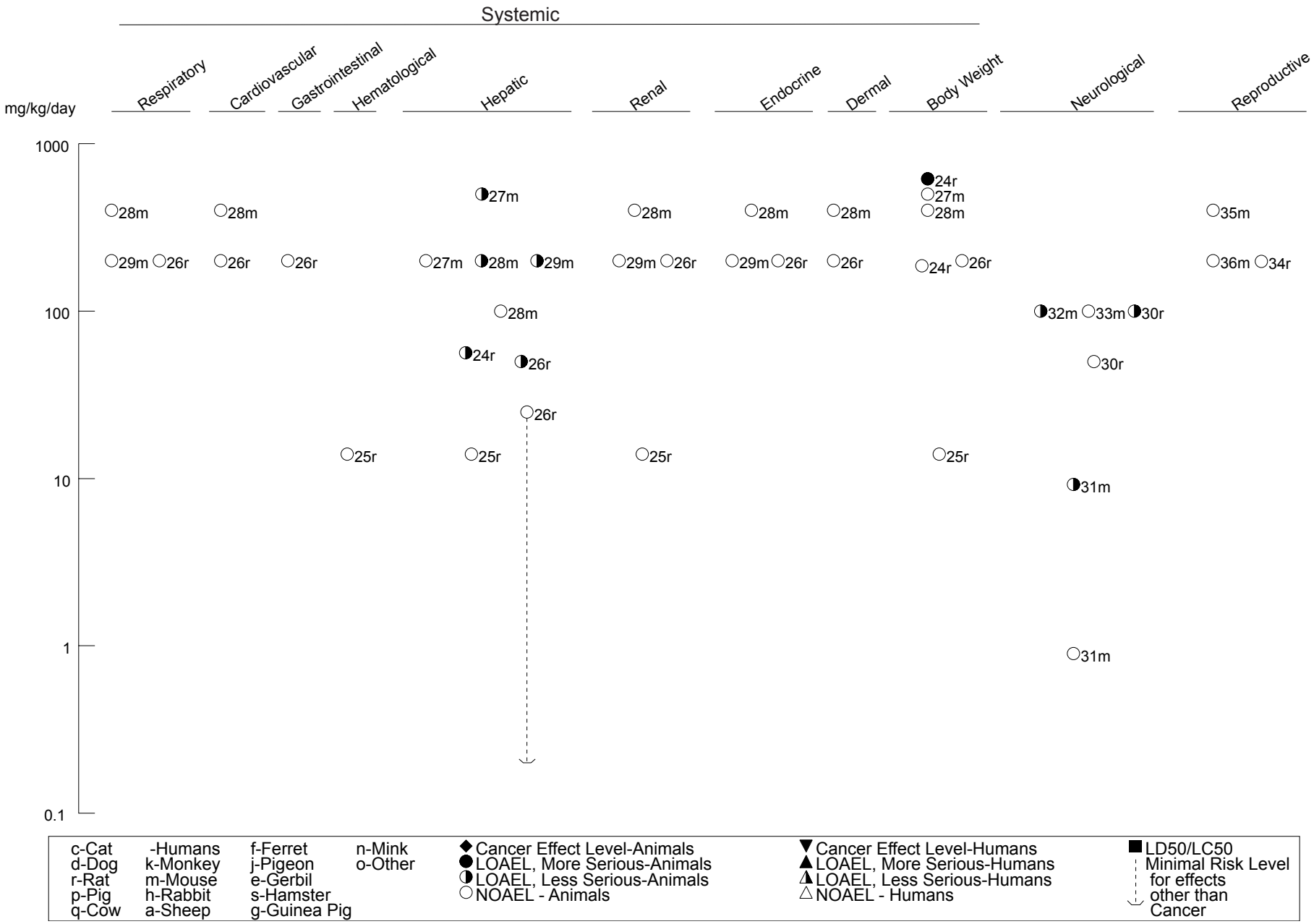

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Figure 3-1. Levels of Significant Exposure to Bromoform - Oral (*Continued*)

Chronic (≥365 days)

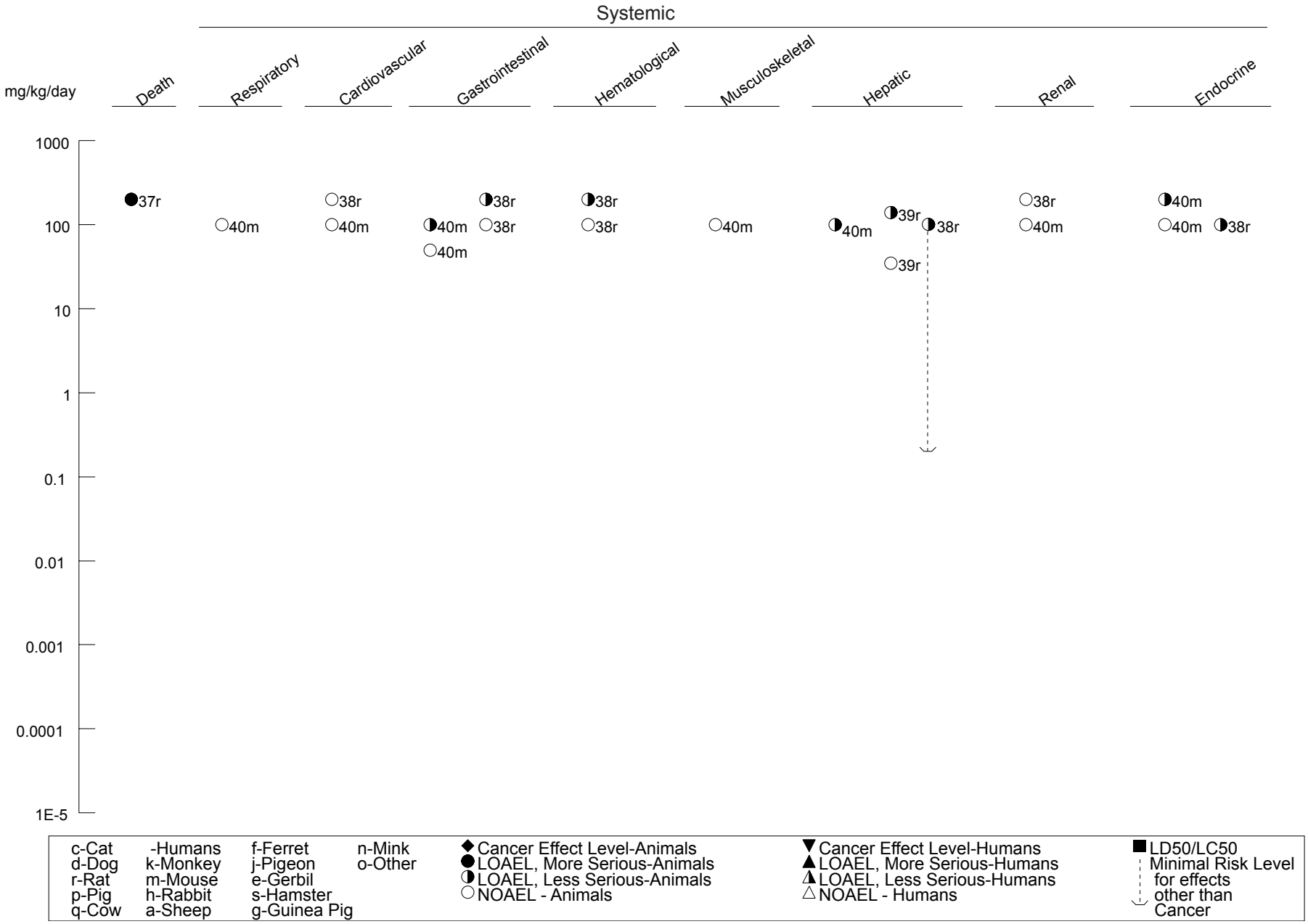

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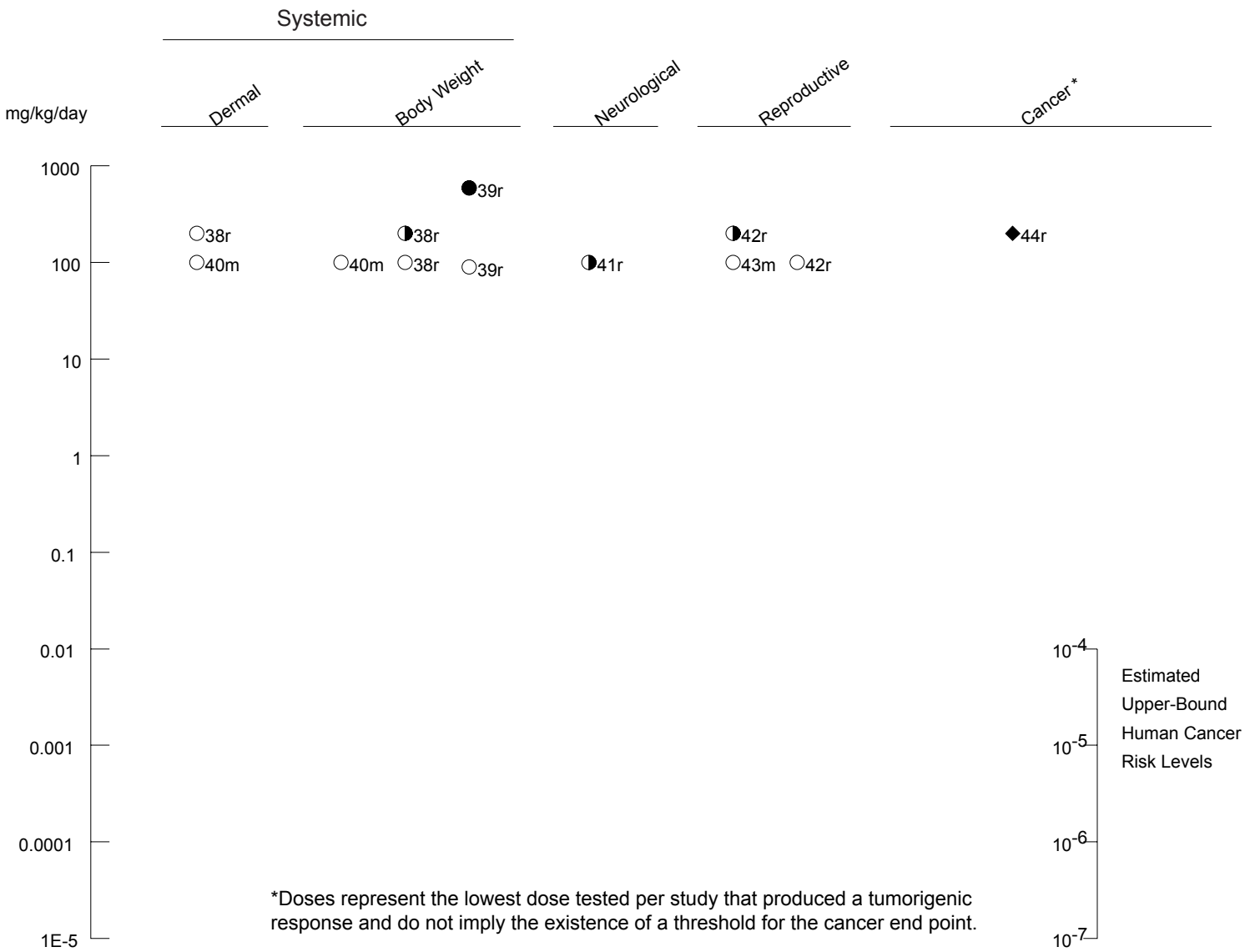
Figure 3-1. Levels of Significant Exposure to Bromoform - Oral (*Continued*)

Chronic (≥365 days)



*Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.

c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	Minimal Risk Level for effects other than Cancer
r-Rat	m-Mouse	e-Gerbil		◑ LOAEL, Less Serious-Animals	◭ LOAEL, Less Serious-Humans	
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	
q-Cow	a-Sheep	g-Guinea Pig				

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Table 3-2 Levels of Significant Exposure to Dibromochloromethane - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Rat (Sprague-Dawley)	1 d (GO)				848 F (LD50)	Chu et al 1982a
2	Rat (Sprague-Dawley)	(G)				1186 M (LD50) 848 F[b] (LD50)	Chu et al. 1980
3	Rat (Sprague-Dawley)	1 d (GO)				3700 M (100% mortality)	Hewitt et al 1983
4	Rat (Fischer- 344)	1 d (GO)				1250 M (4/5 died)	NTP 1985
5	Rat (Fischer- 344)	14 d 1x/d (GO)				500 (8 of 10 died)	NTP 1985
6	Mouse (ICR)	1 d (GW)				800 M[b] (LD50) 1200 F (LD50)	Bowman et al 1978
7	Mouse (B6C3F1)	1 d (GO)				630 M (3/5 died)	NTP 1985
8	Mouse (B6C3F1)	14 d 1x/d (G)				500 (7 of 10 died)	NTP 1985

Table 3-2 Levels of Significant Exposure to Dibromochloromethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
9	Hamster (Golden Syrian)	1 d (G)				145 M (LD50)	Korz and Gatterman 1997
	Systemic						
10	Rat (Sprague-Dawley)	1 d (GO)	Hepatic		2500 M (increased SGPT and OCT levels)		Hewitt et al 1983
			Renal	2500 M			
11	Rat (Fischer- 344)	14 d 1x/d (GO)	Hepatic	250	500 (mottled liver)		NTP 1985
			Renal	250	500 (darkened renal medullae)		
			Bd Wt	125 M		250 M (45% decrease body weight gain)	
12	Rat	1 d (G)	Hepatic	1220			Plaa and Hewitt 1982a
13	Rat (Fischer- 344)	7 d (GW)	Endocr	160 M	310 M (decreased serum testosterone)		Potter et al 1996
			Bd Wt	160 M	310 M (14% decrease in body weight)		
14	Mouse (B6C3F1)	9 doses in 11 day period (GO)	Hepatic		100 F (hepatocellular ballooning and proliferation)		Coffin et al 2000

Table 3-2 Levels of Significant Exposure to Dibromochloromethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
15	Mouse (B6C3F1)	11 days (W)	Hepatic		170 F (hepatocellular ballooning)		Coffin et al 2000
16	Mouse (CD-1)	14 d 1x/d (GO)	Hepatic		37 M[c] (hepatocellular vacuolization)		Condie et al 1983
			Renal		37 M (mesangial hyperplasia)		
			Bd Wt	147 M			
17	Mouse (CD-1)	14 d 1x/d (GW)	Hepatic	125 F	250 F (increased relative and absolute liver weight, decreased serum glucose, and increased SGPT and SGOT)		Munson et al 1982
18	Mouse (B6C3F1)	14 d 1x/d (GO)	Renal	250	500 (reddened renal medullae)		NTP 1985
	Immuno/ Lymphoret						
19	Mouse (CD-1)	14 d 1x/d (GW)		50 F	125 F (impaired humoral immunity)		Munson et al 1982
	Neurological						
20	Rat (Fischer- 344)	14 d 1x/d (GO)		250		500 (lethargy, ataxia)	NTP 1985
21	Rat (Fischer- 344)	1 d (GO)		160	310 (lethargy)		NTP 1985

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Table 3-2 Levels of Significant Exposure to Dibromochloromethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
22	Mouse (ICR)	14 days daily (GW)		10 M			Balster and Borzelleca 1982
23	Mouse (ICR)	1 d (GW)			454 M (ED50 for impaired motor performance)		Balster and Borzelleca 1982 Chlorodibromomethane
24	Mouse (ICR)	1 d (GW)				500 (sedation, anesthesia)	Bowman et al 1978
25	Mouse (B6C3F1)	14 d 1x/d (GO)		250		500 (lethargy, ataxia, and labored breathing)	NTP 1985
	Developmental						
26	Rat (Sprague-Dawley)	9 d Gd 6-15 (GO)		200			Ruddick et al 1983
	INTERMEDIATE EXPOSURE						
	Death						
27	Rat (Fischer- 344)	13 wk 5d/wk (G)				250 (18/ 20 died)	NTP 1985
	Systemic						
28	Rat (Wistar)	30 d (F)	Hepatic	18.3 M	56.2 M (heptocellular vacuolation)		Aida et al 1992
			Bd Wt	173.3 M			

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Table 3-2 Levels of Significant Exposure to Dibromochloromethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
29	Rat (Sprague-Dawley)	28 d (W)	Hemato	12 M			Chu et al 1982a
			Hepatic	12 M			
			Renal	12 M			
			Bd Wt	12 M			
30	Rat (Sprague-Dawley)	90 d (GO)	Resp	200			Daniel et al. 1990
			Cardio	200			
			Gastro	200			
			Hemato	200			
			Hepatic		50 (hepatocellular vacuolization)		
			Renal	50	100 (tubular degeneration)		
			Endocr	200			
			Dermal	200			
			Ocular	200			
			Bd Wt	50		200 (55% decrease in body weight gain)	

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Table 3-2 Levels of Significant Exposure to Dibromochloromethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
31	Rat (Fischer- 344)	13 wk 5d/wk (GO)	Resp	250			NTP 1985
			Cardio	250			
			Gastro	250			
			Musc/skel	250			
			Hepatic	30 M	60 M (hepatocellular vacuolization)		
			Renal	125	250 (toxic nephropathy)		
			Endocr	250			
			Dermal	250			
			Bd Wt	125 M		250 M (47% decreased body weight gain)	
			Other		250 (salivary gland hyperplasia)		
32	Mouse (B6C3F1)	3 wk 5 d/wk (GO)	Hepatic	50 F	100 F[b] (increased relative liver weight) 192 F (hepatocyte hydropic degeneration)		Melnick et al 1998
			Bd Wt	417 F			

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Table 3-2 Levels of Significant Exposure to Dibromochloromethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
33	Mouse (B6C3F1)	13 wk 5d/wk (GO)	Resp	250			NTP 1985
			Gastro	250			
			Hepatic	125 M	250 M (hepatocellular vacuolization)		
			Renal	125 M	250 M (toxic nephropathy)		
			Endocr	250			
			Dermal	250			
			Bd Wt	250			
	Immuno/ Lymphoret						
34	Rat (Sprague-Dawley)	90 d (GO)		100	200 (34-40% decr. in thymus wt.)		Daniel et al. 1990
	Neurological						
35	Rat (Sprague-Dawley)	90 d (GO)		50 F	100 F (decreased absolute brain weight)		Daniel et al. 1990
36	Mouse (ICR)	60 d 1x/d (GW)		100 M	400 M (decreased response rate in operant behavior test)		Balster and Borzelleca 1982
37	Mouse (ICR)	30d 1x/d (GW)		100 M			Balster and Borzelleca 1982 Chlorodibromomethane

Table 3-2 Levels of Significant Exposure to Dibromochloromethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Reproductive						
38	Rat (Sprague-Dawley)	90 d (GO)		100			Daniel et al. 1990
39	Rat (Fischer- 344)	13 wk 5d/wk (GO)		250			NTP 1985
40	Rat (Sprague-Dawley)	15 d (W)		47.8 F			NTP 1996
41	Rat (Sprague-Dawley)	28-34 d (W)		28.2 M 46 F			NTP 1996
42	Mouse (ICR)	2 generations (continuous) (W)		170 F		685 F (decreased fertility)	Borzelleca and Carchman 1982
43	Mouse (B6C3F1)	13 wk 5d/wk (GO)		250			NTP 1985
	Developmental						
44	Mouse (ICR)	2 generations (continuous) (W)		685			Borzelleca and Carchman 1982

Table 3-2 Levels of Significant Exposure to Dibromochloromethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	CHRONIC EXPOSURE						
	Death						
45	Mouse (B6C3F1)	105 wk 5d/wk (GO)				100 M (decreased survival)	NTP 1985
	Systemic						
46	Rat (Fischer- 344)	2 yr 5d/wk (GO)	Resp	80			NTP 1985
			Cardio	80			
			Gastro	80			
			Musc/skel	80			
			Hepatic		40[d] (fatty change)		
			Endocr	80			
			Dermal	80			
			Bd Wt	80			
47	Rat (Wistar)	2 year (F)	Hepatic	20 M	85 M (yellowing of liver; hypertrophy)		Tobe et al 1982
			Bd Wt	20 M	85 M (10% decrease in body weight gain)	540 M (marked decrease in body weight gain)	

Table 3-2 Levels of Significant Exposure to Dibromochloromethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
48	Mouse (B6C3F1)	105 wk 5d/wk (GO)	Resp	100			NTP 1985
			Cardio	100			
			Gastro	100			
			Musc/skel	100			
			Hepatic		50 F (fatty metamorphosis)		
			Renal		100 M (nephrosis)		
			Endocr		50 F (thyroid follicular cell hyperplasia)		
			Dermal	100			
			Bd Wt	50	100 (14-17% decreased terminal body weight)		
	Reproductive						
49	Rat (Fischer- 344)	2 yr 5d/wk (GO)		80			NTP 1985
50	Mouse (B6C3F1)	105 wk 5d/wk (GO)		100			NTP 1985

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Table 3-2 Levels of Significant Exposure to Dibromochloromethane - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Cancer						
51	Mouse (B6C3F1)	105 wk 5d/wk (GO)				100 (CEL: hepatocellular adenoma or carcinoma)	NTP 1985

a The number corresponds to entries in Figure 3-2.

b Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

c Used to derive an acute-duration oral MRL of 0.1 mg/kg/day; dose divided by an uncertainty factory of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

d Used to derive a chronic-duration oral MRL of 0.09 mg/kg/day; dose adjusted for intermittent exposure and divided by an uncertainty factory of 300 (3 for use of a minimal LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Bd Wt = body weight; CNS = central nervous system; d = day(s); F = female; (F) = food; (G) = gavage; Gd = gestation day; Gastro = gastrointestinal; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; (W) = water; wk = week(s); x = time(s)

Figure 3-2. Levels of Significant Exposure to Dibromochloromethane - Oral

Acute (≤14 days)

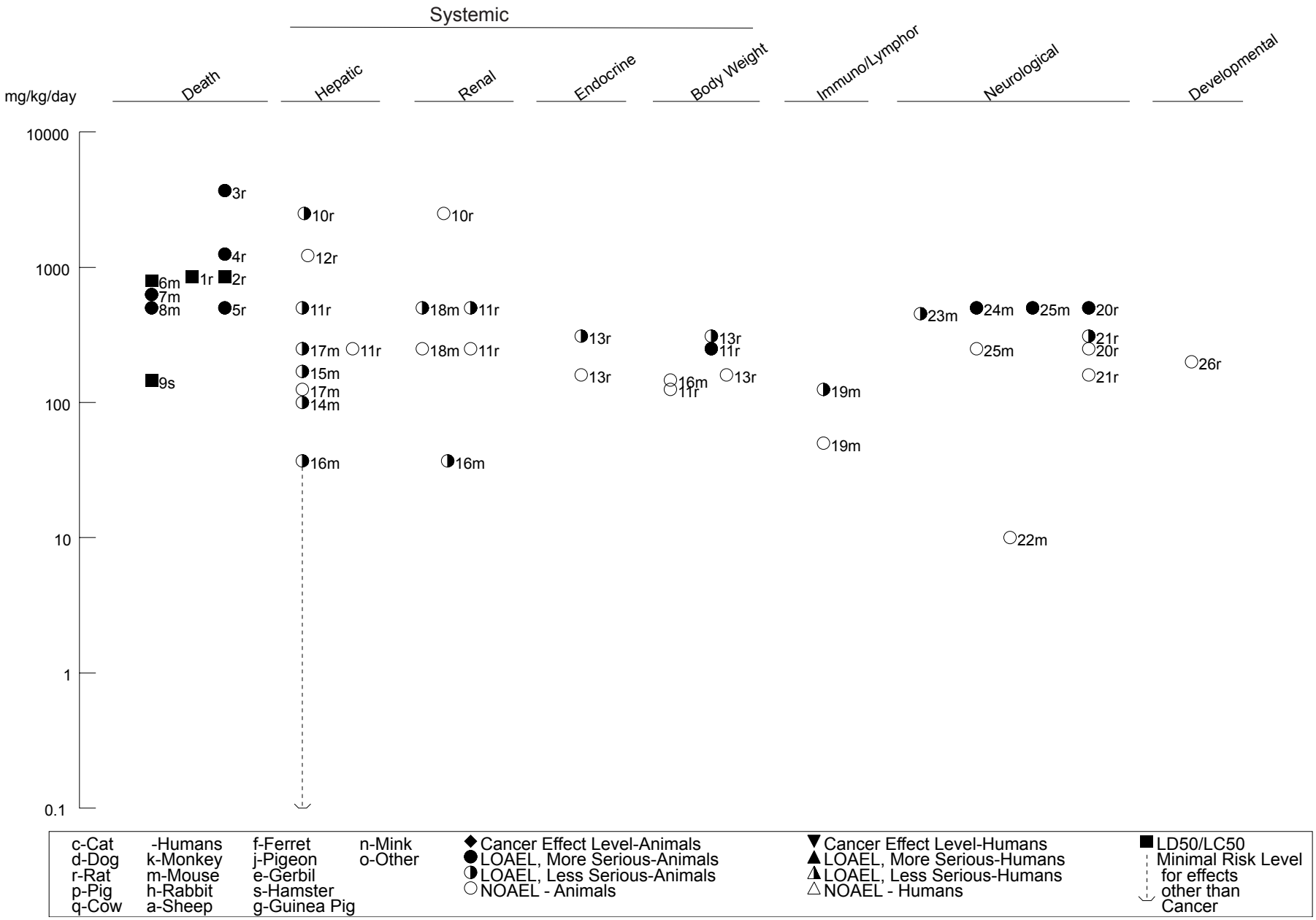

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Figure 3-2. Levels of Significant Exposure to Dibromochloromethane - Oral (*Continued*)

Intermediate (15-364 days)

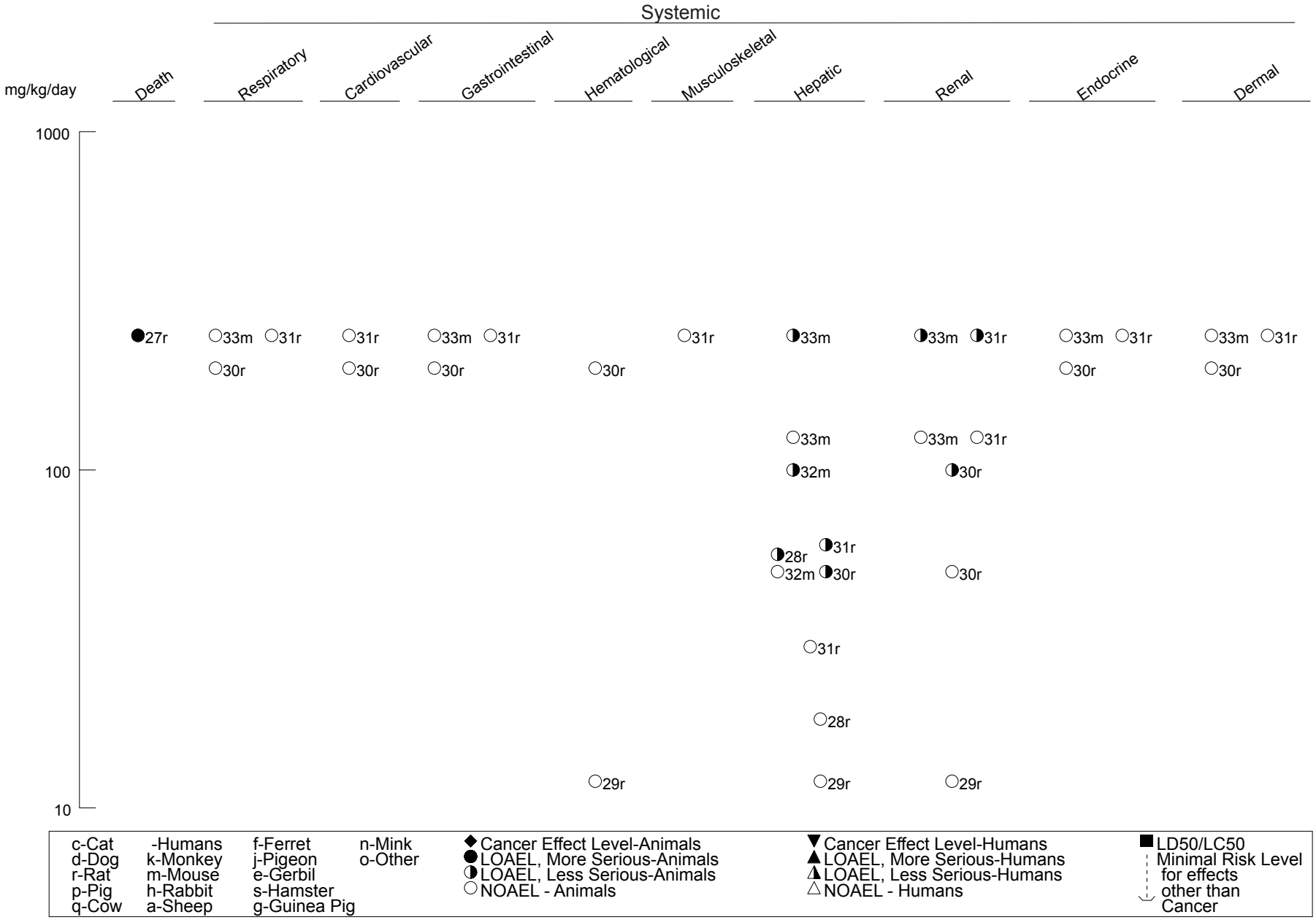

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Figure 3-2. Levels of Significant Exposure to Dibromochloromethane - Oral (*Continued*)

Intermediate (15-364 days)

