



# Toxicological Profile for 1-Bromopropane

August 2017



U.S. Department of Health and Human Services  
Agency for Toxic Substances and Disease Registry

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## **DISCLAIMER**

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

## UPDATE STATEMENT

A Toxicological Profile for 1-Bromopropane, Draft for Public Comment was released in January 2016. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry  
Division of Toxicology and Human Health Sciences  
Environmental Toxicology Branch  
1600 Clifton Road NE  
Mailstop F-57  
Atlanta, Georgia 30329-4027

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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 these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a 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 the protection of public health are identified by ATSDR.

Each profile includes the following:

- (A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic 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.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs 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 was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



Patrick N. Breyse, Ph.D., CIH  
Director, National Center for Environmental Health and  
Agency for Toxic Substances and Disease Registry  
Centers for Disease Control and Prevention

### \*Legislative Background

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "...effectuate and implement the health related authorities" of the statute. This includes the preparation of 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. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the National Priorities List, in an effort to "...establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

## 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 may find the following information helpful for fast answers to often-asked questions.

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### *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 (e.g., 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:

<b>Chapter 1</b>	<b>How Can (Chemical X) Affect Children?</b>
<b>Chapter 1</b>	<b>How Can Families Reduce the Risk of Exposure to (Chemical X)?</b>
<b>Section 3.7</b>	<b>Children's Susceptibility</b>
<b>Section 6.6</b>	<b>Exposures of Children</b>

### **Other Sections of Interest:**

<b>Section 3.8</b>	<b>Biomarkers of Exposure and Effect</b>
<b>Section 3.11</b>	<b>Methods for Reducing Toxic Effects</b>

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### **ATSDR Information Center**

**Phone:** 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)

**Internet:** <http://www.atsdr.cdc.gov>

The following additional materials are available online:

*Case Studies in Environmental Medicine* are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see <https://www.atsdr.cdc.gov/csem/csem.html>).

*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 (see <https://www.atsdr.cdc.gov/MHMI/index.asp>). 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 Exposures*—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 (see <https://www.atsdr.cdc.gov/toxfaqs/Index.asp>).

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### ***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 • Web Page: <https://www.cdc.gov/nceh/>.

*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, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: <https://www.cdc.gov/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 • Web Page: <https://www.niehs.nih.gov/>.

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### ***Clinical Resources (Publicly Available Information)***

*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](mailto: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, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: <http://www.acoem.org/>.

*The American College of Medical Toxicology (ACMT)* is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard,



Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page:  
<http://www.acmt.net>.

*The Pediatric Environmental Health Specialty Units (PEHSUs)* is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at <http://pehsu.net/findhelp.html>.

*The American Association of Poison Control Centers (AAPCC)* provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page:  
<http://www.aapcc.org/>.

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## CONTRIBUTORS

### CHEMICAL MANAGER(S)/AUTHOR(S):

Nickolette Roney, M.P.H.  
Melanie Buser, M.P.H.  
Susan Zells Ingber, A.B., M.S.P.P.  
ATSDR, Division of Toxicology and Human Health Sciences, Atlanta, GA

Fernando Lladós, Ph.D.  
Peter McClure, Ph.D., D.A.B.T.  
Kimberly Zaccaria, Ph.D.  
Courtney Hard, B.A.  
SRC, Inc., North Syracuse, NY

### 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 Environmental Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.
4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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## PEER REVIEW

A peer review panel was assembled for 1-bromopropane. The panel consisted of the following members:

1. Xiaozhong (John) Yu MD, Ph.D., Department of Environmental Health Science, College of Public Health, University of Georgia, Athens, Georgia;
2. James V. Bruckner, Ph.D., Professor of Pharmacology and Toxicology, Department of Pharmaceutical and Biomedical Sciences, College of Pharmacy, University of Georgia, Athens, Georgia; and
3. Gaku Ichihara, M.D., Ph.D., Department of Occupational and Environmental Health Faculty of Pharmaceutical Sciences, Tokyo University of Science, Japan.

These experts collectively have knowledge of 1-bromopropane'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.

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 FOR 1-BROMOPROPANE

This Public Health Statement summarizes the Agency for Toxic Substances and Disease Registry's (ATSDR) findings on 1-bromopropane, including chemical characteristics, exposure risks, possible health effects from exposure, and ways to limit exposure.

The U.S. 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 sites targeted for long-term federal clean-up activities. 1-Bromopropane has not been reported at any EPA NPL sites; however, it is unknown how many of the 1,832 current or former NPL sites have been evaluated for the presence of 1-bromopropane. But the possibility remains that as more sites are evaluated, the sites where 1-bromopropane is found may increase. This information is important because these future sites may be sources of exposure, and exposure to 1-bromopropane may be harmful.

If you are exposed to 1-bromopropane, many factors determine whether you'll be harmed. These include how much you are exposed to (dose), how long you are exposed (duration), how often you are exposed (frequency), and how you are exposed (route of exposure). You must also consider the other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

### WHAT IS 1-BROMOPROPANE?

1-Bromopropane is a colorless liquid. Commercial 1-bromopropane includes not only 1-bromopropane, but also additives that improve its performance in the desired application and stabilizers to inhibit decomposition.

1-Bromopropane was originally used in the production of pesticides, flavors and fragrances, pharmaceuticals, and other chemicals. It is currently used as a solvent in the adhesives, dry cleaning, vapor degreasing, and electronic and metal cleaning industries. 1-Bromopropane production has increased over the last 10 years due to its use as a replacement for other more harmful substances.

More information regarding the identity of 1-bromopropane can be found in Chapters 4 and 5.

### WHAT HAPPENS TO 1-BROMOPROPANE WHEN IT ENTERS THE ENVIRONMENT?

1-Bromopropane quickly evaporates into the air when released to the environment. In air, it is broken down quickly. Half of 1-bromopropane will be broken down in 2 weeks. 1-Bromopropane has been

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detected in ambient air. 1-Bromopropane that enters surface water is slowly broken down. Most of it evaporates into air. 1-Bromopropane released to soil can enter surface water. It is not bound to soil particles, so it may enter groundwater. 1-Bromopropane is not likely to concentrate in the food chain.

More information regarding the levels 1-bromopropane in the environment can be found in Chapter 6.

### **HOW MIGHT I BE EXPOSED TO 1-BROMOPROPANE?**

Exposure to 1-bromopropane is mainly an occupational problem. Use of 1-bromopropane in aerosol applications can lead to dermal and inhalation exposure of workers. Workers using 1-bromopropane as a spray adhesive have the highest exposures. Workers involved in the production of 1-bromopropane, as well as those using it in commercial applications, such as adhesive sprays, degreasing operations for cleaning metals, plastics, and electronic components, dry cleaning, asphalt production, aircraft maintenance, and synthetic fiber manufacturing, also have potential for high exposure.

You may be exposed to 1-bromopropane in air when it is used during aerosol applications, specifically at locations in close proximity to facilities where it is used, processed, or manufactured, where vapor may migrate.

More information regarding exposure and 1-bromopropane can be found in Sections 6.5–6.7.

### **HOW CAN 1-BROMOPROPANE ENTER AND LEAVE MY BODY?**

When you breathe or touch 1-bromopropane (or products containing 1-bromopropane), it can be taken directly into your blood through your lungs and skin. There is no information available to show whether 1-bromopropane can enter the bloodstream if you swallow this substance in liquid form, but based on studies in animals, some of it will likely enter the bloodstream. Factors such as your age, sex, body composition, and overall health will affect what happens to 1-bromopropane once it is in your body. The majority of 1-bromopropane is removed from your body within a day. 1-Bromopropane may leave your body unchanged in the air you breathe or in your urine after it has been changed to breakdown products. More information on how 1-bromopropane can enter and leave your body can be found in Chapter 3.

### **HOW CAN 1-BROMOPROPANE AFFECT MY HEALTH?**

1-Bromopropane may have an effect on your nervous system (brain and nerves). Day-after-day exposure to low concentrations in workplace air has been associated with minor effects, such as headache,



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decreased sensation in the fingers and toes, and a drunk-like feeling. However, workers exposed to higher levels for weeks, months, or years have experienced severe effects requiring hospitalization, including incoordination, weakness, loss of feeling, inability to walk, and damage to nerves. Damage to the nervous system may not be reversible, resulting in long-term effects even after 1-bromopropane exposure is stopped.

Breathing 1-bromopropane may also lead to irritation of your nose and throat. Studies in animals suggest that high 1-bromopropane exposure may damage the liver or kidney, decrease your ability to resist infection, or impair your ability to get pregnant (or get someone pregnant). Evidence for these effects is limited. It is not known whether the same effects will happen in humans.

We do not know if 1-bromopropane causes cancer in humans. 1-Bromopropane has caused tumors in animal studies. Based on the findings in animals, the American Conference of Industrial Hygienists (ACGIH) has assigned 1-bromopropane a classification of “*A3 – Confirmed animal carcinogen with unknown relevance to humans*” and the Department of Health and Human Services (DHHS) has classified 1-bromopropane as “*reasonably anticipated to be a human carcinogen*”. The International Agency for Research on Cancer (IARC) and the EPA have not evaluated the carcinogenicity of 1-bromopropane.

See Chapters 2 and 3 for more information on health effects of 1-bromopropane.

**HOW CAN 1-BROMOPROPANE AFFECT CHILDREN?**

This section discusses potential health effects of 1-bromopropane exposure in humans from when they're first conceived to 18 years of age.

The health effects of 1-bromopropane exposure in children are not known. The nervous system is expected to be a target based on findings in adults. Because the nervous system is still developing in children, they might be more sensitive to nervous system effects seen in adults. However, since exposure to 1-bromopropane occurs mainly in worker settings, children are less likely to be exposed to 1-bromopropane.

It is not known if a fetus or infant can be harmed if a woman is exposed to 1-bromopropane during pregnancy or breastfeeding. Studies in animals have shown effects when mothers were exposed to high levels of 1-bromopropane (500 parts per million [ppm] or higher) during pregnancy and/or nursing.

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However, the exposure levels in these studies were much higher than is expected to occur in human exposures. Therefore, the relevance of these findings to humans is unknown.

More information regarding children's health and 1-bromopropane can be found in Section 3.7.

**HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO 1-BROMOPROPANE?**

If your doctor finds that you have been exposed to significant amounts of 1-bromopropane, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate. You may also contact the state or local health department with health concerns.

Unless you live near a factory/business that uses 1-bromopropane, your household exposure to 1-bromopropane is expected to be minimal. If someone in the household works in a factory or business that produces or uses 1-bromopropane, a change of clothes prior to returning home will decrease the chance of traces of 1-bromopropane entering the home. Although the speed of dermal absorption of 1-bromopropane is unknown, thorough washing of exposed skin including face and hands should decrease the chance of carrying the substance home.

**ARE THERE MEDICAL TESTS TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO 1-BROMOPROPANE?**

1-Bromopropane and its breakdown products (metabolites) can be measured in the urine. However, the detection of 1-bromopropane or its metabolites cannot predict the kind of health effects that might develop from that exposure. Because 1-bromopropane and its metabolites leave the body fairly rapidly, urine tests for these substances need to be conducted within days after exposure.

For more information on the different substances formed by 1-bromopropane breakdown and on tests to detect these substances in the body, see Chapters 3 and 7.

**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

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public health but are not enforceable 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 as “not-to-exceed” levels; that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value usually based on levels that affect animals; levels are then adjusted to help protect humans. Sometimes these not-to-exceed levels differ among federal organizations. Different organizations use different exposure times (e.g., an 8-hour workday or a 24-hour day), different animal studies, or emphasize some factors over others, depending on their mission.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that issued the regulation or recommendation.

Currently, there are no federal recommendations or regulations available for 1-bromopropane.

For more information regarding regulations and recommendations pertaining to 1-bromopropane, see Chapter 8.

**WHERE CAN I GET MORE INFORMATION?**

If you have any questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below. You may also contact your doctor if experiencing adverse health effects or for medical concerns or questions. ATSDR can also provide publicly available information regarding medical specialists with expertise and experience recognizing, evaluating, treating, and managing patients exposed to hazardous substances.

- Call the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636) or
- Write to:  
Agency for Toxic Substances and Disease Registry  
Division of Toxicology and Human Health Sciences  
1600 Clifton Road NE  
Mailstop F-57  
Atlanta, GA 30329-4027

## 1. PUBLIC HEALTH STATEMENT

Toxicological profiles and other information are available on ATSDR's web site:  
<http://www.atsdr.cdc.gov>.

## 2. RELEVANCE TO PUBLIC HEALTH

### 2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO 1-BROMOPROPANE IN THE UNITED STATES

1-Bromopropane is a brominated hydrocarbon that was originally used as an intermediate in the production of pesticides, flavors and fragrances, pharmaceuticals, and other chemicals. It is currently used as a solvent in the adhesives, dry cleaning, vapor degreasing, and electronic and metal cleaning industries. There has been an increased use of 1-bromopropane in the last decade due to its application as a substitute for ozone-depleting substances and suspected carcinogens in various industrial and commercial applications. Due to the increased use of 1-bromopropane, exposure to workers has been increasing, and this has caused some human health concern, such as neurological alterations and reproductive toxicity. Therefore, its use in certain industries is being reevaluated.

The dominant process affecting the overall environmental fate and transport of 1-bromopropane is volatilization. In water, estimated volatilization half-lives for a model river and a model lake were reported as 1.2 hours and 4.4 days, respectively. 1-Bromopropane in air will be degraded by photochemically produced hydroxyl radicals, with 1-bromopropane having a half-life of 14 days. Hydrolysis and biodegradation by microorganisms have also been shown to break down 1-bromopropane in aquatic and terrestrial environments. 1-Bromopropane is not expected to bioaccumulate in aquatic organisms.

Exposure to 1-bromopropane occurs mainly in occupational settings. Use of 1-bromopropane in aerosol applications can lead to dermal and inhalation exposure of workers. Workers using 1-bromopropane as a spray adhesive have the highest dermal and inhalation exposures. Workers involved in the production of 1-bromopropane, as well as those using it in commercial applications, such as adhesive sprays, degreasing operations for cleaning metals, plastics, and electronic components, dry cleaning, asphalt production, aircraft maintenance, and synthetic fiber manufacturing, also have potential for high exposure. The general population may be exposed to 1-bromopropane in air when it is used during aerosol applications due to potential vapor migration, particularly at locations in close proximity to the emissive use of 1-bromopropane.

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**2.2 SUMMARY OF HEALTH EFFECTS**

The preponderance of health effects information on 1-bromopropane is from studies of laboratory animals and human studies in which the main exposure route is inhalation, but dermal exposure may have also occurred in the human studies. As summarized below and detailed in Chapter 3 (Health Effects), the main target organ of concern following 1-bromopropane exposure in humans is the nervous system.

Reported health effects in workers exposed to 1-bromopropane for months or years range from subtle neurological deficits (e.g., decreased vibration sense and paresthesias) at workplace air concentrations as low as 1.28 ppm to frank neurotoxic effects (e.g., ataxia, spastic paraparesis, and symmetric demyelinating polyneuropathy) in workers exposed to concentrations  $\geq 100$  ppm. Although the principal route of exposure was likely inhalation, dermal exposure could have been significant since often no gloves were used when handling 1-bromopropane, or the use of gloves, as noted in some reports, may have enhanced dermal uptake of 1-bromopropane by occlusion effect. Evidence of alterations of the autonomic nervous system has also been presented. A study that followed workers as outpatients for 2 years post-exposure reported persistent symptoms including headache, decreased memory, decreased mood, lower extremities numbness, cramping, paresthesias, weakness, and difficulty walking/poor balance. Clinical signs noted in these individuals included decreased cognition, lower extremities spasticity and weakness, gait ataxia, hyperreflexia, and decreased lower extremities sensation. It was suggested that the pathogenesis of 1-bromopropane neurotoxicity in humans may reflect a central distal axonopathy syndrome.

Results from animal studies support the conclusion that exposure to 1-bromopropane can result in neurotoxicity. Reported effects in acute- and intermediate-duration inhalation studies at concentrations  $\geq 50$  ppm 1-bromopropane included changes in neurobehavior, electrophysiological parameters, and in morphology and biochemistry of the central and peripheral nervous systems. Impaired learning and memory, sedation, and biochemical changes were also reported in rats after 12 days of ingestion of doses of 200 mg 1-bromopropane/kg/day in oral studies that assessed neurological end points in laboratory animals.

Various *in vivo* and *in vitro* mechanistic studies have been conducted to investigate the mechanism(s) involved in the neurotoxic action of 1-bromopropane in animals (see Section 3.5.2, Mechanisms of Toxicity). Proposed mechanisms include changes in neurotransmitter systems, electrophysiological

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alterations, decreased neurogenesis, glial activation, inhibition of anti-apoptotic processes, and oxidative stress; however, no definitive mechanism of action has yet been determined.