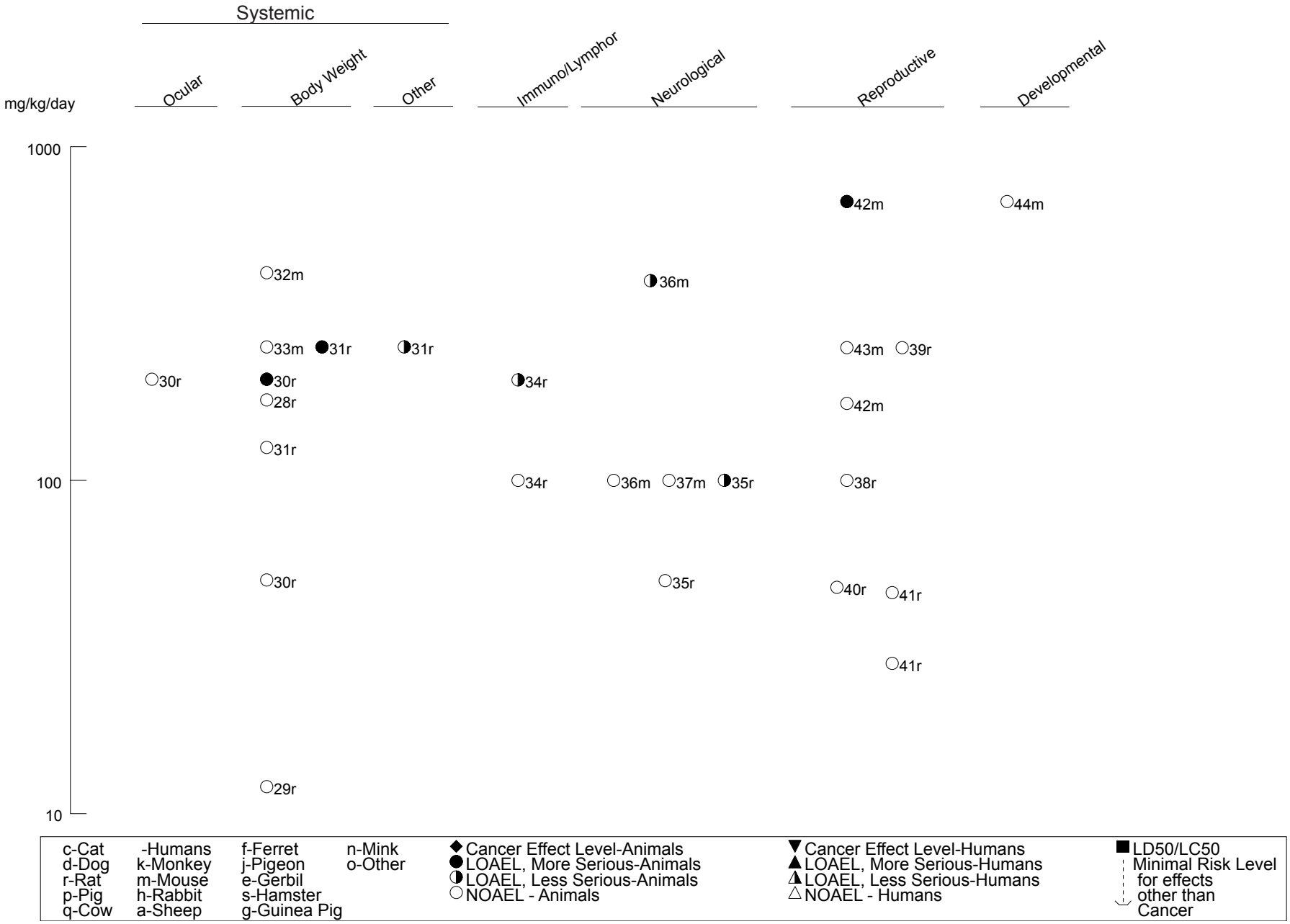

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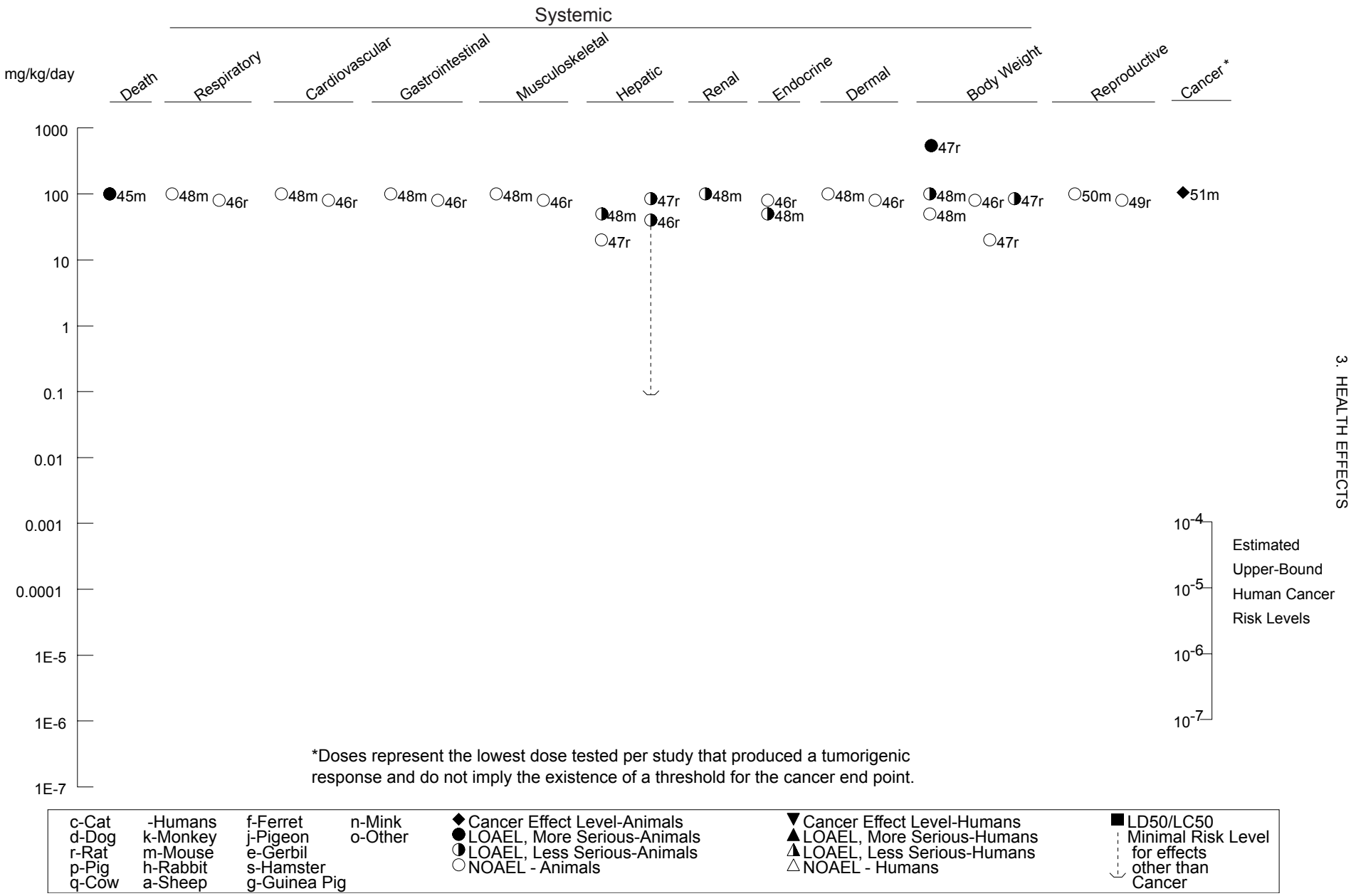
Figure 3-2. Levels of Significant Exposure to Dibromochloromethane - Oral (*Continued*)

Chronic (≥365 days)



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The cause of death following acute oral exposure of animals to bromoform has not been thoroughly investigated, but as in humans, the chief clinical signs observed are those of central nervous system depression (Bowman et al. 1978). While central nervous system depression probably is an important factor in acute lethality, in some cases, death did not occur until several days after an acute exposure (Bowman et al. 1978; NTP 1989a). This suggests that other effects (e.g., hepatic and/or renal injury) may also be important.

Dibromochloromethane. No studies were located regarding death in humans after oral exposure to dibromochloromethane. The acute lethality of dibromochloromethane has been evaluated by several animal studies in rats and mice, with LD_{50} estimates ranging between 800 and 2,650 mg/kg (Bowman et al. 1978; Chu et al. 1980, 1982a; Hewitt et al. 1983; NTP 1985). Korz and Gatterman (1997) reported an LD_{50} of 145 mg/kg for a Golden Syrian hamster; however, the experimental details were not reported to validate the data. Deaths in animals have been reported from single oral doses as low 300–600 mg/kg (NTP 1985).

In intermediate and chronic oral exposure studies, significant increases in mortality has been observed at 250 mg/kg (5 days/week) for exposures of 14–90 days (Chu et al. 1982a; Condie et al. 1983; Daniel et al. 1990; NTP 1985) and at 100 mg/kg (5 days/week) for exposures up to 2 years (NTP 1985).

Differences in mortality from exposure to dibromochloromethane were observed between sexes and species. In mice, males are more sensitive to mortality from dibromochloromethane exposure than females. This is seen in acute exposures (Bowman et al. 1978) and chronic exposure studies (NTP 1985). In contrast, in rats, females are more sensitive to mortality from dibromochloromethane than males, as seen in acute exposures (Chu et al. 1982a).

The cause of death following oral exposure of animals to dibromochloromethane has not been thoroughly investigated. Some of the chief clinical signs observed are those of central nervous system depression and other effects, such as hepatic and/or renal injury (Bowman et al. 1978; NTP 1985).

3.2.2.2 Systemic Effects

Respiratory Effects. Labored breathing has been observed in animals exposed to lethal doses of bromoform and dibromochloromethane (NTP 1985, 1989a); this is likely due to central nervous system depression rather than impaired lung function.

Bromoform. No studies were located regarding respiratory effects in humans after oral exposure to bromoform. NTP (1989a) examined the respiratory tract of rats and mice receiving gavage doses of bromoform for 90 days or 2 years. No histological alterations were observed in the intermediate-duration studies or in female rats and male and female mice in the chronic-duration study. An increased incidence of chronic inflammation of the lungs was observed in male rats exposed to 100 or 200 mg/kg (5 days/week). This inflammation was similar in appearance to that caused by a sialodacryoadenitis (SDA) virus infection, and antibodies to rat SDA virus were detected in study animals. Thus, the inflammation observed was probably secondary to the infection and was not a direct result of bromoform. However, the absence of symptoms in control animals suggested that bromoform-treated rats may have been more susceptible to infection by the virus or slower to recover (NTP 1989a).

Dibromochloromethane. No studies were located regarding respiratory effects in humans after oral exposure to dibromochloromethane. No histological alterations in the respiratory tract were observed in rats and mice administered via gavage up to 250 mg/kg (days/week) for 90 days or 80–100 mg/kg (5 days/week) (NTP 1985).

Cardiovascular Effects.

Bromoform. No studies were located regarding cardiovascular effects in humans or animals after oral exposure to bromoform. Histological examination of rats and mice exposed to up to 100–200 mg/kg (5 days/week) bromoform by gavage for up to 2 years revealed no evidence of adverse effects upon the heart (NTP 1989a). While this indicates that cardiac tissue is not directly injured by bromoform, indirect effects on cardiovascular functions might occur as a consequence of the central nervous system depressant activity of these compounds. However, this has not been studied.

Dibromochloromethane. No studies were located regarding cardiovascular effects in humans after oral exposure to dibromochloromethane. Cardiotoxic (Müller et al. 1997) and histological (NTP 1985) effects were studied in animals. Decreased heart rates and increased blood pressure were observed in male rats following the administration of a single dose (83–667 mg/kg) of dibromochloromethane via gavage (Müller et al. 1997). However, a dose-related trend was not exhibited for these effects (Müller et al. 1997). While this suggests that cardiac function may be impaired by dibromochloromethane exposure, it is unclear if effects are caused by the direct action on cardiac function or if they are indirectly caused as a result of central nervous system depression. No histological alterations to cardiac tissue were observed in

intermediate- and chronic-duration studies of dibromochloromethane administered to rats and mice via gavage (NTP 1985).

Gastrointestinal Effects.

Bromoform. No studies were located regarding gastrointestinal effects in humans after oral exposure to bromoform. NTP (1989a) examined the esophagus, stomach, and intestines of rats and mice orally exposed to bromoform. Stomach nodules were observed in male and female mice following 14 days of exposure to 400 and 600 mg/kg/day, respectively (NTP 1989a). The biological significance of these nodules is not certain, but it is likely that they are a response to a direct irritant effect of bromoform on the gastric mucosa. In chronic-duration studies, histological alterations were observed in male rats and male mice. Forestomach ulcers were observed in male rats at 200 mg/kg (5 days/week) (NTP 1989a) and hyperplasia of the glandular stomach was observed at 100 mg/kg (5 days/week) (NTP 1989a). No stomach lesions were observed in female rats or mice exposed to bromoform at doses up to 200 mg/kg. The histological observations in NTP (1989a) suggest that males may be more sensitive to gastrointestinal effects from acute and chronic bromoform exposures than females. In acute studies, the onset of stomach nodules occurred at a lower dose level in males (400 mg/kg) than in females (600 mg/kg). In chronic studies, gastrointestinal effects were only observed in males. While these observations clearly indicate that the stomach may be affected by bromoform, it is possible that the exposure regimen (bolus dosing, by gavage, in oil) leads to irritant effects in the stomach that might not occur if exposure were continuous at lower concentrations in food or drinking water. However, this has not been investigated.

Dibromochloromethane. No studies were located regarding gastrointestinal effects in humans after oral exposure to dibromochloromethane. No histological changes of the esophagus, stomach, or intestines were observed in mice or rats administered dibromochloromethane via gavage at doses up to 100 mg/kg (5 days/week) for up to 2 years (NTP 1985).

Hematological Effects. Several studies (Chu et al. 1982a, 1982b; Munson et al. 1982; Tobe et al. 1982) have investigated the hematological effects of oral exposure of rats and mice to bromoform and dibromochloromethane. With the exceptions of some minor fluctuations in lymphocyte count following exposure to bromoform (Chu et al. 1982a, 1982b), none of these studies detected any significant effects of dibromochloromethane or bromoform on hemoglobin, hematocrit, red blood cells, or white blood cells.

Musculoskeletal Effects. None of the available studies on the oral toxicity of bromoform or dibromochloromethane have reported effects on the musculoskeletal system. However, detailed electrophysiologic or histopathologic studies on these tissues have not been performed.

Hepatic Effects. The liver is the primary target organ for bromoform and dibromochloromethane-induced toxicity. Oral exposure to bromoform and dibromochloromethane results in an accumulation of fat in the liver, manifested as increased liver weight, hepatocyte vacuoles, alterations in serum cholesterol levels, and decreases in serum triglyceride levels. In addition to fatty liver changes, exposure to bromoform and dibromochloromethane results in focal hepatocellular necrosis. The necrosis is typically observed at higher doses than the fatty liver. The toxicity of both compounds is greater following gavage administration compared to exposure via the diet or drinking water. This is probably due to the large bolus dose overwhelming the liver's ability to detoxify reactive metabolites and the oil vehicle, which likely increases absorption.

Bromoform. Several animal studies have examined the hepatotoxicity of bromoform in rats and mice following gavage, drinking water, or dietary exposure. The most sensitive hepatic end point appears to be fatty degeneration as indicated by centriloblular pallor observed in mice at 145 mg/kg/day for 14 days (Condie et al. 1983) and hepatocellular vacuolization and/or swelling, which has been observed following acute gavage exposure to 200 mg/kg (9 days in an 11-day period) (Coffin et al. 2000), acute drinking water exposure to 300 mg/kg/day (Coffin et al. 2000), intermediate-duration gavage exposure to 50 mg/kg (5 days/week) (NTP 1989a), dietary exposure to 56.4 mg/kg/day (Aida et al. 1992), and chronic gavage exposure to 100 mg/kg (5 days/week) (NTP 1989a). Increases in relative and/or absolute liver weights, although not always consistently found, occur at similar doses (Munson et al. 1982; Tobe et al. 1982). Alterations in clinical chemistry parameters associated with the fatty changes (alterations in serum triglyceride and cholesterol levels) are typically observed at higher doses. Decreases in serum triglyceride levels were observed at 207.5 and 590 mg/kg/day in rats exposed via the diet for 1 or 24 months, respectively (Aida et al. 1992; Tobe et al. 1982); the no effect levels for this end point are 56.4 and 90 mg/kg/day, respectively. An increase in serum total cholesterol was observed in rats exposed to ≥187.2 mg/kg/day in the diet for 1 month (Aida et al. 1992) and a decrease was found in rats exposed to 590 mg/kg/day in the diet for 24 months (Tobe et al. 1982). The data are inadequate to assess whether the difference in the direction of change was related to exposure duration or was an inconsistent finding.

Higher doses of bromoform result in hepatocellular necrosis. Necrosis was observed in rats exposed to 200 mg/kg (5 days/week) for 2 years (NTP 1989a); focal inflammation has also been observed in mice

receiving gavage doses of 280 mg/kg for 14 days (Condie et al. 1983). Significant increases in SGPT and/or SGOT, which is indicative of hepatocellular damage, were observed in mice at 250–289 mg/kg/day for 14 days (Condie et al. 1983; Munson et al. 1982), mice at 500 mg/kg (5 days/week) for 3 weeks (Melnick et al. 1998), and rats at 720 mg/kg/day for 24 months (Tobe et al. 1982). A decrease in serum glucose levels observed in rats exposed to ≥61.9 mg/kg/day for 1 month (Aida et al. 1992) or ≥40 mg/kg/day for 24 months (Tobe et al. 1982) and an increase in hexabarbital sleep time observed in mice at 125 mg/kg/day for 14 days (Munson et al. 1982) are also indicative of liver damage.

There are limited data to assess species differences. The results of the NTP intermediate-duration study (NTP 1989a) suggest that rats may be more sensitive to the hepatotoxicity of bromoform than mice. The NOAEL and LOAEL values for hepatocellular vacuolization were 25 and 50 mg/kg (5 days/week) in rats and 100 and 200 mg/kg in mice. Liver damage was the critical end point used for the derivation of acute-, intermediate-, and chronic-duration oral MRLs for bromoform, as described in the footnotes for Table 3-1 and in Appendix A.

Dibromochloromethane. A variety of hepatic effects have been observed in rats and mice orally exposed to dibromochloromethane. Hepatocellular vacuolization and/or swelling are observed at the lowest adverse effect levels. The LOAEL values for this end point are ≥37 mg/kg in acutely exposed mice (Coffin et al. 2000; Condie et al. 1983), ≥50 mg/kg in rats and mice exposed for an intermediate duration (Aida et al. 1992; Daniel et al. 1990; NTP 1985), and ≥40 mg/kg in rats and mice following chronic exposure (NTP 1985). Clinical chemistry alterations, which are associated with the fatty changes in the liver, include increases in serum cholesterol after a single gavage dose of 1,500 mg/kg (Chu et al. 1982a) or after a 1-month dietary exposure to 56.2 mg/kg/day (Aida et al. 1992), decreases in serum cholesterol at 540 mg/kg/day after a 24-month dietary exposure (Tobe et al. 1982), and decreases in serum triglycerides at 173.3 and 20 mg/kg/day following 1- or 24-month dietary exposures, respectively (Aida et al. 1992; Tobe et al. 1982). Additionally, increases in liver weight were observed in mice administered gavage doses of 250 mg/kg/day for 14 days (Munson et al. 1982) or 100 mg/kg (5 days/week) for 3 weeks (Melnick et al. 1998). The increased incidences of hepatocellular vacuoles observed at 37 mg/kg/day following acute exposure and 40 mg/kg following chronic exposure (NTP 1985) were used to derive acute- and chronic-duration oral MRLs for dibromochloromethane, as described in the footnotes to Table 3-2 and in Appendix A.

At higher doses, oral exposure to dibromochloromethane resulted in hepatocellular necrosis. Necrosis was found in rats and mice exposed to ≥100 mg/kg (Aida et al. 1992; Daniel et al. 1990; NTP 1985) for

intermediate durations. Necrosis was not reported following acute-duration exposure; however, increases in SGOT and/or SGPT (indicative of hepatocellular damage) were found in rats and mice exposed to ≥145 mg/kg (Condie et al. 2000; Hewitt et al. 1983; Munson et al. 1982). Necrosis was not found following chronic exposure in rats and mice exposed to 80 or 100 mg/kg (5 days/week), respectively (NTP 1985). Other liver effects include bile duct hyperplasia in rats exposed to 250 mg/kg (5 days/week) for 13 weeks (NTP 1985), hepatocyte hydropic degeneration in mice exposed to 192 mg/kg (5 days/week) for 3 weeks (Melnick et al. 1998), and decreased serum glucose levels in rats exposed to 540 mg/kg/day for 24 months (Tobe et al. 1982).

Renal Effects.

Bromoform. There is some evidence that oral exposure to bromoform can induce kidney damage. Condie et al. (1983) noted minimal to slight nephrosis and mesangial hypertrophy in male mice exposed to repeated oral doses of 145–289 mg/kg/day of bromoform. In contrast, no significant histopathological alterations were detected by NTP (1989a) in rats or mice receiving gavage of 200 mg/kg (5 days/week) of bromoform for 2 years.

Dibromochloromethane. Histological studies performed by NTP (1985) indicate that oral exposure to dibromochloromethane can cause kidney injury in both rats and mice. The medullae appear to be reddened in both males and females after a single oral dose of 500 mg/kg, but this dose was so high that 7 of 10 animals died. Of greater toxicological concern are effects on the nephron that develop after intermediate or chronic exposure to doses of 50–250 mg/kg/day (NTP 1985). These effects are usually much more apparent in males than females, and are characterized by tubular degeneration and mineralization leading to nephrosis (NTP 1985). These histological findings of nephrotoxicity are supported by the kidney function studies of Condie et al. (1983), which found that ingestion of dibromochloromethane (37–147 mg/kg/day) for 2 weeks by male mice tended to impair uptake of para-amino hippuric acid in renal slices prepared from exposed animals.

Endocrine Effects.

Bromoform. Several endocrine effects have been observed in animals exposed to bromoform; however, none of the effects were consistently found. The observed endocrine effects included enlarged thyroid gland in rats administered a lethal dose of 800 mg/kg/day for 14 days (NTP 1989a), decreased thyroid follicular size and colloid density 90 days after termination of exposure to 360 mg/kg/day (Chu et al. 1982b), thyroid follicular cell hyperplasia in mice administered 200 mg/kg (5 days/week) for 2 years

(NTP 1989a), pituitary gland hyperplasia in rats administered 100 mg/kg (5 days/week) but not 200 mg/kg (NTP 1989a), and decreased serum testosterone levels in rats exposed to 380 mg/kg/day for 7 days (Potter et al. 1996).

Dibromochloromethane. A decrease in serum testosterone levels was observed in rats administered gavage doses of 310 mg/kg/day for 7 days (Potter et al. 1996); a NOAEL of 196 mg/kg/day was also identified. Several studies have examined the potential of dibromochloromethane to induce histological alterations following longer-term exposure. No alterations in endocrine glands were observed following intermediate-duration exposure of rats to 200 or 256 mg/kg/day (Chu et al. 1982b; Daniel et al. 1990) or rats or mice to 250 mg/kg 5 days/week (NTP 1985). Administration of dibromochloromethane via gavage for 2 years resulted in thyroid follicular cell hyperplasia in mice exposed to 50 or 100 mg/kg, 5 days/week; no effects were observed in rats administered 40 or 80 mg/kg (5 days/week) (NTP 1985).

Dermal Effects. Histological studies of tissues from rats and mice exposed to bromoform or dibromochloromethane by gavage for up to 2 years revealed no treatment-related dermal effects (NTP 1985, 1989a).

Ocular Effects. Histological studies of tissues from rats and mice exposed to bromoform or dibromochloromethane by gavage for up to 2 years revealed no treatment-related ocular effects (NTP 1985, 1989a).

Body Weight Effects.

Bromoform. In animals, treatment with bromoform is associated with significant decrements in body weight, without concurrent reduced food intake. The oral database appears to indicate a similar bromoform dose threshold for body weight effects for acute- and intermediate-duration exposures; the threshold appears to be reduced somewhat for long-term exposures. In acute repeated-dose oral gavage studies (Condie et al. 1983; Munson et al. 1982; NTP 1989a), body weight was slightly (4%) decreased compared to controls in female rats at 400 mg/kg/day, decreased by 14% in male rats at 400 mg/kg, but no significant consistently-observed effects on body weight were seen in mice up to 800 mg/kg. Intermediate-duration studies of bromoform appear to present a similar dose-response relationship for body weight effects as the acute studies. Body weights of rats were unaffected by bromoform doses of ≤200 mg/kg administered by gavage, in feed, or in drinking water (Aida et al. 1992; Chu et al. 1982a; NTP 1989a). Body weights of mice treated with 400 mg/kg of bromoform by gavage were slightly (8%) reduced (NTP 1989a). Body weight effects become evident at a lower threshold in chronic studies (NTP

1989a; Tobe et al. 1982). Body weights were decreased by 4–10% in rats and female mice treated with 100 mg/kg of bromoform by gavage, whereas 16–25% decreases in body weight gain were noted at 200 mg/kg (NTP 1989a). A chronic feeding study in rats (Tobe et al. 1982) showed a similar dose-response for body weight effects as the gavage studies; body weight reductions of 15% were observed at 90–150 mg/kg and serious reductions of 30–40% were observed above 365 mg/kg.

Dibromochloromethane. Treatment with dibromochlormethane is also associated with decrements in body weight in animals. The dose responses for body weight effects appear generally similar when dibromochlormethane was administered by gavage, in feed, or in drinking water. In acute repeated-dose oral gavage studies (Chu et al. 1980; Condie et al. 1983; Munson et al. 1982; NTP 1985), body weight was decreased 11 and 20% in male rats at 250 and 400 mg/kg, respectively, but no significant effects on body weight were seen in mice or female rats up to 500 mg/kg. Intermediate-duration studies in which dibromochlormethane was administered by gavage (Daniel et al. 1990; NTP 1985) showed slightly (7%) decreased body weights in male rats at 125 mg/kg, 13–32% decreases in rats of both sexes at 200 mg/kg, and 25–47% decreases in rats of both sexes at 250 mg/kg. In intermediate-duration studies of dibromochlormethane in mice (NTP 1985), body weights were unaffected by gavage doses to 250 mg/kg. In intermediate-duration drinking water studies of dibromochlormethane in rats (Chu et al. 1982a, 1982b), body weights were unaffected at doses below 70 mg/kg, but were reduced by 12% at 224 mg/kg. In a 30-day feeding study (Aida et al. 1992), mean body weight in female rats was decreased by 8% at 330 mg/kg/day. In chronic-duration gavage studies (NTP 1985), body weights were slightly (8–9%) decreased in male rats and female mice at 50–80 mg/kg and decreased by 14–17% in mice at 100 mg/kg. In a chronic-duration feeding study in rats (Tobe et al. 1982), body weights were reduced by 10% at 47–70 mg/kg and by 35% at 200 mg/kg.

3.2.2.3 Immunological and Lymphoreticular Effects

There are limited data on the toxicity of bromoform and dibromochloromethane to the immune and lymphoreticular systems. Munson et al. (1982) examined immune function following exposure to both compounds. Other studies (Daniel et al. 1990; NTP 1985, 1989a) monitored organ weights or examined tissues for histological damage.

Bromoform. Impaired humoral immune function, as tested by the response to sheep red blood cells, was observed in rats and mice exposed to 125 or 250 mg/kg/day bromoform for 14 days (Munson et al. 1982); no adverse effect on cell-mediated immunity was noted. Additionally, it should be noted that male rats

exposed to bromoform for 2 years appeared to have decreased resistance to a common viral infection (NTP 1989a), suggesting (but not proving) that bromoform may have led to functional impairment of the immune system in these animals. No histological alterations were observed in tissues of the immune or lymphoreticular systems in rats and mice exposed to 200 and 400 mg/kg (5 days/week), respectively, for 90 days (NTP 1985) or 100–200 or 200 mg/kg (5 days/week), respectively, for 2 years (NTP 1985).

Dibromochloromethane. Exposure of mice to doses of 125 or 250 mg/kg/day of dibromochloromethane for 14 days resulted in impaired humoral immunity (splenic IgM response to sheep red blood cells) (Munson et al. 1982). Impaired cellular immunity (popliteal lymph node response to sheep red blood cells) was also observed at 250 mg/kg/day. A significant decrease in thymus weight was observed in rats exposed to 300 mg/kg/day for 90 days (Daniel et al. 1990). No histological alterations were observed in immune or lymphoreticular tissues of rats and mice following intermediate or chronic duration to 250 or 80–100 mg/kg (days/week), respectively (NTP 1985).

3.2.2.4 Neurological Effects

Bromoform. Bromoform, like other volatile halogenated hydrocarbons, can lead to marked central nervous system depression. Because of this property, bromoform was used as a sedative in the early 1900s and was commonly administered to children for relief from whooping cough. Several poisonings and a few deaths resulted from accidental overdoses or because of separation of the emulsion (Benson 1907; Burton-Fanning 1901; Dwelle 1903; Stokes 1900; von Oettingen 1955). In mild cases of accidental overdose, clinical signs included rapid breathing, constricted pupils, and tremors; more severe cases of overdose were accompanied by a drunken-like stupor, cyanosis, shallow breathing, and erratic heart rate (Benson 1907; Kobert 1906). Actual doses associated with these neurological symptoms are not known with certainty. Based on experiences with seven cases of accidental bromoform poisonings in children with whooping cough, Burton-Fanning (1901) advised initial treatment volumes of 0.03 mL for children under 1 year, 0.06 mL for those 1–4 years old, and 0.13 ml for children 4–8 years of age, which correspond roughly to doses of 25–60 mg/kg. Dwelle (1903) reported the case of a 33-month-old girl who was prescribed bromoform for relief of whooping cough-induced coughing and vomiting. It is estimated that the girl ingested approximately 700 mg bromoform (60 mg/kg/day) and slept undisturbed that night, suggesting the occurrence of sedative effects.

As with humans, high doses of bromoform result in central nervous system depression in animals; at lower doses, impaired performance on neurobehavioral tests is observed. The severity of the central

nervous system depression was dose-related with anesthesia and shallow breathing occurring at very high, often lethal, doses and ataxia, lethargy, and sedation at lower doses. In rats, lethargy, swallow breathing, and ataxia were observed at 600 and 1,000 mg/kg/day (NTP 1989a) following acute exposure; lethargy was also observed at 100 mg/kg (5 days/week) during a 13-week or 2-year exposure (NTP 1989a). In mice, anesthesia, ataxia, and sedation were observed following a single dose of 1,000 mg/kg (Bowman et al. 1978) and lethargy and ataxia were observed at 600 mg/kg/day for 14 days (NTP 1989a). No overt signs of neurotoxicity were observed at 400 or 100 mg/kg following gavage administration, 5 days/week, for 13 weeks or 2 years (NTP 1989a).

A series of experiments conducted by Balster and Borzelleca (1982) assessed neurobehavioral performance in mice following acute- or intermediate-duration exposure. The ED_{50} for impaired motor performance was 431 mg/kg following a single dose exposure. Intermediate-duration exposure resulted in a decrease in exploratory behavior at 9.2 mg/kg/day for 90 days and a decrease in response rate in an operant behavior test at 100 mg/kg/day for 60 days. No effect on swimming endurance was observed at 9.7 mg/kg/day for 14 days or on passive-avoidance learning at 100 mg/kg/day for 30 days.

Dibromochloromethane. No human data on the neurotoxicity of dibromochloromethane were located. In animals, central nervous system depression, as evidenced by lethargy, ataxia, and sedation occurs at relatively high doses. An acute exposure to 500 mg/kg/day resulted in lethargy, ataxia, sedation, and shallow breathing in rats and mice (Bowman et al. 1978; NTP 1985); lethargy was also observed in rats receiving a single gavage dose of 310 mg/kg (NTP 1985). Intermediate-duration exposure to 250 mg/kg (5 days/week) or chronic exposure to 80–100 mg/kg (5 days/week) did not result in overt signs of neurotoxicity (NTP 1985). Daniel et al. (1990) found a significant decrease in brain weights in rats exposed to 100 or 200 mg/kg/day for 90 days. However, no alterations in brain weight or histopathology were observed at doses as high as 250 mg/kg (5 days/week) for 13 weeks (NTP 1985) or 80 mg/kg (5 days/week) for 2 years (NTP 1985).

Some alterations in neurobehavioral performance were observed in mice (Balster and Borzelleca 1982). An ED_{50} of 454 mg/kg was calculated for impaired motor performance following a single dose exposure and a decrease in response rate in operant behavior test during a 60-day exposure to 400 mg/kg/day. No alterations in swimming endurance (10 mg/kg/day for 14 days), exploratory behavior (10 mg/kg/day for 90 days), or passive avoidance learning (100 mg/kg/day for 30 days) were observed.

3.2.2.5 Reproductive Effects

The reproductive toxicity of bromoform and dibromochloromethane has been assessed in a small number of human and animal studies. A number of studies have examined the potential association between adverse reproductive outcomes, especially spontaneous abortions, stillbirths, and preterm delivery, and consumption of municipal drinking water containing triholomethanes (bromoform, dibromochloromethane, dichloromethane, and chloroform) (Bove et al. 1992, 1995, 2002; Dodds et al. 1999; Kramer et al. 1992; Mills et al. 1998; Nieuwenhuijsen et al. 2000; Savitz et al. 1995; Waller et al. 1999). These studies involved mixed exposures to trihalomethane compounds and most did not provide bromoform or dibromochloromethane exposure data. Two pregnancy outcome studies (Kramer et al. 1992; Waller et al. 1999) have examined risks associated with bromoform or dibromochloromethane drinking water levels. A third study (Windham et al. 2003) examined the risk of altered menstrual cycle function in women exposed to trihalomethanes in drinking water.

A brief discussion of these three studies follows. A discussion of the results of the other studies of trihalomethanes, which do not provide bromoform or dibromochloromethane exposure data, is beyond the scope of this document. It should be noted that collectively, the studies provide insufficient evidence for establishing a causal relationship between exposure to trihalomethane compounds and adverse reproductive outcome.

The Kramer et al. (1992) study is a population case-control study of pregnant white, non-Hispanic women living in communities in Iowa where all drinking water was supplied from a single source. No significant associations between bromoform or dibromochloromethane levels in the drinking water and the risk of prematurity were found. The odds ratios were 1.1 (95% confidence limit of 0.8–1.4) for communities with bromoform levels of 1 μg/L and higher and 1.1 (95% confidence limit of 0.7–1.4) for communities with dibromochloromethane levels of 1–3 μg/L; no cases were found in communities with dibromo-chloromethane levels of 4 μg/L and higher. Similar results were found in the Waller et al. (1999) study. In this study, pregnancy health outcomes were examined in pregnant women living in communities with groundwater, surface water, or mixed sources of drinking water. The risk of spontaneous abortion was not significantly associated with bromoform or dibromochloromethane water levels; the percentage of pregnancies ending with spontaneous abortions were 9.2, 9.8, and 10.3% in communities with bromoform drinking water levels of 0, 1–15, and ≥16 μg/L, respectively, and 9.7, 9.6, and 10.4% for dibromochloromethane levels of 0, 1–30, and ≥31 μg/L, respectively.

Windham et al. (2003) examined the relationship between trihalomethane compounds in drinking water and menstrual cycle function. Menstrual parameter values, such as those of cycle length or phase length, were determined based on biologic measures (hormone levels), rather than by subjective self-reporting, from urine samples collected during an average of 5.6 menstrual cycles from premenopausal women (n=403). The bromoform and dibromochloromethane levels were estimated for each cycle based on residence and utility measurements (quarterly measurements made by water utilities during a 90-day period beginning 60 days before the cycle start date) of individual trihalomethane concentrations made within a relatively narrow time frame around the menstrual cycle start date. Significant associations between exposure to the top quartile of bromoform (≥12 μg/L) and decreasing menstrual cycle and follicular phase length were found. The age, race, body mass index, income, pregnancy history, and caffeine and alcohol consumption-adjusted differences were -0.79 (95% confidence interval of -1.4 to -0.14) for cycle length and -0.78 (-1.4 to -0.14) for follicular phase length. For dibromochloromethane, the differences for the 2–3 quartile (level not reported) and highest quartile (≥20 μg/L) were -0.69 (95% confidence interval of -1.4 to -0.02) and -1.21 (95% confidence interval of -2.0 to -0.38), respectively, for menstrual cycle length and -0.62 (95% confidence interval of -1.3 to 0.05) and -1.1 (95% confidence interval of -1.9 and -0.25, respectively, for follicular phase length. No associations between bromoform or dibromochloromethane concentration and luteal phase length, menses length, or cycle variability were found. Interpretation of the study results is limited due to coexposure to other trihalomethanes.

Bromoform. Data on the reproductive toxicity of bromoform in humans are limited to the trihalomethane studies described above. Animal studies have examined the potential of bromoform to induce histological alterations (NTP 1989a) and impair reproductive function (NTP 1989b). No histological alterations were observed in rats and mice exposed to 200 or 400 mg/kg, respectively, 5 days/week for 13 weeks (NTP 1989a). Dose related incidences of squamous metaplasia of the prostate gland were observed in male rats exposed to 200 mg/kg (5 days/week) for 2 years (NTP 1989a). This lesion may represent a chemical effect associated with concurrent inflammatory lesions in this gland, which occurred at similar rates in all groups of male rats tested, including vehicle controls. Chronic exposure of mice to 200 mg/kg (5 days/week) resulted in no detectable noncancerous histological effects in male reproductive tissues (testes, prostate, and seminal vesicles) (NTP 1989a). No nonneoplastic histological alterations were observed in female rats or mice receiving gavage doses of 200 mg/kg (5 days/week) for 2 years (NTP 1989a). No adverse effects on reproductive performance or fertility were observed in male and female mice receiving gavage doses of 200 mg/kg/day (NTP 1989b).

Dibromochloromethane. Human data on the reproductive toxicity of dibromochloromethane are limited to the trihalomethane studies described above. No histological alterations (testes, prostate, seminal vesicles, ovaries, uterus, and mammary gland examined) were observed in rats or mice receiving gavage doses of up to 250 mg/kg 5 days/week for 13 weeks (Daniel et al. 1990; NTP 1985) or 80 or 100 mg/kg, respectively, 5 days/week for 2 years (NTP 1985). In contrast to these negative findings, female mice exposed to dibromochloromethane in drinking water at a high dose (685 mg/kg/day) experienced a marked reduction in fertility, with significant decreases in litter size, gestational survival, postnatal survival, and postnatal body weight (Borzelleca and Carchman 1982). These effects may have been due to marked maternal toxicity, as evidenced by decreased weight gain, enlarged and discolored livers, and decreased survival. Exposure to lower doses (17 or 170 mg/kg/day) resulted in occasional decreases in one or more of the reproductive parameters monitored, but the effects were not large and were not clearly dose-related. These data are not sufficient to draw firm conclusions about the effects of dibromochloromethane on reproduction, but it appears that reproductive tissues and functions are not markedly impaired at doses that do not cause frank maternal toxicity. This is supported by a reproductive toxicity study conducted by NTP (1996). No alterations in reproductive or fertility indices were observed in female rats exposed to 40.3 mg/kg/day dibromochloromethane in drinking water for 35 days (13 days prior to mating, during mating, and gestation).

3.2.2.6 Developmental Effects

There are limited data on the developmental toxicity of bromoform or dibromochloromethane in humans and animals. Several human studies have examined the potential association between exposure to trihalomethanes in drinking water and birth outcomes (Dodds et al. 1999; Kramer et al. 1992; Savitz et al. 1995). However, only one study (Kramer et al. 1992) examined the risks associated with exposure to individual trihalomethanes in women exposed to tap water containing a number of chlorinated byproducts. In this population-based case control of pregnant white, non-Hispanic women living in communities in Iowa where all drinking water was supplied from a single source, no significant association between exposure to ≥1 μg/L of bromoform or ≥4 μg/L of dibromochloromethane in tap water and increased risk of low birth weight babies and intrauterine growth retardation were found. Interpretation of this study is limited by the co-exposure to other trihalomethane compounds.

Bromoform. Human data on the developmental toxicity of bromoform are limited to the trihalomethane studies discussed above. One animal study (Ruddick et al. 1983) was identified. No significant alterations in the number of resorption sites, fetuses per litter, fetal body weights, fetal malformations, or

visceral anomalies were observed in the offspring of rats administered up to 200 mg/kg/day bromoform in corn oil on gestational days 6–15. Increases in several skeletal anomalies were found in the offspring of rats exposed to bromoform, including the presence of a 14th rib, wavy ribs, interparietal deviations, and sternebra aberrations. The study authors did not conduct a statistical analysis of the data; an independent analysis of the data using Fisher Exact test revealed a significant increase in the incidence (per fetus and number of affected litters) in sternebra aberrations.

Dibromochloromethane. Human data on the developmental toxicity of dibromochloromethane are limited to the trihalomethane studies discussed above. Two animal studies examined the potential of dibromochloromethane to induce developmental effects. In a study by Ruddick et al. (1983) of rats receiving gavage doses of up to 200 mg/kg/day on gestational days 6–15, no alterations in the number of resorption sites, fetuses per litter, fetal body weights, fetal gross malformations, or skeletal or visceral anomalies were found. Borzelleca and Carchman (1982) exposed mice to 685 mg/kg/day of dibromochloromethane in drinking water for several generations and detected no significant effect on the incidence of gross, skeletal, or soft-tissue anomalies.

3.2.2.7 Cancer

No studies were located regarding carcinogenic effects in humans following oral exposure to bromoform or dibromochloromethane. There are a number of epidemiological studies that indicate that there may be an association between chronic ingestion of chlorinated drinking water (which typically contains trihalomethanes including bromoform and dibromochloromethane) and increased risk of rectal, bladder, or colon cancer in humans (Cantor et al. 1987; Crump 1983; Kanarek and Young 1982; Marienfeld et al. 1986), but these studies cannot provide information on whether any effects observed are due to bromoform, dibromochloromethane, or to one or more of the hundreds of other byproducts that are also present in chlorinated water.

Bromoform. A significant increase in the incidence of adenomatous polyps or adenocarcinomas were observed in female rats receiving gavage dose of 200 mg/kg, 5 days/week for 2 years (NTP 1989a); a nonstatistically significant increase was observed in male rats. The incidences of this relatively rare tumor (combined incidences of adenomatous polyps and adenocarcinoma) were 0/50, 0/50, and 3/50 for males administered 0, 100, or 200 mg/kg and 0/50, 1/50, and 8/50 for females. No significant alterations in neoplastic lesions were observed in mice administered up to 100 (males) or 200 (females) mg/kg, 5 days/week for 2 years (NTP 1989a). The International Agency for Research on Cancer (IARC)

concluded that there were inadequate human data and limited animal data and assigned bromoform to weight of evidence category 3, not classifiable as to carcinogenicity in humans (IARC 1991a, 1999a) and EPA classified bromoform as a probable human carcinogen, group B2 (IRIS 2003a). Based on the increased occurrence of neoplastic lesions in the large intestines of female rats, EPA derived an oral slope factor of 7.9x10-3 (mg/kg/day)-1 (IRIS 2003a).

Dibromochloromethane. In mice administered gavage doses of 100 mg/kg, 5 days/week for 2 years, increases in the incidences of hepatocellular adenomas and carcinomas were observed (NTP 1985). The incidence was significantly elevated for hepatocellular adenomas in females (2/50, 4/49, and 11/50 for 0, 50, and 100 mg/kg), hepatocellular carcinoma in males (10/50 and 19/50 for 0 and 100 mg/kg) and combined incidences for hepatocellular adenoma or carcinoma (23/50 and 27/50 for males at 0 and 100 mg/kg and 6/50, 10/49, and 19/50 for females at 0, 50, and 100 mg/kg). No significant alterations in the incidence of neoplastic lesion were observed in male or female rats administered up to 80 mg/kg 5 days/week for 2 years (NTP 1985). The IARC considered the available data on dibromochloromethane carcinogenicity to be not classifiable as to carcinogenicity in humans (group 3) (IARC 1991b, 1999b). EPA classified dibromochloromethane as a possible human carcinogen, group C (IRIS 2003b). Based on the increased combined incidence of hepatocellular adenoma or carcinoma in female mice, EPA derived an oral slope factor of $8.4x10^{-2}$ $(mg/kg/day)^{-1}$ (IRIS 2003b).

3.2.3 Dermal Exposure

No studies were located regarding the following health effects in humans or animals after dermal exposure to bromoform or dibromochloromethane:

3.2.3.1 Death

3.2.3.2 Systemic Effects

3.2.3.3 Immunological and Lymphoreticular Effects

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

3.3 GENOTOXICITY

Bromoform. Numerous studies have examined the *in vivo* and *in vitro* genotoxicity of bromoform; the results of these tests are summarized in Tables 3-3 and 3-4, respectively. The potential for bromoform to induce chromosome aberrations, micronuclei, sister chromatid exchange, and DNA damage was investigated in several studies, often with conflicting results. An increase in chromosome aberrations, in particular chromatid and chromosome breaks, was observed in rats receiving five daily gavage doses of 253 mg/kg/day or a single intraperitoneal dose of 25.3 or 253 mg/kg (Fujie et al. 1990), but not in mice administered up to 800 mg/kg via intraperitoneal injection (NTP 1989a). A significant increase in sister chromatid exchange was observed in the bone marrow cells of mice receiving 25 mg/kg/day gavage doses for 4 days (Morimoto and Koizumi 1983) and mice receiving intraperitoneal doses of 800 mg/kg (NTP 1989a). Increases in micronuclei induction were observed in mice exposed to 800 mg/kg via intraperitoneal injection (NTP 1989a) and newt larvae following a 6-day exposure to 2.5 mg/L (LeCurieux et al. 1995), but not in mice receiving a single intraperitoneal dose of 175–1,400 mg/kg (Hayashi et al. 1988) or 250–1,000 mg/kg via gavage (Stocker et al. 1997). No alterations in unscheduled DNA synthesis were observed in mice administered 324 or 1,080 mg/kg via gavage (Stocker et al. 1997) and no alterations in DNA strand breaks were observed in the kidneys of rats administered 380 mg/kg for 1 day via gavage (Potter et al. 1996). An increase in sex-linked recessive mutations was observed in *Drosophila melanogaster* following feeding but not injection exposure (NTP 1989a); no effect on reciprocal translocations was found.

The results of numerous *in vitro* genotoxicity assays for bromoform are summarized in Table 3-4. Assays assessing the potential of bromoform to induce gene mutations have reported mixed results. Increases (LeCurieux et al. 1995; Simmon and Tardiff 1978; Simmon et al. 1977) and no effect (NTP 1989a; Rapson et al. 1980; Varma et al. 1988) on the occurrence of reverse mutations have been found in *Salmonella tymphimurium*; an increase in forward mutations was also found in *S. tymphimurium* (Roldan-Arjona and Pueyo 1993). The clastogenic activity of bromoform has been tested in one study (Galloway et al. 1985; NTP 1989a) that found no significant alterations with S9 metabolic activation and negative and weakly positive results without metabolic alteration. A significant alteration in mitotic aneuploidy was observed in *Aspergillus nidulans* (Benigni et al. 1993). Other tests of genotoxicity included an increase in sister chromatid exchange in human lymphocytes (Morimoto and Koizumi 1983) and rat erythroblastic leukemia K_3D cells (Fujie et al. 1993), but not in Chinese hamster ovary cells (Galloway et al. 1985; NTP 1989a) or oyster toadfish leukocytes (Maddock and Kelly 1980); SOS induction in *Escherichia coli* (Lecurieux et al. 1995); trifluorotymidine resistance in mouse lymphoma cells (NTP 1989a); and DNA strand breaks in human lymphocytes (Landi et al. 1999).

Table 3-3. Genotoxicity of Bromoform *In Vivo*

End point	Species (test system)	Exposure route	Results	Reference
Nonmammalian systems:				
Sex-linked recessive lethal	*Drosophilia melanogaster*	Feeding	+	Woodruff et al. 1985; NTP 1989a
		Injection	–	
Reciprocal translocation	*D. melanogaster*	Feeding	–	Woodruff et al. 1985; NTP 1989a
Micronuclei	*Pleurodeleswaltl larvae*		+	LeCurieux et al. 1995
Mammalian systems:				
Sister chromatid exchange	Mouse (bone marrow cell)	IP	+	NTP 1989a
	Mouse (bone marrow cell)	oral	+	Morimoto and Koizumi 1983
Chromosomal aberrations	Mouse (bone marrow cell)	IP	–	NTP 1989a
	Rat (bone marrow cell)	IP	+	Fujie et al. 1990
	Rat (bone marrow cell)	Oral	+	Fujie et al. 1990
Micronuclei	Mouse (bone marrow cell)	IP	+	NTP 1989a
	Mouse (bone marrow cell)	Oral	–	Stocker et al. 1996
	Mouse (bone marrow cell)	IP	–	Hayashi et al. 1988
Repairable DNA damage	Rat (liver cells)	Oral	–	Stocker et al. 1996
DNA strand breaks	Rat (kidney cells)	Oral	–	Potter et al. 1996

+ = positive result; -- = negative result; IP = intraperitoneal

Table 3-4. Genotoxicity of Bromoform *In Vitro*

End point	Species (test system)	Results[a] With activation	Results[a] Without activation	Reference
Prokaryotic organisms:				
Reverse gene mutation	*Salmonella tymphimurium*			Simmon and Tardiff 1978; Simmon et al. 1977
	TA100	No data	+	
	TA1535	No data	+	
	S. typhimurium TA100	-	+	LeCurieux et al. 1995
	S. typhimurium			Varma et al. 1988
	TA98	-	–	
	TA100	–	(+)	
	TA1535	–	–	
	TA1537	–	–	
	S. typhimurium TA100	No data	–	Rapson et al. 1980
	S. typhimurium (preincubation assay)			
	TA97	(+)	–	NTP 1989a
	TA98	–, –, (+)	–, –, –	
	TA100	–, –, –	(+), –, –	
	TA1535	–, –, –	–, –, –	
	TA1537	–, –, –	–, –, –	
Forward gene mutation	*S. typhimurium*	No data	(+)	Roldan-Arjona and Pueyo 1993
SOS induction	*Escherichia coli*	+	+	LeCurieux et al. 1995
Eukaryotic organisms:				
Fungi:				
Mitotic aneuploidy	*Aspergillus nidulans*	No data	+	Benigni et al. 1993
Fish:				
Sister-chromatid exchange	Oyster toadfish leukocytes	No data	–	Maddock and Kelly 1980
Mammalian cells:				
Sister-chromatid exchange	Human lymphocytes	No data	+	Morimoto and Koizumi 1983
	Chinese hamster ovary cells	–, –	–, (+)	Galloway et al. 1985; NTP 1989a
	Rat erythroblastic leukemia K_3D cells	+	+	Fujie et al. 1993

Table 3-4. Genotoxicity of Bromoform *In Vitro*

		Results[a]		
End point	Species (test system)	With activation	Without activation	Reference
Chromosomal aberrations	Chinese hamster ovary cells	–, –	–, (+)	Galloway et al. 1985; NTP 1989a
Trifluorothymidine resistance	Mouse lymphoma cells	+	+	NTP 1989a
DNA strand breaks	Human lymphocytes	No data	+	Landi et al. 1999

[a]Results from two or more different contract laboratories are separated by commas
+ = positive result; – = negative result; (+) = marginally positive result

Dibromochloromethane. The genotoxicity of dibromochloromethane has been assessed in a number of *in vivo* and *in vitro* assays presented in Tables 3-5 and 3-6, respectively. *In vivo*, oral exposure to 25–200 mg/kg/day for 4 days resulted in dose-related increases in the frequency of sister chromatid exchanges in mouse bone marrow cells (Morimoto and Koizumi 1983). An increase in the occurrence of chromosomal aberrations was also observed in bone marrow cells of rats receiving a single intraperitoneal injection of 20.8 mg/kg (Fujie et al. 1990); a weak positive response was observed following gavage administration of 10.5–1,041.5 mg/kg/day for 5 days (Fujie et al. 1990). No significant alterations in micronuclei induction (Hayashi et al. 1988), repairable DNA damage (Stocker et al. 1996), or DNA strand breaks (Potter et al. 1996) were observed in mouse bone marrow cells (intraperitoneal injection of 62.5–1,000 mg/kg), rat liver cells (gavage dose of 135 or 450 mg/kg), or rat kidney cells (gavage dose of 310 mg/kg), respectively.

The *in vitro* genotoxicity of dibromochloromethane is summarized in Table 3-5. Mixed results were found in bacterial assays for reverse gene mutations, with some studies finding a significant alteration (Landi et al. 1999; Simmon and Tardiff 1978; Simmon et al. 1977; Varma et al. 1988) and others not finding an effect (LeCurieux et al. 1995; NTP 1985; Zeiger et al. 1987). A significant increase in forward gene mutations was found in mouse lymphoma cells (McGregor et al. 1991). An increase in gene conversion, but not gene reversion, was observed in *Saccharomyces cervisiae* (Nestman and Lee 1985). An increase in mitotic aneuploidy was observed in *A. nidulans* and sister chromatid exchange was observed in human lymphocytes (Morimoto and Koizumi 1983; Sobti 1984), rat liver cells (Sobti 1984), and rat erythroblastic leukemia K_3D cells (Fuije et al. 1993). Additionally, increases in chromosomal aberrations were observed in mouse lymphoma cells (Sofuni et al. 1996) and Chinese hamster lung cells (Matsuoka et al. 1996).

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

There are limited data on inhalation absorption of bromoform or dibromochloromethane. Based on the physical-chemical properties of these compounds, and by analogy with other related halomethanes such as chloroform (Agency for Toxic Substances and Disease Registry 1997), it is expected that bromoform

Table 3-5. Genotoxicity of Dibromochloromethane *In Vivo*

End point	Species (test system)	Exposure route	Results	Reference
Nonmammalian systems:				
Micronuclei	*Pleurodeleswaltl larvae*		–	LeCurieux et al. 1995
Mammalian systems:				
Sister chromatid exchange	Mouse (bone marrow cell)	Oral	+	Morimoto and Koizumi 1983
Chromosomal aberrations	Rat (bone marrow cell)	IP	+	Fujie et al. 1990
	Rat (bone marrow cell)	Oral	(+)	Fujie et al. 1990
Micronuclei	Mouse (bone marrow cell)	IP	–	Hayashi et al. 1988
Repairable DNA damage	Rat (liver cells)	Oral	–	Stocker et al. 1996
DNA strand breaks	Rat (kidney cells)	Oral	–	Potter et al. 1996

+ = positive result; – = negative result; (+) = weak positive; IP = intraperitoneal

Table 3-6. Genotoxicity of Dibromochloromethane *In Vitro*

End point	Species (test system)	Results[a] With activation	Results[a] Without activation	Reference
Prokaryotic organisms:				
Reverse gene mutation	*Salmonella typhimurium* (desiccator sytstem)			Simmon and Tardiff 1978; Simmon et al. 1977
	TA100	No data	+	
	S. typhimurium			LeCurieux et al. 1995
	TA100	–	–	
	S. typhimurium (plate incorporation assay)			Varma et al. 1988
	TA98	+	–	
	TA100	+	–	
	TA1535	+	+	
	TA1537	+	+	
	S. typhimurium (preincubation assay)			NTP 1985; Zeiger et al. 1987
	TA98	–	–	
	TA100	–	–	
	TA1535	–	–	
	TA1537	–	–	
	S. typhimurium			Landi et al. 1999
	TPT100	+	+	
	RSJ100	–	–	
Eukaryotic organisms:				
Fungi:				
Mitotic aneuploidy	*Aspergillus nidulans*	No data	+	Benigni et al. 1993
Gene conversion	*Saccharomyces cervisiae*	–	+	Nestman and Lee 1985
Gene reversion	*S. cerevisiae*	–	–	Nestman and Lee 1985
Mammalian cells:				
Forward gene mutation	Mouse L5178Y lymphoma cells	No data	+	McGregor et al. 1991
Sister-chromatid exchange	Human lymphocytes	No data	+	Morimoto and Koizumi 1983
	Human lymphocytes	No data	+	Sobti 1984
	Rat liver cells	No data	(+)	Sobti 1984
	Rat erythroblastic leukemia K_3D cells	+	+	Fujie et al. 1993

Table 3-6. Genotoxicity of Dibromochloromethane *In Vitro*

End point	Species (test system)	Results[a] With activation	Results[a] Without activation	Reference
Chromosomal aberrations	Mouse L5178Y lymphoma cells	+,+	(+),–	Sofuni et al. 1996
	Chinese hamster lung cells	No data	+	Matsuoka et al. 1996

[a]Results from two or more different contract laboratories are separated by commas
+ = positive result; – = negative result; (+) = marginally positive result

and dibromochloromethane would be well-absorbed across the lung. The occurrence of systemic and neurological effects following inhalation exposure of animals to bromoform (see Section 3.2.1) supports this view. Aggazzotti et al. (1998) examined the uptake of trihalomethanes in five swimmers exposed to trihalomethanes via chlorinated pool water. Although bromoform was detected in the pool water, it was only detected in one of four indoor air samples. Dibromochloromethane was detected in the pool water (0.8 μg/L) and in air samples before swimming (5.2 $\mu g/m^3$) and after swimming (11.4 $\mu g/m^3$). After sitting near the pool for 1 hour, the mean alveolar air level was 0.8 $\mu g/m^3$. After swimming, alveolar air levels were 1.4 $\mu g/m^3$; however, oral and percutaneous exposure also influenced this level. Estimated dibromochloromethane uptake during the 1 hour of sitting near the pool ranged from 1.5 to 2.0 μg/hour; after 1 hour of swimming, the estimated uptake rate ranged from 14 to 22 μg/hour.

Several studies have examined the impact of showering with water contaminated with trihalomethanes on the absorption of individual trihalomethane compounds. Showering involves inhalation exposure to volatilized trihalomethanes, percutaneous exposure, and possibly oral exposure. Several studies have found elevated blood bromoform and/or dibromochloromethane levels following showering (Backer et al. 2000; Lynberg et al. 2001; Miles et al. 2002). A comparative study by Backer et al. (2000) found the highest blood levels of dibromochloromethane after a 10-minute shower, compared to bathing for 10 minutes or drinking 1 L of water in 10 minutes. This difference may be due to differences in total exposure levels, metabolism, or excretion rather than differences in absorption efficiencies.

Several studies have estimated the blood:air partition coefficients for bromoform and dibromochloromethane in humans and rats, these values are summarized in Table 3-7.

3.4.1.2 Oral Exposure

There are limited data on the absorption of bromoform and dibromochloromethane following oral exposure. Most of the available data (Backer et al. 2000; da Silva et al. 1999; Mink et al. 1986) involved exposure to a mixture of trihalomethanes. Elevated blood concentrations of dibromochloromethane were also observed in humans ingesting drinking water containing trihalomethanes (Backer et al. 2000). da Silva et al. (1999) examined bromoform and dibromochloromethane absorption in rats following a single gavage dose. Both compounds were rapidly absorbed with peak plasma levels occurring less than 1 hour postexposure. Oral absorption constants of 0.412 and 0.55 per hour were reported for bromoforom and dibromochloromethane, respectively. A nonlinear relationship between dose (0.25 and

Table 3-7. Partition Coefficients for Bromoform and Dibromochloromethane

	Chemical	Partition coefficient	Species	Reference
Blood:Air				
	Bromoform			
		102.3	Human	Batterman et al. 2002
		161	Rat	Beliveau and Krishnan 2000
		187	Rat	Beliveau et al. 2001b
		198.1	Rat	da Silva et al. 1999
	Dibromochloromethane			
		52.7	Human	Gargas et al. 1989
		49.2	Human	Batterman et al. 2002
		116	Rat	Gargas et al. 1989
		97.5	Rat	Beliveau et al. 2001b
Fat:Air				
	Bromoform	4,129	Rat	da Silva et al. 1999
	Dibromochloromethane	1,919	Rat	Gargas et al. 1989
Liver:Air				
	Bromoform	210.3	Rat	da Silva et al. 1999
	Dibromochloromethane	126	Rat	Gargas et al. 1989
Muscle:Air				
	Bromoform	115.1	Rat	da Silva et al. 1999
	Dibromochloromethane	55.6	Rat	Gargas et al. 1989

0.50 mmol/kg; 63 and 126 mg/kg bromoform and 52 and 104 mg/kg dibromochloromethane) and areas under the blood concentration versus time curves (AUCs) were found, suggesting metabolism saturation. The AUCs (20–360 minutes postexposure) for 63 and 126 mg/kg bromoform were 48.6 and 190.4 μM/hour; for 52 and 104 mg/kg dibromochlormethane, the AUCs (20–360 minutes) were 31.2 and 85.6 μM/hour. When bromoform and dibromochloromethane were administered along with chloroform and dichlorobromomethane (0.25 mmol/kg of each trihalomethane), the AUC was significantly higher than when administered singly.

Mink et al. (1986) found that 60–90% of the bromoform and dibromochloromethane administered in a mixture of trihalomethanes in corn oil to rats (100 mg trihalomethane/kg) or mice (150 mg trihalomethane/kg) were recovered in expired air, urine, or in internal organs. This indicates that gastrointestinal absorption was at least 60–90% complete. This is consistent with the ready gastrointestinal absorption observed for other halomethanes such as chloroform (Agency for Toxic Substances and Disease Registry 1997). As noted by Withey et al. (1983), the rate of halocarbon uptake from the gastrointestinal tract may be slower when compounds are given in oil than when they are given in water.

3.4.1.3 Dermal Exposure

No studies were located regarding dermal absorption of bromoform or dibromochloromethane in humans or animals. As discussed under Inhalation Exposure, showering, which involves both inhalation and dermal exposure with water contaminated with trihalomethanes, can result in significantly elevated blood bromoform and dibromochloromethane levels. Xu et al. (2002) reported dermal absorption coefficients of 0.21 and 0.20 cm/hour for aqueous solutions of bromoform and dibromochloromethane, respectively. These values were determined *in vitro* using excess breast skin tissues at two temperature settings (20 and 25 °C).

3.4.2 Distribution

Several studies have estimated the tissue:air partition coefficients for bromoform and dibromochloromethane in humans and rats; these values are summarized in Table 3-7. *In vitro* data, suggest that hemoglobin is the primary ligand for bromoform, and presumably dibromochloromethane, in the blood (Béliveau and Krishnan 2000b).

3.4.2.1 Inhalation Exposure

No studies were located regarding the distribution of bromoform or dibromochloromethane in humans or animals following inhalation exposure. However, adverse effects involving several organs (liver, kidney, central nervous system) indicate distribution to these sites.

3.4.2.2 Oral Exposure

The distribution of bromoform and dibromochloromethane in tissues following oral exposure has not been thoroughly investigated. Analysis of bromoform levels in the organs of a child who died after an accidental overdose revealed concentrations of 10–40 mg/kg tissue in intestine, liver, kidney, and brain, with somewhat higher levels in lung (90 mg/kg) and stomach (130 mg/kg) (Roth 1904, as cited in von Oettingen 1955). This suggests that bromoform is distributed fairly evenly from the stomach to other tissues.

In animals, Mink et al. (1986) found that only about 1–2% of a single oral dose of ^{14}C-labeled dibromochloromethane or bromoform as part of a trihalomethane mixture was retained in the soft tissues of rats 8 hours after dosing. The tissues which contained measurable amounts of the radiolabel were the brain, kidney, liver, lungs, muscle, pancreas, stomach (excluding contents), thymus, and urinary bladder. The relative amount of radiolabel in each tissue was not mentioned. Similar results were noted in mice, except that blood also contained a significant fraction of the total dose (10% in the case of bromoform). The chemical form of the material in the tissues (parent, metabolite, or adduct) was not reported. The form in blood also was not determined, but studies by Anders et al. (1978) suggest that some or all may have been carbon monoxide bound to hemoglobin (see Section 3.4.3).

3.4.2.3 Dermal Exposure

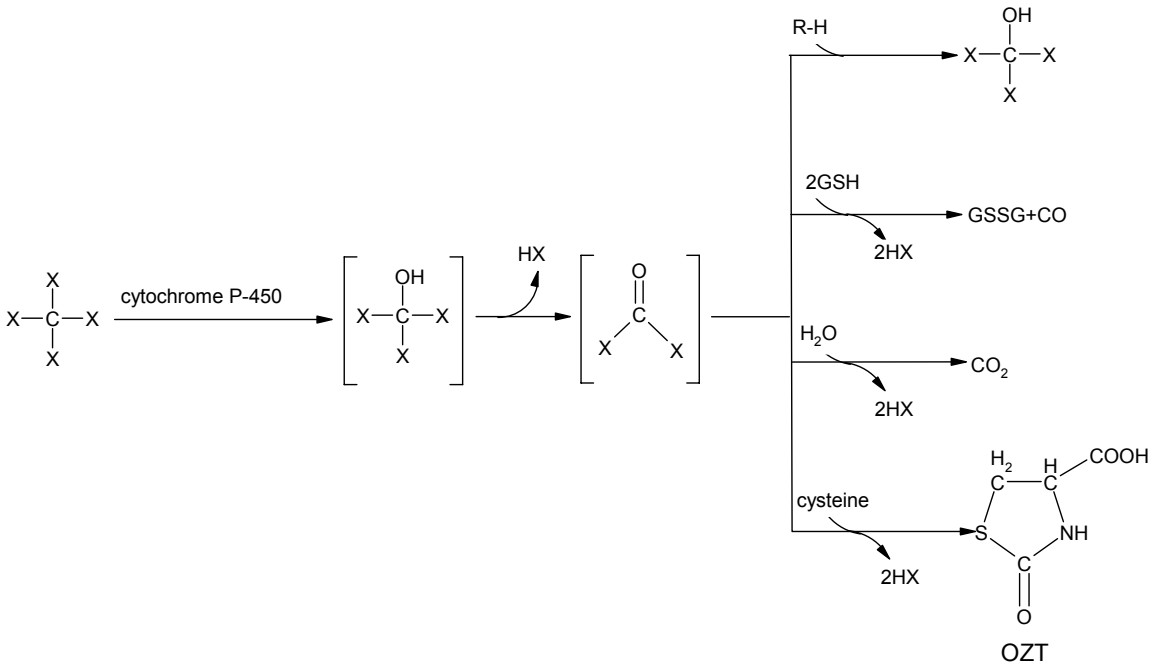
No studies were located regarding the distribution of bromoform or dibromochloromethane in humans or animals following dermal exposure.