Limited data are available regarding non-neoplastic health effects in humans exposed to 1-bromopropane other than neurological effects. Preliminary health surveys and occupational case studies suggest that 1-bromopropane may be a respiratory tract irritant. These data are supported by findings of respiratory tract lesions in rats and mice exposed to  $\geq 125$  or  $\geq 62.5$  ppm 1-bromopropane, respectively, for intermediate-duration periods. Limited human clinical chemistry data do not indicate that the liver or kidney are sensitive targets of 1-bromopropane, although animal studies suggest that liver and/or kidney damage may occur with repeated exposure to concentrations  $\geq 50$  ppm. Limited reproductive data available in two NIOSH Health Hazard Evaluation reports and two preliminary health surveys are inadequate to assess the reproductive toxicity of 1-bromopropane in humans. The available animal data, however, show that 1-bromopropane exposure can adversely affect the male and female reproductive systems (sperm damage, altered hormone concentrations, altered estrous cycles, altered reproductive development) at exposure concentrations  $\geq 50$  ppm.

There are no developmental studies in humans exposed to 1-bromopropane. Studies in rats suggest that maternal exposure to  $\geq 500$  ppm 1-bromopropane can result in reduced body weight in the offspring. 1-Bromopropane was not teratogenic in animal studies. No human data are available regarding immune system effects, but one inhalation and one oral study in animals suggest that 1-bromopropane exposure can suppress immune responses. Available data do not provide consistent evidence for exposure-related effects in other organ systems (cardiovascular, dermal, endocrine, gastrointestinal, hematological, or ocular); therefore, non-neoplastic effects in these systems following exposure to 1-bromopropane are unlikely to occur.

There are no cancer studies in humans exposed to 1-bromopropane. The potential carcinogenicity of 1-bromopropane has been examined in 2-year inhalation bioassays with F-344 rats and B6C3F1 mice. 1-Bromopropane was a multi-site carcinogen in rats, significantly increasing the incidence of large intestine adenomas in females (500 ppm), skin keratoacanthoma in males ( $\geq 250$  ppm), skin keratoacanthoma, basal cell adenoma, or squamous cell carcinoma in males ( $\geq 125$  ppm), malignant mesothelioma in males (500 ppm), and pancreatic islet adenoma in males ( $\geq 125$  ppm). In mice, exposure to 1-bromopropane significantly increased the incidence of combined alveolar/bronchiolar adenoma or carcinoma in females ( $\geq 62.5$  ppm). Based on the findings from the NTP bioassay, ACGIH has assigned 1-bromopropane a classification of “A3 – *Confirmed animal carcinogen with unknown relevance to*

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*humans,*” and the Department of Health and Human Services has classified 1-bromopropane as “*reasonably anticipated to be a human carcinogen*”. IARC and the EPA have not evaluated the carcinogenicity of 1-bromopropane.

### 2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been established for 1-bromopropane. 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.

#### *Inhalation MRLs*

- An MRL of 1 ppm (5 mg/m<sup>3</sup>) has been derived for acute-duration inhalation exposure (14 days or less) to 1-bromopropane.

The MRL is based on a BMCL<sub>1SD</sub> of 97.40 ppm for neurological effects in rats exposed intermittently to 1-bromopropane for 14 days (Honma et al. 2003). No adequate data in humans are available. The only acute-duration inhalation studies in humans were a few case studies reporting subjective symptoms in workers within 2 weeks of 1-bromopropane introduction into the workplace. Symptoms included respiratory irritation, headache, nausea, and lower extremity numbness, pain, and weakness; the geometric mean air concentration was 107 ppm for glue sprayers (range 58–254 ppm) (Raymond and Ford 2007). Acute animal inhalation studies included two single-exposure studies evaluating lethality (Elf AtoChem S.A. 1997; Kim et al. 1999), a single-exposure study evaluating sperm motility (Garner et



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al. 2007), a 1-week study evaluating neurogenesis and endocrine end points (Zhang et al. 2013), a 1-week study evaluating morphological and biochemical changes in the brain (Wang et al. 2002), and a 3-week study that also provided results of neurobehavioral tests conducted in rats during the first 2 weeks of exposure (Honma et al. 2003). Garner et al. (2007) reported significantly reduced sperm motility in mice following a single 6-hour exposure to 800 ppm 1-bromopropane for 6 hours. It should be noted, however, that because the initial concentration of 800 ppm 1-bromopropane decreased steadily during the 6-hour exposure period, the true LOAEL may have been somewhat lower. Wang et al. (2002) reported morphological changes in the medulla oblongata and posterior tibial nerve in rats exposed to 800 ppm 1-bromopropane, but not  $\leq 400$  ppm, for 1 week (Wang et al. 2002). However, only one rat/group was assessed for morphological alterations. Wang et al. (2002) also reported several biochemical changes in the central nervous system of rats following exposure to  $\geq 200$  ppm 1-bromopropane. The toxicological significance of these changes is unknown because there were no clear associations between biochemical and morphological changes. Other reported neurological effects included decreased activity and ataxia after single exposures to  $\geq 1,800$  ppm, but not 300 ppm; however, only qualitative data were provided in that study (Kim et al. 1999). In the Zhang et al. (2013) study, there were no exposure-related changes in hippocampal neurogenesis, adrenal weight, or plasma corticosterone levels in male rats intermittently exposed to 1,000 ppm 1-bromopropane (the highest exposure concentration tested) for 1 week. Honma et al. (2003) conducted several neurobehavioral tests in male F-344 rats following exposure to  $\leq 1,000$  ppm 1-bromopropane 8 hours/day, 7 days/week for 3 weeks. All tests were conducted at various times after the 3-week exposure period except a traction test that was also conducted on exposure days 1, 7, and 14. The traction test was used to measure forelimb grip strength. No statistically significant differences in grip strength were observed between exposed rats (10, 50, 200, 1,000 ppm 1-bromopropane) and controls on days 1 or 7. On day 14, however, rats exposed to 1,000 ppm 1-bromopropane showed a statistically significant decrease in grip strength compared to lower exposure groups and controls, thus defining a no-observed-adverse-effect level (NOAEL) and LOAEL of 200 and 1,000 ppm, respectively, for neurological effects in an acute-duration inhalation study. Because all data were presented graphically, the means and standard errors (standard deviations [SDs] were subsequently calculated) for traction time (assessed on day 14) were extracted digitally using GrabIt! software (version XP2) for benchmark dose (BMD) analysis. The  $BMCL_{1SD}$  of 97.40 ppm from the selected model (Exponential model 4) was duration-adjusted (8/24 hours) to calculate a  $BMCL_{[HEC]}$  of 32.3 ppm. Applying an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability) to the  $BMCL_{[HEC]}$  of 32.3 ppm yields an acute-duration inhalation MRL of 1 ppm for 1-bromopropane. A duration adjustment (8/24 hours) seemed appropriate in the absence of information regarding whether

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Haber's Law is applicable under the experimental conditions of the study. Further details of the MRL derivation are presented in Appendix A.

- An MRL of 0.1 ppm (0.5 mg/m<sup>3</sup>) has been derived for intermediate-duration inhalation exposure (15–364 days) to 1-bromopropane.

Adequate human data are not available. There are three publications of human cases exposed for intermediate durations (from weeks to months) that provide exposure levels. A case discussed by Ichihara et al. (2002) (case 3) was a woman who showed signs of staggering and numbness and paresthesias in the feet, thighs, lower back, and hips, and complained of headaches after 2 months of using 1-bromopropane as a solvent with a spray gun. Estimates of the exposure levels using a passive sampler indicated that the daily time-weighted average (TWA) concentration ranged from 60 to 261 ppm with an average of 133±67 ppm (SD). An MRL cannot be based on a single case. Raymond and Ford (2007) reported that four workers developed severe ataxia, sensory motor, and cognitive impairments soon after the introduction of 1-bromopropane into their workplace as a furniture adhesive. A survey conducted by the National Institute of Occupational Safety and Health (NIOSH) 9 months after the four workers became ill showed that the workers could have been exposed to a mean concentration of 1-bromopropane of 107 ppm (range 58–254 ppm). This study is not suitable for MRL derivation because of the small size of the cohort, the fact that the workers studied had elevated urinary arsenic concentrations from unknown sources, a major confounder, and lack of exposure data at the time of the illnesses. In a brief communication, Wang et al. (2015) reported that 6 out of 20–25 workers in a golf-club cleaning business in Taiwan developed neurological symptoms, including tingling pain, soreness in the lower extremities, and paresthesia after exposure to 1-bromopropane for 3–10 months. Workers were assigned to wash and dry golf clubs with the solvent. The mean of three measurements of 1-bromopropane in air over the platform of the washing tank was 128.8 ppm (range 97.3–188.6 ppm). Because only qualitative data were presented, no personal air sampling was available, and dermal contact with 1-bromopropane may have been considerable (no data on the use of gloves were provided), this study is inadequate for MRL derivation.

Examination of the intermediate-duration inhalation database in animals suggests that the liver and the nervous system might be targets for 1-bromopropane toxicity. Four studies identified the lowest LOAEL of 50 ppm 1-bromopropane. At this exposure concentration, Kim et al. (1999) reported hepatocyte vacuolization in Sprague-Dawley rats exposed intermittently for 8 weeks; Liu et al. (2009) reported hepatocellular degeneration and focal necrosis and alterations in sperm parameters in BALB/cA mice exposed intermittently for 4 weeks, Zong et al. (2016) reported mild hepatocyte degeneration in rats

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exposed intermittently for 4 weeks, and Honma et al. (2003) reported increased spontaneous locomotor activity in Fischer-344 rats exposed intermittently for 3 weeks. The 50 ppm exposure concentration was the lowest concentration tested in the Kim et al. (1999), Liu et al. (2009), and Zong et al. (2016) studies, whereas Honma et al. (2003) identified a NOAEL of 10 ppm for neurological effects. Of these three studies, the Honma et al. (2003) study appears to be the most appropriate for MRL derivation for the following reasons: (1) the nervous system is the most sensitive target for 1-bromopropane in humans as evidenced in studies in workers and case reports (no adverse hepatic effects have been reported in individuals showing clear signs of neurotoxicity) and (2) it identified a NOAEL for neurological effects. In the Honma et al. (2003) study, spontaneous locomotor activity was monitored in groups of male F-344 rats (4/group) following 3 weeks of daily 8-hour whole-body exposures to 0, 10, 50, or 200 ppm 1-bromopropane vapors. After the 3-week exposure period, rats were tested once per day for 6 consecutive days. Significant increases in spontaneous locomotor activity relative to controls occurred in the groups exposed to 50 ppm 1-bromopropane on post-exposure days 1, 2, and 3 and in the group exposed to 200 ppm on post-exposure days 1, 2, 3, and 4. No significant difference from controls was observed in rats exposed to 10 ppm 1-bromopropane. The spontaneous locomotor activity results were presented graphically; however, the data were not amenable for extraction using GrabIt! Software (version XP2). Thus, the NOAEL/LOAEL approach was used to identify the point of departure (POD) for the MRL. The data (Figure 3 in the study) are presented as changes in spontaneous locomotor activity relative to pre-exposure levels (assigned as 100% activity) for each day post-exposure that the test was performed (up to 6 days post-exposure). The selection of which post-exposure day (1 to 6) to model to compare treated and controls would have been entirely arbitrary. The NOAEL of 10 ppm was duration-adjusted (8/24) to calculate the NOAEL<sub>[HEC]</sub> of 3.33 ppm. Applying an uncertainty factor of 30 (3 for dosimetric adjustment and 10 for human variability) resulted in an intermediate-duration inhalation MRL of 0.1 ppm for 1-bromopropane. A duration adjustment (8/24 hours) seemed appropriate in the absence of information regarding whether Haber's Law is applicable under the experimental conditions of the study. Further details of the MRL derivation are presented in Appendix A.

- An MRL of 0.02 ppm (0.1 mg/m<sup>3</sup>) has been derived for chronic-duration inhalation exposure (365 days or more) to 1-bromopropane.

This MRL was based on a minimal LOAEL of 1.28 ppm for mild neurological impairment (increased vibration sense threshold in toes, indicating decreased vibration sense) in female workers from three 1-bromopropane production facilities in China employed for an average duration of ~40 months (Li et al. 2010). The study examined a number of neurological parameters in a population of workers and age-, sex-, and region-matched controls in three 1-bromopropane production plants in China. The final analysis

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comprised 120 women (60 exposed and 60 referents) and 52 men (26 exposed and 26 referents). Median individual TWA exposure to 1-bromopropane ranged from 0.07 to 106.4 ppm for females and from 0.06 to 114.8 ppm for males. After conducting multiple analyses, the vibration sense threshold showed the clearest dose-related effect, with significant increases (indicative of decreased vibration sense) in all exposed female groups. No significant differences between controls and individual male groups were seen regarding neurological parameters in this analysis. The minimal LOAEL of 1.28 ppm for increased vibration sense threshold (decreased vibration sense) in females was adjusted for continuous exposure ( $1.28 \text{ ppm} \times 5 \text{ days/7 days} \times 12 \text{ hours/24 hours} = 0.46 \text{ ppm}$ ) and was divided by an uncertainty factor of 30 (3 for use of minimal LOAEL and 10 to account for human variability) to derive the MRL of 0.02 ppm ( $0.1 \text{ mg/m}^3$ ). However, the confidence in the MRL is low due to a number of limitations of the principal study, most notably potential underestimation of 1-bromopropane exposure levels and concerns regarding the sensitivity of the vibration sense measurement method utilized in the study. However, after careful review of limitations and criticisms, as well as the available human and animal data, this study was considered to be the best available study on which to base the chronic MRL. In support, basing an MRL on the most sensitive animal study identifying a LOAEL for respiratory lesions (Morgan et al. 2011; NTP 2011) would yield an MRL of 0.03 ppm ( $0.15 \text{ mg/m}^3$ ), which is essentially equivalent to the MRL based on the selected human study. The rationale for selecting the Li et al. (2010) study as the principal study for the derivation of the chronic inhalation MRL, despite acknowledged limitations, is discussed in detail in Appendix A.

ACGIH (2014, 2016) has recommended a Threshold Limit Value (TLV) of 0.1 ppm 1-bromopropane based on the same end point from the Li et al. (2010) study. This value is designed to be protective for healthy adult workers exposed daily over a working lifetime.

***Oral MRLs***

- An MRL of 0.2 mg 1-bromopropane/kg/day has been derived for acute-duration (14 days or less) oral exposure to 1-bromopropane

This MRL was based on a  $\text{BMDL}_{\text{LSD}}$  of 19.75 mg 1-bromopropane/kg/day for impaired memory in the Morris water maze test in Wistar rats exposed to 0, 200, 400, or 800 mg 1-bromopropane/kg/day via gavage for 12 days (Zhong et al. 2013). On days 8–12, cognitive function (spatial learning and memory) was assessed with the Morris water maze test and dose-related impairments were observed in learning and memory measures. On day 5, when the escape platform was removed to assess memory, all exposure groups showed a significant decrease in the number of times they crossed the former location of the

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escape platform. A LOAEL of 200 mg/kg/day was identified for this study based on impaired spatial learning and memory (increased swimming distance, altered search pattern, decreased number of crossings of the escape platform); no NOAEL was identified. All data were presented graphically. The SDs could not be extracted from day 1–4 figures, either because they overlapped between dose groups (total swimming distance) or they were not reported (distribution of search patterns); therefore, these data could not be used for BMD analysis. However, the means and standard deviations for the number of crossings of the escape platform (assessed on day 5) were extracted digitally using GrabIt! software (version XP2) for BMD analysis. Alternate data extraction of the means and SDs using DigitizeIt software resulted in BMDLs that differed by <17% on average, which would yield the same MRL. The BMDL<sub>1SD</sub> of 19.75 mg 1-bromopropane/kg/day from the selected model (Hill) was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 to account for human variability) to derive an MRL of 0.2 mg 1-bromopropane/kg/day. Further details regarding the Zhong et al. (2013) study can be found in Appendix A. A more recent study by the same groups of investigators confirmed the previous results and reported that treatment of male Wistar rats with  $\geq 200$  mg 1-bromopropane/kg/day for 12 days impaired spatial memory and spatial learning ability (Guo et al. 2015). In this study, rats exposed to  $\geq 200$  mg 1-bromopropane/kg/day in the Morris Water Maze showed a significantly dose-related decreased percent of time at the target platform; the NOAEL was 100 mg 1-bromopropane/kg/day. Modeling of these data yielded a BMDL<sub>1SD</sub> (POD) of 77.94 mg 1-bromopropane/kg/day, which is higher than the BMDL<sub>1SD</sub> of 19.75 mg 1-bromopropane /kg/day used to derive the current MRL. Therefore, it is still more appropriate (more protective) to use data from Zhong et al. (2013) to derive an acute-duration oral MRL for 1-bromopropane.

No intermediate-duration oral MRL was derived for 1-bromopropane due to a lack of adequate studies. No chronic-duration oral MRL was derived for 1-bromopropane due to a lack of oral studies for chronic durations.

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### 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 1-bromopropane. 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 (e.g., death, systemic, immunological, neurological, reproductive, developmental, 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

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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 1-bromopropane are indicated in Table 3-1 and Figure 3-1.

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.

Unless otherwise stated, all animal studies mentioned in Section 3.2 tested commercial-grade 1-bromopropane (purity  $\geq 99\%$ ).