3.4.3 Metabolism

The metabolism of bromoform, dibromochloromethane, and other trihalomethanes has been investigated by Anders and colleagues (Ahmed et al. 1977; Anders et al. 1978; Stevens and Anders 1979, 1981). The main reactions, which are not believed to be route-dependent, are shown in Figure 3-3. The first step in the metabolism of trihalomethanes is oxidation by the cytochrome P-450 mixed function oxidase system of liver. This has been demonstrated *in vitro* using isolated rat liver microsomes (Ahmed et al. 1977), and *in vivo*, where the rate of metabolism is increased by cytochrome P-450 inducers (phenobarbital) and decreased by cytochrome P-450 inhibitors (SKF-525A) (Anders et al. 1978). The product of this reaction is presumed to be trihalomethanol, which then decomposes by loss of hydrogen and halide ions to yield the dihalocarbonyl. Although this intermediate has not been isolated, its formation has been inferred by the detection of 2-oxothiazolidine-4-carboxylic acid (OZT) in an *in vitro* microsomal system metabolizing bromoform in the presence of cysteine (Stevens and Anders 1979). The dihalocarbonyl molecule (an analogue of phosgene) is highly reactive, and may undergo a number of reactions, including: (a) direct reaction with cellular nucleophiles to yield covalent adducts; (b) reaction with two moles of glutathione (GSH) to yield carbon monoxide and oxidized glutathione (GSSG); and (c) hydrolysis to yield CO_2. The amount of trihalomethane metabolized by each of these pathways has not been studied in detail, but it appears that conversion to CO_2 is the main route. However, this depends on the species, the trihalomethane being metabolized, and metabolic conditions (cellular glutathione levels). Mink et al. (1986) found that mice oxidized 72% of an oral dose of dibromochloromethane and 40% of an oral dose of bromoform to CO_2. In contrast, rats oxidized only 18% of dibromochloromethane and 4% of bromoform to CO_2. The fraction of the dose converted to carbon monoxide has not been quantified, but dramatically increased levels of carboxyhemoglobin have been reported following oral exposure of rats to bromoform (Anders et al. 1978; Stevens and Anders 1981). Mink et al. (1986) reported that about 10% of a dose of bromoform was present in blood in mice; the form of the label was not investigated, but it may have been carboxyhemoglobin.

Metabolism of trihalomethanes by cytochrome P-450 can also lead to the production of highly reactive trihalomethyl free radicals, especially under hypoxic conditions (O'Brien 1988). Radical formation from bromoform has been observed both in isolated hepatocytes incubated with bromoform *in vitro* and in the liver of rats exposed to bromoform *in vivo* (Tomasi et al. 1985). Although it has not been studied, it seems likely that this pathway would also generate trihalomethyl radicals from dibromochloromethane. While metabolism to free radicals is a minor pathway in the sense that only a small fraction of the total dose is converted, it might be an important component of the toxic and carcinogenic mechanism of dibromochloromethane and bromoform. Figure 3-4 shows how free radical generation can lead to an

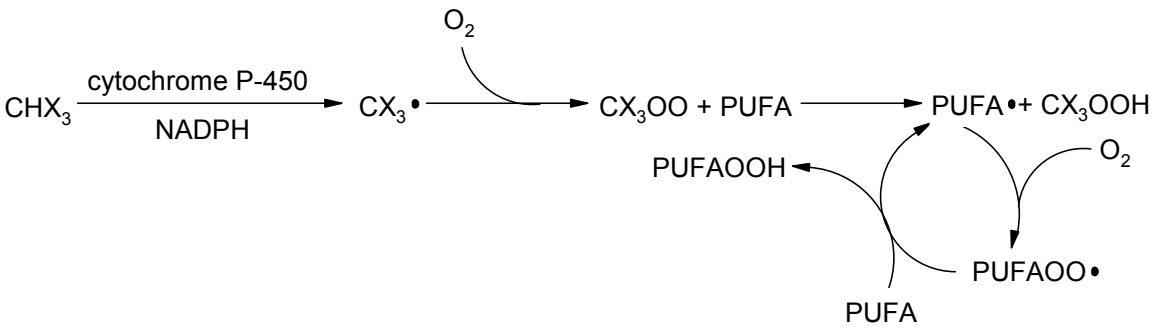
Figure 3-3. Proposed Pathway of Trihalomethane Metabolism in Rats*



*Adapted from Stevens and Anders 1981

X = halogen atom (chlorine, bromine); R = cellular nucleophile (protein, nucleic acid); GSH = reduced glutathione; GSSG = oxidized glutathione; OZT = oxothiazolidine carboxylic acid

Figure 3-4. Proposed Pathway of Trihalomethyl-radical-mediated Lipid Peroxidation*



*Adapted from O'Brien 1988

X = halogen atom (chlorine, bromine, iodine); PUFA = polyunsaturated fatty acid

autocatalytic peroxidation of polyunsaturated fatty acids (PLJFAs) in cellular phospholipids (O'Brien 1988). Peroxidation of cellular lipids has been observed in rat kidney slices incubated with bromoform *in vitro*, although lipid peroxidation was not detectable in liver slices (Fraga et al. 1987). Lipid peroxidation is considered to be a likely cause of cell injury for other halogenated compounds such as carbon tetrachloride (Agency for Toxicological Substances and Disease Registry 1994), but the significance of this pathway in the toxicity of dibromochloromethane and bromoform remains to be determined.

Development of the general metabolic scheme for trihalomethanes shown in Figure 3-3 relied primarily on the use of chloroform and bromoform as model substrates. However, some metabolic data specific to dibromochloromethane are available from a series of experiments conducted in rats by Pankow et al. (1997). Increased levels of the metabolites bromide (in plasma) and carbon monoxide (as detected by formation of carboxyhemoglobin in blood) and dependence of their rate of production on hepatic GSH concentration in rats treated with dibromochloromethane are consistent with the metabolic scheme for the oxidative pathway shown in Figure 3-3. Observation of increased hepatic levels of GSSG in dosed rats by Pankow et al. (1997) is also consistent with the proposed scheme. The observation of (1) partial inhibition of bromide and carboxyhemoglobin production in dosed rats co-administered diethyldithiocarbamate (a potent inhibitor of P-450 isoform CYP2E1) and (2) stimulation of production in rats pretreated with isoniazid (a potent inducer of CYP2E1) indicates that cytochrome P-450 isoform CYP2E1 is at least partially responsible for oxidative metabolism of dibromochloromethane. Pretreatment with phenobarbital (an inducer of CYP2B1/2 in the rat) increased the concentration of bromide in plasma, suggesting that CYP2B1/2, as well as CYP2E1, catalyzes metabolism of dibromochloromethane in the rat.

Recent studies suggest that brominated trihalomethanes, including bromoform and dibromochloromethane, may be metabolized by one or more pathways dependent on glutathione conjugation catalyzed by glutathione S-transferase (De Marini et al. 1997; Pegram et al. 1977) in addition to the oxidative and reductive pathways described above. Transfection of *Salmonella typhimurium* test strain TA1535 with the gene for rat glutathione S-transferase theta 1-1 increased the mutagenicity of bromoform and dibromochloromethane (by 95- and 85-fold, respectively) in reverse mutation assays when compared to mutagencity in TA1535 transfected with a nonfunctional form of the gene (De Marini et al. 1997). The mutational spectra and site specificity for bromoform, dibromochloromethane, and bromodichloromethane (a structurally-related brominated trihalomethane) were closely similar, suggesting bioactivation of all three compounds via common metabolic intermediates. The mutagenic metabolites were not identified in this study, but S-(1-halomethyl)glutathione, S-(1,1-dihalomethyl)

glutathione, or their further metabolites were presumed on the basis of data reported for other halomethanes to be capable of reacting with DNA to produce the observed mutations (De Marini et al. 1997).

The formation of reactive metabolites by conjugation of bromoform or dibromochloromethane via glutathione S-transferase theta-mediated pathways has not been examined in mammalian test systems. However, the metabolism of bromodichloromethane via glutathione conjugation has been investigated *in vitro* using cytosols prepared from human, rat, and mouse liver (Ross and Pegram 2003). Conjugation of bromodichloromethane with glutathione in mouse liver cytosol was time- and protein-dependent, was not affected by an inhibitor of alpha-, mu-, and pi-class glutathione S-transferases, and was correlated with activity toward 1,2-epoxy-3-(4'-nitrophenoxy)propane (a substrate specific for theta-class glutathione S-transferases). Conjugation activity toward bromodichloromethane in hepatic cytosols isolated from different species followed the rank order mouse, followed by rat, then human. The initial conjugate formed was S-chloromethyl glutathione. This compound was unstable and degraded to multiple metabolites including S-hydroxymethyl glutathione, S-formyl glutathione, and formic acid. These data demonstrate that glutathione conjugation of bromodichloromethane occurs in mammalian liver cytosols and is likely catalyzed by glutathione S-transferase theta. These findings are significant because production of reactive glutathione conjugates from bromodichloromethane may result in formation of DNA adducts and thus cause genotoxicity. Because there is structural similarity among the brominated trihalomethanes and evidence for common pathways of bioactivation (De Marini et al. 1997), the findings of Ross and Pegram (2003) support the idea that glutathione conjugation of bromoform and dibromochloromethane leading to formation of reactive metabolites also occurs in the liver of rodents and humans.

Comparison of catalytic efficiencies for recombinant rat CYP2E1 and glutathione S-transferase theta 1-1 using bromodichloromethane as a substrate (data on bromoform or dibromochloromethane are not available) suggest that glutathione conjugation is likely to be a quantitatively minor hepatic pathway *in vivo* (Ross and Pegram 2003). Although metabolism via this pathway may be minor from the standpoint that only a small fraction of the total dose is converted, it might be an important component of the mechanism for dibromochloromethane and/or bromoform toxicity in extrahepatic tissues where GSTT1-1 is expressed in conjunction with lower levels of CYP2E1.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

No studies were located regarding excretion of bromoform or dibromochloromethane by humans or animals following inhalation exposure.

3.4.4.2 Oral Exposure

In rats and mice given a single oral dose of ^{14}C-labeled bromoform or dibromochloromethane as part of a trihalomethane mixture (100 mg/kg in rats and 150 mg/kg in mice), excretion occurred primarily by exhalation of bromoform or dibromochloromethane or of CO_2 (Mink et al. 1986). In mice, 39.68 and 71.58% of the administered radiolabelled bromoform and dibromochloromethane, respectively, were exhaled as CO_2 and 7.18 and 12.31% as unmetabolized compound, respectively. In contrast, 4.3 and 18.2% of bromoform and dibromochloromethane were exhaled as CO_2 in rats and 66.9 and 48.1% of parent compound. Only 1–5% of the dose was excreted in urine (the chemical form in urine was not determined). The elimination half-times of bromoform and dibromochloromethane were 0.8 and 1.2 hours, respectively, in rats at 8 or 2.5 hours, respectively, in mice.

3.4.4.3 Dermal Exposure

No studies were located regarding excretion of bromoform or dibromochloromethane by humans or animals following dermal exposure.

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

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

pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste

sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-5 shows a conceptualized representation of a PBPK model.

PBPK models have not been developed for bromoform or dibromochloromethane. da Silva et al. (1999) developed a model to simulate the venous blood concentration of each trihalomethane after simultaneous exposure to the four trihalomethanes. This model, which simulates competitive inhibition of hepatic metabolism, is discussed in Section 3.9. Although da Silva et al. (1999) also described models in rats following single administration of bromoform or dibromochloromethane, these models involved optimizing metabolic parameters across the dose range used in the study and were not developed as stand-alone models.

3.5 MECHANISMS OF ACTION

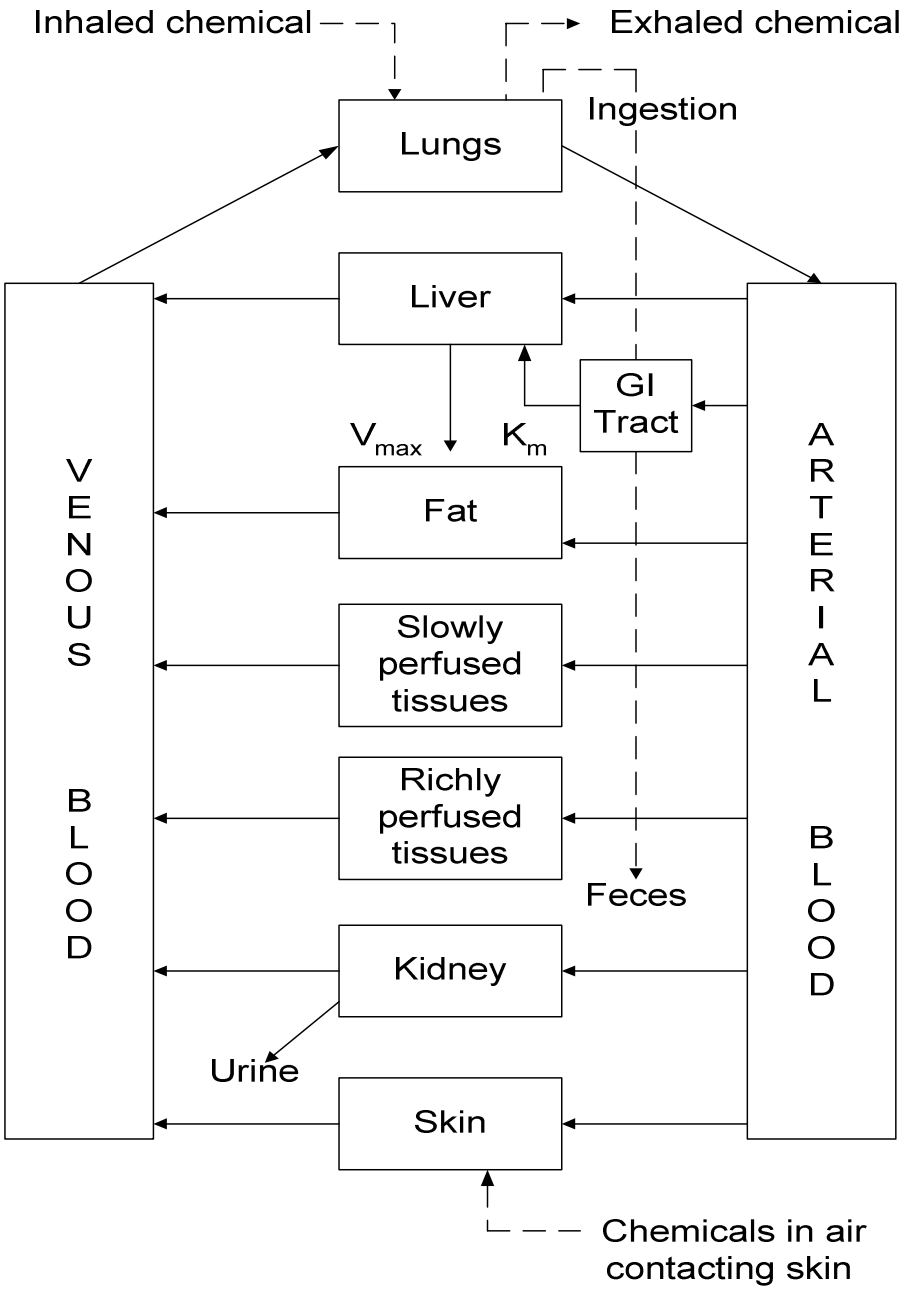
3.5.1 Pharmacokinetic Mechanisms

Bromoform and dibromochloromethane can be absorbed by inhalation (Graham 1915; Merzbach 1928), ingestion (Backer et al. 2000; Mink et al. 1986), and dermal (Backer et al. 2000; Xu et al. 2002) routes of exposure. In humans and laboratory animals, bromoform and dibromochloromethane are generally absorbed quickly (Backer et al. 2000). Primarily because of their high blood:air partition coefficients, these chemicals pass with some ease through most tissue and cellular barriers in the body and are widely distributed throughout the body. Although bromoform and dibromochloromethane are lipophilic, they do not appear to accumulate in adipose tissue (Stanley 1986). Bromoform and dibromochloromethane are thought to be metabolized by at least two route-independent pathways: oxidation by cytochrome P450 mixed function oxidase system (Ahmed et al. 1977; Anders et al. 1978) and conjugation via glutathione S-transferase (DeMarini et al. 1997; Pegram et al. 1977). Bromoform and dibromochloromethane are primarily excreted via exhalation as the parent compound or carbon dioxide (Mink et al. 1986).

3.5.2 Mechanisms of Toxicity

The mechanisms by which bromoform and dibromochloromethane cause damage in target tissues is not fully understood, but there is strong evidence that metabolism to reactive intermediates is a prerequisite

Figure 3-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

for toxicity. Subsequent interaction of the reactive intermediates with key cellular molecules leads to impaired function and/or cell death.

Several mechanisms for cell injury by trihalomethanes have been proposed based on the combined experimental database for chloroform and the brominated trihalomethanes. These include: (1) oxidative metabolism by CYP2E1 to produce dihalocarbonyls, which deplete glutathione content, and alkylate cellular macromolecules to produce necrosis; (2) reductive dehalogenation under conditions of low physiological oxygen tension to produce highly reactive dihalomethyl free radicals that covalently bind to proteins or lipids; and (3) glutathione-dependent metabolism to DNA-reactive intermediates, which results in adduct formation and mutation. Toxicity of bromoform and dibromochloromethane may result from metabolism by one or more of these pathways. Bromine is generally a better leaving group than chlorine, suggesting that the degree of bromine substitution will influence the rate of metabolism among chlorinated and brominated trihalomethanes and the flux through specific pathways.

Although mechanistic data on bromoform and dibromochloromethane are lacking, the requirement for metabolism of these compounds to toxic intermediates is supported by studies of chloroform and bromodichloromethane. In a representative study, Ilett et al. (1973) observed covalent binding of radiolabeled material to proteins in the liver and kidney following administration of [^{14}C]chloroform to mice. The amount of binding was correlated with the extent of renal and hepatic necrosis both in normal animals and in male mice pretreated with an inhibitor or inducer of microsomal enzymes. Autoradiograms showed that the bound radioactivity was located mainly in necrotic lesions. In other studies, Brown et al.(1974) reported that pretreatment of rats with phenobarbital (a cytochrome P450 inducer) resulted in increased formation of covalent adducts and increased hepatic toxicity following chloroform exposure. Pohl et al. (1980) reported that the level of covalent binding correlated directly with injury to the liver tissue and concluded that phosgene was the metabolite responsible for the covalent binding to liver macromolecules. Tyson et al. (1983) confirmed that covalent binding to proteins in rats was more prevalent in areas of necrosis than in less damaged areas. More recently, Constan et al. (1999) evaluated toxicity in male B6C3F$_1$, SV/129 wild-type (CYP2E1 +/+), and SV/129 null (CYP2E1 -/-) mice exposed to chloroform by inhalation. Parallel groups of control and treated mice B6C3F$_1$ and wild-type SV/129 mice were also treated with an irreversible cytochrome P450 inhibitor. Extensive hepatic and renal necrosis occurred in B6C3F$_1$ and SV/129 mice exposed to chloroform. Chloroform-exposed animals that received the inhibitor were completely protected against hepatic and renal toxicity and pathological changes were absent in null mice, demonstrating that metabolism is necessary for toxicity.

The data linking metabolism of brominated trihalomethanes to toxicity are less extensive than those for chloroform. No data were located specifically for bromoform or dibromochloromethane. Pretreatment of female rats and mice with inhibitors of CYP2E1 metabolism reduced the acute renal and hepatic toxicity of bromodichloromethane (Thornton-Manning et al. 1994). Depletion of glutathione by pretreatment of male F344 rats with butathione sulfoximine (BSO) increased the incidence and severity of hepatic and renal lesions (Gao et al. 1996). Addition of glutathione to hepatic microsomal and S9 preparations and renal microsomes under aerobic conditions decreased covalent binding of [^{14}C]bromodichloromethane to proteins. Addition of glutathione to hepatic or renal microsomes under anaerobic conditions decreased binding of [^{14}C]bromodichloromethane to lipids (Gao et al. 1996). These data demonstrate a protective role of glutathione that is consistent with metabolism of bromodichloromethane to one or more reactive species.

Studies in animals indicate that bromoform and dibromochloromethane have carcinogenic potential (NTP 1985, 1989a). The mechanism of action for tumor induction by these chemicals is unknown and may involve contributions from more than one of the proposed pathways described above. Pathway 1 (oxidative metabolism to dihalocarbonyl) may not be directly genotoxic, but may lead to increased risk of cancer as a result of cytotoxicity and subsequent regenerative hyperplasia, as observed for chloroform (ILSI 1997). Pathways 2 (reductive metabolism) and 3 (glutathione-dependent metabolism) may lead to direct DNA damage *in vivo*. The relative contribution of these pathways to the carcinogenic potential of bromoform and dibromochloromethane has not been determined.

Three studies have examined cytotoxicity and regenerative hyperplasia in the liver of female B6C3F1 mice (Coffin et al. 2000; Melnick et al. 1998) or the kidney of male F344 rats (Potter et al. 1996) following exposure to bromoform or dibromochloromethane. These studies are of limited use for understanding the mechanism of bromoform carcinogenesis because they do not address cytotoxicity or regeneration in the large intestine, the target tissue for tumor induction. Dibromochloromethane induced cytotoxicity and cell proliferation in the liver of female B6C3F1 mice, but the LOAEL values reported by Melnick et al. (1998) and Coffin et al. (2000) were inconsistent (400 mg/kg/day vs. 100 mg/kg/day). Therefore, a threshold for induction of cellular proliferation cannot be clearly identified for comparison with the liver tumor incidence data in female B6C3F1 mice (NTP 1985). The reason for the discrepancy between studies is unknown, but might be related to the use of different techniques or different time points for measurement of labeling index (a method for estimating cell proliferation). These data do not allow a conclusion regarding the role of cytotoxicity and regenerative cell proliferation in the

development of hepatic tumors in mice exposed to dibromochloromethane. Melnick et al. (1998) modeled dose response data for cell proliferation and serum enzyme activity (as a composite) and for tumor induction in the liver of B6C3F1 mice using an empirical Hill equation model. The dose-response curves for these processes had different shapes, suggesting that they were not causally associated.

Positive results for mutagenicity and cytogenetic damage have been observed in some standard assays (see Section 3.3), suggesting that some metabolites of bromoform and dibromochloromethane interact directly with DNA. Reductive metabolism (Melnick et al. 1998) and glutathione conjugation of brominated trihalomethanes have been proposed as a source of DNA reactive intermediates (De Marini et al. 1997; Ross and Pegram 2003), but the available data are too limited to fully evaluate the contribution of these pathways to the genotoxicity and carcinogenicity of bromoform and dibromochloromethane. Studies of bromodichloromethane metabolism in hepatic cytosols prepared from rat, mouse, and liver microsomes suggest that metabolism of brominated trihalomethanes via a glutathione-dependent pathway is likely to be a minor pathway in the liver (Ross and Pegram 2003). It is unknown whether the small amounts formed in the liver are toxicologically significant. It is possible that glutathione-dependent pathways are of greater toxicological significance in extrahepatic tissues where concentrations of CYP2E1 are lower, such as the distal large intestine (Ross and Pegram 2003).

3.5.3 Animal-to-Human Extrapolations

Most of the available data on the toxicity and toxicokinetic properties of bromoform and dibromochloromethane come from studies in rats and mice. There are very limited human data, and the only end point that has been examined is neurotoxicity; high doses of bromoform result in central nervous system depression in humans and laboratory animals. Data from other trihalomethanes, particularly chloroform (Agency for Toxic Substances and Disease Registry 1997), suggest that the available laboratory animal toxicity and toxicokinetic data for bromoform and dibromochloromethane would also be applicable for humans. A potential difference between species is quantitative and qualitative differences in Phase I metabolism of trihalomethanes. In rats, trihalomethanes are substrates of cytochrome P450 enzyme isoforms CYP2E1, CYP2B1, CY2B2, and CYP1A2 (Allis et al. 2001; Pankow et al. 1997). CYP2E1 and CPY1A2 are also expressed in human tissues; however, the relevance of metabolism by CYP2B1/2 to human health is presently uncertain, since these isoforms have not been reported in human adult or fetal tissues (Juchau et al. 1998; Nelson et al. 1996). CYP2B6 is the only active member of the CYP2B subfamily in man, although the CYP2B7 gene has also been found in the genome (Czerwinski et al. 1994).

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the Environmental Protection Agency (EPA) to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), which in 1998 completed its deliberations and made recommendations to EPA concerning *endocrine disruptors.* In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997a, 1997b). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

There is little evidence to suggest that bromoform or dibromochloromethane has the potential to distrupt the normal functioning of the neuroendocrine axis. There are some suggestive data that these chemicals have the potential to alter reproductive hormone levels. An ecological study found significant correlations between bromoform and dibromochloromethane concentrations in drinking water and

alterations in menstrual cycle length (Windham et al. 2003); however, the women were exposed to a number of other potentially toxic compounds in the drinking water and the data are inadequate for establishing causality. In rats administered 300–380 mg/kg/day bromoform or dibromochloromethane, significant decreases in serum testosterone levels were observed.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and

sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

There are limited data on the toxicity of bromoform and dibromochloromethane. In the early 1900s, bromoform was used as a sedative for the treatment of whooping cough (Benson 1907; Burton-Fanning 1901; Dwelle 1903; Stokes 1900; von Oettingen 1955). Sedation was observed at the prescribed dosage; higher doses often resulted in central nervous system depression. Central nervous system depression has also been observed in adult animals following oral exposure to bromoform (Bowman et al. 1978; NTP 1989a) or dibromochloromethane (Bowman et al. 1978; NTP 1985). There is no indication that children are more susceptible than adults to this effect.

Animal data provide strong evidence that the liver is the critical target of bromoform and dibromochloromethane toxicity (Aida et al. 1992; Coffin et al. 2000; Condie et al. 1983; NTP 1985, 1989a; Tobe et al. 1982). These animal studies were conducted in adults and no animal studies using juveniles were located. The available data suggest that the hepatotoxicity of bromoform and dibromochloromethane is due to tissue damage from reactive intermediates that are generated during metabolism. In rats, trihalomethanes are substrates for several cytochrome P450 enzyme isoforms, including CYP2E1, CYP2B1, CYP2B2, and CYP1A2 (Allis et al. 2001; Pankow et al. 1997) in Phase I reactions and glutathione S-transferase theta (GSTT) (DeMarini et al. 1997; Pegram et al. 1987; Ross and Pegram 2003) in Phase II reactions. As discussed in EPA (2001a), CYP2E1 levels increase rapidly during the first 24 hours after birth and levels in children between 1 and 10 years of age are similar to those in adults.

Similarly, GSTT levels in children older than 1 year are similar to adults. These data provide some suggestive evidence that exposure during early childhood would result in the formation of similar reactive intermediates and metabolites as in adults.

The potential of bromoform and dibromochloromethane to induce developmental effects cannot be conclusively established from the existing database. A significant alteration in the occurrence of sternebra aberrations were observed in the offspring of rats administered 200 mg/kg/day bromoform in corn oil during gestation (Ruddick et al. 1983). A similar exposure to dibromochloromethane did not result in any significant alterations. Similarly, no developmental alterations were observed in mouse offspring exposed to 685 mg/kg/day dibromochloromethane in drinking water for several generations (Borzelleca and Carchman 1982).

There are no specific biomarkers of exposure or effect for bromoform or dibromochloromethane that have been validated in children or adults exposed as children. No studies were located regarding interactions of bromoform or dibromochloromethane with other chemicals in children. Additionally, there are no pediatric-specific methods of reducing peak absorption or reducing body burden following exposure to bromoform or dibromochloromethane. In the absence of these data, it is assumed that there are no age-related differences in biomarkers, interactions, or mitigation of effects.

3.8 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).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. 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 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 bromoform or dibromochloromethane are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by bromoform or dibromochloromethane are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10 “Populations That Are Unusually Susceptible”.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Bromoform and Dibromochloromethane

The most straightforward means of identifying exposure to bromoform or dibromochloromethane in a person is measurement of parent compound in blood or expired air. Sensitive and specific gas chromatographic-mass spectrophotometric methods available for this purpose are described in Section 7.1. Quantification of exposure is complicated by the relatively rapid clearance rate of these compounds from the body, both by exhalation and metabolic breakdown. Data are not available on clearance rates in humans, but in animals, clearance of parent is nearly complete within 8 hours (see Section 3.4.4). Consequently, this approach is best suited for detecting recent exposures (within 1–2 days).

No data are available on blood or breath levels of bromoform or dibromochloromethane in acutely exposed individuals. However, studies involving exposure to trihalomethanes in water have found elevated alveolar air levels of dibromochloromethane following a 1-hour exposure to volatilized trihalomethanes from swimming pool water (Aggazzotti et al. 1998) and elevated blood bromoform and dibromochloromethane levels following a 10-minute shower or 10-minute bath (Backer et al. 2000). Background concentrations in people not exposed to bromoform or dibromochloromethane except through chlorinated drinking water are about 0.6 ppb (Antoine et al. 1986), while levels in expired breath are undetectable (Wallace et al. 1986a, 1986b). In a study of blood trihalomethane concentrations in women living in areas with trihalomethane in tap water (Miles et al. 2002), a simple linear relationship between blood levels and tap water levels of trihalomethanes was not found. For bromoform and dibromochloromethane, no significant correlations were found between tap water levels of these compounds and blood levels before showering. After showering, a significant correlation between bromoform levels in the tap water and blood levels were found; however, the correlation coefficient (0.450) is relatively low, suggesting that a number of variables affected blood bromoform levels. Although bromoform and dibromochloromethane are lipophilic, they do not appear to accumulate in adipose tissue (Stanley 1986), so measurement of parent levels in this tissue is not likely to be valuable as a biomarker of exposure.

The principal metabolites of bromoform and dibromochloromethane are CO_2, CO, Cl^-, and Br^-. None of these metabolites are sufficiently specific to be useful as a biomarker of exposure. It is suspected that reactive intermediates formed during metabolism may produce covalent adducts with proteins or other cellular macromolecules (see Section 3.4.3), but these putative adducts have not been identified nor has any means for their quantification been developed.

3.8.2 Biomarkers Used to Characterize Effects Caused by Bromoform and Dibromochloromethane

There are limited data on the toxicity of bromoform and dibromochloromethane in humans. Exposure to bromoform can result in sedation; it is likely that the same is true for dibromochloromethane. However, generalized central nervous system depression is too nonspecific to be useful as a biomarker of effects from bromoform or dibromochloromethane exposure. Studies in animals indicate the liver and the kidneys are also affected, resulting in fatty liver, increased serum enzyme levels, and nephrosis. Effects on liver and kidney can be evaluated using a variety of laboratory and clinical tests (CDC/ATSDR 1990),

but these are also too nonspecific to be valuable in recognizing early effects caused by low level exposure to these two chemicals.

3.9 INTERACTIONS WITH OTHER CHEMICALS

It is well-known that exposure to alcohols, ketones, and a variety of other substances can dramatically increase the acute toxicity of halomethanes such as carbon tetrachloride (Agency for Toxic Substances and Disease Registry 1994) and chloroform (Agency for Toxic Substances and Disease Registry 1997). Several studies have been performed to determine if the toxic effects of bromoform and dibromochloromethane are similarly affected by these agents.

Hewitt et al. (1983) found that pretreatment of rats with a single oral dose of acetone resulted in a l0–40-fold potentiation of the hepatotoxic effects of a single oral dose of dibromochloromethane given 18 hours later. Similarly, pretreatment of rats for one to three days with chlordecone resulted in a 7–60-fold potentiation of the hepatotoxic effects of a single oral dose of dibromochloromethane (Plaa and Hewitt 1982a, 1982b). In contrast, chlordecone pretreatment had relatively little potentiating effect on the hepatotoxicity of bromoform (Agarwal and Mehendale 1983; Plaa and Hewitt 1982a).

The mechanism by which chemicals such as acetone and chlordecone potentiate halomethane toxicity is not known, but it is generally considered that at least some of the effect is due to stimulation of metabolic pathways that yield toxic intermediates. If so, the findings above support the hypothesis that the toxicity of dibromochloromethane is mediated at least in part by metabolic generation of reactive intermediates, but that metabolism is relatively less important in bromoform toxicity.