#### **3.2.1 Inhalation Exposure**

In occupational studies and case reports described below, exposure to 1-bromopropane occurred primarily via the inhalation route, but dermal exposure may have also occurred. Since (in most cases) it is not known whether the workers were using protective clothing and/or respirators, the specific contribution of each route of exposure is not possible to determine. Therefore, the reader should keep in mind that both inhalation and dermal routes combined may have contributed to the effects described.

##### **3.2.1.1 Death**

No reports of deaths in humans following inhalation exposure to 1-bromopropane were located in the available literature.

Lethal exposure concentrations have been identified in rats in acute-duration studies and in mice in intermediate-duration studies. In male and female rats exposed for 4 hours to concentrations of 1-bromopropane vapors ranging from 11,000 to 17,000 ppm, the combined  $LC_{50}$  was 14,374 ppm (95%



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confidence interval [CI], 13,624–15,596) (Kim et al. 1999). No rats died in the 11,000-ppm exposure group, and all rats exposed to 17,000 ppm 1-bromopropane died during the 14-day observation period. Necropsy did not reveal gross alterations. Light microscopy showed that some exposed rats had cytoplasmic vacuolization of hepatocytes. In another study of male and female rats exposed for 4 hours to concentrations of 1-bromopropane vapors ranging from 6,040 to 8,500 ppm, the combined  $LC_{50}$  was 7,000 ppm (Elf AtoChem S.A. 1997). At necropsy, pulmonary lesions consisting of edema and “emphysema” were observed.

In intermediate-duration studies, exposure to 500 ppm 1-bromopropane vapors 6 hours/day, 5 days/week resulted in significant lethality in male and mice during the first 2 weeks of exposure (Anderson et al. 2010; NTP 2011). No deaths occurred in mice exposed to 250 ppm 1-bromopropane. The cause of death was not specified in these studies, but NTP stated that in the 14-week study, lethargy and abnormal breathing were observed in moribund mice on week 1. Since the 16-day and 14-week NTP studies also tested rats exposed up to 2,000 and 1,000 ppm 1-bromopropane, respectively, and there were no compound-related deaths, mice appear to be considerably more sensitive than rats to the acute toxicity of 1-bromopropane.

The  $LC_{50}$  from Kim et al. (1999) and the lethal doses from Anderson et al. (2010) and NTP (2011) are listed in Table 3-1 and plotted in Figure 3-1.

### 3.2.1.2 Systemic Effects

The highest NOAEL values and all LOAEL values for each reliable study for systemic effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

**Respiratory Effects.** One preliminary health survey and several case reports of workers experiencing frank neurotoxicity following exposure to 1-bromopropane indicate that occupational exposure to 1-bromopropane can cause mild respiratory irritation. In a preliminary health survey, 10/24 female and 6/13 male workers from a Chinese 1-bromopropane factory reported nose and/or throat irritation; workers were exposed to 1–171 ppm 1-bromopropane for 1–115 months (Ichihara et al. 2004a). In three female workers from a cushion company who were hospitalized for neurological symptoms following exposure to 1-bromopropane for 8–9 hours/day for  $\geq 3$  months, two of the women complained of sore throat, hoarseness, and/or sinus irritation (Ichihara et al. 2002). The mean daily time-weighted exposure level was  $133 \pm 67$  ppm (range 60–261 ppm). Raymond and Ford (2007) reported sinusitis in a woman who

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Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
ACUTE EXPOSURE								
Death								
1	Rat (Wistar)	4 hr				7000 (4-hour LC50)	Elf AtoChem S.A. 1997 1-Bromopropane	
2	Rat (Sprague- Dawley)	4 hr				14374 (4-hour LC50)	Kim et al. 1999 1-Bromopropane	
3	Mouse (B6C3F1)	4-10 wk 5 d/wk 6 hr/d				500 F (3/8 died in the first week)	Anderson et al. 2010 1-Bromopropane	
4	Mouse (B6C3F1)	2 wk 5 d/wk 6 hr/d				500 M (4/5 deaths during first week)	NTP 2011 1-Bromopropane	
5	Mouse (B6C3F1)	14 wk 5 d/wk 6 hr/d				500 (4/10 males and 5/10 females died in the first 2 weeks)	NTP 2011 1-Bromopropane	
Systemic								
6	Rat (Sprague- Dawley)	14 d Gd 6-19 6 hr/d	Bd Wt	100 F	498 F (14.3% reduction in net body weight change on Gd 6-20)	996 F (24.6% reduction in net body weight change on Gd 6-20)	BSOC 2001b 1-Bromopropane	

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments	
					Less Serious (ppm)	Serious (ppm)			
7	Rat (Wistar)	4 hr	Resp	6040		6920	(pulmonary edema and emphysema)	Elf AtoChem S.A. 1997 1-Bromopropane	
			Hemato	7280 M					
			Bd Wt	7280 M					
				7020 F					
8	Rat (Wistar)	7 d 8 hr/d	Bd Wt	800 M				Wang et al. 2002 1-Bromopropane	
9	Rat (Wistar)	7 d 8 hr/d	Endocr	1000 M				Zhang et al. 2013 1-Bromopropane	Endocrine NOAEL is for adrenal gland weight and plasma corticosterone.
			Bd Wt	800 M	1000 M (11% reduction in final body weight)				
Neurological									
10	Human	< 2 wks (Occup)			107 F (subjective complaints of headache, dizziness, numbness, weakness)			Raymond and Ford 2007 1-Bromopropane	Case reports (n=2)
11	Rat (Fischer- 344)	14 d 8 hr/d		<sup>b</sup> 200 M	1000 M (reduced forelimb grip strength)			Honma et al. 2003 1-Bromopropane	

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
12	Rat (Sprague- Dawley)	4 hr			11000	(decreased activity, ataxia)	Kim et al. 1999 1-Bromopropane	
13	Rat (Sprague- Dawley)	1 hr		300	1800	(decreased activity; mild ataxia)	Kim et al. 1999 1-Bromopropane	
14	Rat (Wistar)	7 d 8 hr/d		1000 M			Zhang et al. 2013 1-Bromopropane	NOAEL is for neurogenesis in the hippocampus.
<b>Reproductive</b>								
15	Rat (Sprague- Dawley)	14 d Gd 6-19 6 hr/d		996 F			BSOC 2001b 1-Bromopropane	
16	Rat (Wistar)	4 hr		8500 M			Elf AtoChem S.A. 1997 1-Bromopropane	NOAEL is for histopathology of the testes.
17	Mouse (C57BL/6N)	6 hr			800 M	(37% reduced sperm motility)	Garner et al. 2007 1-Bromopropane	CYP2E1-null mice showed only a 12% reduction in sperm motility.

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
Developmental								
18	Rat (Sprague-Dawley)	14 d Gd 6-19 6 hr/d		498	996	(7.4% reduced fetal weight)	BSOC 2001b 1-Bromopropane	
INTERMEDIATE EXPOSURE								
Systemic								
19	Rat (Sprague-Dawley)	13 wk 5 d/wk 6 hr/d	Resp	600			Albemarle Corporation 1997 1-Bromopropane	NOAELs are for clinical chemistry, urinalysis, and organ weight/histology
			Cardio	600				
			Gastro	600				
			Hemato	600				
			Musc/skel	600				
			Hepatic	400 M	600 M (vacuolation of centrolobular hepatocytes and increased liver weight)			
			Renal	600				
			Endocr	600				
			Dermal	600				
			Ocular	600				
			Bd Wt	600				
			Metab	600				

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
20	Rat (Wistar)	6 wk 7 d/wk 8 hr/d	Cardio	400 M	1000 M (15-20% increase in systolic blood pressure)		Banu et al. 2007 1-Bromopropane	
			Bd Wt	400 M		1000 M (Body weight reduced 30% at exposure cessation)		
21	Rat (Sprague- Dawley)	2-gen 70 d 6 hr/d	Resp	750			BSOC 2001a 1-Bromopropane	
			Hepatic	100 M	250 M (hepatocellular vacuolization in F0 and F1 males)			
			Renal	250 F	500 F (transitional renal epithelial hyperplasia and pelvic mineralization in F0 females)			
			Endocr	500 M	750 M (20% decrease absolute weight of F1 male adrenals and pituitary)			
			Bd Wt	250 F	500 F (12-14% reduced body weight F0 and F1 dams on Gd 20)			
22	Rat (Wistar)	42 d 8 hr/d	Bd Wt	400 F	800 F (11% reduced maternal body weight on postnatal day 21)		Furuhashi et al. 2006 1-Bromopropane	

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
23	Rat (Fischer- 344)	3 wk 7 d/wk 8 hr/d	Bd Wt	200 M	1000 M (12% weight loss during exposure period)		Honma et al. 2003 1-Bromopropane	
24	Rat (Wistar)	4 wk 7 d/wk 8 hr/d	Cardio		1000 M (approximately 15% increase in systolic blood pressure)		Huang et al. 2016 1-Bromopropane	
			Hepatic		1000 M (21.8% increase in absolute liver weight)			
			Bd Wt		1000 M (12.2% reduction in body weight)			
25	Rat (Wistar)	12 wk 7 d/wk 8 hr/d	Resp	800 M			Ichihara et al. 2000a 1-Bromopropane	NOAELs are for organ weight and histopathology.
			Cardio	800 M				
			Hemato	800 M				
			Musc/skel	800 M				
			Hepatic	800 M				
			Renal	800 M				
			Endocr	800 M				
			Bd Wt	400 M	800 M (final body weight reduced 12%)			

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
26	Rat (Wistar)	12 wk 7 d/wk 8 hr/d	Musc/skel	400 M		800 M (alteration in myofilaments in soleus muscle)	Ichihara et al. 2000b 1-Bromopropane	
			Bd Wt	400 M	800 M (12% reduction in terminal body weight)			
27	Rat (Wistar)	4-12 wk 5 d/wk 6 hr/day	Hepatic		700 M (47-49% decrease plasma ALT activity)		Ishida et al. 2002 1-Bromopropane	No microscopic examination of the liver was conducted.
28	Rat (Sprague- Dawley)	8 wk 5 d/wk 6 hr/day	Resp	1800			Kim et al. 1999 1-Bromopropane	
			Cardio	1800				
			Hemato	1800 M				
			Hepatic		50 (hepatocyte vacuolization)			
			Renal	300 F	1800 F (tubular casts in the kidneys)			
			Endocr	1800				
			Bd Wt	1800				



## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
29	Rat (Fischer- 344)	16 d 5 d/wk 6 hr/d	Hepatic		125 F (increased relative and absolute liver weight)		NTP 2011 1-Bromopropane	
			Renal		125 F (increased relative kidney weight)			
			Bd Wt	1000 M		2000 M (final body weight reduced 27%)		

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
30	Rat (Fischer- 344)	14 wk 5 d/wk 6 hr/d	Resp	1000			NTP 2011 1-Bromopropane	NOAELs are for tissue histopathology and organ weight. Vacuolization in hepatocytes at >=250 ppm.
			Cardio	1000				
			Gastro	1000				
			Hemato	1000				
			Musc/skel	1000				
			Hepatic	62.5 F	125 F (significant increase in absolute and relative liver weight)			
			Renal	500 F	1000 F (increased absolute and relative kidney weight)			
			Endocr	1000				
			Dermal	1000				
			Ocular	1000				
31	Rat (Fischer- 344)	20 d 8 hr/d	Bd Wt	500 M	1000 M (12% reduction in final body weight)		Sekiguchi et al. 2002 1-Bromopropane	
			Bd Wt	1000 F				

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
32	Rat (Sprague- Dawley)	13 wk 5 d/wk 6/hr/d	Bd Wt	1250			Sohn et al. 2002 1-Bromopropane	
33	Rat (Wistar)	4 wk 7 d/wk 8 hr/d	Bd Wt	800 M	1000 M (15% reduction in terminal body weight)		Subramanian et al. 2012 1-Bromopropane	
34	Rat (Wistar)	12 wk 7 d/wk 8 hr/d	Bd Wt	400 M	800 M (12% reduction in terminal body weight)		Wang et al. 2003 1-Bromopropane	
35	Rat (Wistar)	12 wk 7 d/wk 8 hr/d	Hepatic		200 F (significant increase in absolute and relative liver weight)		Yamada et al. 2003 1-Bromopropane	
			Renal		200 F (significant increase in absolute and relative kidney weight)			
			Endocr	800 F				
			Bd Wt	400 F		800 F (final body weight reduced 30%)		

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
36	Rat (Wistar)	7 wk 7 d/wk 8 hr/d	Hemato	1000 M			Yu et al. 1998 1-Bromopropane	Hepatic and renal NOAELs are for organ histopathology.
			Hepatic	1000 M				
			Renal	1000 M				
			Bd Wt		1000 M (19% reduced body weight)			
37	Rat (Wistar)	7 wk 7 d/wk 8 hr/d	Hemato	1000 M			Yu et al. 2001 1-Bromopropane	NOAELs are for tissue histopathology
			Hepatic	1000 M				
			Renal	1000 M				
			Bd Wt		1000 M (19% reduced terminal body weight)			
38	Rat (Wistar)	4 wk 7 d/wk 8 hr/d	Endocr	1000 M			Zhang et al. 2013 1-Bromopropane	Endocrine NOAEL is for adrenal gland weight and serum corticosterone.
			Bd Wt	800 M	1000 M (10% reducton in final body weight)			

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
39	Mouse (BALB/cA)	4 wk 7 d/wk 8 h/d	Hepatic		50 M (hepatocellular degeneration and focal necrosis)		Liu et al. 2009 1-Bromopropane	
			Bd Wt	250 M				
40	Mouse (C57BL/6J)	4 wk 7 d/wk 8 hr/d	Hepatic		100 M (liver necrosis)		Liu et al. 2010 1-Bromopropane	Nfr2-null mice were more susceptible than the wild type to 1-BP-induced liver toxicity.
41	Mouse (B6C3F1)	17 d 5 d/wk 6 hr/d	Resp		125 (minimal grade necrosis and regeneration in bronchioles)		NTP 2011 1-Bromopropane	Nasal lesions observed in olfactory and respiratory epithelium at 500 ppm and higher.
			Cardio	500 M	1000 M (decreased absolute and relative heart weight)			
			Hepatic	250 M		500 M (moderate to marked centrilobular necrosis)		
			Renal	500 F	1000 F (increased absolute and relative kidney weight)			
			Bd Wt	2000				

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
42	Mouse (B6C3F1)	14 wk 5 d/wk 6 hr/d	Resp	250	500	(cytoplasmic vacuolization in nasal respiratory epithelium, trachea, and bronchioles)	NTP 2011 1-Bromopropane	NOAELs are for tissue histopathology and organ weight
			Cardio	500				
			Gastro	500				
			Hemato	500				
			Musc/skel	500				
			Hepatic	250		500 (necrosis and hepatocyte degeneration)		
			Renal	250	500	(increased absolute and relative kidney weight)		
			Endocr	250 F		500 F (moderate to marked necrosis of adrenal cortex)		
			Dermal	500				
			Ocular	500				
			Bd Wt	500				
43	Mouse C57BL/6J	4 wk 8 hr/d	Hepatic		50 M (mild centrilobular hepatocyte degeneration)	250 M (severe liver necrosis, hemorrhage, and hepatocyte degeneration).	Zong et al. 2016 1-Bromopropane	
			Bd Wt	250 M				

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
Immuno/ Lymphoret								
44	Rat (Sprague- Dawley)	13 wk 5 d/wk 6 hr/d		600			Albemarle Corporation 1997 1-Bromopropane	NOAEL is for organ weight/histology
45	Rat (Fischer- 344)	4-10 wk 5 d/wk 6 hr/d		250 F	500 F (decreased CD4+/CD8- cells in spleen at 10 weeks)		Anderson et al. 2010 1-Bromopropane	Suppression of IgM response to SRBC at 1,000 ppm (10 wks)
46	Rat (Sprague- Dawley)	2-gen 70 d 6 hr/d		750			BSOC 2001a 1-Bromopropane	Increased brown pigment in the spleen considered not toxicologically significant.
47	Rat (Wistar)	12 wk 7 d/wk 8 hr/d		800 M			Ichihara et al. 2000a 1-Bromopropane	NOAEL is for organ weight and histopathology of the spleen and thymus.
48	Rat (Sprague- Dawley)	8 wk 5 d/wk 6 hr/day		1800			Kim et al. 1999 1-Bromopropane	NOAEL is for histopathology of thymus and spleen.
49	Rat (Fischer- 344)	14 wk 5 d/wk 6 hr/d		1000			NTP 2011 1-Bromopropane	NOAEL is for histopathology of lymphoreticular tissues.

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
50	Rat (Wistar)	12 wk 7 d/wk 8 hr/d		800 M			Yamada et al. 2003 1-Bromopropane	NOAEL is for weight and histopathology of spleen and thymus.
51	Mouse (B6C3F1)	4-10 wk 5 d/wk 6 hr/d			125 F (suppression of IgM response to SRBC at 10 weeks)		Anderson et al. 2010 1-Bromopropane	
52	Mouse (B6C3F1)	14 wk 5 d/wk 6 hr/d		500			NTP 2011 1-Bromopropane	NOAEL is for histopathology of lymphoreticular tissues.
<b>Neurological</b>								
53	Human	2-12 mo				133 F (ataxia, numbness, weakness, autonomic dysfunction, mood changes)	Ichihara et al. 2002 1-Bromopropane	Case reports (n=3)
54	Rat (Sprague-Dawley)	13 wk 5 d/wk 6 hr/d		600			Albemarle Corporation 1997 1-Bromopropane	NOAEL is for FOB, motor activity, and organ weight/histology
55	Rat (Wistar)	6 wk 7 d/wk 8 hr/d		400 M	1000 M (decreased hindlimb muscle strength)		Banu et al. 2007 1-Bromopropane	



## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
56	Rat (Sprague- Dawley)	2-gen 70 d 6 hr/d		750			BSOC 2001a 1-Bromopropane	NOAEL is for histopathology of the brain of the F0 generation.
57	Rat (Wistar)	4 wk 5 d/wk 6 h/d				1500 M (ataxic gate, convulsions)	Fueta et al. 2002 1-Bromopropane	
58	Rat (Wistar)	8 wk 5 d/wk 6 hr/d			700 M (increased excitability in hippocampal neurons)		Fueta et al. 2004 1-Bromopropane	Experiments were conducted ex vivo in hippocampal slices.
59	Rat (Wistar)	12 wk 5 d/wk 6 hr/d		200 M	400 M (increased excitability in hippocampal neurons)		Fueta et al. 2007 1-Bromopropane	Experiments were conducted ex vivo in hippocampal slices.
60	Rat (Fischer- 344)	3 wk 8 hr/d		<sup>c</sup> 10 M	50 M (increased spontaneous locomotor activity)		Honma et al. 2003 1-Bromopropane	
61	Rat (Wistar)	12 wk 7 d/wk 8 hr/d			200 M (significantly reduced hindlimb grip strength)		Ichihara et al. 2000b 1-Bromopropane	Morphological and physiological changes in peripheral nerve occurred at 800 ppm.
62	Rat (Sprague- Dawley)	8 wk 5 d/wk 6 hr/day		1800			Kim et al. 1999 1-Bromopropane	NOAEL is histopathology of the brain.

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
63	Rat (Fischer- 344)	4 wk 7 d/wk 8 hr/d		400 M	800 M (decrease density of noradrenergic axons in brain areas)		Mohideen et al. 2011 1-Bromopropane	
64	Rat (Fischer- 344)	4 wk 7 d/wk 8 hr/d			400 M (morphological alterations in astrocytes in cerebellum)		Mohideen et al. 2013 1-Bromopropane	
65	Rat (Fischer- 344)	14 wk 5 d/wk 6 hr/d		1000			NTP 2011 1-Bromopropane	NOAEL is for histopathology of the brain.
66	Rat (Sprague- Dawley)	13 wk 5 d/wk 6 hr/d		1250			Sohn et al. 2002 1-Bromopropane	NOAEL is for histopathology of central and peripheral nervous tissues.
67	Rat (Wistar)	4 wk 7 d/wk 8 hr/d		800 M	1000 M (morphological alterations in cerebellar microglia)		Subramanian et al. 2012 1-Bromopropane	
68	Rat (Wistar)	12 wk 5 d/wk 6 hr/d			400 M (increased excitability in hippocampal neurons)		Ueno et al. 2007 1-Bromopropane	Excitability was tested in hippocampal slices.

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
69	Rat (Wistar)	7 wk 7 d/wk 8 hr/d				1000 M (hindlimb paralysis)	Yu et al. 1998 1-Bromopropane	Motor nerve conduction velocity was decreased 18%.
70	Rat (Wistar)	7 wk 7 d/wk 8 hr/d				1000 M (peripheral nerve degeneration)	Yu et al. 2001 1-Bromopropane	
71	Rat (Wistar)	4 wk 7 d/wk 8 hr/d		600 M		900 M (reduced neurogenesis in hippocampus)	Zhang et al. 2013 1-Bromopropane	NOAEL and LOAEL are TWA exposure concentrations over study duration.
72	Mouse (B6C3F1)	14 wk 5 d/wk 6 hr/d		500			NTP 2011 1-Bromopropane	NOAEL is for histopathology of the brain.
<b>Reproductive</b>								
73	Rat (Sprague-Dawley)	13 wk 5 d/wk 6 hr/d		600			Albemarle Corporation 1997 1-Bromopropane	NOAEL is for organ weight/histology
74	Rat (Wistar)	6 wk 7 d/wk 8 hr/d			400 M (23% reduced epididymal sperm count)	1000 M (>30% reduced absolute reproductive organs weight)	Banu et al. 2007 1-Bromopropane	

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
75	Rat (Sprague- Dawley)	2-gen 70 d 6 hr/d		100	250 M (reduced absolute prostate weight in F0 males)  250 F (increased estrous cycle length in F1 females)	750 (100% infertility)	BSOC 2001a 1-Bromopropane	
76	Rat (Wistar)	12 wk 7 d/wk 8 hr/d			200 M (26-27% reduced absolute and relative seminal vesicles weight)		Ichihara et al. 2000a 1-Bromopropane	
77	Rat (Sprague- Dawley)	8 wk 5 d/wk 6hr/d		300 F	1800 F (27-30% increased relative ovaries weight)		Kim et al. 1999 1-Bromopropane	No effects were reported in the testes.
78	Rat (Fischer- 344)	14 wk 5 d/wk 6 hr/d		500 M  125 F	1000 M (reduced sperm count and motility)  250 F (alterations in estrus cycles length)		NTP 2011 1-Bromopropane	
79	Rat (Fischer- 344)	20 d 8 hr/d		1000 F			Sekiguchi et al. 2002 1-Bromopropane	NOAEL is for effects on estrous cycles and spontaneous ovulation.

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
80	Rat (Wistar)	12 wk 7 d/wk 8 hr/d			200 F (decreased ovarian antral follicle counts)		Yamada et al. 2003 1-Bromopropane	
81	Rat (Wistar)	7 wk 7 d/wk 8 hr/d		1000 M			Yu et al. 1998 1-Bromopropane	NOAEL is for testes histopathology.
82	Rat (Wistar)	7 wk 7 d/wk 8 hr/d		1000 M			Yu et al. 2001 1-Bromopropane	NOAEL is for histopathology of the testes.
83	Mouse (BALB/cA)	4 wk 7 d/wk 8 h/d			50 M (decreased sperm count and motility; increased abnormal sperm)		Liu et al. 2009 1-Bromopropane	
84	Mouse (B6C3F1)	14 wk 5 d/wk 6 hr/d		250	500 (decreased sperm per gram cauda; estrus cycles alterations)		NTP 2011 1-Bromopropane	
<b>Developmental</b>								
85	Rat (Sprague- Dawley)	2-gen 70 d 6 hr/d		250	500 (decreased F1 and F2 pups born and litter size; reduced [14-18%] F2 pup weight on Pnd 14 and 21)		BSOC 2001a 1-Bromopropane	Male F1 pup weight reduced 13.7% on Pnd 28 at 500 ppm.

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
86	Rat (Wistar)	20 d GD 1-20 6 hr/d			700 (7.5 to 9.5% reduced pup weights on Pnd 14).		Fueta et al. 2015 1-Bromopropane	1-BP suppressed wet dog shakes induced by kainate.
87	Rat (Wistar)	42 d Gd 0-21 Ld 1-21 8 hr/d		100		800 (significantly decreased survival during lactation)	Furuhashi et al. 2006 1-Bromopropane	
<b>CHRONIC EXPOSURE</b>								
<b>Systemic</b>								
88	Human	~40 mo (Occup)	Hemato	22.58			Li et al. 2010	Values listed are median exposure levels. Hepatic and renal NOAELs are for serum chemistry.
			Hepatic	22.58				
			Renal	22.58				
			Endocr	1.28 F	6.6 F	(83% increase in serum TSH)		
89	Human	4-9 yr (Occup)	Hemato	197			NIOSH 2002 1-Bromopropane	The NOAEL listed is the geometric mean.

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
90	Human	~ 29 mo (Occup)	Hemato	45.7			NIOSH 2003a 1-Bromopropane	The NOAELs listed are the geometric means. The kidney NOAEL is for serum chemistry.
			Renal	45.7				
91	Rat (Fischer- 344)	105 wk 5 d/wk 6 hr/d	Resp		125	(glandular hyperplasia in the nose [both sexes], chronic active nasal inflammation [females])	Morgan et al. 2011; NTP 2011 1-Bromopropane	NOAELs are for tissues histopathology. Various respiratory tract lesions in the nose, larynx, trachea, and lungs were observed at 250 ppm and higher.
			Cardio	500				
			Gastro	500				
			Musc/skel	500				
			Hepatic	500				
			Renal	500				
			Endocr	500				
			Dermal	500				
			Ocular	500				
			Bd Wt	500				

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
92	Mouse (B6C3F1)	105 wk 5 d/wk 6 hr/d	Resp		62.5	(various histological alterations in the nasal respiratory epithelium, larynx, trachea, and bronchioles)	Morgan et al. 2011; NTP 2011 1-Bromopropane	NOAELs are for tissue histopathology. Lesions of the olfactory epithelium were observed in females at 125 ppm and higher.
			Cardio	250				
			Gastro	250				
			Musc/skel	250				
			Hepatic	250				
			Renal	250				
			Endocr	250				
			Dermal	250				
			Ocular	250				
			Bd Wt	250				
Immuno/ Lymphoret								
93	Rat (Fischer- 344)	105 wk 5 d/wk 6 hr/d		500			Morgan et al. 2011; NTP 2011 1-Bromopropane	NOAEL is for histopathology of lymphoreticular tissues.
94	Mouse (B6C3F1)	105 wk 5 d/wk 6 hr/d		250			Morgan et al. 2011; NTP 2011 1-Bromopropane	NOAEL is for histopathology of lymphoreticular tissues.



## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
Neurological								
95	Human	~40 mo (Occup)			1.28 <sup>d</sup> F (increased vibration sense threshold)		Li et al. 2010	LOAEL value listed is the median exposure level.
96	Human	> 3 yr (Occup)				108 (inability to walk, spastic paraparesis, sensory loss, hyperreflexia)	Majersik et al. 2007 1-Bromopropane	Case reports (n=5)
97	Human	4-9 yr (Occup)			117.1 (subjective complaints of neurotoxicity)		NIOSH 2002 1-Bromopropane	No referent group was included; LOAEL value listed is the geometric mean.
98	Human	~ 29 mo (Occup)			45.7 (Subjective complaints of anxiety, nervousness)		NIOSH 2003a 1-Bromopropane	The LOAEL listed is for the geometric mean.
99	Human	18 mo 5-6 d/wk 8.5-9.5 hr/d (Occup)				533 M (severe ataxia, motor and sensory impairments, axonal damage)	Samukawa et al. 2012 1-Bromopropane	Case report
100	Rat (Fischer- 344)	105 wk 5 d/wk 6 hr/d		500			Morgan et al. 2011; NTP 2011 1-Bromopropane	NOAEL is for histopathology of the brain.

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
101	Mouse (B6C3F1)	105 wk 5 d/wk 6 hr/d		250			Morgan et al. 2011; NTP 2011 1-Bromopropane	NOAEL is for histopathology of the brain.
<b>Reproductive</b>								
102	Human	4-9 yr (Occup)		168.9			NIOSH 2002 1-Bromopropane	The NOAEL (geometric mean) is for lack of self-reported reproductive issues.
103	Human	~ 29 mo (Occup)		45.7 F			NIOSH 2003a 1-Bromopropane	The NOAEL (geometric mean) is based on a lack of self-reported reproductive issues.
104	Rat (Fischer- 344)	105 wk 5 d/wk 6 hr/d		500			Morgan et al. 2011; NTP 2011 1-Bromopropane	NOAEL is for histopathology of reproductive organs.
105	Mouse (B6C3F1)	105 wk 5 d/wk 6 hr/d		250			Morgan et al. 2011; NTP 2011 1-Bromopropane	NOAEL is for histopathology of the reproductive organs.
<b>Cancer</b>								
106	Rat (Fischer- 344)	105 wk 5 d/wk 6 hr/d				125 M (CEL: skin keratoacanthoma; basal cell adenoma or carcinoma)	Morgan et al. 2011; NTP 2011 1-Bromopropane	125 ppm also CEL for pancreatic islet adenoma in males.

## 3. HEALTH EFFECTS

Table 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL		Reference Chemical Form	Comments
					Less Serious (ppm)	Serious (ppm)		
107	Mouse (B6C3F1)	105 wk 5 d/wk 6 hr/d				62.5 F (CEL: combined alveolar/bronchiolar adenoma or carcinoma)	Morgan et al. 2011; NTP 2011 1-Bromopropane	

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

b Used to derive an acute-duration inhalation minimal risk level (MRL) of 1 ppm for 1-BP based on a BMCL1SD of 97.40 ppm. The BMCL1SD was adjusted for intermittent exposure and multiplied by the ratio of the animal-to-human blood: gas partition coefficients to calculate a human equivalent concentration (HEC). The BMCL[HEC] was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

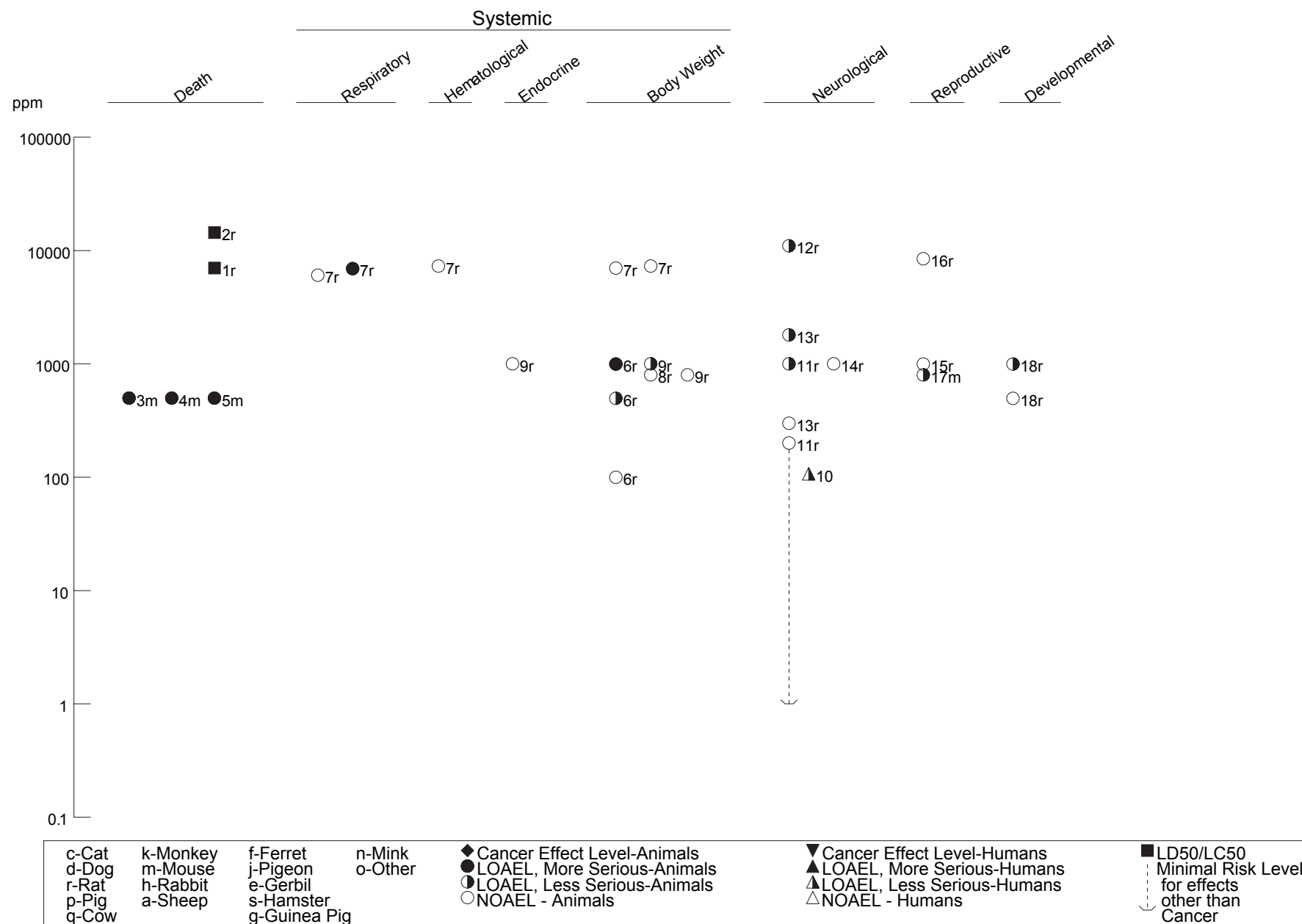
c Used to derive an intermediate-duration inhalation MRL of 0.1 ppm for 1-BP based on a NOAEL of 10 ppm. The NOAEL was adjusted for intermittent exposure and multiplied by the ratio of the animal-to-human blood: gas partition coefficients to calculate a human equivalent concentration (HEC). The NOAEL[HEC] was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

d Used to derive a chronic-duration (365 days or more) inhalation MRL of 0.02 ppm for 1-BP. The minimal LOAEL of 1.28 ppm was adjusted for continuous exposure ( $1.28 \text{ ppm} \times 5 \text{ days/7 days} \times 12 \text{ hours/24 hours} = 0.46 \text{ ppm}$ ) and was divided by an uncertainty factor of 30 (3 for use of minimal LOAEL and 10 for human variability) to derive the MRL of 0.02 ppm.