Harris et al. (1982) found that exposure of rats to a combination of bromoform and carbon tetrachloride resulted in more liver injury (judged by release of hepatic enzymes into serum) than would be predicted by the effects of each chemical acting alone. The mechanism of this interaction is not certain, but may be related to dihalocarbonyl formation and lipid peroxidation (Harris et al. 1982).

A PBPK model has been developed by da Silva et al. (1999) that examined the influence of exposure to a mixture of trihalomethanes (bromoform, dibromochloromethane, dichlorobromomethane, and chloroform) on the kinetics of individual compounds. When all four trihalomethanes were administered together (1.0 mmol/kg), the area under the blood concentration versus time curve was significantly higher as compared to the AUC after administration of a single compound (0.25 mmol/kg). For bromoform and

dibromochloromethane, the AUCs after the single 0.25 mmol/kg dose were 48.6 and 31.2 μM/hour and after the 1.0 mmol/kg mixture of trihalomethanes, the AUCs were 127.3 and 128.6 μM/hour. These data suggest that there is metabolic interation between the trihalomethanes; likely competitive inhibition of hepatic metabolism.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to bromoform or dibromochloromethane than will most persons exposed to the same level of bromoform or dibromochloromethane in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of bromoform or dibromochloromethane, or compromised function of organs affected by bromoform or dibromochloromethane. Populations who are at greater risk due to their unusually high exposure to bromoform or dibromochloromethane are discussed in Section 6.7, Populations With Potentially High Exposures.

Studies of bromoform and dibromochloromethane toxicity in animals reveal that there may be some quantitative and qualitative differences in susceptibility between sexes and between species (see Section 3.2). The basis for these differences is not known, but one likely factor is sex and species-dependent differences in metabolism (see Section 3.4.3). On this basis, it is reasonable to assume that there could be some differences in susceptibility between humans as a function of sex, race, or age. However, there are no studies that provide data on this point. Studies in animals (discussed in Section 3.9) also suggest that humans exposed to alcohols, ketones, or other drugs (e.g., barbiturates, anticoagulants) that influence halomethane metabolism might be more susceptible to the toxic effect of dibromochloromethane and perhaps bromoform as well. Persons with existing renal or hepatic disease might also be more susceptible, since these organs are adversely affected by exposure to bromoform and dibromochloromethane.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to bromoform or dibromochloromethane. 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 bromoform or dibromochloromethane. When specific exposures have occurred, poison control centers

and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to bromoform or dibromochloromethane:

Haddad LM, Shannon MW and Winchester JF, eds. 1998. Clinimal management of poisoning and drug overdose. Philadelphia, PA: W.B. Saunders Co., 913-939, 992-1000.

Viccellio P, ed. 1998. Emergency toxicology. Philadelphia, PA: Lippincott-Raven Publishers, 925-932.

3.11.1 Reducing Peak Absorption Following Exposure

Human exposure to bromoform or dibromochloromethane may occur by inhalation, ingestion, or dermal contact. General recommendations for reducing absorption of these chemicals include removing the exposed individual from the contaminated area and removing the contaminated clothing. If the eyes and skin were exposed, they should be flushed with water. In order to reduce absorption of ingested bromoform and dibromochloromethane, emesis may be considered unless the patient is comatose, is convulsing, or has lost the gag reflex. Controversy exists concerning use of emesis because of the rapid onset of central nervous system depression, the risk of aspiration of stomach contents into the lungs, and the relative ineffectiveness of this method. In comatose patients with absent gag reflexes, an endotracheal intubation may be performed in advance to reduce the risk of aspiration pneumonia. Gastric lavage may also be used.

3.11.2 Reducing Body Burden

Trihalomethanes levels in human blood have a short half-life of approximately 0.5 hours (Lynberg et al. 2001). Bromoform or dibromochloromethane were not stored to any appreciable extent in the rat and were mostly metabolized to CO_2 (see Section 3.4). The elimination half-life of bromoform was reported to be 0.8 hours in the rat and 8 hours in the mouse (Mink et al. 1986). The half-lives of dibromochloromethane were 1.2 and 2.5 hours in rats and mice, respectively (Mink et al. 1986). Despite an expected relatively fast clearance of from the body, toxic effects may develop in exposed individuals. No method is commonly practiced to enhance the elimination of the absorbed dose of bromoform or dibromochloromethane.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The primary targets of bromoform and dibromochloromethane are the liver, kidneys, and central nervous system. It is believed that the mechanism of bromoform and dibromochloromethane toxicity to the liver and kidneys involves metabolism to reactive intermediates. No methods for interfering with the mechanism of action have been developed for these compounds. Studies using two other trihalomethanes (chloroform and dichlorobromomethane) provide suggestive evidence that administration of agents which inhibit cytochrome P450 decreases hepatotoxicity. Co-administration of chloroform and 1-aminobenzo-triazole (an irreversible cytochrome P450 inhibitor) (Constan et al. 1999) or dibromochloromethane and a CYP2E1 inhibitor (Thornton-Manning et al. 1994) resulted a reduction of acute hepatic and renal toxicity.

3.12 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 bromoform or dibromochloromethane 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 bromoform or dibromochloromethane.

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

Figure 3-6. Existing Information on Health Effects of Bromoform

	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
	Systemic									
Inhalation										
Oral	●					●				
Dermal										

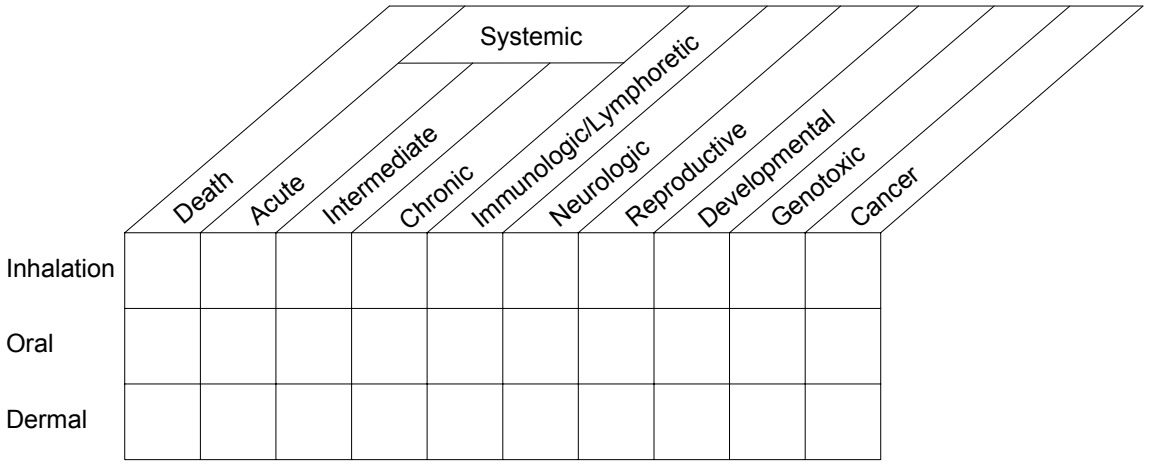
Human

	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
	Systemic									
Inhalation	●	●	●			●				
Oral	●	●	●	●	●	●	●	●	●	●
Dermal										

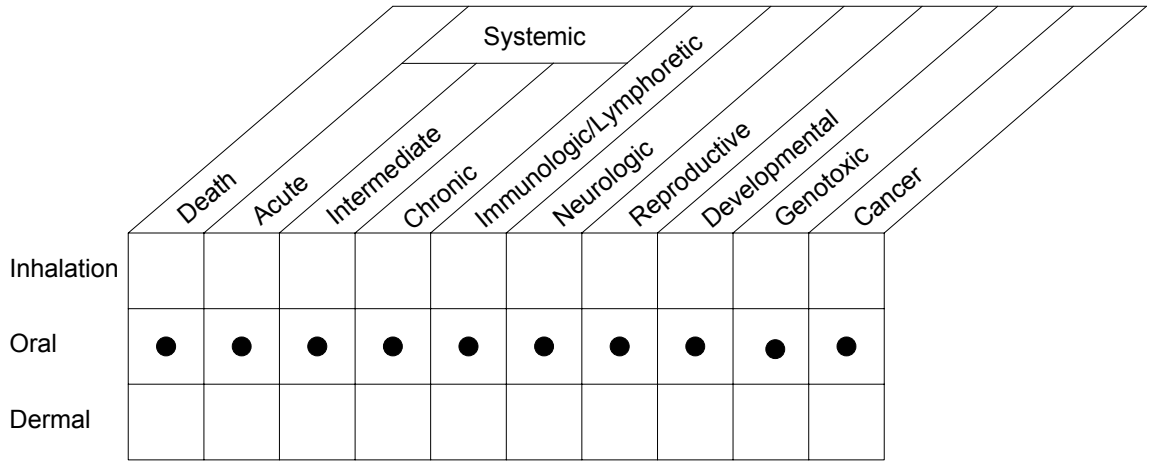
Animal

● Existing Studies

Figure 3-7. Existing Information on Health Effects of Dibromochloromethane



Human



Animal

● Existing Studies

3.12.1 Existing Information on Health Effects of Bromoform and Dibromochloromethane

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to bromoform and dibromochloromethane are summarized in Figures 3-6 and 3-7, respectively. The purpose of these figures is to illustrate the existing information concerning the health effects of bromoform or dibromochloromethane. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

As shown in Figure 3-6, there are limited data on the toxicity of bromoform following inhalation exposure. No human data were located and laboratory animal studies are limited to lethality studies, which found central nervous system depression, and acute and intermediate duration studies, which are only available as abstracts. Human data on the oral toxicity of bromoform are limited to reports of children taking bromoform for the treatment of whooping cough; effects are limited to death and central nervous system depression and the exposure levels are poorly characterized. A number of laboratory animal studies have examined the oral toxicity of bromoform, and data are available for all end points. However, in many cases, the available data for a particular end point are limited to a single study or use a route of administration (e.g., gavage) that may not be relevant to human environmental exposure to bromoform. The dermal toxicity of bromoform has not been studied in humans or animals.

As shown in Figure 3-7, there are no human toxicity data for dibromochloromethane following inhalation, oral, or dermal exposure. Additionally, there are no laboratory animal data on dibromochloromethane following inhalation or dermal exposure. For the oral route of exposure, data are available for all end points. As noted for bromoform, information on a particular end point comes from a single study, and most studies used a gavage in oil administration route, which may not be relevant for human environmental exposure to dibromochloromethane.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. The available data on the acute toxicity of bromoform in humans are limited to reports of children prescribed bromoform for the treatment of whooping cough. Following ingestion, the children were said to sleep undisturbed through the night, suggestive of sedation (Dwelle 1903); accidental overdoses resulted in symptoms of central nervous system depression (Benson 1907; Burton-Fanning 1901; Dwelle 1903; Stokes 1900; von Oettingen 1955). No human data were located discussing human toxicity following inhalation or dermal exposure to bromoform or after inhalation, oral, or dermal exposure to dibromochloromethane. Inhalation and oral exposure animal studies confirm that high oral doses of bromoform (Balster and Borzelleca 1982; Bowman et al. 1978; Graham 1915; Mertzbach 1928; NTP 1989a) or dibromochloromethane (Balster and Borzelleca 1982; NTP 1985) can result in central nervous system depression. At lower doses, the liver and possibly the kidney appear to be the primary targets of toxicity for both compounds. Nonlethal animal inhalation data are limited to a study published in Russian that found liver and kidney effects in rats (Dykan 1964). The inhalation data are inadequate to define the threshold for these effects or identify the critical target of toxicity; additional inhalation studies that examine a wide range of end points and exposure concentrations would be useful for establishing the critical targets of toxicity of bromoform and dibromochloromethane following inhalation exposure and establishing concentration-response relationships. There is a more extensive database following oral exposure, which allows for the derivation of acute-duration oral MRLs for bromoform and dibromochloromethane. Following oral exposure to bromoform, increases in liver weight (Munson et al. 1982), centrilobular pallor (Condie et al. 1983), and hepatocellular vacuolization and/or swelling (Coffin et al. 2000) have been observed. Other effects of bromoform observed in acute-duration animal studies include mesangial nephrosis (Condie et al. 1983), impaired humoral immune function (Munson et al. 1982), and developmental effects (Ruddick et al. 1983). As with bromoform, the most sensitive effects of dibromochloromethane following acute oral exposure are liver and kidney damage; the liver effects consisted of mottled liver, hepatocellular vacuolization and/or swelling, and increases in SGPT and SGOT levels (Coffin et al. 2000; Condie et al. 1983; Munson et al. 1982; NTP 1985) and kidney effects included mesangial hyperplasia and darkened renal medullae (Condie et al. 1983; NTP 1985). At higher doses, impaired humoral immunity (Munson et al. 1982), decreased body weight gain (NTP 1985; Potter et al. 1996), and decreased serum testosterone levels (Potter et al. 1996) were observed.

No data are available in humans or animals following dermal exposure to bromoform or dibromochloromethane. Contact with concentrated solutions of these chemicals might be expected to produce effects similar to those following ingestion or inhalation, and might also result in skin or eye irritation. Studies on this would be useful, although contact with concentrated bromoform or dibromochloromethane is considered extremely unlikely for members of the general population or residents near waste sites. Studies on the effects of dermal contact with lower levels of the compounds in water or soil would be valuable, since people might be exposed by these routes near waste sites.

Intermediate-Duration Exposure. No human data are available on the intermediate-duration toxicity of bromoform or dibromochloromethane following inhalation, oral, or dermal exposure. Animal data are limited to a study reporting liver and kidney effects in rats exposed to bromoform for 2 months (Dykan 1962); however, this study is currently only available as an abstract. No intermediate-duration animal inhalation exposure data are available for dibromochloromethane. Further studies on the intermediate-duration inhalation toxicity of these compounds would be valuable in assessing human health risks from airborne exposures near waste sites, although available data suggest that exposures in air near such sites are likely to be low. The available intermediate-duration oral exposure animal studies strongly identify the liver as the most sensitive target for bromoform and dibromochloromethane. Hepatocellular vacuolization and/or swelling have been observed at the lowest adverse effect levels (Aida et al. 1992; Daniel et al. 1990; NTP 1985, 1989a). Other effects observed in animals exposed to higher doses of bromoform include lethargy (NTP 1989a), impaired performance on neurobehavioral tests (Balster and Borzelleca 1982), and decreased body weight gain (Aida et al. 1992). Exposure to higher doses of dibromochloromethane also resulted in kidney damage (tubular degeneration and nephropathy) (Daniel et al. 1990; NTP 1985), impaired performance on neurobehavioral tests (Balster and Borzelleca 1982), and impaired fertility (Borzelleca and Carchman 1982). These animal data were considered adequate for derivation of an intermediate MRL for bromoform. An MRL was not derived for dibromochloromethane because the resultant MRL would be higher than the MRL for acute duration exposure. Additional studies using a number of dose levels would provide additional information on the threshold of hepatic toxicity and possible allow for the derivation of an intermediate-duration MRL for dibromochloromethane. There are no data on dermal exposure, and studies on intermediate-duration dermal exposure to the compounds in water or soil would be useful in evaluating human health risk at waste sites

Chronic-Duration Exposure and Cancer. No human studies examining the chronic toxicity of bromoform or dibromochloromethane were located, although a number of studies examining health outcomes in areas with elevated trihalomethanes in tap water have been located. Chronic animal inhalation data are not available for either chemical, and would be useful, especially for dibromochloromethane, since it is significantly more volatile (vapor pressure=76 mmHg) than bromoform (vapor pressure=5 mmHg). Chronic-duration studies that identify the critical targets of toxicity and establish concentration-response relationships would be useful for deriving chronic-duration inhalation MRLs for bromoform and dibromochloromethane. In the absence of such data, extrapolation of observations from the oral route might be possible using appropriate toxicokinetic models. The chronic oral toxicity of bromoform (NTP 1989a; Tobe et al. 1982) and dibromochloromethane (NTP 1985; Tobe et al. 1982) has been investigated in several studies, and the data are sufficient to identify hepatotoxicity as the most sensitive end point and to derive MRL values for both chemicals. However, in both cases, chronic oral MRLs are based on LOAELs for hepatotoxicity, so further studies to define the NOAELs would be helpful in reducing uncertainty in the MRL calculations. No data exist for dermal exposure, and further studies (focusing on exposure in water or soil) would be valuable.

The carcinogenic effects of chronic oral exposure to bromoform (NTP 1989a) and dibromochloromethane (NTP 1985) have been investigated in well designed studies in both rats and mice, and the data suggest that both chemicals have carcinogenic potential. However, effects were limited or equivocal in some cases, so additional studies to strengthen the weight of evidence would be valuable. Of particular interest would be studies of the carcinogenic effects when exposure is via drinking water rather than by gavage, since drinking water is the most likely route of human exposure, and exposure by gavage (especially using oil as a medium) may not be a good model for this. Also of value would be studies on the mechanism of carcinogenicity and on the identity of carcinogenic metabolites. For example, studies on methylene chloride and other volatile halocarbons indicate that metabolism via a glutathione pathway may be important in carcinogenicity (e.g., Anderson et al. 1987; Reitz et al. 1989). Studies to determine if dibromochloromethane or bromoform are metabolized by a similar pathway would be helpful in evaluating carcinogenic mechanism and risk.

Genotoxicity. There have been a number of studies that indicate bromoform and dibromochloromethane are genotoxic, both in prokaryotic (LeCurieux et al. 1995; Roldan-Arjona and Pueyo 1993; Simmon and Tardiff 1978; Simmon et al. 1977; Varma et al. 1988) and eukaryotic (Benigni et al. 1993; Fujie et al. 1993; Landi et al. 1999; Matsuoka et al. 1996; McGregor et al. 1991; Morimoto and Koizumi 1983; Nestman and Lee 1985; Sobti 1984; Sofuni et al. 1996) organisms. However, a

number of other studies have failed to detect significant genotoxic potential for these compounds (Maddock and Kelly 1980; NTP 1985, 1989a). The basis for this inconsistency is not entirely obvious, but might be related to the efficacy of the test system to activate the parent compound to genotoxic metabolites. Several *in vivo* studies have also found genotoxic effects following exposure to bromoform (Fujie et al. 1990; Morimoto and Koizumi 1983; NTP 1989a) or dibromochloromethane (Fujie et al. 1990; Morimoto and Koizumi 1983), although other studies have not found effects (Hayashi et al. 1988; Potter et al. 1996; Stocker et al. 1996). Further studies to define conditions under which these compounds are and are not genotoxic *in vitro* and *in vivo* may help clarify both the mechanism of genotoxicity and the relevance of this to human health risk. Studies on the genotoxic effects of bromoform and dibromochloromethane on germ cells (sperm or ova) would also be valuable.

Reproductive Toxicity. A number of ecological studies have examined the reproductive toxicity to women ingesting drinking water contaminated with trihalomethanes (Bove et al. 1992, 1995; Dodds et al. 1999; Kramer et al. 1992; Mills et al. 1998; Nieuwenhuijsen et al. 2000; Savitz et al. 1995; Waller et al. 1999). Three of these studies (Kramer et al. 1992; Waller et al. 1999; Windham et al. 2003) measured bromoform and dibromochloromethane levels; however, the contribution of the other trihalomethanes to the observed effects cannot be determined from the existing data. Collectively, the trihalomethane studies provide insufficient evidence to establish a causal relationship between exposure to trihalomethanes and adverse reproductive outcome. Animal data are limited to several studies that examined reproductive tissues for histological alterations or examined reproductive function following oral exposure to either compound. No histological alterations were observed in reproductive tissues following chronic exposure to bromoform (NTP 1989a) or dibromochloromethane (NTP 1985). No significant alterations in reproductive performance or fertility were observed in males or females exposed to bromoform (NTP 1989b). For dibromochloromethane, one study found a marked reduction in fertility at a maternally toxic dose level (Borzelleca and Carchman 1982), but no effects on reproductive performance or fertility were observed at lower doses (NTP 1986). Multigeneration studies involving oral exposure to bromoform and dibromochloromethane would provide useful data on the reproductive potential of these chemicals. Based on the oral studies, it does not seem likely that effects would occur following inhalation or dermal exposure except at very high levels, but inhalation and dermal exposure studies to confirm this important point would be valuable.

Developmental Toxicity. Several ecological studies have examined the relationship between exposure to trihalomethanes in tap water and the birth outcomes (Dodds et al. 1999; Kramer et al. 1992; Savitz et al. 1995). The Kramer et al. (1992) study reported levels for individual trihalomethanes, but this

study, as well as the other studies, does not provide sufficient evidence for establishing a relationship between trihalomethane exposure and adverse birth outcomes. No other human studies were located for bromoform or dibromochloromethane. No inhalation or dermal exposure animal developmental toxicity studies were located. There are limited data on the developmental toxicity of bromoform and dibromochloromethane following oral exposure in animals. A minor skeletal abnormality was observed in the offspring of rats exposed to bromoform during gestation (Ruddick et al. 1983). No developmental effects were observed in studies of rat and mouse offspring exposed to dibromochloromethane (Borzelleca and Carchman 1982; Ruddick et al. 1983). Additional oral studies on the developmental effects of both bromoform and dibromochloromethane in animals would be valuable to determine whether these skeletal abnormalities are produced consistently, and whether they lead to significant adverse effects in the neonate. If so, then similar studies by the inhalation and dermal routes would also be valuable to define safe inhalation levels for developmental effects.

Immunotoxicity. The immunotoxic effects of bromoform and dibromochloromethane have been investigated in one 14-day oral study (Munson et al. 1982). That study indicated that both chemicals can lead to changes in several immune cell-types in mice. Similar studies in other species would be valuable in determining if this is a common response. In addition, longer duration studies and tests of the functional consequence of these changes (e.g., resistance to infectious disease) would be especially valuable in assessing the biological significance of these effects. If these studies indicate the immune system is a target, then similar studies by inhalation and dermal exposure routes would also be valuable.

Neurotoxicity. Numerous studies, both in humans and animals, reveal that central nervous system depression is a rapid effect following either oral or inhalation exposure to bromoform; more limited data indicate that dibromochloromethane also causes this effect. While central nervous system depression appears to be reversible within a short time after exposure ceases, the possibility of permanent neurological damage from high doses has not been thoroughly studied. Histological studies by NTP indicate that sub-depressant doses of bromoform (NTP 1989a) and dibromochloromethane (NTP 1985) do not lead to detectable histological changes in the brain, but similar data are not available following narcotizing doses. In addition to histological studies, functional studies capable of detecting lasting neurological changes would be valuable. One study of this sort (Balster and Borzelleca 1982) indicates that both bromoform and dibromochloromethane can cause some behavioral changes (impaired motor performance, decreased exploratory behavior [bromoform only], and decreased response rate in tests of operant behavior) at high doses. Further studies along these lines, perhaps employing more sensitive tests of electrophysiological or neurobehavioral changes, would be helpful in determining if this is an effect of concern to exposed humans.

Epidemiological and Human Dosimetry Studies. No epidemiological or human dosimetry studies are currently available for bromoform or dibromochloromethane. Since only very small quantities of these chemicals are produced or used in this country (see Chapter 5), it does not seem likely that a sufficiently large subpopulation of exposed workers exists to serve as the basis for a meaningful epidemiological study. Epidemiological studies of populations exposed to low levels of bromoform and dibromochloromethane in chlorinated drinking water cannot provide specific data on the human health risks of dibromochloromethane or bromoform, since chlorinated drinking water contains hundreds of different contaminants.

Biomarkers of Exposure and Effect.

Exposure. The only known biomarker of exposure to bromoform or dibromochloromethane is the level of parent compound in blood or in expired air. However, data on blood or breath levels in humans following acute exposure are lacking, due to the rarity of such events. Since both bromoform and dibromochloromethane are rapidly cleared from the body by exhalation or metabolism, measurements of parent compounds in blood or breath are likely to be useful only for a short time (1–2 days) after an exposure. Monitoring of humans continuously exposed to the trace levels normally present in chlorinated water reveal very low to nondetectable levels in blood or expired air. The main metabolites of these compounds (CO_2, CO, Cl^-, Br^-) are not sufficiently specific to be useful for biomonitoring of exposure. Identification of stable and specific biomarkers of exposure (e.g., halomethyl adducts) would be valuable in evaluating the exposure history of people around waste sites and other sources where above-average levels might be encountered.

Effect. No specific biomarkers of bromoform- or dibromochloromethane-induced effect are known. Neurological, hepatic, and renal effects caused by these chemicals can be detected by standard clinical or biochemical tests, but abnormal function in these tissues can be produced by a number of common diseases in humans, so detection of abnormal function is not proof that the effect was caused by bromoform or dibromochloromethane. Efforts to identify more specific and sensitive biomarkers of bromoform and dibromochloromethane-induced effects would be useful, especially biomarkers (e.g., specific DNA adducts) that might be predictive of carcinogenic risk.

Absorption, Distribution, Metabolism, Excretion. Limited data indicate that bromoform and dibromochloromethane are rapidly and efficiently taken up from the gastrointestinal tract, but further studies to confirm and refine available estimates would be valuable. Toxicokinetic studies to date have

generally employed exposure by gavage in corn oil, so studies involving exposure via an aqueous vehicle would be especially valuable. No toxicokinetic data exist for inhalation exposure, so quantitative estimates of the inhalation absorption fraction, tissue distribution, and excretion rate would be beneficial. Also, data on dermal absorption would be helpful, especially from soil or from dilute aqueous solutions, since this is how humans are most likely to experience dermal contact near waste sites.

The pathways of bromoform and dibromochloromethane metabolism have been investigated in several laboratories, but quantitative data on the amount of chemical passing through each pathway are limited, and the chemical identity of products appearing in urine has not been studied. Of particular interest would be studies that seek to clarify the role of metabolism in toxicity, the mechanism by which metabolites and adducts lead to toxic effects, and the importance of protective mechanisms such as cellular antioxidants. This would include careful dose-response studies to determine if either activating or protective pathways are saturable.

Comparative Toxicokinetics. Available toxicity data indicate that target tissues of bromoform and dibromochloromethane are similar in humans, rats, and mice. Limited data suggest that effect levels are generally similar across species, but some distinctions are apparent. Toxicokinetic studies have revealed differences between rats and mice regarding metabolic patterns and clearance rates and these might underlie the differences in toxicity between tissues, sexes, and species. Additional comparative studies in animals, with special emphasis on differences in metabolism, would be useful in understanding these differences, and in improving inter-species extrapolation. In addition, *in vitro* studies of metabolism by human liver cells would be valuable in determining which animal species has the most similar pattern of metabolism and is the most appropriate model for human toxicity. Data from studies of this sort could then be used to support physiologically-based toxicokinetic models.

Methods for Reducing Toxic Effects. Further research is needed to determine strategies designed to selectively inhibit the specific P450 isozymes involved in the metabolism of bromoform or dibromochloromethane to reactive intermediates, and thus reduce the toxic effects. Because bromoform or dibromochloromethane are thought to be metabolized by glutathione conjugation (DeMarini et al. 1997; Pegram et al. 1977; Ross and Pegram 2003), further research is needed to determine if administration of sulfhydryl compounds, such as L-cysteine, reduced GSH or N-acetylcysteine, as glutathione surrogates might provide protection against nephrotoxicity or hepatotoxicity induced due to depleted glutathione stores. Research on using dietary supplements for mitigating adverse effects of

chronic exposure to bromoform or dibromochloromethane would be helpful, especially in the case of chronic exposure from chlorinated drinking water.

Children's Susceptibility. The available human data for bromoform are mostly from case reports of accidental orally-administered overdose in children. No data exist on the toxicity of dibromochloromethane following oral administration in children, or of bromoform or dibromochloromethane following inhalation or dermal exposure in children. The developmental effects of oral exposure to bromoform and dibromochloromethane have not been extensively investigated, but limited data suggest that these chemicals have relatively low toxicity on the developing fetus (Borzelleca and Carchman 1982; Ruddick et al. 1983). However, these studies did not examine neurodevelopmental end points that may be a sensitive target. Additional animal studies assessing the neurodevelopmental toxicity of bromoform and dibromochloromethane would be useful. Toxicokinetic studies examining how aging can influence absorption rates would be useful in assessing children's susceptibility to the toxicity of bromoform or dibromochloromethane.

Child health data needs relating to exposure are discussed in 6.8.1 Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

No ongoing studies on the health effects of bromoform or dibromochloromethane were listed in the Federal Research in Progress database searched on June 23, 2003 (FEDRIP 2003).

4. CHEMICAL AND PHYSICAL INFORMATION

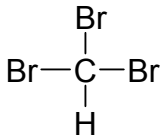
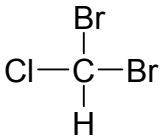
4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of bromoform and dibromochloromethane is located in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of bromoform and dibromochloromethane is located in Table 4-2.

Table 4-1. Chemical Identity of Bromoform and Dibromochloromethane

Characteristic	Bromoform	Dibromochloromethane	Reference
Synonyms	Tribromomethane; methenyltribromide; methane, tribromo-	Chlorodibromomethane dibromochloromethane; methane, dibromochloro-; methane, chlorodibromo-	HSDB 2003a, 2003b
Registered trade name(s)	No data	No data	
Chemical formula	$CHBr_3$	$CHBr_2Cl$	O'Neil et al. 2001
Chemical structure			
Identification numbers:			
CAS registry	75-25-2	124-48-1	O'Neil et al. 2001
NIOSH RTECS	PB5600000	PA6360000	RTECS 2003
EPA hazardous waste	U225	No data	RTECS 2003
OHM/TADS	8100034	No data	HSDB 1988
DOT/UN/NA/IMCO shipping	UN2515 IMCO 6.1	No data	HSDB 2003a, 2003b HSDB 2003a, 2003b
HSDB	2517	2763	HSDB 2003a, 2003b
NCI	C55130	C55254	RTECS 2003
Beilstein reference number	1731048	1731046	RTECS 2003
Beilstein handbook reference	4-01-00-00082	4-01-00-0081	RTECS 2003
Wisesser line notation	EYEE	GYEE	RTECS 2003

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

Table 4-2. Physical and Chemical Properties of Bromoform and Dibromochloromethane

Property	Bromoform	Dibromochloromethane	Reference
Molecular weight	252.73	208.28	O'Neil et al. 2001
Color	Colorless	Colorless to pale yellow	Verschueren 2001
Physical state	Liquid	Liquid	Verschueren 12001
Melting point	8.0 °C	-20 °C	Lide 2000
Boiling point	149.1 °C	120 °C	Lide 2000
Density at 20 °C	2.899	2.451	Lide 2000
Odor	Sweet, similar to chloroform	No data	Verschueren 2001
Taste	Similar to chloroform	No data	Lewis 1997
Odor threshold:			
Water	0.51 mg/L	No data	Amoore and Hautala 1983
Air	13.45 mg/m^3	No data	Amoore and Hautala 1983
Solubility:			
Water	3.10x10^3 mg/L (25 °C)	2.7x10^3 mg/L (20 °C)	Horvath 1982; Heikes 1987
Organic solvents	Miscible in ethanol, benzene, petroleum ether, acetone, oils	Soluble in ethanol, ether, acetone	Lide 2000
Corrosivity	Will attack some forms of plastics, rubber, and coatings.	No data	HSDB 2003a
Partition coefficients:			
Log octanol/water	2.4	2.16	CITI 1992; Sangster 1994
Log K_{oc}	2.06[a]	1.92[a]	Mabey et al. 1982
Vapor pressure at 20 °C	5 mmHg	76 mmHg	Mabey et al. 1982
Vapor density	8.7 (air=1)	No data	IARC 1991a, 1991b
Henry's law constant	5.6x10^{-4} atm-m^3/mol	9.9x10^{-4} atm-m^3/mol	Mabey et al. 1982
Surface tension	41.53 dynes/cm	No data	Lewis 1997
Heat of vaporization	46.05 KJ/mol (25 °C)	No data	Lide 2000
Autoignition temperature	No data	No data	
Flashpoint	No data	No data	
Flammability limits	Non-flammable	Non-flammable	HSDB 2003a, 2003b
Conversion factor	1 ppm = 10 mg/m^3 1 mg/m^3 = 0.097 ppm	1 ppm = 8.5 mg/m^3 1 mg/m^3 = 0.12 ppm	IARC 1991a, 1991b

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Bromoform may be prepared from acetone and sodium hypobromite, by treating chloroform with aluminum bromide, or by electrolysis of potassium bromide in ethyl alcohol (HSDB 2003a; Stenger 1978).