ALT = alanine aminotransferase; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = Female; FOB = functional observation battery; Gastro = gastrointestinal; Gd = gestational day; gen = generation; Hemato = hematological; hr = hour(s); IgM = immunoglobulin M; Immuno/Lymphoret = immunological/lymphoreticular; LC50 = lethal concentration, 50% kill; Ld = lactation day; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolism; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Occup = occupational; Resp = respiratory; SRBC = sheep red blood cell; TWA = time-weighted average; wk = week(s)

## 3. HEALTH EFFECTS

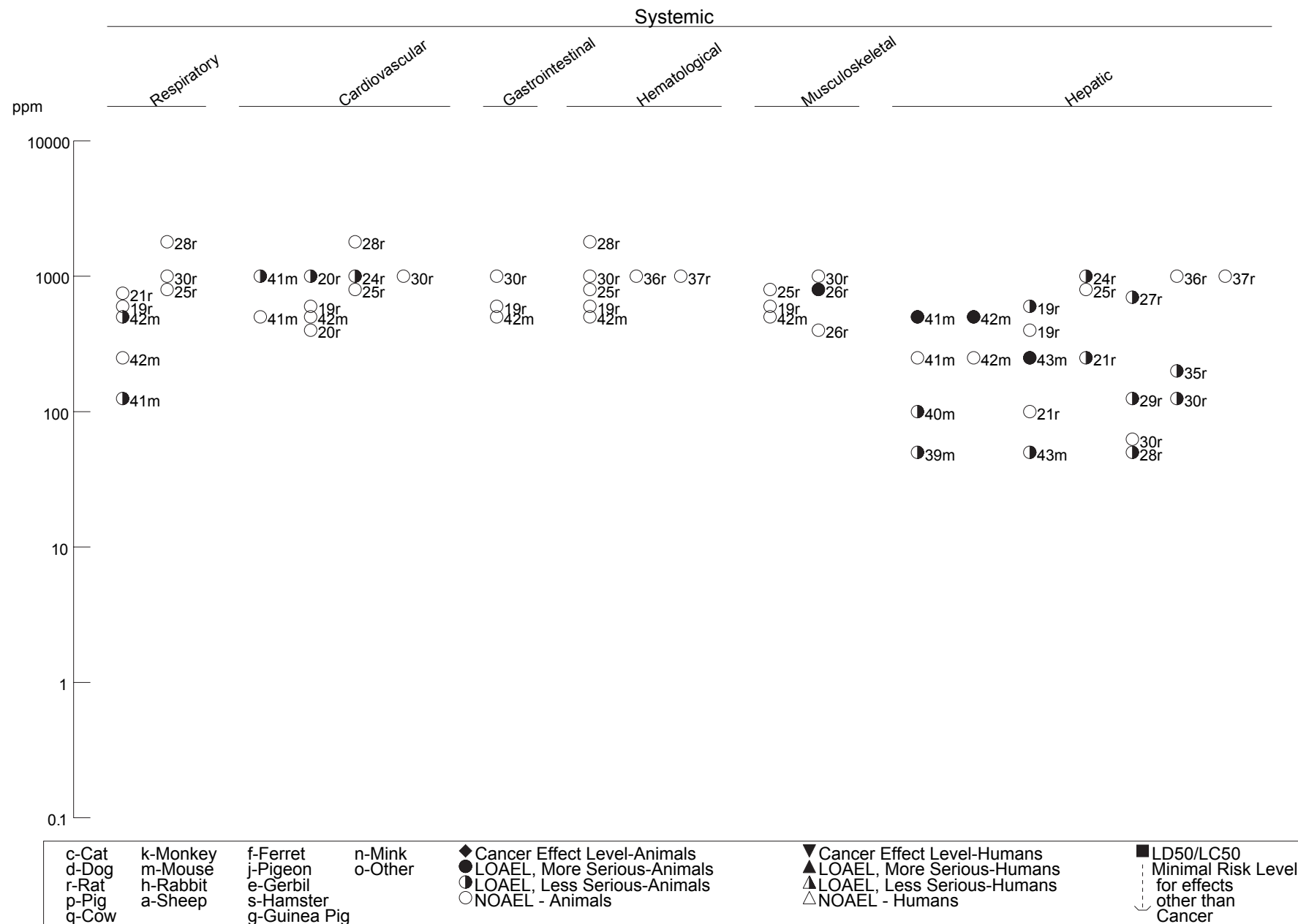
Figure 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation

Acute ( $\leq 14$  days)

## 3. HEALTH EFFECTS

Figure 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (*Continued*)

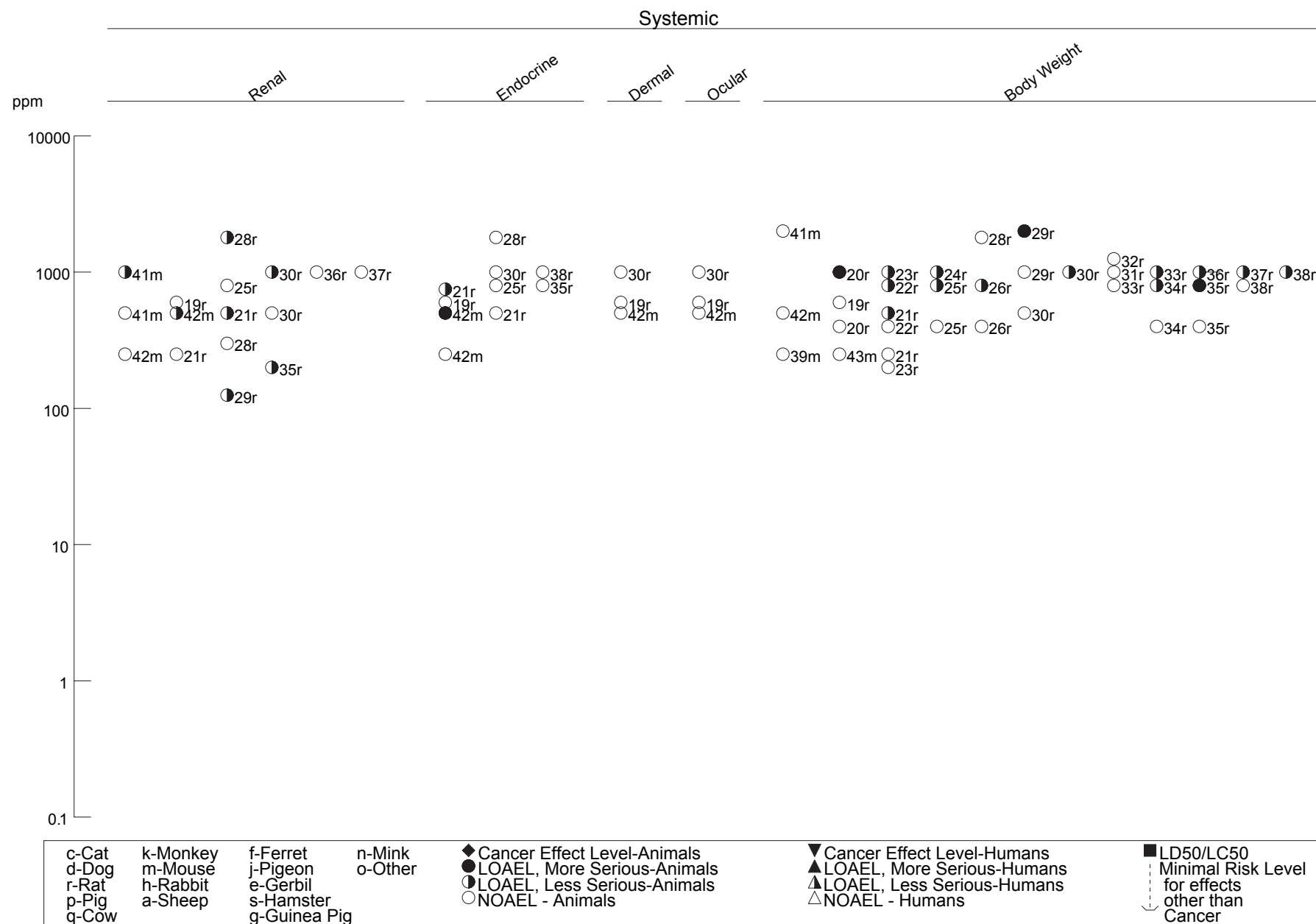
Intermediate (15-364 days)



## 3. HEALTH EFFECTS

Figure 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (*Continued*)

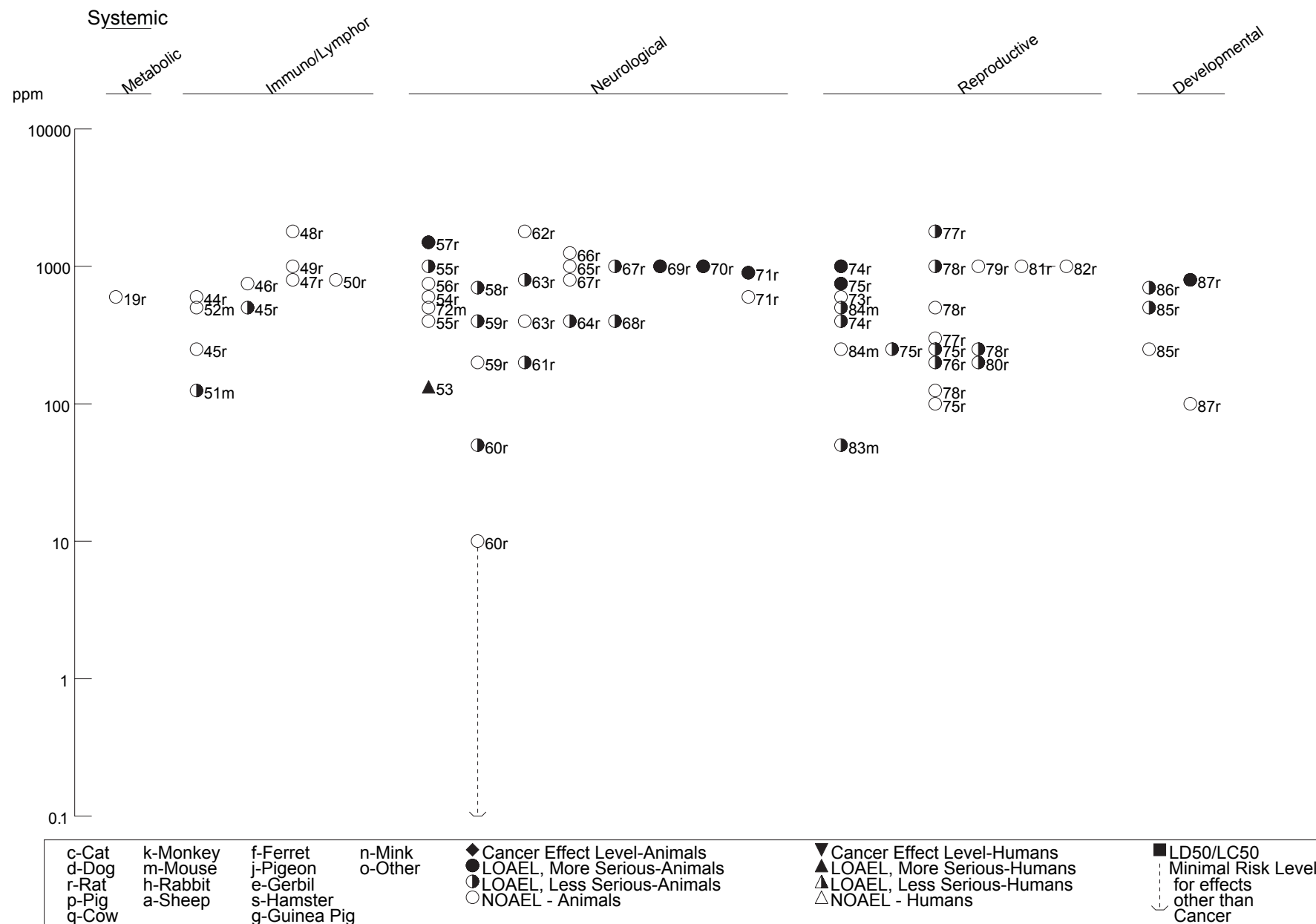
Intermediate (15-364 days)



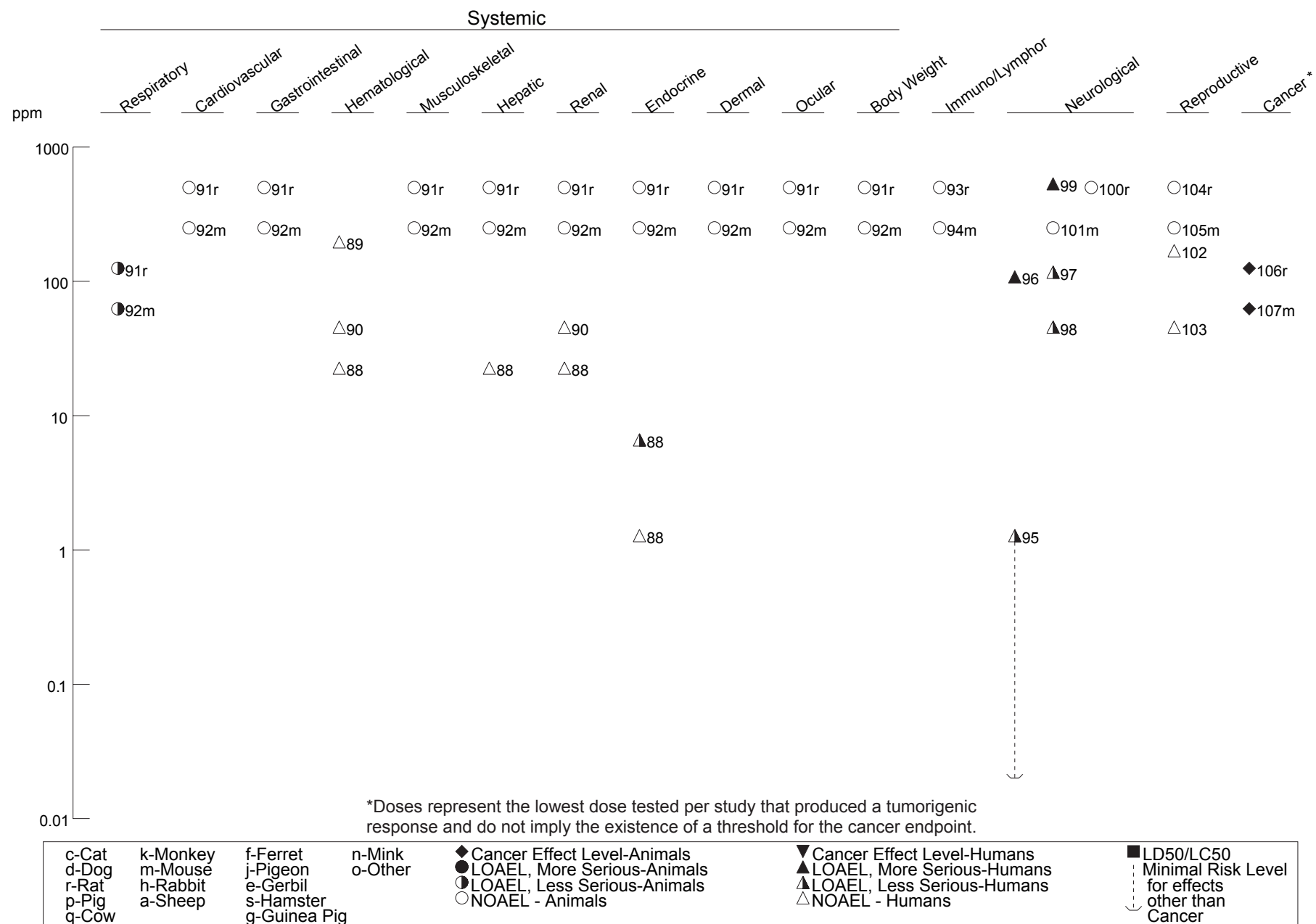
## 3. HEALTH EFFECTS

Figure 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (Continued)

Intermediate (15-364 days)



## 3. HEALTH EFFECTS

Figure 3-1 Levels of Significant Exposure to 1-Bromopropane - Inhalation (*Continued*)Chronic ( $\geq 365$  days)



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developed neurological signs and symptoms 2 weeks after 1-bromopropane was introduced into her workplace. The geometric mean air concentration of 1-bromopropane was 107 ppm for glue sprayers (range 58–254 ppm). It should be mentioned that the woman had been a furniture gluer for 18 months prior to the introduction of 1-bromopropane into the workplace and had been in good health prior to the introduction of 1-bromopropane into the workplace.

In general, except for a chronic study, studies in rats and mice have used exposure concentrations higher than those associated with respiratory irritation in workers and have reported mainly histological alterations in the respiratory tract, with some inconsistencies between studies. Some studies provided data on lung weight. It also appears that mice are more susceptible than rats. Pulmonary lesions consisting of edema and “emphysema” were reported in rats exposed to  $\geq 6,920$  ppm, a lethal concentration, for 4 hours (Elf AtoChem S.A. 1997). Nasal lesions, including minimal necrosis of the respiratory epithelium and suppurative inflammation were observed in 1–2/5 male rats exposed to  $\geq 500$  ppm 1-bromopropane for 16 days, but no such lesions were observed in females exposed to doses up to 2,000 ppm for 16 days or males or females exposed to concentrations up to 1,000 ppm for 14 weeks (NTP 2011). No changes were observed in lung weights in the NTP studies in rats. In other intermediate-duration rat studies, no exposure-related changes in lung weight or histology were observed in rats intermittently exposed to concentrations up to 1,800 ppm 1-bromopropane (Albemarle Corporation 1997; BSOC 2001a; Ichihara et al. 2000a; Kim et al. 1999).

In intermediate-duration mouse studies, histopathological changes were observed in various levels of the respiratory tract of mice following intermittent exposure to 500 ppm 1-bromopropane for 14 weeks, including cytoplasmic vacuolization of the nasal respiratory epithelium and cytoplasmic vacuolization in the trachea and lung bronchioles (4/10 males, 5/10 females); incidences in the control group were 0/10 (NTP 2011). Absolute and relative lung weights were also increased in females exposed to 500 ppm 1-bromopropane. Exposure-related effects were not observed at  $\leq 250$  ppm. In the accompanying 17-day study, histopathological changes in the lungs were observed in all mice exposed to  $\geq 125$  ppm 1-bromopropane (lowest concentration tested), including bronchiole necrosis, regeneration, and vacuolization and perivascular inflammation (NTP 2011). Histopathological changes in the nose were observed at  $\geq 500$  ppm, including olfactory epithelium atrophy, necrosis, and regeneration and respiratory epithelial necrosis and cytoplasmic vacuolization (NTP 2011).

In a chronic-duration study, respiratory tract lesions were observed in rats exposed to  $\geq 125$  ppm and mice exposed to  $\geq 62.5$  ppm 1-bromopropane for 105 weeks (lowest concentrations tested) (Morgan et al. 2011;

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NTP 2011). Observed lesions in rats included glandular hyperplasia and chronic suppurative inflammation of the nose; chronic active inflammation of the nose, larynx, and trachea; chronic suppurative inflammation of the lungs; metaplasia of the olfactory epithelium; squamous metaplasia of the larynx; and epithelial hyperplasia of the trachea. In mice, observed lesions included regeneration of bronchioles; cytoplasmic vacuolization in the nasal respiratory epithelium, bronchioles, larynx, and trachea; hyperplasia in nasal respiratory epithelium; and metaplasia and atrophy in nasal olfactory epithelium.

Limited human data suggest that exposure to 1-bromopropane can cause respiratory tract irritation at exposure levels that might be found in occupational settings; however, definite levels at which respiratory lesions might occur in humans are unknown. Studies in animals suggest that mice can develop respiratory tract lesions at exposure levels reported in some occupational studies and may be a better animal model than rats for this end point.

**Cardiovascular Effects.** Only one report was located that provided some information regarding cardiovascular assessment in humans following likely exposure to 1-bromopropane at work. Raymond and Ford (2007) reported that a woman who developed neurological signs and symptoms 2 weeks after 1-bromopropane was introduced into her workplace had a normal electrocardiogram. The geometric mean air concentration was 107 ppm for glue sprayers (range 58–254 ppm). It should be mentioned that the woman had been a furniture gluer for 18 months prior to the introduction of 1-bromopropane into the workplace.

No generalizations can be made from the single case report mentioned above, and the available studies in animals have examined mostly histology of the heart, but not cardiovascular function. The animal studies indicate that morphological alterations of the heart are unlikely to occur following exposure to 1-bromopropane. Changes in heart weight were reported in one animal study. A significant decrease in absolute and relative heart weight was observed in male mice intermittently exposed to  $\geq 1,000$  ppm 1-bromopropane for 17 days; no exposure-related changes were observed in heart weight in males at  $\leq 500$  ppm or in females at  $\leq 2,000$  ppm (NTP 2011). No exposure-related changes in heart histology were observed in mice at concentrations up to 2,000 ppm 1-bromopropane for 17 days or 500 ppm for 14 weeks (NTP 2011). In rats, no exposure-related changes in heart weight or histology were observed in three strains intermittently exposed to concentrations up to 1,800 ppm 1-bromopropane for 8–14 weeks (Albemarle Corporation 1997; Ichihara et al. 2000a; Kim et al. 1999; NTP 2011).

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A significant increase (15–20%) in systolic blood pressure (measured with a tail cuff) was reported in conscious male Wistar rats exposed to 1,000 ppm 1-bromopropane intermittently for 4–6 weeks (Banu et al. 2007; Huang et al. 2016). The blood pressure was still elevated 5 weeks after exposure ceased, but returned to control values by 8 weeks after exposure terminated. No significant effects were reported in rats exposed to 400 ppm 1-bromopropane. Biochemical assays in homogenates of left ventricle and aortic tissues showed that markers of oxidative stress were significantly elevated in exposed rats, which led Huang et al. (2016) to suggest that oxidative stress, through activation of NADPH oxidase pathways, might be a mechanism for 1-bromopropane-induced increased blood pressure.

In the only available chronic-duration study, no exposure-related changes in heart histology were observed in rats or mice intermittently exposed to concentrations up to 500 or 250 ppm 1-bromopropane, respectively, for 105 weeks (Morgan et al. 2011; NTP 2011).

The limited human data are insufficient to determine if 1-bromopropane exposure causes cardiovascular effects. While animal studies showed that morphological alterations of the heart did not occur following exposure to 1-bromopropane, no conclusions can be drawn regarding cardiovascular function that would support or refute the findings of the case report.

**Gastrointestinal Effects.** Several single case reports or reports of a small number of workers experiencing frank neurotoxicity following exposure to 1-bromopropane reported gastrointestinal effects, including diarrhea and nausea/vomiting, at mean air concentrations of 107–133 ppm (Ichihara et al. 2002; Raymond and Ford 2007). These effects are considered secondary to neurological effects (see Section 3.2.1.4, Neurological Effects for more details).

No exposure-related histopathological lesions were observed in the gastrointestinal tract in intermediate-duration studies in rats or mice intermittently exposed to concentrations up to 1,000 or 500 ppm 1-bromopropane, respectively, or in chronic-duration studies in rats or mice exposed intermittently to concentrations up to 500 or 250 ppm, respectively (Albemarle Corporation 1997; Morgan et al. 2011; NTP 2011). The limited information from animal studies suggests that the gastrointestinal tract is not a sensitive target for airborne 1-bromopropane.

**Hematological Effects.** The available human occupational studies show mixed results regarding hematological effects in 1-bromopropane workers. For example, a study was conducted of 60 female and 26 male Chinese individuals who had been exposed to the chemical in three 1-bromopropane production

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factories for 3–4 years (Li et al. 2010). Based on assessments of individual exposures, median exposure concentrations for low-, mid-, and high-dose females were 1.28, 6.60, and 22.58 ppm, respectively; median exposure concentrations for the low- and high-dose males were 1.05 and 12.5 ppm, respectively. The results of hematological tests showed small (8–20%) but significant decreases between exposed female groups and matched controls for white blood cell count, red blood cell count, hemoglobin, and hematocrit. However, no clear dose-response relationships were apparent and the effects were not significant in male workers. Regression analysis adjusting for alcohol exposure and pair-matching for age, sex, and region in selecting controls showed significant negative trends for red blood cell count, hematocrit, and platelets in females; no significant trends were reported in males. The same regression analysis on the product of exposure levels and duration of exposure (cumulative exposure) showed significant increases in mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) and significant decreases in red blood cell count and hematocrit in female workers. In a review of the Li et al. (2010) study, Smith et al. (2011) noted that since hematological parameters experience temporal fluctuations related to menstrual cycle, lack of control for the latter could have led to misleading results. Additionally, reported hematological values in female workers were within reported reference ranges for hematological parameters (CDC 2005); values for other parameters were not reported by study authors.

The findings of Li et al. (2010) are not supported by findings from two earlier surveys of workers in the United States exposed to 1-bromopropane during the spray application of solvent-based adhesives (NIOSH 2002, 2003a). Neither survey found exposure-related hematological effects in the workers who were exposed to concentrations of 1-bromopropane ranging from 7 to 381 ppm. Although exposure levels were monitored using full-shift personal breathing zone samples in both studies, these studies are limited due to relatively small sample sizes (69 subjects in one study and 13 the other) and lack of control for potential confounding factors (e.g., age).

Single case reports or reports of a small number of workers experiencing frank neurotoxicity following exposure to 1-bromopropane suggest that hematological parameters are not particularly sensitive to 1-bromopropane exposure. For example, Samukawa et al. (2012) stated that routine blood tests (assuming that included standard hematological parameters) of a worker that may have been exposed to up to 553 ppm 1-bromopropane for 18 months were within normal limits. Raymond and Ford (2007) reported that a woman who developed neurological signs and symptoms 2 weeks after 1-bromopropane was introduced into her workplace had normal complete blood count. The geometric mean concentration of 1-bromopropane for glue sprayers was 107 ppm (range, 58–254 ppm). One of the cases described by Majersik et al. (2007) was that of a woman who worked as a foam cushion gluer for 4 years prior to

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showing neurotoxic signs and symptoms. The investigators stated that a complete blood count showed “variant lymphocytes.” However, no further details were provided. The mean concentration of 1-bromopropane in the workplace air during gluing operations was 130 ppm (range 91–176 ppm) and a TWA of 108 ppm (range 92–127 ppm).

Studies in rats and mice exposed to 1-bromopropane have described alterations in hematological parameters of questionable biological significance and at exposure levels considerably higher than those measured in the human studies mentioned above. For example, nose-only exposure of male Wistar rats to 7,280 ppm 1-bromopropane for 4 hours resulted in a significant increase in polymorphonuclear neutrophils 24 hours after exposure ceased, but not 14 days after exposure (Elf AtoChem S.A. 1997). Other hematological parameters were not significantly altered by exposure to 1-bromopropane in this study.

Significant hematological alterations observed in male rats exposed intermittently to 1,800 ppm 1-bromopropane for 8 weeks included a 28% decrease in white blood cell count, 8% decrease in red blood cell count, 12% decrease in hematocrit, 3% decrease in MCV, 8% increase in MCH, and 11% increase in mean corpuscular hemoglobin concentration (MCHC) (Kim et al. 1999). Some of these parameters were also altered at 50 ppm, but none were altered at 300 ppm. The study authors did not consider these changes to be biologically relevant, as they were mostly within the normal range for rats. Similarly, no biologically relevant changes were observed in hematological parameters in females exposed to concentrations up to 1,800 ppm (Kim et al. 1999). Similarly, significant, but minor changes in hematology observed in male rats intermittently exposed to concentrations  $\geq 400$  ppm for 12 weeks, including a 3% increase in MCV and a 2.4–3.5% decrease in MCHC, were not considered biologically relevant (Ichihara et al. 2000a). No exposure-related hematological changes were reported in rats or mice intermittently exposed to concentrations up to 1,000 or 500 ppm, respectively, for 7–14 weeks (Albemarle Corporation 1997; NTP 2011; Yu et al. 1998, 2001).

Available human and animal data are limited, but suggest that clinically relevant hematological changes are not likely to occur in humans following exposure to 1-bromopropane. Hematological parameters were not assessed in the chronic-duration study; therefore, it is unknown whether the findings of Li et al. (2010) in 1-bromopropane workers would also occur in animals following prolonged exposure to low levels of 1-bromopropane (Morgan et al. 2011).

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**Musculoskeletal Effects.** No information was located regarding musculoskeletal effects in humans exposed to 1-bromopropane.

Animal studies provide limited relevant data. Irregular banding of the striated muscle fibers of the soleus muscle was observed in male rats intermittently exposed to 800 ppm for 12 weeks, and electron microscopy revealed loss of regular linearity in the Z line and zigzag arrangement of the myofilaments; no changes were observed at  $\leq 400$  ppm (Ichihara et al. 2000b). In other intermediate-duration studies, no exposure-related musculoskeletal effects were observed in rats or mice intermittently exposed to concentrations up to 1,000 or 500 ppm, respectively (Albemarle Corporation 1997; Ichihara et al. 2000a; NTP 2011).

In the only available chronic-duration study, no exposure-related musculoskeletal effects were observed in rats or mice intermittently exposed to concentrations up to 500 or 250 ppm, respectively, for 105 weeks (Morgan et al. 2011; NTP 2011).

From these limited data, it would appear that neither skeletal muscle nor bone are sensitive targets for 1-bromopropane toxicity.

**Hepatic Effects.** Limited information is available regarding hepatic effects in humans exposed to 1-bromopropane. No evidence of adverse liver effects was observed in the Chinese cohort of workers exposed to 1-bromopropane studied by Li et al. (2010) as described above. In that study, liver function was assessed by clinical chemistry tests. The median exposure level in 60 female workers was 6.6 ppm with a range of 0.07–106.4 ppm. The corresponding values for 26 exposed male workers were 4.6 and 0.06–114.8 ppm. Raymond and Ford (2007) reported that a woman who developed neurological signs and symptoms 2 weeks after 1-bromopropane was introduced into the workplace had hepatic clinical chemistry parameters within normal ranges. The geometric mean air concentration was 107 ppm for glue sprayers (range 58–254 ppm).

Unlike the limited human data, findings from animal studies indicate that the liver might be a target of 1-bromopropane at much higher exposure levels. A study aimed at determining an  $LC_{50}$  for 1-bromopropane in rats reported cytoplasmic vacuolization of hepatocytes in some exposed rats exposed to 11,000–17,000 ppm for 4 hours; however, there was no dose-response relationship (Kim et al. 1999).

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Intermediate-duration studies in rats and mice have reported histological alterations consisting mostly of hepatocyte vacuolization and occasionally hepatocyte degeneration and necrosis at the higher exposure concentrations. Studies in rats identified LOAELs of 250 ppm (NTP 2011), 800 ppm (Yamada et al. 2003), and 600 ppm (Albemarle Corporation 1997); corresponding NOAELs were 125, 400, and 400 ppm 1-bromopropane. In general, male rats appeared to be affected at lower exposure concentrations than females. In these studies, exposure durations were  $\geq 12$  weeks. In an 8-week study, hepatocyte vacuolization was observed in rats exposed intermittently to 50–1,800 ppm 1-bromopropane; however, the study authors stated that findings were not dose-related, but incidence data were not provided (Kim et al. 1999). However, hepatocyte vacuolization was observed in parental male rats exposed to 250 ppm 1-bromopropane in a 2-generation reproductive study (BSOC 2001a). In shorter-duration studies (2–7 weeks), no exposure-related changes in liver histology were observed in rats exposed to concentrations up to 2,000 ppm (NTP 2011; Yu et al. 1998, 2001). LOAELs reported in mice include 50 ppm (lowest exposure concentration tested) for mild hepatocyte changes (Zong et al. 2016), 100 ppm (lowest exposure concentration tested) for hepatic necrosis (Liu et al. 2010), and 500 ppm for hepatocyte degeneration (NTP 2011). A NOAEL of 250 ppm 1-bromopropane was identified in NTP (2011).

Significant increases in liver weight (7–48%) have been reported in rats exposed intermittently for 2–14 weeks to  $\geq 125$  ppm 1-bromopropane but not at  $\leq 62.5$  ppm (Albemarle Corporation 1997; Huang et al. 2016; Kim et al. 1999; NTP 2011; Yamada et al. 2003). However, a study reported no exposure-related changes in liver weight in male rats following intermittent exposure to concentrations up to 800 ppm for 12 weeks (Ichihara et al. 2000a). In BALB/cA mice, which have an increased metabolic capacity for 1-bromopropane, absolute liver weights were significantly increased by 22% following exposure to 250 ppm 1-bromopropane for 4 weeks; no changes were observed at  $\leq 110$  ppm (Liu et al. 2009). In other mouse strains, liver weight was significantly increased by 13–43% following intermittent exposure to  $\geq 300$  ppm for 2–14 weeks; no exposure-related changes were observed at  $\leq 250$  ppm (Liu et al. 2009, 2010; NTP 2011).

The results of monitoring clinical chemistry parameters have been mixed and not always consistent with histopathological findings. Early, transient changes in clinical chemistry (decreased albumin, total protein, and alanine aminotransferase [ALT] activity) that were observed in rats intermittently exposed to 62.5–1,000 ppm for 14 weeks were attributed to the effects of 1-bromopropane on hepatic protein metabolism; however, the 25–30% increase in succinate dehydrogenase (SDH) activity in male rats exposed to  $\geq 500$  ppm might have been indicative of mild hepatotoxicity (NTP 2011). Serum activities of liver enzymes were significantly decreased in male rats exposed to  $\geq 50$  ppm for 8 weeks (Kim et al.