Bromoform is currently produced by Geoliquids, Inc., Prospect Heights, Illinois and Sigma-Aldrich Fine Chemicals (SRI 2002). Bromoform was produced formerly by Dow Chemical Company, Midland, Michigan. In 1975, production of bromoform in the United States was estimated to be <500 kkg and the 1977 production was estimated at 50 to 500 kkg (1 kkg=1,000 kg or 1 metric ton) (NTP 1989a; Orrell and Mackie 1988; Perwak et al. 1980). More recent production data were not found.

The Toxics Release Inventory lists one facility in Arkansas that manufactures or processed bromoform (TRI01 2003). The minimum amount of bromoform at this facility site is 1,000 pounds, and the maximum amount is 9,999 pounds. This facility uses bromoform for ancillary purposes.

Dibromochloromethane can be prepared by the addition of dibromochloroacetone to 5N sodium hydroxide (IARC 1991b). It can also be prepared by reaction of a mixture of chloroform and bromoform with triethylbenzylammonium chloride and sodium hydroxide (IARC 1991a). Available information indicates that dibromochloromethane is no longer produced commercially in the United States (SRI 2002).

Both bromoform and dibromochloromethane are inadvertently generated during water chlorination when chlorine reacts with endogenous organic materials such as humic and fulvic acid (Rook 1977). When chlorine is added to water, hypochlorous acid is formed (Wallace 1997). Hypochlorous acid reacts with humic or fulvic acids in the water to produce chloroform or it can oxidize any bromide ion that is present to form hypobromous acid, which leads to the formation of bromoform, dibromochloromethane, or bromodichloromethane. It is estimated that 17 kkg of bromoform and 204 kkg of dibromochloromethane were generated in this way in 1978 (Perwak et al. 1980). According to a model generated by Clark et al. (1996), higher bromide to chloride ratios promote the bromine substitution reaction over the chlorine substitution reaction with organic matter in chlorinated water. At higher bromide concentrations, levels of chloroform decreased, while levels of bromoform increased. Dibromochloromethane was found to

increase to a maximum level for bromide concentrations of 2.5 mg/L and then decline with increasing bromide concentration (Clark et al. 1996).

5.2 IMPORT/EXPORT

Orrell and Mackie (1988) estimated that 6–9 kkg of bromoform were imported by Freeman Industries in the late 1980s. No current information was located on the import of bromoform and dibromochloromethane, but it is likely that little, if any, is imported.

5.3 USE

Bromoform is used in geological assaying as a heavy liquid for mineral ore separations based on differences in specific gravity (Verschueren 2001). It is used in the electronics industry in quality assurance programs (Orrell and Mackie 1988). Bromoform has been used as a catalyst, initiator, or sensitizer in polymer reactions and in the vulcanization of rubber (HSDB 2003a). As a solvent, bromoform has been used for waxes, greases, and oils as well as for liquid-solvent extractions and nuclear magnetic resonance (NMR) studies (Lewis 1997; NTP 1989a). Former uses of bromoform include a fire-resistant chemical ingredient, a gauge fluid ingredient, an intermediate in chemical syntheses, and a sedative and antitussive agent (HSDB 2003a; Perwak et al. 1980).

Dibromochloromethane is used in laboratory quantities only and there is no current commercial use for this compound (Perwak et al. 1980). Dibromochloromethane was used formerly as a chemical intermediate in the production of fire extinguishing agents, aerosol propellants, refrigerants, and pesticides (IARC 1991b).

5.4 DISPOSAL

Because bromoform and dibromochloromethane are listed as hazardous substances, land disposal of wastes containing these compounds is controlled by a number of federal regulations (see Chapter 8). Wastes containing dibromochloromethane or bromoform may be incinerated by rotary kiln, liquid injection, or fluidized bed methods. CERCLA reportable quantities for bromoform and dibromochloromethane released to the environment are those quantities equal to or greater than 100 pounds or 45.4 kg.

The amount of bromoform and dibromochloromethane released or disposed of through industrial and/or laboratory use of these chemicals is not known, but is considered to be insignificant compared to the amount inadvertently generated by water chlorination processes (EPA 1987c; HSDB 2003a; Perwak et al. 1980).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Bromoform has been identified in at least 141 of the 1,636 hazardous waste sites while dibromochloromethane has been identified in at least 172 of the 1,636 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2003). However, the number of sites evaluated for bromoform and dibromochloromethane is not known. The frequency of these sites can be seen in Figures 6-1 and 6-2, respectively. Of these sites, 138 of the 141 bromoform sites are located within the United States, 1 is located in the Virgin Islands (not shown), and 2 are located in the Commonwealth of Puerto Rico (not shown). For dibromochloromethane, 170 of the 171 sites are located within the United States, 1 is located in the Virgin Islands, and 1 is located in the Commonwealth of Puerto Rico.

The principal route of human exposure to dibromochloromethane and bromoform is from the consumption of chlorinated drinking water. These chemicals are thought to form in the water as by-products from the reaction of chlorine with dissolved organic matter and bromide ions. Dibromochloromethane and bromoform concentrations in water are quite variable, but average levels are usually <5 μg/L.

Most dibromochloromethane and bromoform tend to volatilize from water when exposed to the air. The fate of these chemicals in air has not been investigated, but it is likely they are relatively stable, with half-lives of about 1–2 months. Most measurements of the concentration of these chemicals in air indicate that levels are quite low (<10 ppt).

Neither chemical is strongly adsorbed from water by soil materials, and it is likely that both readily migrate in groundwater. Neither chemical appears to be easily biodegradable under aerobic conditions, but they may readily biodegrade under anaerobic conditions.

Figure 6-1. Frequency of NPL Sites with Bromoform Contamination

Figure 6-2. Frequency of NPL Sites with Dibromochloromethane Contamination

6.2 RELEASES TO THE ENVIRONMENT

Bromoform and dibromochloromethane have been identified in a variety of environmental media (air, surface water, groundwater, soil, and sediment) collected at 141 and 172 of the 1,636 NPL hazardous waste sites, respectively (HazDat 2003).

According to the 2001 Toxics Release Inventory (TRI), one facility, Teris L.L.C. of 309 American Circle Union in El Dorado, Arizona, has reported a total of seven releases of bromoform to the environment (TRI01 2003). All of the releases at this facility were on-site air emissions. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

6.2.1 Air

Bromoform has been identified in air samples collected at 7 of the 141 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2003). Dibromochloromethane has been identified in air samples collected at 1 of the 172 NPL hazardous waste sites where it was detected in some environmental media.

The average concentration of dibromochloromethane in uncontrolled emissions from 40 medical waste incinerators in the United States and Canada was 0.96 μg/kg waste (Walker and Cooper 1992). The average concentration in controlled emissions was 536 μg/kg waste.

No other studies were located regarding the amount of bromoform and dibromochloromethane released into the atmosphere from laboratories, chemical plants, or chemical waste sites. However, since neither compound is produced or used in large quantities (Perwak et al. 1980), atmospheric emissions from these sources are probably small.

6.2.2 Water

Bromoform has been identified in surface water samples and groundwater samples collected at 15 and 102 of the 141 hazardous waste sites, respectively, where it was detected in some environmental media. Dibromochloromethane has been identified in surface water samples and groundwater samples collected

at 15 and 143 of the 172 hazardous waste sites, respectively, where it was detected in some environmental media (HazDat 2003).

The principal source of bromoform and dibromochloromethane in the environment is chlorination of water containing organic materials (Bellar et al. 1974; EPA 1980a; Peters et al. 1994; Rook 1977; Symons et al. 1975, 1993). It has been estimated that the total amounts of bromoform and dibromochloromethane generated by chlorinating U.S. drinking water in 1978 were 17 and 204 kkg, respectively (Perwak et al. 1980).

Bromoform and dibromochloromethane were detected in the distribution systems of three water treatment plants that each use different methods of water chlorination (LeBel et al. 1997). Mean monthly concentrations of dibromochloromethane were 0.2 μg/L in samples from the chlorine-chloramine treatment plant, 0.3 μg/L in samples from the chlorine-chlorine treatment plant, and 0.1 μg/L in samples from the ozone-chlorine treatment plant. Mean monthly bromoform concentrations were <0.1 μg/L in samples from all three plants. Bromoform levels were 1.4, 3.7, and 2.1 mg/L in California State Project Water samples after ozonation at the Los Angeles Aqueduct Filtration Plant in 1987 at ozone doses of 1.0, 2.0, and 4.0 mg/L, respectively (Glaze et al. 1989).

Release of dibromochloromethane and bromoform into groundwater has been shown to occur as a consequence of the yearly aquifer storage and recovery (ASR) in the Las Vegas Valley. As an example, it is estimated that up to 16.3×10^6 m^3 water was injected into the underlying aquifer during the winter months of 1995–1996, when demand for water by neighboring Las Vegas was low (Thomas et al. 2000). Because the recharge water is chlorinated before injection, byproducts of this disinfection process are introduced into the groundwater at concentrations measured during the 1995–1996 ASR recharge seasons of 18 μg/L for dibromochloromethane and 2.6 μg/L for bromoform in the recharge water. During the water recovery phase beginning in the spring of 1996, initial concentrations of dibromochloromethane and bromoform in water recovered from one recharge well (#14) in the spring of 1996 were below detection limits (0.5 μg/L) but were much higher, 15 and 2.4 μg/L, respectively, in a second well (#51). Dibromochloromethane and bromoform levels in water recovered from the second well fell during the remaining spring and summer months decreasing to concentrations of 1.5 and 0.6 μg/L, respectively, in September of 1996. The differences in the concentrations of dibromochloromethane and bromoform between wells 14 and 51, and the decrease in concentrations observed in water recovered from well 51 during the spring and summer recovery months of 1996, were attributed to both dilution of the

recharge water in the aquifer with natural water from the surrounding aquifer basin and biotransformation of the trihalomethanes within the aquifer.

Dibromochloromethane and bromoform may also occur as a consequence of chlorinating industrial waste waters (Perry et al. 1979). Staples et al. (1985) reported that bromoform was detected in 60 of 1,346 samples of industrial waste effluent, at a median concentration of <5 μg/L, and dibromochloromethane was detected in 84 of 1,298 samples at a median concentration of <2.4 μg/L. These values are not significantly higher than those for typical chlorinated water (see Section 5.4.2), suggesting that industrial discharge may not be a major source of release.

Bromoform and dibromochloromethane were detected in New York City municipal wastewater samples taken from 1989 to 1993 (Stubin et al. 1996). Influent concentrations ranged from 7 to 40 μg/L for bromoform with a frequency of detection of 4% and 9 μg/L for dibromochloromethane with a frequency of detection of 1%. Effluent concentrations ranged from 3 to 11 μg/L for bromoform with a frequency of detection of 11% and from 2 to 15 μg/L for dibromochloromethane with a frequency of detection of 8%. Moschandreas et al. (1997) studied samples from 14 New York City waste water pollution control plants to determine the organic compound concentrations in the waste water at each of the plants. Bromoform was detected with concentrations of 0.4–10 μg/L in raw influent samples, 2.0–9.0 μg/L in primary influent samples, 1.0–10 μg/L in primary effluent samples, 0.3–11 μg/L in aeration tank samples, 0.4–12 μg/L in superficial of return activated sludge samples, and 0.2–12 μg/L in plant effluent samples. Only the plant effluent concentration range (0.3–5.0 μg/L) was reported for dibromochloromethane.

Although most raw water samples collected from different points of the Great Lakes in 1990 contained trihalomethanes at concentrations <2 μg/L, mean concentrations in treated water samples from four of the six locations were above 25 μg/L (Henshaw et al. 1993). The low trihalomethane concentrations of the other two locations are attributed to the use of alternative methods of water treatment such as ammonia addition and potassium permanganate disinfection.

The average concentration of dibromochloromethane in sewage treatment effluents in England and Wales in 1995 was 0.2007 μg/L with a frequency of detection of 30.4% (Stangroom et al. 1998a). The average concentration of dibromochloromethane in trade effluents in England and Wales in 1995 was 7.91 μg/L with a frequency of detection of 63%.

Mean dibromochloromethane concentrations were determined to be 2 ng/L in water and sediment samples taken from the anoxic fjord Idefjorden between Norway and Sweden near the city of Halden, Norway (Abrahamsson and Klick 1989). Dibromochloromethane was detected in effluent water from a nearby paper pulp mill.

Class et al. (1986) observed trace levels of dibromochloromethane and bromoform and other halogenated methanes in seawater (0.1–6 ng/L) and in the air (0.1–20 ppt) at several locations in the Atlantic. Other studies have reported atmospheric bromoform concentration ranges of 1.9–16.3 pptv off the coast of Galway, Ireland, 0.28–2.9 pptv in the West Pacific Islands, 0.32–7.1 pptv in the Asian Seas, and 1.0–37.4 pptv off the Antarctic Peninsula (Carpenter et al. 1999). Dibromochloromethane was also detected off the coast of Galway, Ireland with an atmospheric concentration ranging from 0.3 to 1.8 pptv. The presence of these compounds can be attributed to biosynthesis and release of bromochloromethanes by macroalgae (Carpenter et al. 1999; Class et al. 1986; Gschwend et al. 1985). Gschwend et al. (1985) estimated that marine algae could be a major global source of volatile organobromides. More recently, Carpenter and Liss (2000) estimated that macroalgae produce around 70% of the world's bromoform, which is greater than what was previously estimated due to updated seaweed biomass estimates. However, Class et al. (1986) states that this source accounts for <1% of the anthropogenic burden of total organohalogens in the atmosphere.

6.2.3 Soil

Bromoform has been identified in soil and sediment samples collected at 25 and 4 of the 141 NPL hazardous waste sites, respectively, where it was detected in some environmental media. Dibromochloromethane has been identified in soil and sediment samples collected at 20 and 5 of the 172 NPL hazardous waste sites, respectively, where it was detected in some environmental media (HazDat 2003).

Soils and other unconsolidated surficial materials may become contaminated with bromoform and dibromochloromethane by chemical spills, the landfilling of halomethane-containing solid wastes, or the discharge of chlorinated water. However, no data were located to suggest that land releases are a significant source of the chemicals in the environment.

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Bromoform and dibromochloromethane are slightly volatile liquids, and tend to exist primarily as vapors in the atmosphere. The vapor pressure of bromoform is 0.007 atm at 20 °C (Mabey et al. 1982), and the vapor pressure of dibromochloromethane at 20 °C is approximately 0.1 atm (Mabey et al. 1982). The half-time of evaporation from flowing, aerated water (e.g., rivers and streams) has been estimated to range from 1 to 581 hours for bromoform and from 0.7 to 398 hours for dibromochloromethane (Kaczmar et al. 1984; Mackay et al. 1982).

Both dibromochloromethane and bromoform are moderately soluble in water (Callahan et al. 1979; Heikes 1987), and so each may be removed from the air by being dissolved into clouds or raindrops. Estimates of the Henry's law constant (H) (the tendency of a chemical to partition between its vapor phase and water) for bromoform range from 4.3 to 5.6×10^{-4} atm-m^3/mole, and from 8.7 to 9.9×10^{-4} atm-m^3/mole for dibromochloromethane (Mabey et al. 1982; Mackay and Shiu 1981; Munz and Roberts 1987; Nicholson et al. 1984). The magnitude of these values suggest that the two halomethanes will tend to partition to both water and air.

It is not known if either compound can be adsorbed by airborne particulate matter that is subject to atmospheric dispersion, gravitational settling, or wash-out by rain. Particle adsorption is probably not an important transport mechanism because these chemicals occur at such low concentrations in the atmosphere.

Bromoform and dibromochloromethane have a minor tendency to be adsorbed by soils and sediments. Calculated and measured values of K_{oc} (the organic carbon/water partition coefficient, an index of the relative mobility of a material in water-soil systems) for bromoform range from 62 to 126 (Hassett et al. 1983; Hutzler et al. 1986; Mabey et al. 1982). These relatively low values imply that bromoform will exhibit only a minor affinity for soil materials and will tend to be highly mobile (Roy and Griffin 1985). This low tendency for adsorption to soil has been confirmed in laboratory studies by Curtis et al. (1986) and in field studies by Roberts et al. (1986).

A similar K_{OC} value of 57 has been estimated for dibromochloromethane, based on its measured water solubility (Heikes 1987). No studies were located on the adsorption of dibromochloromethane by soils or

soil materials, but it is likely that dibromochloromethane will have properties generally similar to those of bromoform.

Bromoform and dibromochloromethane may be slightly bioconcentrated by aquatic organisms. The octanol/water partition coefficient (K_{OW}) (an index of the partitioning of a compound between octanol and water) is approximately 240 for bromoform and 170 for dibromochloromethane (Mabey et al. 1982). The magnitudes of these values suggest that the chemicals will tend to partition to fat tissues of aquatic organisms. No studies were located regarding the bioconcentration factor (BCF) for dibromochloromethane or bromoform, but based on measured BCFs for similar compounds (Kenaga 1980), the BCF of dibromochloromethane and bromoform may be on the order of 2–10. It is not known if these chemicals can be transferred through food chains to higher trophic levels, but this seems unlikely to be of major concern.

6.3.2 Transformation and Degradation

6.3.2.1 Air

Based on the behavior of similar compounds, it seems likely that bromoform and dibromochloromethane may be degraded by photooxidative interactions with atmospheric OH radicals. Radding et al. (1977) proposed that the atmospheric half-life of bromoform and dibromochloromethane is approximately 1–2 months, but this has not been confirmed by direct experimental measurements.

6.3.2.2 Water

Both dibromochloromethane and bromoform are relatively stable in water, with estimated hydrolytic rate constants of 3.2×10^{-11} sec^{-1} and 8×10^{-11} sec^{-1} (Mabey and Mill 1978). These rate constants correspond to hydrolytic half-lives of 686 and 274 years for bromoform and dibromochloromethane, respectively.

No information was located on oxidation or photolysis of these chemicals in water, but it is not expected that either is a significant degradative pathway.

It has been found that dibromochloromethane and bromoform undergo only limited biodegradation (10–25%) under aerobic conditions, although the rate may increase somewhat after microbial adaptation

(Bouwer et al. 1981; Tabak et al. 1981a). Bromoform, at initial concentrations ranging from 132 to 177 μg/L, underwent >99% reduction in a continuous-flow biofilm column seeded with primary settled sewage with 1.5 hours packed-bed detention time (Cobb and Bouwer 1991). Under anaerobic conditions, dibromochloromethane and bromoform have been found to be readily biodegraded in the presence of methane-producing bacteria (Bouwer and McCarty 1983a; Bouwer et al. 1981), and under denitrifying and sulfate-reducing conditions in batch and column experiments (Bouwer and McCarty 1983b; Bouwer and Wright 1986). There is also some field evidence that trihalomethanes degrade in anaerobic groundwater (Bouwer et al. 1981), with half-lives estimated to be between 21 and 42 days (Bouwer and McCarty 1984). Increased degradation rates were observed for bromoform and dibromochloromethane under conditions similar to those found inside ferrogenic aquifers, especially at higher pH (Kenneke et al. 2003; Pecher et al. 2002). Bouwer and Wright (1986) reported that one degradation product of bromoform was dibromomethane, but there was no additional information on the identity or fate of environmental degradation by-products. Bromoform was not degraded in enriched seawater cultures taken from beds of the giant kelp, *M. pyrifera* off the coast of California after 40 days (Goodwin et al. 1997).

6.3.2.3 Sediment and Soil

No studies were located regarding the biodegradation of dibromochloromethane or bromoform in soil. It is expected that observations regarding biodegradation rates in aerobic and anaerobic aqueous media (above) will be generally applicable to degradation rates in moist soils.

6.3.2.4 Other Media

No information was located on the transformation and degradation of bromoform or dibromochloromethane in other media.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

6.4.1 Air

Dibromochloromethane and bromoform are usually found in air only at very low concentrations. Brodinsky and Singh (1983) tabulated data on dibromochloromethane and bromoform levels in ambient

air from five urban locations across the United States. For dibromochloromethane, 63 of 89 samples were below the detection limit, the mean value was 3.8 ppt (32 ng/m^3), and the highest value was 27 ppt (230 ng/m^3). For bromoform, 60 of 78 samples were below the detection limit, the mean value was 3.6 ppt (37 ng/m^3) and the highest value was 71 ppt (730 ng/m^3). The mean concentration of bromoform in ambient air samples collected in the Arctic Circle was 5.1 ppt (53 ng/m^3) (Berg et al. 1984). Forty-six air samples collected near four chemical plants in Arkansas contained a mean bromoform concentration of 0.9 ppt (9 ng/m^3) (Pellizzari 1978). The mean dibromochloromethane concentration was 0.08 ppt (0.8 ng/m^3), but 54 of 56 measurements were <0.05 ppt (0.5 ng/m^3). Fischer et al. (2000) found a nearly constant mixing ratio of bromoform at 0.5 parts per trillion by volume (pptv) in the marine troposphere of the Atlantic across 30 °W longitude. In the coastal region of South America, bromoform concentrations were 2.4 pptv. A high concentration of bromoform (2.0 pptv) was found in an air sample taken near Cape Verde Island. Air mixing ratios for bromoform in samples taken above the waters of the equatorial Pacific during the third joint Soviet-American Gases and Aerosols (SAGA 3) experiment ranged from 0.68 to 3.28 pptv using the charcoal or Tenax adsorption method and from 0.5 to 6.7 pptv using the canister collection method (Atlas et al. 1993). Air mixing ratios for dibromochloromethane ranged from 0.09 to 0.49 pptv using the charcoal or Tenax adsorption method. Dibromochloromethane was not measured with the canister collection method.

During the Urban Air Toxics Monitoring Program, concentrations of bromoform and dibromochloromethane at 13 air monitoring sites located in Vermont, New Jersey, Louisiana, and Texas were <1 parts per billion by volume (ppbv) (no detection limit given) (Mohamed et al. 2002). Bromoform was not detected in air samples from three permanent sites in Arizona (Tucson, Payson, and Casa Grande) during the Arizona Hazardous Air Pollutants Monitoring Program, though the detection limit was not specified (Zielinska et al. 1998). Bromoform was detected at a fourth permanent site in Phoenix with a maximum concentration of 0.02 ppbv, although the average bromoform concentration at this site was below the detection limit. The mean, minimum, and maximum concentrations of dibromochloromethane in air samples taken during the Southern California Ozone Study in 1997 were 0.02 ppbv (210 ng/m^3), 0.04 ppbv (420 ng/m^3), and 0.01 ppbv (105 ng/m^3), respectively at a residential/industrial site in Mexicali, Mexico (Zielinska et al. 2001). Dibromochloromethane was not detected at a residential site in Rosarito, Mexico (no detection limit given). Dibromochloromethane was detected at 24 ppb (0.210 mg/m^3) in Finnish industrial air samples medical industry preparing solutions and at 1.6 ppb (0.014 μg/m^3) in suburban air from Turku, Finland (Kroneld 1989a, 1989b). Dibromochloromethane was not detected in countryside air samples taken from the Islands of Inio at the southwest coast of Finland.

Bromoform was detected with an occurrence rate of 54% in indoor air samples taken from 26 houses, although actual concentrations were not given (Kostiainen 1995). Air from 13 houses in Katusushika Ward, Tokyo, Japan were sampled during a survey of indoor pollution by volatile organohalogen compounds in February 1995 (Amagai et al. 1999). Thirty houses were sampled in July 1995. Bromoform was detected in all 13 houses during the February survey. In July, it was detected in 22 out of 30 houses. Dibromochloromethane was detected in all houses during both the February and July surveys. Mean concentrations of dibromochloromethane in February 1995 were 0.016 μg/m^3 in outdoor air, 0.095 μg/m^3 in living room air, 0.122 μg/m^3 in kitchen air, 0.096 μg/m^3 in bedroom air, and 0.701 μg/m^3 in bathroom air. Mean concentrations of dibromochloromethane in July 1995 were 0.007 ug/m^3 in outdoor air, 0.050 μg/m^3 in living room air, 0.065 μg/m^3 in kitchen air, 0.042 μg/m^3 in bedroom air, and 0.372 μg/m^3 in bathroom air. Mean concentrations of bromoform in February 1995 were 0.009 ug/m^3 in outdoor air, 0.016 μg/m^3 in living room air, 0.018 μg/m^3 in kitchen air, 0.015 μg/m^3 in bedroom air, and 0.091 μg/m^3 in bathroom air. Mean concentrations of bromoform in July 1995 were 0.010 μg/m^3 in outdoor air, 0.013 μg/m^3 in living room air, 0.013 μg/m^3 in kitchen air, 0.012 μg/m^3 in bedroom air, and 0.034 μg/m^3 in bathroom air.

Kerger et al. (2000) evaluated airborne concentrations of common trihalomethane compounds in bathrooms during showering and bathing in three urban homes supplied with chlorinated tap water. Samples were collected prior to, during, and after the water-use event for 16 shower and 7 bath events. The increases in average airborne concentration of dibromochloromethane were 0.5 μg/m^3 per μg/L during showers and 0.15 μg/ m^3 per μg/L during baths.

No studies were located regarding atmospheric concentrations of bromoform or dibromochloromethane in the workplace. Dibromochloromethane was detected in air samples at two hazardous waste sites, but the amounts were not quantified (LaRegina et al. 1986).

6.4.2 Water

Dibromochloromethane and bromoform are rarely measurable in nonchlorinated water (Cech et al. 1981; Staples et al. 1985; Varma et al. 1984), but both are very frequently found in chlorinated water. The levels of bromoform and dibromochloromethane in finished (chlorinated) drinking water have been investigated in several studies (see Table 6-1). Except for a few cases, the concentrations of bromoform and dibromochloromethane in drinking water were <100 μg/L, with mean concentrations generally <10 μg/L.

Table 6-1. Occurrence of Bromoform and Dibromochloromethane in Finished Drinking Water

Frequency of detection percent	Concentration (μg/L) Range	Mean	Location	Reference
Bromoform				
10	ND–92	≈0.4	National	Symons et al. 1975
27	ND–3.0	≈0.5	13 Cities	Keith et al. 1976
34	NR	12	National	Brass et al. 1977
67	NR–4.4	0.4	Midwest	ORVWSC 1979
NR	ND–258	≈7	Texas	Glaze and Rawley 1979
100	4–17	9	Texas	Smith et al. 1980
26	NR–110	NR	National	Westrick et al. 1984
NR	1–10	NR	Iowa	Kelley et al. 1985
8	ND–1.6	0.1	Michigan	Furlong and D'Itri 1986
NR	NR	0.8–8	California	Wallace et al. 1986b
Dibromochloromethane				
86	<0.1–2	0.9	Ohio	Bellar et al. 1974
NR	3-32	NR	5 Cities	Coleman et al. 1975
37	ND–110	2.7	National	Symons et al. 1975
85	ND–15.0	≈0.4	13 Cities	Keith et al. 1976
65	ND–9.0	2.9	Iowa	Morris and Johnson 1976
86	NR	14	National	Brass et al. 1977
99	NR–33	5.6	Midwest	ORVWSC 1979
NR	ND–128	≈20	Texas	Glaze and Rawley 1979
100	11–31	20	Texas	Smith et al. 1980
42	NR–63	NR	National	Westrick et al. 1984
NR	1–28	NR	Iowa	Kelley et al. 1985
75	ND–40	4.1	Michigan	Furlong and D'Itri 1986
NR	NR	1–2	New Jersey	Wallace et al. 1986a
NR	NR	8–28	California	Wallace et al. 1986b

μg = microgram; L = liter; ND = not detected; NR = not reported

Bromoform and dibromochloromethane were detected in approximately 90% of samples from 5,320 wells in 21 states from 1985 to 1995 according to data collected by the United States Geological Survey (USGS) National Water-Quality Assessment Program, although actual concentrations were not given (Lapham et al. 2000). Bromoform and dibromochloromethane were detected in 27 and 39 out of 7,712 California drinking water wells, respectively, during monitoring studies conducted from 1984 to 1990 (Lam et al. 1994). Maximum concentrations were 78 μg/L for bromoform and 30 μg/L for dibromochloromethane. Dibromochloromethane was detected in 5 out of 6 samples from 178 active public supply wells in the Los Angeles physiographic basin, California above the laboratory reporting limit of 0.18 μg/L in August through September, 2000 (Shelton et al. 2001). Bromoform was detected in four out of four samples above the laboratory reporting limit of 0.06 μg/L. Clark et al. (1994) collected drinking water samples from different points along the North Marin Water District, which serves the greater Novato area in California. Bromoform and dibromochloromethane were detected in the samples with concentrations ranging from 2.4 to 11.4 μg/L and from <0.1 to 7.5 μg/L, respectively.

The State of California's Water Quality Monitoring Database contains data for public drinking water systems that use either groundwater or surface water sources (Storm 1994). Analysis of these data shows that bromoform was detected in 145 out of 11,765 samples (1.2%) and dibromochloromethane was detected in 171 out of 11,782 samples (1.5%). Mean concentrations in samples with detected dibromochloromethane and bromoform were 8.95 and 7.63 μg/L, respectively. Occurrence data from approximately 22,000 public water systems (source water: 88% groundwater and 12% surface water) from a cross-section of 24 states were selected from the Unregulated Contaminant Information System database (Round 1 monitoring data) (EPA 2001a). Dibromochloromethane and bromoform were detected in these systems with 99th percentile values of 12.7 and 7.3 μg/L, respectively. Occurrence data from approximately 27,000 public water systems (source water: 89% groundwater and 11% surface water) from a cross-section of 22 states were selected from the Safe Drinking Water Information System database (Round 2 monitoring data). Dibromochloromethane and bromoform were detected in these systems with 99th percentile values of 9.7 and 6.5 μg/L, respectively.

It is usually found that halomethanes occur at higher concentrations in drinking water derived from surface sources than those from groundwater supplies because the former tends to contain more dissolved organic matter (Bellar et al. 1974; Cech et al. 1981; Glaze and Rawley 1979; Page 1981). The total trihalomethane content of finished water from a given facility can be extremely variable as a function of time (Arguello et al. 1979; Smith et al. 1980), with lower levels of halomethanes usually occurring during the winter.

The mean concentration of dibromochloromethane was 0.74 μg/L in cold season samples from the Elizabethtown, New Jersey water distribution system (Chen and Weisel 1998). Dibromochloromethane levels rose to 1.7 μg/L in warm season samples. Bromoform was not found above the detection limit (0.10 μg/L) in cold season samples from the distribution system, but it was detected in warm season samples with a mean concentration of 0.27 μg/L. Summer concentration ranges in treated water immediately prior to distribution in a 1993 national Canadian survey conducted by Health Canada were <0.1–19.8 μg/L for dibromochloromethane and <0.1–4.2 μg/L for bromoform (Ritter et al. 2002). Winter concentration ranges were <0.1–9.0 μg/L for dibromochloromethane and <0.1–3.3 μg/L for bromoform. Bromoform was detected in the influent, treated, and distribution stages from 47 municipal water treatment plants in Ontario, Canada at concentrations of 0.5, 0–7.0, and 0.2–8.5 μg/L, respectively. Dibromochloromethane was detected in samples from plant effluents of 35 Finnish waterworks with concentrations ranging from <0.05 to 3 μg/L (Nissinen et al. 2002). One exception was a comparatively high concentration of 43 μg/L measured at one of the plants. Bromoform concentrations were <0.05 μg/L in samples from all plants except for three (0.48, 0.31, and 27 μg/L). Concentrations of bromoform and dibromochloromethane in samples from two Finnish waterworks rose in the spring, changed little over summer and fall, and then dropped during winter.

Bromoform and dibromochloromethane were detected in water samples from seven out of nine household residences in the Lower Rio Grande Valley during the spring of 1993 with concentrations ranging from 1.0 to 14.1 μg/L and from 3.3 to 17.3 μg/L, respectively (Berry et al. 1997). These compounds were detected in water samples from five out of nine residences in the same region during the summer of 1993 with concentrations ranging from 1.6 to 31.7 μg/L and from 1.8 to 49.9 μg/L, respectively.