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1999). In females, aspartate aminotransferase (AST) activity was not significantly affected, ALT was decreased at  $\geq 300$  ppm, and lactic dehydrogenase (LDH) was decreased at 300 ppm but not 1,800 ppm (Kim et al. 1999). The lack of a dose-response relationship, at least in females, is consistent with an apparent lack of dose-response reported for histological alterations in this study. No biologically significant exposure-related changes were observed in hepatic clinical chemistry parameters in male or female rats exposed up to 600 ppm 1-bromopropane for 13 weeks; this exposure concentration induced hepatocyte vacuolization in male rats (Albemarle Corporation 1997). In male rats, plasma ALT levels were significantly decreased by 27–49% following intermittent exposure to  $\geq 700$  ppm for 3–12 weeks, but no changes were observed in plasma AST; no histological examination of the liver was conducted in this study (Ishida et al. 2002).

In a chronic-duration study, no exposure-related changes in non-neoplastic liver histology were observed in rats or mice intermittently exposed to concentrations up to 500 or 250 ppm, respectively, for 105 weeks (Morgan et al. 2011; NTP 2011).

The limited human data available suggest that the liver is not a sensitive target for 1-bromopropane toxicity. However, animal data suggest that at high enough concentrations, the liver may be a target of 1-bromopropane toxicity.

**Renal Effects.** The available studies of humans exposed to 1-bromopropane suggest that inhaled 1-bromopropane did not significantly alter renal function under the exposure conditions. A significant trend for increased blood urea nitrogen (BUN) was reported in male and female Chinese workers exposed to 1-bromopropane in the study conducted by Li et al. (2010); however, all reported values for BUN (as well as serum creatinine) were within reported reference values (Ichihara et al. 2011). In the Li et al. (2010) study, median exposure concentrations for low-, mid-, and high-dose females (20/group) were 1.28, 6.60, and 22.58 ppm, respectively; median exposure concentrations for low- and high-dose males (13/group) were 1.05 and 12.5 ppm, respectively. In the 2003 NIOSH survey described earlier under Hematological Effects, no exposure-related changes were observed in renal clinical chemistry values between adhesive-spray line workers exposed to a geometric mean (range) of 45.7 ppm (7–281 ppm) and 30 unexposed workers exposed to a geometric mean (range) of 1.1 ppm (0.1–4.9 ppm) (NIOSH 2003a). Similarly, in case studies, two women who developed neurological signs and symptoms 2 weeks after 1-bromopropane was introduced into their workplace had renal clinical chemistry and urinalysis parameters within normal ranges; however, one woman developed polyuria (Raymond and Ford 2007). The geometric mean air concentration was 107 ppm for glue sprayers (range 58–254 ppm). It should be



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mentioned that the women had been furniture gluers for  $\geq 40$  months prior to the introduction of 1-bromopropane into the workplace.

No information regarding renal effects was located in the available acute-duration studies in animals.

Intermediate-duration inhalation studies in animals provide information regarding kidneys' histological appearance, weight, and urinalysis parameters. Some animal studies suggest that exposure to high concentrations of 1-bromopropane may induce adverse renal effects.

Results of microscopic examination of the kidneys have been mixed. For instance, no significant alterations have been reported in rats at  $\leq 600$  ppm 1-bromopropane (Albemarle Corporation 1997; Kim et al. 1999; Yamada et al. 2003), but mild dilation of proximal tubules was seen in female rats exposed to 800 ppm (Yamada et al. 2003), tubule casts were reported in female exposed to 1,800 ppm for 8 weeks (Kim et al. 1999), and transitional renal epithelial hyperplasia and pelvic mineralization were reported in parental generation female rats exposed to 500 ppm 1-bromopropane (BSOC 2001a). In contrast, no exposure-related changes in kidney histology were observed in female rats exposed up to 2,000 ppm 1-bromopropane for 2–14 weeks (NTP 2011). Similarly, no exposure-related changes were observed in kidney histology in male rats at up to 2,000 ppm or mice at up to 500 ppm for 2–14 weeks (Albemarle Corporation 1997; Ichihara et al. 2000a; Kim et al. 1999; NTP 2011; Yu et al. 1998, 2001).

Results of monitoring kidney weight were mixed. The lowest LOAEL in rats was 125 ppm 1-bromopropane for a 20% increase in absolute kidneys weight in females in a 16-day study (NTP 2011), whereas the lowest LOAEL in mice was 500 ppm 1-bromopropane for a 12% increase in kidney weight in a 14-week study (NTP 2011). No NOAEL was identified in the rat study and the NOAEL in the mouse study was 250 ppm. Because other studies did not report significant alterations in kidney weights at higher exposure concentrations or effects were not dose-related, no generalizations can be made, suggesting that kidney weight is not a reliable biomarker of 1-bromopropane toxicity.

Two studies provided information regarding urinalysis in rats exposed to 1-bromopropane, and based on the results, it seems that exposure to 1-bromopropane did not induce toxicologically significant alterations. One 8-week study reported increased urobilinogen, bilirubin, ketone bodies, and leukocytes in females exposed to  $\geq 300$  ppm and decreased urobilinogen and increased ketone bodies in males exposed to 1,800 ppm (Kim et al. 1999). However, no data were shown, and the investigators stated that most values were within normal limits. In the other study, no exposure-related changes in urinalysis were

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observed in male or female rats exposed up to 600 ppm 1-bromopropane (the highest concentration tested) for 13 weeks (Albemarle Corporation 1997).

In a chronic-duration study, no exposure-related changes in kidney histology were observed in rats or mice intermittently exposed to concentrations up to 500 or 250 ppm, respectively, for 105 weeks (Morgan et al. 2011; NTP 2011).

The limited human data available suggest that the kidney is not a sensitive target for 1-bromopropane toxicity. Results from some animal studies suggest that at high enough concentrations, the kidney may be a target of 1-bromopropane toxicity. These concentrations, however, are considerably higher than those reported in occupational studies.

**Endocrine Effects.** A small number of human studies provide information on endocrine effects after exposure to 1-bromopropane. Based on these limited data, it appears that 1-bromopropane does not have endocrine effects in humans. In a study of Chinese workers exposed to 1-bromopropane conducted by Li et al. (2010), regression analyses that included exposure level and duration showed significant trends for increased serum TSH and follicle-stimulating hormone (FSH) in female workers. Neither serum estradiol levels in females nor serum testosterone levels in males were significantly associated with exposure to 1-bromopropane.

In a case study of female foam cushion gluers experiencing frank neurotoxicity following exposure to 1-bromopropane vapors 30–40 hours/week for  $\geq 3$  years, no exposure-related changes in serum TSH were observed (Majersik et al. 2007). The mean concentration of 1-bromopropane in the workplace air during gluing operations was 130 ppm (range 91–176 ppm). Similarly, Raymond and Ford (2007) reported that a woman who developed neurological signs and symptoms 2 weeks after 1-bromopropane was introduced into her workplace had normal thyroid function tests. The geometric mean air concentration in this case was 107 ppm for glue sprayers (range 58–254 ppm).

Studies in animals have examined mostly the microscopic appearance and weight of endocrine glands and, consistent with the limited human data, do not suggest that the endocrine system is a particularly sensitive target for 1-bromopropane toxicity.

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The only relevant information in an acute-duration study is that no changes in adrenal weight or plasma corticosterone levels were observed in male rats exposed intermittently to concentrations up to 1,000 ppm 1-bromopropane for 1–4 weeks (Zhang et al. 2013).

Intermediate-duration studies identified a LOAEL of 500 ppm 1-bromopropane for moderate to marked necrosis of the adrenal cortex in female mice exposed for 14 weeks; the NOAEL was 250 ppm (NTP 2011). No exposure-related non-neoplastic changes were observed in other endocrine glands. Studies in several strains of rats exposed intermittently to up to 1,800 ppm 1-bromopropane did not report exposure-related histopathological lesions in endocrine glands (Albemarle Corporation 1997; BSOC 2001a; Ichihara et al. 2000a; Kim et al. 1999; NTP 2011; Yamada et al. 2003).

Several intermediate-duration studies provide information on endocrine gland weight. The lowest LOAEL was 50 ppm 1-bromopropane for a 30% increase in relative weight of the left adrenal in male rats exposed for 8 weeks (Kim et al. 1999). However, exposure to higher concentrations did not show a clear dose-response relationship, and no significant changes occurred in the right adrenal or in the adrenal gland from females exposed to the same concentrations (Kim et al. 1999). Therefore, the significance of the effect is questionable at best. Other studies in rats that tested exposure concentrations in the range of 200–800 ppm 1-bromopropane also reported increases in adrenal weight in rats, but the results were inconsistent between studies, or no dose-response was apparent (Albemarle Corporation 1997; Yamada et al. 2003). In other intermediate-duration exposure studies, no exposure-related changes in adrenal or pituitary weight were observed in rats intermittently exposed to concentrations up to 1,000 ppm (Ichihara et al. 2000a; Zhang et al. 2013).

In chronic studies, no exposure-related, non-neoplastic changes were observed in endocrine glands from rats or mice intermittently exposed to concentrations up to 500 and 250 ppm 1-bromopropane, respectively, for 105 weeks (Morgan et al. 2011; NTP 2011).

The limited human data and the animal data available do not suggest that endocrine end points are particularly sensitive targets for 1-bromopropane toxicity.

**Dermal Effects.** No information was located regarding dermal effects in humans following inhalation exposure to 1-bromopropane.

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No exposure-related non-neoplastic skin lesions were observed in intermediate-duration studies in rats or mice intermittently exposed to concentrations up to 1,000 or 500 ppm, respectively, or in chronic-duration studies in rats or mice exposed intermittently to concentrations up to 500 or 250 ppm, respectively (Albemarle Corporation 1997; Morgan et al. 2011; NTP 2011).

**Ocular Effects.** No information was located regarding ocular effects in humans following inhalation exposure to 1-bromopropane. However, symptoms of eye irritation were common among Chinese workers exposed to concentrations  $\geq 56.9$  ppm 1-bromopropane (Ichihara et al. 2004a). It is assumed that the eye irritation was due to vapors of 1-bromopropane making direct contact with the eye.

No exposure-related changes were observed in ophthalmic or microscopic examinations of the eyes of rats intermittently exposed to concentrations up to 600 ppm 1-bromopropane for 13 weeks (Albemarle Corporation 1997). Similarly, no exposure-related non-neoplastic lesions were observed in the eyes of rats or mice intermittently exposed to concentrations up to 1,000 or 500 ppm 1-bromopropane, respectively, for 14 weeks, or 500 or 250 ppm, respectively, for 105 weeks (Morgan et al. 2011; NTP 2011).

**Body Weight Effects.** Studies in humans and in rats show that repeated exposure to 1-bromopropane can produce weight loss. Several single case reports or reports of a small number of workers experiencing frank neurotoxicity following exposure to 1-bromopropane also reported body weight loss (Ichihara et al. 2002; Raymond and Ford 2007). In general, weight loss (11–25 pounds in some cases) occurred in a relatively short period of time prior to hospitalization for neurological symptoms. In one case, weight loss was accompanied by diarrhea and nausea/vomiting (Ichihara et al. 2002). In two additional cases, it was noted that the subjects complained of dysphagia (difficulty swallowing), which suggested a disorder of the glossopharyngeal nerve, vagus nerve, or medulla oblongata (Ichihara et al. 2002). The mean daily time-weighted exposure level in one workplace was  $133 \pm 67$  ppm (range 60–261 ppm). In cases reported by Raymond and Ford (2007), the geometric mean air concentration of 1-bromopropane was 107 ppm for glue sprayers (range 58–254 ppm).

In an acute 4-hour nose-only inhalation study in rats, exposure of males to 7,280 ppm 1-bromopropane or females to 7,029 ppm 1-bromopropane did not result in significant alterations in body weight over a 14-day observation period following exposure (Elf AtoChem S.A. 1997). Intermittent exposure of pregnant rats to 498 or 996 ppm 1-bromopropane on gestational days (GDs) 6–19 resulted in 14.3 and

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24.6% reductions in net weight (weight at termination [GD 20] minus weight on GD 6), respectively; the NOAEL was 100 ppm 1-bromopropane (BSOC 2001b).

In intermediate-duration studies, body weight effects following inhalation exposure to 1-bromopropane differed between rat strains. In general, the relative strain susceptibility was Wistar > F-344 > Sprague Dawley. In male and female Wistar rats exposed intermittently for 1–14 weeks, final body weight decreases of 9.8–30% compared to controls were consistently reported at exposure concentrations  $\geq 1,000$  ppm 1-bromopropane, and decreased body weight was also occasionally observed in animals exposed to 700–800 ppm 1-bromopropane; no significant body weight effects were observed  $\leq 400$  ppm 1-bromopropane (Banu et al. 2007; Furuhashi et al. 2006; Honma et al. 2003; Huang et al. 2016; Ichihara et al. 2000a, 2000b; Ishida et al. 2002; Subramanian et al. 2012; Wang et al. 2002, 2003; Yamada et al. 2003; Yu et al. 2001; Zhang et al. 2013). Male F-344 rats exposed intermittently to  $\geq 1,000$  ppm 1-bromopropane for 2–105 weeks showed decreases in final body weight of 12–27% relative to controls; no significant body weight effects were observed in F-344 males exposed to  $\leq 500$  ppm or in females exposed to  $\leq 2,000$  ppm (Morgan et al. 2011; NTP 2011; Sekiguchi et al. 2002). None of the studies in Wistar or F-344 rats provided information regarding food consumption. In Sprague-Dawley rats, no significant changes ( $\leq 10\%$  compared to controls) in body weight or food consumption were observed in males or females intermittently exposed to concentrations up to 1,800 ppm for 8–13 weeks (Albemarle Corporation 1997; Kim et al. 1999; Sohn et al. 2002). However, male Sprague-Dawley from the parental generation in a 2-generation study exposed to 750 ppm 1-bromopropane were 12.8% lighter at termination than controls (BSOC 2001a). In addition, pregnant rats from the parental and F1 generations exposed to 500 ppm 1-bromopropane had body weights reduced 12–14% on GD 20; no significant effects were reported at 250 ppm 1-bromopropane (BSOC 2001).

No body weight effects were observed in four mouse strains intermittently exposed to concentrations up to 2,000 ppm for 2–14 weeks (Liu et al. 2009; NTP 2011; Zong et al. 2016). Similarly, no body weight effects were observed in mice exposed to concentrations up to 250 ppm for 105 weeks (Morgan et al. 2011; NTP 2011).

Human and rat studies indicate that exposure to 1-bromopropane can reduce body weight gain. Observed weight effects may be secondary to nausea and anorexia, or other neurological effects in exposed humans (see Section 3.2.1.4, Neurological Effects, for more details). In Wistar rats, exposure to  $\geq 1,000$  ppm 1-bromopropane has been reported to induce a decline in consciousness (Honma et al. 2003), so

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decreased food intake due to sedation may explain, at least in part, the reported decreased weight gain at these exposure levels.

**Metabolic Effects.** Limited data from reports of workers experiencing frank neurotoxicity following exposure to 1-bromopropane do not suggest metabolic effects of 1-bromopropane. In the 2003 NIOSH survey previously described in the Hematological Effects section, no exposure-related changes were observed in electrolyte levels between adhesive-spray line workers exposed to a geometric mean of 45.7 ppm 1-bromopropane (range, 7–281 ppm) and 30 unexposed workers exposed to a geometric mean of 1.1 ppm 1-bromopropane (range, 0.1–4.9 ppm) (NIOSH 2003a). Similarly, Raymond and Ford (2007) reported normal electrolyte and glucose levels in four workers who developed neurological signs and symptoms 2 weeks after 1-bromopropane was introduced into the workplace. The geometric mean air concentration was 107 ppm for glue sprayers (range, 58–254 ppm). It should be mentioned that the workers had been furniture gluers for up to 18 years prior to the introduction of 1-bromopropane into the workplace. In a case study of a female foam cushion gluer experiencing frank neurotoxicity following exposure to 1-bromopropane vapors for 30–40 hours/week for  $\geq 3$  years, no exposure-related changes in glucose levels were observed (Majersik et al. 2007). The mean concentration of 1-bromopropane in the workplace air during gluing operations was 130 ppm (range, 91–176 ppm).

Only one study in animals that assessed metabolic end points was located. No exposure-related changes in electrolyte or glucose levels were observed in male or female rats intermittently exposed up to 600 ppm 1-bromopropane for 13 weeks (Albemarle Corporation 1997).

### 3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after inhalation exposure to 1-bromopropane.

Only one study was located that evaluated immune function in animals exposed to 1-bromopropane via inhalation. In that study, the IgM plaque-forming response to immunization with SRBCs was reduced by up to ~60% in splenocytes harvested from female rats and mice exposed intermittently to 1,000 ppm and  $\geq 125$  ppm, respectively, for 4–10 weeks (Anderson et al. 2010). Other exposure-related changes observed in mice at  $\geq 125$  ppm included reduced absolute spleen weight, reduced spleen cellularity, decreased CD3+ cells in the spleen, and increased natural killer (NK) cells in the spleen. No mouse NOAEL was identified. In rats, several significant changes were observed in spleen cell subpopulations

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in rats at  $\geq 500$  ppm, including decreased CD4<sup>-</sup>/CD8<sup>+</sup>, CD45/B220<sup>+</sup>, and CD3<sup>+</sup> cells and increased NK cells. The NOAEL in rats was 250 ppm.