Trihalomethanes may also form in chlorinated swimming pools (Beech et al. 1980). For freshwater pools, chloroform and dichlorobromomethane were usually the predominant THM species present, with dibromochloromethane and bromoform averaging 3–15 and 1–2 μg/L, respectively. However, in saline pools (which have a higher bromide ion content than freshwater pools), bromoform was the major THM present (average concentration of 650 μ/L), with lower concentrations (5–27 μg/L) of dibromochloromethane, bromodichloromethane, and chloroform. Concentrations of bromoform and dibromochloromethane were 1.8–2.9 and 3.5–17 μg/L, respectively, in samples taken from three chlorinated sandy bottom swimming areas in September (Mansour et al. 1999).

Dibromochloromethane and bromoform have also been detected in water near hazardous waste sites, although this is not common. Data from the Contract Laboratory Program (CLP) Statistical Data Base (CLPSD 1988) indicated that bromoform was detected in surface water at two of 862 hazardous-waste sites; the median concentration was 7 μg/L. Dibromochloromethane was detected in only one sample (45 μg/L). Bromoform was detected in groundwater samples collected at four sites; the median concentration was 26 μg/L. Based on monitoring data from 479 disposal site groundwater investigations that were conducted across the United States, bromoform was detected in groundwater samples from 10 hazardous waste disposal sites and dibromochloromethane has been detected in groundwater samples from 8 hazardous waste disposal sites (Plumb 1991). Actual concentrations of bromoform and dibromochloromethane were not given.

In a random survey of 954 community water systems, bromoform and dibromochloromethane were detected (minimum reporting limit of 0.2 μg/L) in 3.4 and 5.5%, respectively, of source water samples (Delzer and Ivahnenko 2003). Both bromoform and dibromochloromethane were detected more frequently in groundwater sources than surface water sources. Concentrations of bromoform in groundwater ranged from 0.19 to 2.61 μg/L with a median value of 0.26 μg/L; in surface water, the concentrations ranged from 0.03 to 0.06 μg/L with a median value of 0.05 μg/L. For dibromochloromethane, concentrations in groundwater ranged from 0.02 to 2.43 μg/L with a median value of 0.04 μg/L; in surface water, the concentrations ranged from 0.02 to 0.15 μg/L with a median value of 0.03 μg/L. In a study of over 21 cities throughout the United States conducted between 1991–1995, dibromochloromethane was detected (minimum reporting limit of 0.2 μg/L) in 3.4% of stormwater and 0.5% of shallow groundwater samples (Lopes and Bender 1998). The presence of dibromochloromethane in these samples was attributed to the irrigation of lawns, gardens, and parks with chlorinated water, the draining of swimming pools, and uses of chlorinated water that result in its introduction to stormwater catchments.

Dibromochloromethane has been detected at concentrations ranging from 1.1 to 36.3 ng/L in the Scheldt River estuary, Germany during May 1998; from 0.2 to 22.7 ng/L in Scheldt River estuary, Germany during October 1998; from below the detection limit to 39.0 ng/L in the Thames River estuary, England during February 1999; from below the detection limit to 7.7 ng/L in the Loire River estuary, France during September 1998; and from below the detection limit to 9.8 ng/L in the Rhine River estuary, Germany during November 1997 (Christof et al. 2002). Bromoform and dibromochloromethane were detected in water samples from the Southampton Water estuary at concentrations of 10–2,597 and 10–2,200 ng/L, respectively (Bianchi et al. 1991).

6.4.3 Sediment and Soil

Staples et al. (1985) reported that bromoform was not detected in any of 353 sediment samples analyzed. No data were available for dibromochloromethane. Data from the Contract Laboratory Program Statistic Data Base (CLPSD 1988) indicated dibromochloromethane and bromoform were detected in soils in only 2 of 862 hazardous waste sites; the median concentrations were 17 μg/kg (bromoform) and 15 μg/kg (dibromochloromethane). Bromoform and dibromochloromethane were detected in sediment samples from the Southampton Water estuary at concentrations ranging from 75 to 62,609 and from 150 to 27,350 ng/kg, respectively (Bianchi et al. 1991). During a monitoring study of volatile halogenated organic compounds in the Klosterhede State Forest District in Jutland, Denmark, bromoform was the only brominated compound detected in soil air samples and only in the upper soil layer with a concentration of 0.25 ng/L (Laturnus et al. 2000b).

6.4.4 Other Environmental Media

The use of chlorinated water in the manufacture of commercially bottled drinks has raised concern over the presence of trihalomethanes in these drinks (McNeal et al. 1995). Levels of dibromochloromethane in bottled water and in carbonated soft drinks ranged from 0.5 to 2 ng/g in a survey of soft drinks, juices, beers, bottled water, and canned foods purchased from Washington, DC markets in 1991–1992. Bromoform was not found in any of the samples above a detection limit of 0.1 ng/g. Dibromochloromethane was found in pasteurized milk from a suburban area of Turku, Finland (Kroneld and Reunanen 1990).

Neither bromoform nor dibromochloromethane were detected in oyster, clam, or sediment samples from the Ariho and Yoshingaga Rivers in Japan (Gotoh et al. 1992). No detection limit was given.

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Because of the variability of dibromochloromethane and bromoform concentrations in water and air, it is not possible to derive precise estimates of typical human exposure levels. However, based on the typical ranges of dibromochloromethane and bromoform concentrations measured in water and air, it is likely that most individuals will be exposed to average doses of <1 μg/kg/day (Table 6-2), of which nearly all is due to water. Limited data suggest that exposure levels around chemical factories or waste sites are not likely to be much higher, but this can only be evaluated on a site-by-site basis.

Table 6-2. Summary of Typical Human Exposure to Bromoform and Dibromochloromethane

Parameter	Exposure medium	
	Water	Air
Typical concentration in medium	1–20 μg/L	0–0.1 μg/m^3
Assumed intake of medium by 70-kg adult	2 L/day	20 m^3/day
Assumed absorption fraction	1.0	0.5
Estimated dose to 70-kg adult	0.03–0.6 μg/kg/day	0.0–0.01 μg/kg/day

μg = microgram; kg = kilogram; L = liter; m^3 = cubic meters

The range of dibromochloromethane concentrations in tap water, in blood samples before showering, and in blood samples after showering in Cobb County, Georgia were <1–4, 0.001–0.003, and 0.003–0.029 μg/L, respectively (Miles et al. 2002). Concentrations in tap water, in blood samples before showering, and in blood samples after showering samples from Corpus Christi, Texas were 5–20, 0.002–0.031, and 0.011– >0.093 μg/L, respectively. Bromoform was detected in the Cobb County, Georgia samples at concentrations of <1 μg/L in tap water, 0.001–0.0052 μg/L in blood before showering, and 0.0001–0.0059 μg/L in blood after showering. Concentrations of dibromochloromethane in tap water, in blood samples before showering, and in blood samples after showering from Corpus Christi, Texas ranged from 2–17, 0.001–0.02, and 0.006–0.064 μg/L, respectively. Breath samples of individuals taken within 5 minutes after a shower with high dibromochloromethane and bromoform water concentrations contained dibromochloromethane at a mean concentration of 4.8 $\mu g/m^3$ and bromoform at a mean concentration of 2.3 $\mu g/m^3$ (Weisel 1999). Breath samples taken 5–20 minutes after a shower with high water concentration contained dibromochloromethane at a mean concentration of 2.8 $\mu g/m^3$ and bromoform at a mean concentration of 1.2 $\mu g/m^3$. Breath samples taken >20 minutes after a shower with high water concentration contained dibromochloromethane at a mean concentration of 1 $\mu g/m^3$ and bromoform at a mean concentration of 0.6 $\mu g/m^3$. Breath samples from individuals after a shower with low water concentration contained dibromochloromethane with a mean concentration of 1 $\mu g/m^3$ at different collection times and bromoform with a mean concentration of 0.6 $\mu g/m^3$ at different collection times.

Dibromochloromethane was found in human kidney and lung tissue at 0.6 and 0.06 μg/kg, respectively, in samples taken in the city of Turku, Finland in 1987 (Kroneld 1989a). It was also detected in air samples from that region.

Blood samples taken from 16 individuals in the Lower Rio Grande Valley during the spring of 1993 had a maximum dibromochloromethane concentration of 0.05 μg/L (38% frequency of detection) and a maximum bromoform concentration of 0.07 μg/L (19% frequency of detection) (Buckley et al. 1997). Blood samples taken during the Third National Health and Nutrition Examination Survey, which included over 1,000 individuals, had a maximum dibromochloromethane concentration of 0.024 μg/L (14.5% frequency of detection) and a maximum bromoform concentration of 0.034 μg/L (9.9% frequency of detection) (Buckley et al. 1997; Needham et al. 1995).

Exposure to dibromochloromethane and bromoform may be above average for persons who swim in chlorinated swimming pools. Beech (1980) estimated that the total dose for a 6-year-old boy who swam

for 3 hours in a pool containing 500 μg/L of trihalomethanes could be as high as 2.8 mg (130 μg/kg). About 60% of this dose was attributed to dermal absorption, with about 30% resulting from inhalation. In freshwater pools, only a small fraction of this would be dibromochloromethane or bromoform, but in a saltwater pool, a large fraction would be expected to be bromoform (Beech et al. 1980).

No studies were located regarding human exposure levels in the workplace.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in 3.7 Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

No information was located regarding the exposures of children to bromoform or dibromochloromethane. Exposures of children to bromoform and dibromochloromethane through inhalation are expected to vary depending on the length of time a child spends indoors and the concentrations of these compounds in indoor air. The concentrations of bromoform and dibromochloromethane will depend on the source of household water, exchange rate of indoor and outdoor air, frequency and duration of showers, and emission rates of these compounds from other household sources (e.g., dishwasher, washing machines, etc.). Dermal exposures of children to bromoform and dibromochloromethane are expected to be lower than, or similar to, those found for adults, depending on frequency and duration of bathing or showering. However, the primary routes of exposure to bromoform and dibromochloromethane are expected to be through drinking water or consumption of beverage or food products that contain water that has been disinfected through chlorination. It is expected that a child's exposure to bromoform and dibromochloromethane will depend predominantly on the source and amount of drinking water consumed per day. Exposure of newborns and infants to bromoform and dibromochloromethane, whose diets are

supplemented with human breast milk, cow's milk, or infant formulas, is not known, since measurements of these compounds are not available in these media. Swimming is expected to provide an additional source of exposure for children who spend time in chlorinated swimming pools (Beech et al. 1980).

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The environmental medium most likely to be contaminated with bromoform and dibromochloromethane is chlorinated water. Therefore, any person who is in frequent contact with such water could have above average exposures. This includes individuals who drink large quantities of water, such as workers in hot climates, or individuals with swimming pools or saunas, where contact could occur by inhalation or by dermal contact. Since bromoform and dibromochloromethane levels in water depend on the organic content of the source water before chlorination, individuals whose water source is high in organics are likely to have finished water with higher-than-average bromoform and dibromochloromethane levels.

Workers in chemical production facilities or laboratories where bromoform and dibromochloromethane is made or used would also have potentially high exposures to the chemicals, most likely by inhalation or dermal exposure. Persons living near hazardous-waste sites may have potentially high exposures to bromoform and dibromochloromethane, but this can only be evaluated on a case-by-case basis.

6.8 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 bromoform and dibromochloromethane are 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 bromoform and dibromochloromethane.

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

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of dibromochloromethane and bromoform have been well studied, and reliable values for key parameters are available for use in environmental fate and transport models. On this basis, it does not appear that further studies of the physical-chemical properties of dibromochloromethane and bromoform are essential.

Production, Use, Release and Disposal. Available data indicate that neither bromoform nor dibromochloromethane is produced or used in significant quantities in the United States. Nevertheless, a listing of laboratories or industries that use small amounts in research or testing would be valuable in identifying locations where the potential for environmental releases or human exposure exists. Also, information on the means of disposal of waste chemicals would be valuable in identifying environmental media likely to be affected at such sites. Federal regulations do restrict disposal of dibromochloromethane and bromoform to land or in industrial effluents.

Environmental Fate. The fate of dibromochloromethane and bromoform in the environment has not been thoroughly studied, although the physical-chemical properties indicate that both are likely to partition to air and water. Volatilization rates have been calculated for flowing rivers and streams, but direct measurements of half-times of volatilization would be useful, both for surface waters and for household water (showers, baths, cooking, etc.). Adsorption of these compounds to soils and sediments has been studied and does not appear to be a significant factor. Consequently, transport in surface or groundwater are likely to be important. Studies to confirm these expectations and provide more precise descriptions of the environmental behavior of these compounds would be valuable in assessing human exposure near specific sources of release.

Degradation of dibromochloromethane and bromoform in air has not been studied, but is expected to occur by reaction with hydroxyl radicals. Studies to measure the atmospheric half-times of these compounds would be valuable in estimating long-term trends in atmospheric levels, but such studies are probably not essential in estimating exposure near specific sources. Neither chemical undergoes chemical degradation in water, but both are subject to microbial breakdown in water (especially anaerobic groundwater) or moist soils. Further data on the rate of microbial degradation of dibromochloromethane and bromoform in water and soil would be valuable, with special attention to how these rates depend on environmental conditions (oxygen level, pH, etc.).

Bioavailability from Environmental Media. Both dibromochloromethane and bromoform are known to be absorbed following oral and inhalation exposure. No data are available regarding dermal absorption, but it seems likely that uptake across the skin may occur. No data were located regarding the relative bioavailability of dibromochloromethane and bromoform in water, soil or air. Because of their physical and chemical properties, it is expected that the bioavailability of dibromochloromethane and bromoform are not significantly reduced by environmental media, but studies to substantiate this presumption would be helpful.

Food Chain Bioaccumulation. There are few data on bioconcentration of dibromochloromethane or bromoform by plants or aquatic organisms, and no data were located on the bioaccumulation of bromoform and dibromochloromethane in the food chain. This lack of data may not be a major limitation because the general levels of the chemicals in water and soil appear to be quite low, and based on the Koc of these chemicals, there appears to be a low likelihood of food chain buildup.

Exposure Levels in Environment Media. There are several studies on the atmospheric concentrations of bromoform and dibromochloromethane in urban and rural environments, but many of the samples did not have detectable levels. No data on levels in air near waste sites were located. More research in this area using more sensitive analytical methods would be helpful, although it is anticipated that typical atmospheric levels will usually be low enough that air is not the principal route of exposure. Data are available on dibromochloromethane and bromoform in a number of chlorinated drinking water systems, and these compounds have been detected in surface water and groundwater near a few hazardous waste sites. Further studies on the levels of these compounds in water and soil around waste sites would be valuable in evaluating the risk to human health posed by these contaminants.

Exposure Levels in Humans. There are no data on levels of dibromochloromethane or bromoform in blood, breath or other tissues from humans residing near waste sites. Low levels of bromoform have been detected in blood of humans, presumably as the result of exposure through ingestion of chlorinated drinking water. Levels in expired breath and in adipose tissue appear to be too low to measure reliably for the general population. Direct measurement of typical human intake from water and air (especially indoor air) would be helpful in obtaining more accurate estimates of typical human dose levels. Similar data on inhalation and dermal doses would be useful for bromoform and dibromochloromethane in and around swimming pools (especially indoor pools).

Exposures of Children.

Child health data needs relating to susceptibility are discussed in 3.12.2 Identification of Data Needs: Children's Susceptibility.

No formal studies of children's inhalation, dermal, or oral exposures to bromoform and dibromochloromethane were located in the literature. Based on the concentrations of bromoform and dibromochloromethane measured in indoor air and in drinking water that has been disinfected by chlorination, studies are needed to assess the inhalation, dermal, and oral exposures of children to these and other disinfection by-products. Data on inhalation and dermal doses would be useful for bromoform and dibromochloromethane in and around swimming pools (especially indoor pools).

Exposure Registries. No exposure registries for bromoform and dibromochloromethane were located. These compounds are not currently among the compounds for which subregistries have been established in the National Exposure Registry. These compounds will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to the exposure to these compounds.

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2003) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1. These studies are summarized in Table 6-3.

Table 6-3. Ongoing Studies on the Potential for Human Exposure to Bromoform[a]

Investigator	Affiliation	Research description	Sponsor
Hudson SM	North Carolina State University, Raleigh, North Carolina	Development of a low cost but high value short fiber by direct shear precipitation of chitosan solutions; synthesis of a hybrid material based on chitosan fibrids by graft co-polymerization techniques; investigation of the suitability of transition metal-carbonyl complexes as initiators for graft copolymerization for polysaccharides.	National Research Institute
Harrington, J; Simpson WR	Pennsylvania State University, University Park, Pennsylvania; University of Alaska Fairbanks Campus, Fairbanks, Alaska	Development and testing of a radiation-transfer model for snow photochemistry. This will help quantify the extent of photochemical processing of trace compounds within snow and will help in interpreting ice core climate records and understanding atmospheric chemistry in snow-covered regions. The study will include measurements of photolysis rates for bromoform.	National Science Foundation
Meyer GJ	Johns Hopkins University, Baltimore, Maryland	Development of new reductive and oxidative dehalogenation chemistries and the elucidation of their fundamental mechanisms; application of these new findings to the sensing, remediation, and determination of the environmental fate of organohalide pollutants. The study will provide a pedagogical platform that informs and educates the next generation of environmental chemists.	National Science Foundation
Rathbun RE	U.S. Geological Survey, North-Central Colorado	To study the fundamentals of volatilization, dispersion, and sorption on sediments of organic substances in water; to develop sub-models of these processes including methods for measuring or estimating the process rate coefficients; and to integrate these sub-models in overall transport and fate models for organic substances in streams. The study will include measurements of trihalomethanes.	U.S. Geological Survey

[a]Source: CRIS 2003; FEDRIP 2003

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring bromoform and dibromochloromethane, its metabolites, and other biomarkers of exposure and effect to bromoform and dibromochloromethane. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

As is true for most volatile organic compounds, the preferred analytical technique for dibromochloromethane and bromoform is gas chromatography (GC) (Ashley et al. 1996; Djozan and Assadi 1995; Fishbein 1985). A number of devices are suitable for detection and quantification of dibromochloromethane and bromoform as they emerge from the GC, including flame ionization detection (GC/FID), halogen-sensitive detection (GC/HSD) or electron-capture detection (GC/ECD). In general, HSD or ECD are preferable because of their high sensitivity for halogenated compounds. When absolute confidence in compound identity is required, mass spectrometry (GC/MS) is the method of choice.

The most variable aspect of analyses of this sort is the sample preparation procedure used to separate dibromochloromethane and bromoform from the test medium in order to prepare a sample suitable for GC analysis. As volatile organic compounds of relatively low water solubility, both dibromochloromethane and bromoform are easily lost from biological and environmental samples, so appropriate care must be exercised in handling and storing such samples for chemical analysis. Brief summaries of the methods available for extraction and detection of these compounds in biological and environmental samples are provided below.

7.1 BIOLOGICAL MATERIALS

Separation of dibromochloromethane and bromoform from biological samples is most often achieved by headspace analysis, purge-and-trap collection, solvent extraction, or direct collection on adsorbent resins.

Headspace analysis offers speed, simplicity, and good reproducibility, but partitioning of the analyte between the headspace and the sample matrix is dependent upon the nature of the matrix and must be determined separately for each different kind of matrix (Walters 1986).

Purge-and-trap collection is well suited to biological samples such as blood or urine that are readily soluble in water (Ashley et al. 1996; Peoples et al. 1979). This method consists of bubbling an inert gas through a small volume of the sample and collecting the vapor in a trap packed with sorbent. The analytes are then removed from the trap by heating it and backflushing the analytes onto a gas chromatographic column. The two materials most widely used for adsorption and thermal desorption of volatile organic compounds collected by the purge and trap technique are Carbotrap®, consisting of graphitized carbon black, and Tenax®, a porous polymer of 2,6-diphenyl-p-phenylene oxide (Fabbri et al. 1987).

For water-insoluble materials such as fat or other tissues, the most common separation procedure is extraction with an organic solvent such as diethyl ether (Zlatkis and Kim 1976). Homogenization of tissue with the extractant and lysing of cells usually improves solvent extraction efficiency.

Analytical methods for the determination of bromoform and dibromochloromethane in biological materials are summarized in Table 7- l.

7.2 ENVIRONMENTAL SAMPLES

Dibromochloromethane and bromoform may be isolated from environmental samples using the same methods and principles as those used for biological materials, followed by gas chromatographic analysis. The most convenient procedure for most liquid and solid samples is the purge-and-trap method. Arthur et al. (1992) used solid phase micro extraction to separate volatile halogenated compounds from water samples. The organic analytes partition between the water sample and the stationary phase coating of a fused silica fiber before they are thermally desorbed in a GC injector. Djozan and Assadi (1995) introduced a gas stripping cryogenic trapping technique for separating volatile halogenated compounds from drinking water samples. In this method, a purified gas passes through the water sample in a stripping column where it removes volatile compounds from a water sample. The effluent from the column is dried, trapped in a cold trapping coil, and then released to the GC system by warming. Membrane inlet mass spectrometry (MIMS) is another technique for separating organohalogen compounds from drinking water (Bocchini et al. 1999). With this method, volatile organic compounds

Table 7-1. Analytical Methods for Determining Bromoform and Dibromochloromethane in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Accuracy (percent recovery)	Reference
Adipose tissue	Extraction, bulk lipid removal, Florisil fractionation	HRGC/MS	0.1 μg/g	NR	Mack and Stanley 1985
Adipose tissue	Heated dynamic headspace purge-and-trap	HRGC/MS	1 ng/g (DBCM) 2 ng/g (TBM)	NR	Stanley 1986
Adipose tissue	Purge from liquified fat at 115 °C, trap on Tenax/silica gel, thermal desorption	GC/HSD	<2 μg/L	83–107 (TBM) 90–118 (DBCM)	Peoples et al. 1979
Blood	Purge from blood onto Tenax, thermal desorption onto column maintained at -20 °C	GC/MS	≈0.1 ng/mL	NR	Antoine et al. 1986
Blood	Extract with n-pentane	HRGC/ECD	0.1 μg/L (DBCM)	NR	Kroneld 1985
Blood	Purge from blood at 30 °C, trap onto Tenax, thermal desorption	GC/MS	0.021μg/L (TBM)	102–108 (TBM)	Ashley et al. 1992
Blood	Purge from blood at 30 °C, trap onto Tenax, thermal desorption	GC/MS	0.017μg/L (DBCM)	91–104 (DBCM)	Ashley et al. 1992
Blood, tissue	Macerate tissue in water, warm blood or tissue, pass inert gas through, trap on Tenax, thermal desorption	GC/MS	3 ng/mL (blood) 6 ng/g (tissue)	NR	Pellizzari et al. 1985b
Blood serum	Purge from water-serum mixture containing antifoam reagent at 115 °C, trap on Tenax/silica gel, thermal desorption	GS/HSD	<2 μg/L	79–100 (TBM) 78–100 (DBCM)	Peoples et al. 1979
Breath	Trap on Tenax, dry over calcium sulfate, thermal desorption	GC/MS	1–5 μg/m^3	92±15 (TBM) 93±13 (DBCM)	Wallace et al. 1986b

μg = microgram; DBCM = dibromochloromethane; ECD = electron capture detector; g = gram; GC = gas chromatography; HRGC = high resolution gas chromatography; HSD = halide specific detector; L = liter; m^3 = cubic meters; mg = milligram; mL = milliliter; MS = mass spectrometry; ng = nanogram; NR = not reported; TBM = bromoform

from the drinking water sample diffuse through a hollow-fiber membrane into a mass spectrometer. The advantages of this method are that sample pre-treatment is not required, response times are fast, and trace analysis of the pollutants can be preformed on-line. Halocarbons can also be removed from water by adsorption on synthetic polymers contained in cartridges, followed by thermal desorption of the analyte (Pankow et al. 1988). Among the products used for this purpose are Tenax-GC® and Tenax-TA®. A similar procedure is used for air, in which the air is passed through an adsorbent canister, followed by thermal desorption (Pankow et al. 1998).

Analytical methods for the determination of dibromochloromethane and bromoform in environmental samples are given in Table 7-2.

7.3 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 bromoform and dibromochloromethane 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 bromoform and dibromochloromethane.

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

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Sensitive and specific methods exist for the determination of dibromochloromethane and bromoform in blood, expired air, and adipose tissue. These methods are presumably sensitive enough to measure levels in humans exposed to doses of the chemicals that produce sedation or cause injury to liver

Table 7-2. Analytical Methods for Determining Bromoform and Dibromochloromethane in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Accuracy (percent recovery)	Reference
Drinking water	Solvent extraction with pentane, direct injection of extract	HRGC/ECD	<0.5 μg/L	NR	Fayad and Iqbal 1985
Drinking water	Gas stripping and cryogenic trapping system	GC/FID	0.05 μg/L (DBCM)	75±7.7 (DBCM)	Djozan and Assadi 1995
Drinking water	Adsorption to and diffusion through a polymeric hollow-fiber membrane	MIMS	0.5 μg/L (TBM)	NR	Bocchini et al. 1999
Drinking water	Adsorption to and diffusion through a polymeric hollow-fiber membrane	MIMS	0.5 μg/L (DBCM)	NR	Bocchini et al. 1999
Drinking water	Purge and trap, thermal desorption	GC/MS	0.1μg/L	89–90 (TBM)	Eichelberger et al. 1990
Drinking water	Purge and trap, thermal desorption	GC/MS	0.1μg/L	95–100 (TBM)	Eichelberger et al. 1990
Air	Coconut shell charcoal sorption, carbon disulfide desorption	GC/FID	10 μg/sample	NR	NIOSH 1984
Air	Coconut shell charcoal sorption, carbon disulfide desorption	GC/FID	10 μg/sample (TBM)	14.0 (TBM)	NIOSH 1994
Air	Carbotrap/Carboxen filled glass cartridge adsorption/thermal desorption	GC/MS	0.02 ppbv (TBM)	95–102 (TBM)	Pankow et al. 1998
Air	Carbotrap/Carboxen filled glass cartridge adsorption/thermal desorption	GC/MS	0.04 ppbv (DBCM)	96–99 (DBCM)	Pankow et al. 1998
Water	Purge and trap	GC/MS	10 μg/L	NR	EPA 1980b
Water	Purge and trap	GC/HSD	0.20 μg/L (TBM)	89±9 (TBM)	EPA 1982a
			0.09 μg/L (DBCM)	98±7 (DBCM)	
Water	Purge and trap	GC/MS	4.7 μg/L (TBM)	105±16 (TBM)	EPA 1982b
			3.1 μg/L (DBCM)	104±14 (DBCM)	
Water	Purge and trap	GC/HSD	0.5 μg/L	97 (DBCM)	APHA 1985a
				101 (DBCM)	
Water	Purge and trap	GC/MS	<2 μg/L	82 (TBM)	APHA 1985b

Table 7-2. Analytical Methods for Determining Bromoform and Dibromochloromethane in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Accuracy (percent recovery)	Reference
Water	Solvent extraction (isooctane)	GC/ECD	2 μg/L	NR	ASTM 1988
Water	Solid phase micro extraction	GC/MS	4.7 μg/L (TBM)		Arthur et al. 1992
Water	Solid phase micro extraction	GC/MS	3.1 μg/L (DBCM)		Arthur et al. 1992
Contaminated soil	Purge and trap	GC/HSD	2 μg/kg (TBM)	96[b] (TBM)	EPA 1986a
			0.9 μg/kg (DBCM)	94[b] (DBCM)	
Wastes, non-water miscible	Purge and trap	GC/HSD	250 μg/kg (TBM)	96[b] (TBM)	EPA 1986a
			113 μg/kg (DBCM)	94[b] (DBCM)	
Solid waste	Purge and trap	GC/MS	5 μg/kg	118[b] (TBM)	EPA 1986b
				101[b] (DBCM)	

[a]Value refers to both DBCM and TBM unless noted otherwise.
[b]This recovery is typical at concentrations of around 100 μg/L or higher. Recoveries may deviate at lower concentrations.

μg = microgram; DBCM = dibromochloromethane; ECD = electron capture detector; FID = flame ionization detector; g = gram; GC = gas chromatography; HRGC = high resolution gas chromatography; HSD = halide specific detector; kg = kilogram; L = liter; MS = mass spectrometry; NR = not reported; TBM = bromoform

and kidney. However, data on this are lacking due to absence of cases. The methods are also suitable for measuring background levels in the general population, although increased sensitivity would be useful for analysis of expired air and adipose tissue. The major limitation to these methods is that only recent exposures can be detected, so work to identify and quantify a more stable biomarker of exposure (e.g., a halomethyl adduct) would be valuable.

Effect. No chemical or biochemical biomarkers of effect are recognized, aside from nonspecific indices of hepatic or renal dysfunction, Efforts to identify a specific biomarker of effect (in particular, an effect such as alkylation of DNA that may be related to cancer risk) would be valuable in evaluating potential health risk to exposed humans.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Reliable and specific methods exist for measuring parent dibromochloromethane and bromoform in air, water, soil and solid wastes. Humans could be exposed to these compounds by contact with any of these media, although ingestion of or dermal contact with contaminated water appears to be the most likely route near a chemical waste site. Existing methods are readily able to detect concentration values in environmental media that are likely to lead to significant noncancer health effects, but might not be sensitive enough to measure levels that pose low levels of cancer risks. However, since no chemical-specific cancer potency values are available for these components, this is not certain.

7.3.2 Ongoing Studies

No ongoing studies on analytical methods were identified in a search of the Federal Research in Progress database (FEDRIP 2003).

8. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding bromoform and dibromochloromethane in air, water, and other media are summarized in Table 8-1.

An acute-duration oral MRL of 0.7 mg/kg/day has been derived for bromoform. This MRL is based on a NOAEL of 72 mg/kg/day and a LOAEL of 145 mg/kg/day for centrilobular pallor in mice receiving gavage doses of bromoform for 14 days (Condie et al. 1983). The MRL was derived by dividing the NOAEL by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

An intermediate-duration oral MRL of 0.2 mg/kg/day has been derived for bromoform. This MRL is based on a NOAEL of 50 mg/kg for hepatocellular vacuolization in rats administered gavage doses of bromoform in corn oil 5 days/week for 13 weeks (NTP 1989a). The MRL was derived by dividing the duration adjusted NOAEL of 18 mg/kg/day by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

A chronic-duration oral MRL of 0.2 mg/kg/day has been derived for bromoform. This MRL is based on a LOAEL of 100 mg/kg for hepatocellular vacuolization in rats administered gavage doses of bromoform in corn oil 5 days/week for 2 years (NTP 1989a). The MRL was derived by dividing the duration adjusted LOAEL of 71 mg/kg/day by an uncertainty factor of 300 (3 for use of a minimal LOAEL, 10 for animal to human extrapolation, and 10 for human variability).

An acute-duration oral MRL of 0.1 mg/kg/day has been derived for dibromochloromethane. This MRL is based on a LOAEL of 37 mg/kg for hepatocellular vacuolization in mice administered gavage doses of dibromochloromethane in corn oil for 14 days (Condie et al. 1983). The MRL was derived by dividing the LOAEL by an uncertainty factor of 1,000 (3 for use of a minimal LOAEL, 10 for animal to human extrapolation, and 10 for human variability).

A chronic-duration oral MRL of 0.09 mg/kg/day has been derived for dibromochloromethane. This MRL is based on a LOAEL of 40 mg/kg for fatty changes in the liver of rats administered gavage doses of dibromochloromethane in corn oil for 2 years (NTP 1985). The MRL was derived by dividing the duration-adjusted LOAEL of 28 mg/kg/day by an uncertainty factor of 300 (10 for use of a minimal LOAEL, 10 for animal to human extrapolation, and 10 for human variability).

Table 8-1. Regulations and Guidelines Applicable to Bromoform and Dibromochloromethane

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification		IARC 1999a, 1999b
	Bromoform	Group 3[a]	
	Dibromochloromethane	Group 3[a]	
WHO	Drinking water guideline		WHO 1996
	Bromoform	100 mg/L	
	Dibromochloromethane	100 mg/L	
NATIONAL			
Regulations and Guidelines:			
a. Air:			
ACGIH	TLV (8-hour TWA)		ACGIH 2003
	Bromoform[b]	0.5 ppm	
NIOSH	REL (10-hour TWA)		NIOSH 2003
	Bromoform[c]	0.5 ppm	
	IDLH	850 ppm	
OSHA	PEL (8-hour TWA) for general industry		OSHA 2003a 29 CFR 1910.1000, Table Z-1
	Bromoform[d]	0.5 ppm	
	PEL (8-hour TWA) for construction industry		OSHA 2003c 29 CFR 1926.55, Appendix A
	Bromoform[d]	0.5 ppm	
	PEL (8-hour TWA) for shipyard industry		OSHA 2003b 29 CFR 1915.1000
	Bromoform[d]	0.5 ppm	
USC	Hazardous air pollutant	Bromoform	USC 2003
b. Water			
EPA	Drinking water health advisories		EPA 2002a, 2002b
	Bromoform		
	1-day (10-kg child)	5.0 mg/L	
	10-day (10-kg child)	2.0 mg/L	
	DWEL[e]	0.7 mg/L	
	10^{-4} Cancer risk[f]	0.4 mg/L	
	Dibromochloromethane		
	1-day (10-kg child)	6.0 mg/L	
	10-day (10-kg child)	6.0 mg/L	
	DWEL[e]	0.7 mg/L	
	Lifetime[g]	0.06 mg/L	
	10^{-4} Cancer risk[f]	0.04 mg/L	
	Effluent guidelines and standards; toxic pollutants pursuant to Section 307 (a)(1) of the Clean Water Act	Bromoform	EPA 2003c 40 CFR 401.15

Table 8-1. Regulations and Guidelines Applicable to Bromoform and Dibromochloromethane

Agency	Description	Information		Reference
NATIONAL *(cont.)*				
EPA	National primary drinking water regulations			EPA 2003f 40 CFR 141.12
	MCL for total trihalo methanes[h]	0.10 mg/L		
	Pollutants of initial focus in the Great Lakes Water Quality Initiative	Bromoform and dibromochloromethane		EPA 2003m 40 CFR 132, Table 6
c. Food				
FDA	Bottled drinking water allowable concentrations for total trihalomethanes[i]	0.10 mg/L		FDA 2003 21 CFR 165.110
d. Other				
ACGIH	Carcinogenicity classification	A3[j]		ACGIH 2003
EPA	Carcinogenicity classification			IRIS 2003a, 2003b
	Bromoform	B2[k]		
	Dibromochloromethane	C[l]		
	RfD			IRIS 2003a, 2003b
	Bromoform	2.0×10^{-2} mg/kg/day		
	Dibromochloromethane	2.0×10^{-2} mg/kg/day		
	Community right-to-know; release report; effective date of reporting			EPA 2003i 40 CFR 372.65
	Bromoform	01/01/87		
	Identification and listing of hazardous waste; hazardous waste number			EPA 2003d 40 CFR 261, Appendix VIII
	Bromoform	U225		
	Land disposal restrictions; universal treatment standards	Waste water (mg/L)	Non-waste water mg/kg)	EPA 2003e 40 CFR 268.48
	Bromoform	0.63	15	
	Dibromochloromethane	0.57	15	
	Municipal solid waste landfills; hazardous constituents	Suggested method	PQL (µg/L)	EPA 2003a 40 CFR 258, Appendix II
	Bromoform	8010	2	
		8021	15	
		8260	5	
	Dibromochloromethane	8010	1	
		8021	0.3	
		8260	5	

Table 8-1. Regulations and Guidelines Applicable to Bromoform and Dibromochloromethane

Agency	Description	Information		Reference
NATIONAL *(cont.)*				
	Reportable quantity of hazardous substance in accordance with Section 307 (a) of the Clean Water Act, Section 112 of RCRA, and Section 112 of the Clean Air Act			EPA 2003b 40 CFR 302.4
	Bromoform	100 pounds		
	Reportable quantity of hazardous substance in accordance with Section 112 of RCRA			EPA 2003b 40 CFR 302.4
	Dibromochloromethane	100 pounds		
	Standards for the management of specific hazardous waste and types of hazardous waste management facilities			EPA 2003g 40 CFR 266, Appendix V
		Risk specific doses ($\mu g/m^3$)		
	Bromoform	7.0×10^{-1}		
	Standards for owners or operators of hazardous waste TSD facilities; maximum concentration for groundwater protection			EPA 2003h 40 CFR 264, Appendix IX
		Suggested method	PQL (µg/L)	
	Bromoform	8010	2	
		8240	5	
	Dibromochloromethane	8010	1	
		8240	5	
	TSCA; chemical information rules	Effective date	Sunset date	EPA 2003k 40 CFR 712.30
	Bromoform	03/11/94	05/10/94	
	TSCA; health and safety data reporting	Effective date	Sunset date	EPA 2003j 40 CFR 716.120
	Bromoform	06/01/87	06/01/97	
	Dibromochloromethane	06/01/87	06/01/87	
	TSCA; identification of specific chemical substance and mixture testing requirements for			EPA 2003l 40 CFR 799.5055
	Bromoform	Hydrolysis testing		
STATE				
a. Air	No data			
b. Water				
Arizona	Drinking water guideline			HSDB 2003a, 2003b
	Bromoform	0.19 µg/L		
	Dibromochloromethane	0.19 µg/L		

Table 8-1. Regulations and Guidelines Applicable to Bromoform and Dibromochloromethane

Agency	Description	Information	Reference
STATE *(cont.)*			
Florida	Drinking water guideline		HSDB 2003a, 2003b
	Bromoform	4.0 μg/L	
	Dibromochloromethane	1.0 μg/L	
Minnesota	Drinking water guideline		HSDB 2003a, 2003b
	Bromoform	40 μg/L	
	Dibromochloromethane	10 μg/L	
New Hampshire	Drinking water guideline		HSDB 2003a
	Bromoform	4.0 μg/L	
Wisconsin	Drinking water guideline		HSDB 2003a, 2003b
	Bromoform	4.4 μg/L	
	Dibromochloromethane	60 μg/L	
c. Food	No data		
d. Other	No data		

[a]Group 3: not classifiable as to its carcinogenicity to humans
[b]Skin notation: refers to the potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, either by contact with vapors or, of probable greater significance, by direct skin contact with the substance.
[c]Skin designation: indicates the potential for dermal absorption; skin exposure should be prevented as necessary through the use of good work practices and gloves, coveralls, goggles, and other appropriate equipment.
[d]Skin designation
[e]DWEL: a lifetime exposure concentration protection of adverse, non-cancer health effects, that assumes all of the exposure to a contaminant is from drinking water.
[f]Lifetime: the concentration of a chemical in drinking water that is not expected to cause any adverse noncarcinogenic effects for a lifetime of exposure. The Lifetime HA is based on exposure of a 70-kg adult consuming 2 L water/day.
[g]10^{-2} Cancer risk: the concentration of a chemical in drinking water corresponding to an excess estimated lifetime cancer risk of 1 in 10,000.
[h]Total trihalomethanes (the sum of the concentrations of bromoform, dibromochloromethane, bromodichloromethane, and chloroform) applies to subpart H community water systems which serve a population of 10,000 people or more until December 31, 2001. This level applies to community water systems that use only groundwater not under the direct influence of surface water and serves a population of 10,000 people or more until December 31, 2003. Compliance with the MCL for total trihalomethanes is calculated pursuant to 40 CFR 141.30. After December 31, 2003, this section no longer applies.
[i]Total trihalomethanes: sum of the concentration in mg/L of the trihalomethane compounds (bromoform, dibromochloromethane, bromodichloromethane, and chloroform), rounded to two significant figures.
[j]A3: confirmed animal carcinogen with unknown relevance to humans
[k]B2: probable human carcinogen
[l]C: possible human carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; CFR = Code of Federal Regulations; DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; PQL = practical quantitation level; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfD = reference dose; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TSD = treatment, storage, and disposal; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

The EPA (IRIS 2003a) assigned bromoform an oral reference dose (RfD) of 2.00×10^{-2} mg/kg/day with an uncertainty factor of 1,000 based on hepatic lesions in rats (NTP 1989a). The EPA (IRIS 2003b) assigned dibromochloromethane an oral RfD of 2.00×10^{-2} mg/kg/day with an uncertainty factor of 1,000 based on hepatic lesions in rats (NTP 1985).

The EPA has assigned the following weight-of-evidence classifications: bromoform is assigned a classification of B2 (probable human carcinogen) (IRIS 2003a); and dibromochloromethane is assigned a classification of C (possible human carcinogen) (IRIS 2003b).

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

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

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

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

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by 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.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

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

Biomarkers—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.

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.

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

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research but are not actual research studies.

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

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.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

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

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

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

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

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 occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (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.

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

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

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

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

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

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

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

Immunological Effects—Functional changes in the immune response.

***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 has been reported to have caused death in humans or animals.

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

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

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

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

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

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

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

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

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

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

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

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

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. 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.

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

Organophosphate or Organophosphorus Compound—A phosphorus containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

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

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

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a

variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

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

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

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 μg/m^3 for air).

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

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

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily 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 no-observed-adverse-effect level (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 the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a 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.

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

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

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

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

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

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

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

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

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

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

Toxic Dose$_{(50)}$ (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.

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

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

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

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

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

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

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

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Bromoform
CAS Number: 75-25-2
Date: September 2003
Profile Status: Final Draft
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to Figure: 13
Species: Mice

Minimal Risk Level: 0.7 [X] mg/kg/day [ ] mg/m^3

Reference: Condie LW, Smallwood CL, Laurie RD. 1983. Comparative renal and hepatotoxicity of halomethanes: Bromodichloromethane, bromoform, chloroform, dibromochloromethane and methylene chloride. Drug Chem Toxicol 6:563-578.

Experimental design:

Groups of 5–16 male CD-1 mice received daily gavage doses of 0, 72, 145, or 289 mg/kg/day bromoform in corn oil for 14 days. Body weight was measured on days 1 and 14. Blood was collected for clinical chemistry at study termination. Renal cortical slices of kidney tissue were collected for measurement of para-aminohippurate (PAH) uptake, and samples of liver and kidney tissue were collected for histopathological examination.

Effects noted in study and corresponding concentrations:

No significant alterations in body weight gain were observed. PAH uptake by kidney slices was decreased by 30% in the 289 mg/kg/day group; a significant increase in SGPT was also observed at this dose. Minimal to moderate liver and kidney histological alterations were observed. Liver effects included centrilobular pallor at 145 and 289 mg/kg/day and focal inflammation at 289 mg/kg/day. Kidney effects consisted of epithelial hyperplasia at 289 mg/kg/day and mesangial nephrosis at 145 and 289 mg/kg/day.

Concentration and end point used for MRL derivation:

The MRL is based on a NOAEL of 72 mg/kg/day and a LOAEL of 145 mg/kg/day for hepatice centrilobular pallor in mice.

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: NA

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL:

Several acute-duration studies support the identification of the liver as the most sensitive target of bromoform toxicity. The observed effects include hepatocellular vacuolization and swelling (Chu et al. 1982a; Coffin et al. 2000), centrilobular pallor (Condie et al. 1983), increased absolute and relative liver weights (Munson et al. 1982), alterations in serum chemistry enzymes such as SGPT (Munson et al. 1982), and impaired liver function (Munson et al. 1982). The highest NOAEL for liver effects is 72 mg/kg/day in mice (Condie et al. 1983); in this study, centrilobular pallor (Condie et al. 1983), which was considered to be indicative of liver degeneration, was observed at 145 mg/kg/day. At 125 mg/kg/day, increases in liver weight were observed (Munson et al. 1982) and hepatocellular vacuolization and swelling were observed at 200 mg/kg (164 mg/kg/day) (Coffin et al. 2000). Other adverse effects that have been observed at similar or higher dose levels include mesangial nephrosis at 145 mg/kg/day (NOAEL of 72 mg/kg/day) (Condie et al. 1983), impaired immune function at 125 mg/kg/day (NOAEL of 50 mg/kg/day) (Munson et al. 1982), skeletal anomalies in the offspring of rats exposed to 200 mg/kg/day (NOAEL of 100 mg/kg/day) (Ruddick et al. 1983), and central nervous system depression at ≥600 mg/kg (Balster and Borzelleca 1982; Bowman et al. 1978; NTP 1989a). Although several adverse effects have been reported at 100–200 mg/kg/day, the liver was selected as the critical target because the adverse liver effects are consistently observed in animals following acute-, intermediate-, and chronic-duration exposure.

Agency Contact (Chemical Managers): John Risher, Dennis Jones

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Bromoform
CAS Number: 75-25-2
Date: September 2003
Profile Status: Final Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to Figure: 26
Species: Rat

Minimal Risk Level: 0.2 [X] mg/kg/day [ ] mg/m^3

Reference: NTP. 1989a. Toxicology and carcinogenesis studies of tribromomethane (bromoform) in F344/N rats and B6C3F1 mice (gavage studies). National Toxicology Program. Technical Report Series No. 350. Research Triangle Park, NC: U.S. Department of Health and Human Services.

Experimental design:

Groups of F344/N male and female F344/N rats (10/sex/group) received gavage doses of 0, 12, 25, 50, 100, or 200 mg/kg bromoform in corn oil 5 days/week for 13 weeks. The rats were observed twice per day and weighed weekly. At sacrifice, all animals were necropsied and tissues from the vehicle control and high dose groups were examined histologically.

Effects noted in study and corresponding concentrations:

None of the rats died before the end of the study. Final mean body weights were similar in dosed and control groups. Lethargy was observed in all male rats exposed to 100 or 200 mg/kg and in all females exposed to 200 mg/kg. Hepatocellular vacuolization was observed in male rats (3/10, 6/10, 5/10, 8/10, 8/10, and 10/10 in the 0, 12, 25, 50, 100, and 200 mg/kg groups, respectively); the response reached statistical significance (Fisher exact one-tailed p-value of 0.03) at 50 mg/kg/day. Severity data were not reported for this lesion, but the study authors noted that vacuoles were more numerous in the 200 mg/kg group. Corresponding hepatic effects were not observed in females.

Concentration and end point used for MRL derivation:

The MRL is based on a NOAEL of 25 mg/kg (duration-adjusted to 18 mg/kg/day) and a LOAEL of 50 mg/kg (duration-adjusted to 36 mg/kg/day) for hepatic lesions (hepatocellular vacuolization).

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: NA

Was a conversion used from intermittent to continuous exposure?

The NOAEL was adjusted for intermittent exposure:
25 mg/kg x 5 days/7 days = 18 mg/kg/day

Other additional studies or pertinent information that lend support to this MRL:

A number of animal studies have identified the liver as the critical target of bromoform oral toxicity. An intermediate-duration study in rats (Aida et al. 1992) supports the identification of 50 mg/kg as the critical dose. In this study, a LOAEL of 56.4 mg/kg/day was identified for hepatocellular vacuolization and swelling in rats exposed to bromoform in the diet for 1 month. At a higher dose (207.5 mg/kg/day), a decrease in serum triglycerides and an increase in serum cholesterol levels were found; these findings are consistent with the liver histological alterations. Mice appear to be less sensitive to the toxicity of bromoform than rats. NOAEL and LOAEL values of 100 and 200 mg/kg (5 days/week) for hepatocellular vacuolization were identified in the intermediate-duration mouse NTP study (NTP 1989a). Melnick et al. (1998) found hydropic degeneration and increases in SGPT and sorbitol dehydrogenase levels in mice receiving gavage doses of 500 mg/kg, 5 days/week for 3 weeks. Acute- and chronic-duration studies have also identified the liver as the most sensitive target of toxicity.

Agency Contact (Chemical Managers): John Risher, Dennis Jones

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Bromoform
CAS Number: 75-25-2
Date: September 2003
Profile Status: Final Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to Figure: 38
Species: Rat

Minimal Risk Level: 0.2 [X] mg/kg/day [ ] mg/m^3

Reference: NTP. 1989a. Toxicology and carcinogenesis studies of tribromomethane (bromoform) in F344/N rats and B6C3F1 mice (gavage studies). National Toxicology Program. Technical Report Series No. 350. Research Triangle Park, NC: U.S. Department of Health and Human Services.

Experimental design:

Groups of male and female F344/N rats (50/sex/group) were administered via gavage 0, 100, or 200 mg/kg bromoform in corn oil 5 days/week for 103 weeks. Animals were observed for clinical signs throughout the study. Body weights were measured weekly for 12 weeks and monthly thereafter. At termination, all study animals were necropsied. Full histopathological examination was performed on all control and high dose animals and on low dose males. Selected tissues including esophagus, gross lesions, kidney, liver, lymph nodes, mammary gland, pancreas, pituitary gland, salivary glands, thyroid gland, trachea, and uterus were examined in low-dose females.

Effects noted in study and corresponding concentrations:

Significantly increased mortality was observed in male rats exposed to 200 mg/kg after week 91 (36–78% vs. 26–32%). Survival was comparable to vehicle controls in males exposed to 100 mg/kg and in females exposed to 100 or 200 mg/kg. Bromoform-related clinical signs included lethargy in both sexes and aggressiveness in males. After 15 weeks, the difference between control body weights and body weights of males exposed to 200 mg/kg males was consistently ≥10%; terminal body weights were 21% lower than controls. In the females exposed to 200 mg/kg, the difference in body weights was ≥10% after week 41; terminal body weights were 25% lower than controls. Body weights in the 100 mg/kg groups were typically within 10% of controls. Bromoform-related hepatic lesions included fatty change (characterized as hepatocellular vacuolization) in 23/50, 49/50, and 50/50 males exposed to 0, 100, or 200 mg/kg, respectively, and 19/50, 39/49, and 46/50 females; chronic active inflammation (male: 0/50, 29/50, and 23/50; female: 9/50, 8/49, and 27/50); and necrosis (male: 7/50, 3/50, and 20/50; female: 11/50, 3/49, and 2/50). Other lesions with significantly increased incidences included salivary gland duct squamous metaplasia at 100 and 200 mg/kg (males: 0/50, 15/50, and 31/48; females: 0/49, 10/49, and 16/50) and chronic active inflammation (male: 0/50, 14/50, and 22/48; female: 0/49, 9/49, and 18/50); ulcers of the forestomach in males at 200 mg/kg (1/49, 5/50, and 10/50); chronic active inflammation in the lungs in males at 100 and 200 mg/kg (1/50, 7/50, and 15/50); squamous metaplasia in the prostate gland at 200 mg/kg (2/49, 6/46, and 12/50); hyperplasia of the anterior lobe of the pituitary gland in males at 100 mg/kg (9/48, 26/50, and 15/50); and spleen pigmentation in females at 200 mg/kg (7/49, 6/28, and 29/50), which was characteristic of hemosiderin. The occurrence of ulcers in the forestomach may have resulted from gavage bolus dose delivery. Lesions observed in the lungs and salivary glands were reported to be consistent with infection by sialodacryloadenitis (SDA) virus. However, since the

occurrence of these lesions was clearly dose-related, the study authors concluded that they were likely to represent a combination of viral and chemical-related effects.

It should be noted that the study authors did not report statistical analysis data for nonneoplastic lesions. An independent statistical analysis was conducted; statistical significance was determined using a Fisher exact test, one tailed $p<0.05$).

Concentration and end point used for MRL derivation:

The MRL is based on a LOAEL of 100 mg/kg (duration-adjusted to 71 mg/kg/day) for histopathological changes (vacuolization) in the liver.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: NA

Was a conversion used from intermittent to continuous exposure? Yes.

The LOAEL was adjusted for intermittent exposure:
100 mg/kg x 5 days/7 days = 71 mg/kg/day

Other additional studies or pertinent information that lend support to this MRL:

Two studies have examined the chronic toxicity of bromoform (NTP 1989a; Tobe et al. 1982). Both studies identified the liver as the most sensitive target of toxicity. Both the NTP (1989a) rat and mouse studies identified LOAEL values of 100 mg/kg (5 days/week) for hepatocellular vacuolization. The rat study was selected over the mouse study because the effects were observed in both sexes. This study is supported by a 2-year dietary study conducted by Tobe et al. (1982). Yellowing of the liver and increases in absolute and liver weights were observed in female rats exposed to 140 mg/kg/day; histological examinations were not conducted. Alterations in several clinical chemistry parameters are also indicative of liver damage. Increases in SGOT and SGPT and decreases in serum triglycerides and cholesterol were observed at 590–720 mg/kg/day. A number of intermediate-duration studies (Aida et al. 1992; Chu et al. 1982b; Melnick et al. 1998; NTP 1989a) support the identification of the liver as the critical target of bromoform toxicity.

Agency Contact (Chemical Managers): John Risher, Dennis Jones

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Dibromochloromethane
CAS Number: 124-48-1
Date: September 2003
Profile Status: Final Draft
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Key to Figure: 16
Species: Mouse

Minimal Risk Level: 0.1 [X] mg/kg/day [ ] mg/m^3

Reference: Condie LW, Smallwood CL, Laurie RD. 1983. Comparative renal and hepatotoxicity of halomethanes: Bromodichloromethane, bromoform, chloroform, dibromochloromethane and methylene chloride. Drug Chem Toxicol 6:563-578.

Experimental design:

Groups of 5–16 male CD-1 mice received daily gavage doses of 0, 37, 74, or 147 mg/kg/day dibromochloromethane in corn oil for 14 days. Body weight was measured on days 1 and 14. Blood was collected for clinical chemistry at study termination. Renal cortical slices of kidney tissue were collected for measurement of para-aminohippurate uptake, and samples of liver and kidney tissue were histopathological examination.

Effects noted in study and corresponding concentrations:

No deaths or treatment-related clinical signs were reported. No significant alterations in body weight gain were observed. Para-aminohippurate uptake by kidney slices was decreased by approximately 30% in the 147 mg/kg/day group; a significant increase in SGPT was also observed at this dose. Minimal to moderate liver and kidney histological alterations were observed. Liver effects included hepatocellular vacuolization at 37 mg/kg/day and higher (1/16, 3/5, 4/10, and 8/10 in the 0, 37, 74, and 147 mg/kg/day groups, respectively) and mitotic figures at 147 mg/kg/day (0/16, 0/5, 2/10, and 4/10). Kidney effects consisted of mesangial hypertrophy was observed at 37 mg/kg/day and higher (0/16, 4/5, 7/10, and 7/10).

Concentration and end point used for MRL derivation:

The MRL is based on a LOAEL of 37 mg/kg/day for hepatocellular vacuolization (Condie et al. 1983).

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: NA

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL:

There are numerous studies that support the identification of the liver as the critical target of dibromochloromethane toxicity. Hepatocellular vacuolization and/or swelling were observed in mice exposed to 100 and 300 mg/kg (9 doses in an 11-day period) (Coffin et al. 2000), at ≥50 mg/kg in rats and mice exposed to dibromochloromethane for an intermediate duration (Aida et al. 1992; Daniel et al. 1990; NTP 1985) and in rats and mice exposed to ≥40 for 2 years (NTP 1985). At higher doses, hepatocellular necrosis is observed (Aida et al. 1993; Daniel et al. 1990; NTP 1985) in rats and mice exposed to ≥100 mg/kg for intermediate durations.

The Condie et al. study (1983) also identified the 37 mg/kg/day dose as a LOAEL for kidney effects, mesangial cell hyperplasia. Other animal studies have also found kidney lesions following oral exposure to dibromochloromethane. Nephropathy, characterized by tubular cell degeneration and tubular cast formation was noted in 80% of male rats and 100% of female rats, but was not found in the controls or other dose groups exposed to dibromochloromethane in corn oil for 13 weeks (NTP 1985). The liver was selected as the critical target because the results of other studies suggest that it may be the more sensitive target of toxicity.

Agency Contact (Chemical Managers): John Risher, Dennis Jones

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Dibromochloromethane
CAS Number: 124-48-1
Date: September 2003
Profile Status: Final Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to Figure: 46
Species: Rat

Minimal Risk Level: 0.09 [X] mg/kg/day [ ] mg/m^3

Reference: NTP. 1985. Toxicology and carcinogenesis studies of dibromochloromethane in F344/N rats and B6C3F1 mice (gavage studies). National Toxicology Program. Technical Report Series No. 282. Research Triangle Park, NC: U.S. Department of Health and Human Services.

Experimental design:

Groups of 50 male and 50 female F344/N rats received 0, 40, or 80 mg/kg gavage doses of dibromochloromethane in corn oil 5 days/week for 2 years. Clinical signs were recorded weekly. Body weights were recorded weekly for the first twelve weeks of the study and monthly thereafter. Necropsy was performed on all animals. Histopathological examination was conducted on tissues from all dose groups.

Effects noted in study and corresponding concentrations:

Survival was comparable in all study groups. Body weight gain was within 10% of controls throughout the study. In the liver, fatty change (male: 27/50, 47/50, and 49/50; female: 12/50, 23/50, and 50/50) and "ground glass" cytoplasmic changes (male: 8/50, 22/50, and 34/50; female: 0/50, 1/50, and 12/50) were observed. A dose-related increase in nephrosis was observed in female rats (7/50, 11/50, and 14/50); however, the incidences in exposed rats was not statistically higher than in vehicle controls assessed using the Fisher exact test.

It should be noted that the study authors did not report statistical analysis data for nonneoplastic lesions. An independent statistical analysis was conducted; statistical significance was determined using a Fisher exact test, one tailed $p<0.05$).

Concentration and end point used for MRL derivation:

The MRL is based on a LOAEL of 40 mg/kg (duration-adjusted to 28 mg/kg/day) for liver histopathology (fatty change) (NTP 1985).

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 3 for use of a minimal LOAEL
[X] 10 for extrapolation from animals to humans

[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: NA

Was a conversion used from intermittent to continuous exposure?

The LOAEL was adjusted for intermittent exposure:
40 mg/kg x 5 days/7 days = 28 mg/kg/day

Other additional studies or pertinent information that lend support to this MRL:

The identification of the liver as the critical target is supported by numerous acute-duration studies in rats and mice exposed to ≥37 mg/kg (Chu et al. 1982a; Coffin et al. 2000; Condie et al. 1983; Hewitt et al. 1983; Munson et al. 198; NTP 1985), 50 mg/kg for intermediate durations (Aida et al. 1992; Daniel et al. 1990; Melnick et al. 1998; NTP 1985), and 40 mg/kg for chronic durations (NTP 1985; Tobe et al. 1982). The identification of the LOAEL of 40 mg/kg for fatty changes in the liver is supported by the NTP (1985) mouse study and a rat study by Tobe et al. (1982). Fatty metamorphosis was found in mice receiving gavage doses of 50 mg/kg, 5 days/week for 2 years (NTP 1985). Necrosis was observed at 100 mg/kg. In the Tobe et al. (1982) study, groups of rats were exposed to dibromochloromethane in diet for 2 years. No histological examinations were conducted; however, hypertrophy and yellowing of the liver was found at 85 mg/kg/day. Alterations in a number of clinical chemistry parameters, which are indicative of liver damage, were also observed. Decreases in serum triglycerides were observed at 20 mg/kg/day and decreases in serum cholesterol were observed at 540 mg/kg/day.

Agency Contact (Chemical Managers): John Risher, Dennis Jones

APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical 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 chemical.

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

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, 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 chapter covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter. If data are located in the scientific literature, a table of genotoxicity information is included.

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

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

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

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

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "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 the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgment, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgment or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen 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. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, 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. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of no-observed-adverse-effect levels (NOAELs), lowest-observed-adverse-effect levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 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 3-1

(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 exists, 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 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

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

(3) 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 (see key number 18).

(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 derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 3-1).

(5) Species The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/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 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(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, 1 systemic effect (respiratory) was investigated.

(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 "b").

(9) LOAEL A lowest-observed-adverse-effect level (LOAEL) is the lowest dose 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 respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in Chapter 9 of the profile.

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

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

LEGEND

See Figure 3-1

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

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

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

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

(16) NOAEL In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. 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 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived

from the 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.

SAMPLE

1 → **TABLE 3-1. 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							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89-104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79-103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

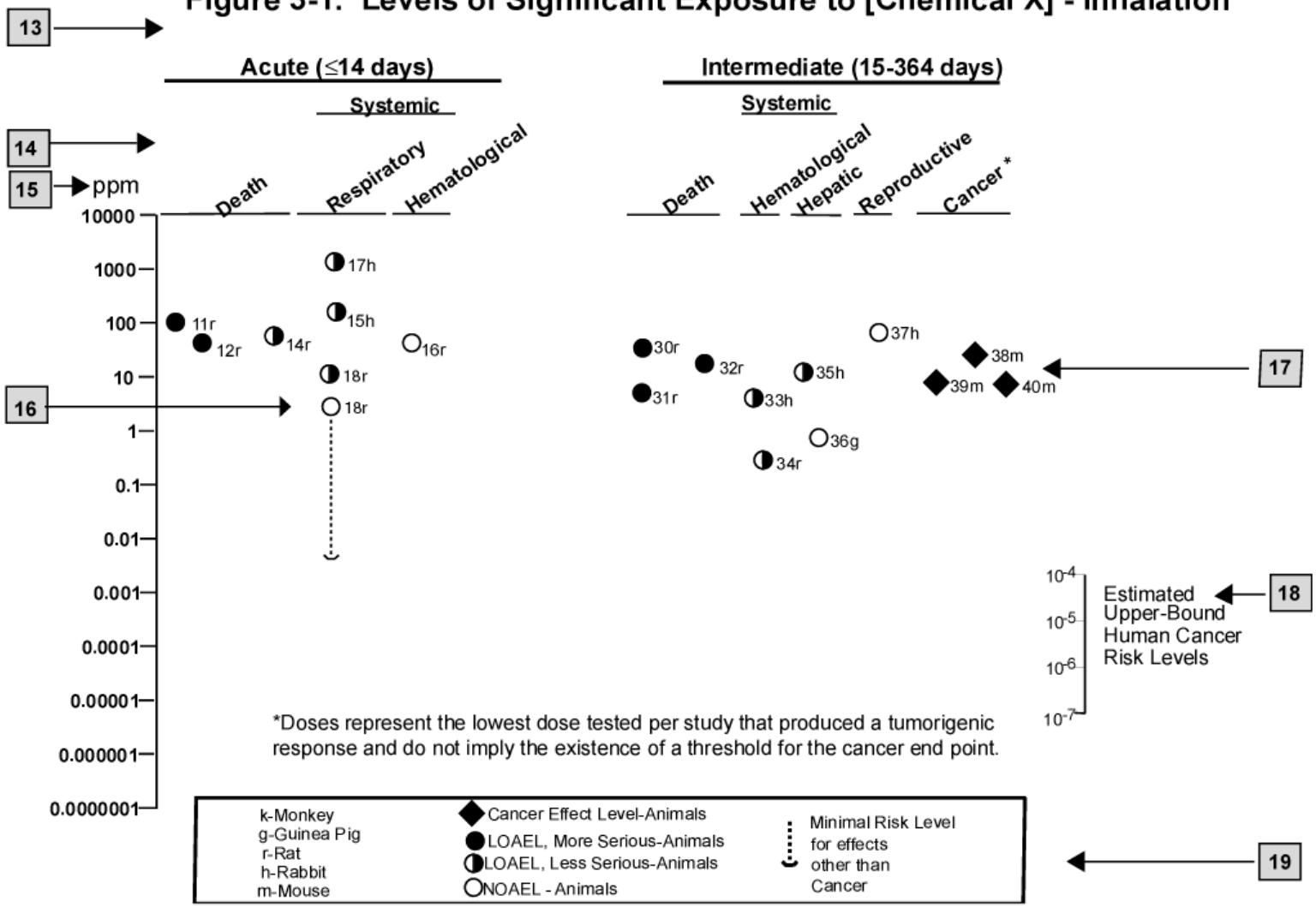
12 →

[a] The number corresponds to entries in Figure 3-1.

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

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



DRAFT FOR PUBLIC COMMENT

APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACOEM	American College of Occupational and Environmental Medicine
ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AOEC	Association of Occupational and Environmental Clinics
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotranferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/NA/IMCO	Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code

DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	*Federal Register*
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LDH	lactic dehydrogenase
LH	luteinizing hormone
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MFO	mixed function oxidase
mg	milligram

MIMS	membrane inlet mass spectrometry
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
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
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic

PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	reportable quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

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