No other animal studies evaluating immune function were located. However, several studies examined immune organ weight or histology following inhalation exposure to 1-bromopropane; however, no exposure-related changes were observed in intermediate-duration studies in rats or mice exposed intermittently to concentrations up to 1,800 or 500 ppm, respectively, or in chronic-duration studies in rats or mice exposed intermittently to concentrations up to 500 or 250 ppm, respectively (Albemarle Corporation 1997; BSOC 2001a; Ichihara et al. 2000a; Kim et al. 1999; Morgan et al. 2011; NTP 2011; Yamada et al. 2003).

The limited evidence from animal inhalation studies indicates that 1-bromopropane can suppress immune responses in two different species, indicating that immune suppression may be a concern following 1-bromopropane exposure in humans.

#### 3.2.1.4 Neurological Effects

Exposure to 1-bromopropane can induce neurotoxicity in humans as evidenced by reports of exposure at work and occupational studies involving larger cohorts.

Neurological parameters were evaluated in Chinese 1-bromopropane production workers and unexposed controls (no monitoring data were available in the control factories, but these factories did not use 1-bromopropane) from the Li et al. (2010) occupational study described in the Hematological Effects section. Median exposure concentrations for the low-, mid-, and high-exposure females were 1.28, 6.60, and 22.58 ppm, respectively; median exposure concentrations for the low- and high-dose males were 1.05 and 12.5 ppm, respectively. Comprehensive neurological evaluations were conducted that included measurements of motor and sensory parameters as well as performance in various neurobehavioral tests. Using regression analysis of median group exposure levels, adjusting for alcohol exposure and pair-matching for age, sex, and region in selecting controls, significant trends were observed in tibial distal latency, vibration sense in the toes, and Benton test in female workers. Significant increases in tibial distal latency and vibration sense threshold were also associated with cumulative exposure in female workers. Regression analyses also showed impaired results in a test of motor coordination in males. When workers were stratified by exposure groups (control, low-, mid-, and high-exposure), analysis of variance (ANOVA) showed significant decreases in vibration sense, tibial distal latency, and sural

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sensory nerve conduction velocity between exposed females and controls. The vibration sense threshold showed the clearest dose-related effect, with significant increases (indicative of decreased vibration sense) in all exposed female groups. No significant differences between controls and individual male groups were seen regarding neurological parameters in this analysis. No information was provided regarding work position, which could have contributed to numbness and decreased sensations. The minimal LOAEL of 1.28 ppm for reduced vibration sense in female workers was used as the basis for the chronic-duration inhalation MRL. However, the confidence in the MRL is low due to a number of limitations of the principal study. Key limitations identified by the investigators or pointed out by others (Smith et al. 2011) included: (1) the cross-sectional study design; (2) potential selection bias for the control group; (3) potential underestimation of 1-bromopropane exposure levels; (4) co-exposure to low levels of 2-bromopropane in the exposed group of workers; (5) lack of biomonitoring data for controls; (6) lack of control of the temperature of the skin of the legs may have impacted measurements of nerve conduction velocity; (7) abnormally high control values for tibial nerve distal latency; (8) concerns regarding the sensitivity of the vibration sense measurement method utilized in the study; and (9) no data on menstrual cycle of females. However, after careful review of limitations and criticisms, as well as the available human and animal data, this study was considered to be the best available study on which to base the chronic MRL. In support, the most sensitive animal study yielded an MRL of 0.03 ppm (0.15 mg/m<sup>3</sup>) based on respiratory lesions (Morgan et al. 2011; NTP 2011), which is essentially equivalent to the MRL based on the selected human study. The rationale for selecting the Li et al. (2010) study as the principal study for the derivation of the chronic inhalation MRL, despite acknowledged limitations, is discussed in more detail in Appendix A. The results of the neurological testing of 1-bromopropane workers from one of the three factories included in the Li et al. (2010) study had been published previously by Ichihara et al. (2004b).

Other occupational studies evaluating neurological effects include two NIOSH Health Hazard Evaluation reports of workers exposed to 1-bromopropane during the spray application of solvent-based adhesives (NIOSH 2002, 2003a). These studies, however, are limited due to small sample sizes, lack of control for potential confounding factors (e.g., age), and/or lack of unexposed referent group. In the first report, study subjects were exposed to a geometric mean (range) 168.9 ppm (60–381.2 ppm) 1-bromopropane. All workers surveyed (n=42) presented with symptoms suggestive of excessive exposure to solvents. Those exposed to the higher levels of 1-bromopropane (169.8–197 ppm) reported more frequently having a headache at least once per week, having painful tingling in the hands, having a tremor, and “feeling drunk” when not drinking than those with the lower exposure levels. Thirty-two persons were subjected to further analyses of symptoms. The results showed that for each of the symptoms evaluated, the



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concentrations of 1-bromopropane in air were not statistically different between those individuals reporting the symptom compared to those not reporting the symptom. In the second NIOSH report, the cohort included 10 female and 3 male workers exposed to a geometric mean (range) of 45.7 ppm (7–281 ppm) and 30 unexposed workers exposed to a geometric mean (range) of 1.1 ppm (0.1–4.9 ppm). Exposed workers complained more frequently of tremor, headache, feeling "drunk," fatigue, and anxiety; using personal breathing zone (PBZ) data, employees reporting anxiety, headache, and feeling "drunk" had statistically significant higher PBZ concentrations of 1-bromopropane compared to those not reporting those symptoms. Nerve conduction studies performed in 29 individuals were judged by a physician to be normal, 4 were incomplete but without abnormalities, and 4 were considered borderline. The remaining five tests were considered abnormal; two of them were among the workers exposed to 1-bromopropane, but neither one was among the most heavily exposed workers. This yielded a prevalence ratio of 1.5 (95% CI, 0.3–7.9) for abnormal nerve conduction. Assessment of the combined (n=9) borderline tests (n=4) and abnormal tests (n=5) showed that only two of them were exposed to 1-bromopropane and seven were not. Overall, the results of this survey found no relationship between abnormal nerve conduction and exposure to 1-bromopropane.

Case reports have described neurological effects in subjects exposed to 1-bromopropane for periods ranging from a few weeks to years. In most cases, dermal exposure could have been significant since often no gloves were used when handling 1-bromopropane, or the use of gloves, as noted in some reports, may have enhanced dermal uptake of 1-bromopropane by occlusion effect. In an early case described by Sclar (1999), a subject exposed for 2 months to a solvent containing mainly 1-bromopropane developed numbness and progressive weakness of the extremities. Nerve conduction studies showed evidence of primary, symmetric demyelinating polyneuropathy. Samukawa et al. (2012) reported that a subject who used 1-bromopropane as a cleaning agent for metal parts for 18 months complained of numbness and pain of the lower extremities, weakness, and gait disturbance. Conduction velocity was decreased in motor and sensory nerves. Examination of a biopsy of the sural nerve showed axonal damage. The mean TWA level of exposure for this subject was estimated to be 553 ppm 1-bromopropane (range, 353–663 ppm). Others have reported similar effects (Ichihara et al. 2002; Majersik et al. 2007; MMWR 2008; Raymond and Ford 2007; Wang et al. 2015). Diarrhea, urinary incontinence, and abnormal sweating were signs reported in the three cases described by Ichihara et al. (2002), suggesting alterations in the autonomic nervous system. The daily exposure concentration measured with a passive sampler attached to one subject for 11 days was  $133 \pm 67$  ppm (mean  $\pm$  SD). Majersik et al. (2007) reported six cases of neurotoxicity occurring in foam cushion gluers exposed to 1-bromopropane vapors from spray adhesives. Five patients were exposed 30–40 hours/week over a period of 3 years, whereas the sixth patient had been

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employed for 3 months; none used protective clothing. Lower extremity pain or paresthesias developed subacutely in all of the patients. Five of them complained of difficulty walking and, upon examination, had spastic paraparesis, distal sensory loss, and hyperreflexia. Analysis of air samples collected at the workplace during gluing operations revealed a mean concentration of 1-bromopropane of 130 ppm (range, 91–176 ppm) with a 7-hour TWA of 108 ppm (range, 92–127 ppm). A 2-year follow-up of three of the patients revealed persistent symptoms that included headache, decreased memory, decreased mood, lower extremities numbness, cramping, paresthesias, weakness, and difficulty walking/poor balance. Clinical signs noted in these individuals included decreased cognition, lower extremities spasticity and weakness, gait ataxia, hyperreflexia, and decreased lower extremities sensation. Majersik et al. (2007) suggested that the pathogenesis of 1-bromopropane neurotoxicity in humans may reflect a central distal axonopathy syndrome. It should be noted that decreased vibration sense, particularly in the lower extremities, was reported in several of the cases described above (Ichihara et al. 2002; Majersik et al. 2007; Raymond and Ford 2007; Samukawa et al. 2012; Sclar 1999). Vibration sense in the toes appeared to be the most sensitive neurological end point in 1-bromopropane workers studies by Li et al. (2010), and was significantly decreased in workers exposed to a median concentration  $\geq 1.28$  ppm 1-bromopropane.

Many studies have examined the effects of 1-bromopropane on the nervous system of animals. These studies have provided information regarding biochemical, morphological, and physiological aspects of both the peripheral nervous system and the central nervous system. For the most part, these studies support the findings in humans.

A study aimed at determining an  $LC_{50}$  for 1-bromopropane in rats reported decreased activity and ataxia within 1 hour after a 4-hour exposure to  $\geq 11,000$  ppm 1-bromopropane (Kim et al. 1999). The same investigators reported that male and female rats exposed to 1,800 ppm 1-bromopropane for 6 hours showed decreased activity and mild ataxia after 1 hour of exposure; no such signs were observed in rats exposed to 300 ppm 1-bromopropane. In another study, daily exposure of male rats to 1,000 ppm 1-bromopropane 8 hours/day for 14 days significantly reduced forelimb grip strength, but no significant effect was seen at  $\leq 200$  ppm 1-bromopropane or at 1,000 ppm when tested following exposure on day 1 or 7 (Honma et al. 2003). The Honma et al. (2003) study was used to derive an acute-duration inhalation MRL for 1-bromopropane. A more detailed description of the Honma et al. (2003) study can be found in Appendix A.

An acute-duration study in male rats examined neurochemical (8 rats/group) and morphological effects (1 rat/group) of 1-bromopropane in rats exposed up to 800 ppm 1-bromopropane 8 hours/day for 7 days

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(Wang et al. 2002). Observed morphological alterations included the preterminal axon swelling with thin myelin sheath in the gracile nucleus of the medulla oblongata and swelling and masses of myelin sheath, hypertrophy of Schwann cell cytoplasm, and decreased frequency of Schmidt-Lanterman incisures in the posterior tibial nerve. Morphological changes were not observed in the medulla or tibial nerve at  $\leq 400$  ppm or the cerebellum, dorsal root ganglion, or thoracic spinal cord at  $\leq 800$  ppm. It should be mentioned, however, that only 1 rat per group ( $n=9$ ) was used for morphological analyses, therefore, the findings may not be representative. Biochemical findings in this study included decreased creatine kinase (CK) activity in the brain stem and spinal cord at  $\geq 200$  ppm, increased total glutathione through the central nervous system at  $\geq 200$  ppm, and reduced levels of the neuronal marker protein  $\gamma$ -enolase in the cerebrum and cerebellum at  $\geq 400$  ppm. These findings suggest that biochemical end points are affected at lower exposures than morphological structures if the morphological findings are representative of the various exposure groups.

In intermediate-duration studies, the lowest LOAEL for neurological effects was 50 ppm 1-bromopropane for increased spontaneous locomotor activity in male F-344 rats exposed intermittently for 3 weeks; the NOAEL was 10 ppm 1-bromopropane (Honma et al. 2003). The increase in spontaneous locomotor activity was used to derive an intermediate-duration inhalation MRL for 1-bromopropane. Other effects occurring at higher exposure concentrations included increased ambulation and rearing, altered performance in a water maze test, and decreased muscle strength; however, concentrations up to 1,000 ppm did not significantly alter passive avoidance behavior, preening behavior, or motor coordination (Honma et al. 2003). Other studies in rats have reported reduced limb grip strength at  $\geq 200$  ppm 1-bromopropane and altered gait at  $\geq 800$  ppm (Ichihara et al. 2000b; Yu et al. 1998, 2001). Male rats exposed to 1,500 ppm 1-bromopropane intermittently for 4 weeks showed frank effects such as ataxic gait and convulsions (Fueta et al. 2002). A study that assessed the reversibility of the effects of 1-bromopropane reported a significant decrease (about 68%) in hindlimb muscle strength in male Wistar rats following exposure to 1,000 ppm 1-bromopropane for 6 weeks, which was still evident (about 40% reduction) 14 weeks after exposure terminated (Banu et al. 2007). In a 13-week study in rats, however, no exposure-related changes were observed in motor activity or a functional observation battery assessed during weeks 4, 8, and 13 of exposure to 1-bromopropane at concentrations up to 600 ppm (Albemarle Corporation 1997). No significant histopathological changes were observed in rats or mice exposed at up to 1,800 or 500 ppm, respectively, 1-bromopropane 6 hours/day, 5 days/week for 8–14 weeks (Kim et al. 1999; NTP 2011; Sohn et al. 2002). Neurobehavior was not assessed in these studies.

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Some functional deficits described above could be explained by basic electrophysiological changes such as alterations in nerve conduction velocity. For example, motor nerve conduction velocity was significantly decreased and distal latency was increased in male Wistar rats after several weeks of exposure to  $\geq 800$  ppm 1-bromopropane (Ichihara et al. 2000b; Yu et al. 2001). In turn, decreased nerve conduction velocity could be due to morphological changes such as swelling of the axons and alteration of the myelin sheath, as observed by Ichihara et al. (2000b) and Yu et al. (1998, 2001). In Sprague-Dawley rats, a strain in which no functional deficits or morphological alterations of the brain were found by Albemarle Corporation (1997) and BSOC (2001a), a study of similar duration and exposure conditions as those used by Ichihara et al. (2000b) and Yu et al. (2001) reported no morphological alterations in peripheral nerves of male or female rats exposed to up to 1,250 ppm 1-bromopropane; however, no nerve conduction velocity experiments were conducted (Sohn et al. 2002). The mechanism(s) underlying the apparent strain differences are unknown.

Studies have also examined morphological and biochemical alterations in various brain areas following exposure to 1-bromopropane. For example, intermittent exposure of male rats to  $\geq 800$  ppm 1-bromopropane vapors for 4 weeks resulted in a significant reduction in the density of noradrenergic axons in the dorsal and ventral medial prefrontal cortex and the amygdala but induced no significant changes in the dentate gyrus in the hippocampus (Mohideen et al. 2011). In contrast, exposure to 1-bromopropane did not affect the density of serotonergic neurons in any of the three areas studied. A more recent study in rats reported that exposure to 1,000 ppm 1-bromopropane for 4 weeks produced pyknosis and shrinkage of Purkinje cells and nuclei of granular cells of the cerebellum (Mohideen et al. 2013). Immunostaining showed that exposure to  $\geq 400$  ppm 1-bromopropane significantly increased the number of astrocytes in the middle cerebellar peduncle, suggesting astrocyte activation. Exposure to 1-bromopropane also induced significant elongation of processes in astrocytes in the cerebellum in all exposed groups. There was no clear demyelination in the cerebellum or hippocampus. Cerebellar glia cells were also affected in a study in male rats exposed to 1,000 ppm 1-bromopropane 8 hours/day, 7 days/week for 4 weeks (Subramanian et al. 2012). In these rats, microglia appeared larger and had longer ramified processes in the high-dose group. Microscopy also showed shrinkage of Purkinje cells in the high-dose group. No such effects were reported in rats exposed to 800 ppm 1-bromopropane. Morphological changes were paralleled by exposure-concentration-related increases in markers of oxidative stress in the cerebellum, as well as reactive oxygen species and nitric oxide content, suggesting that these biochemical changes may play a role in the neurotoxicity of 1-bromopropane. Other biochemical changes observed in various brain regions following exposure to  $\geq 200$  ppm 1-bromopropane for 1–4 weeks included alterations in amino acids involved in transamination and alterations in levels of neurotransmitters or their metabolites or

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precursors from the gamma-aminobutyric acid (GABA), serotonergic, dopaminergic, noradrenergic, and glutamatergic systems (Suda et al. 2008; Zhang et al. 2013); see Section 3.4.2, Mechanisms of Toxicity, for more details, in particular the possible role of the hippocampus in 1-bromopropane-induced neurotoxicity.

In a chronic-duration inhalation study of 1-bromopropane, exposure of male and female rats to up to 500 ppm 1-bromopropane or of male and female mice to up to 250 ppm 1-bromopropane did not induce gross or microscopic alterations in brain (Morgan et al. 2011; NTP 2011). No other neurological end points were assessed in these studies.

The available data clearly indicate that the nervous system is a target for 1-bromopropane toxicity in humans and animals. Data in humans show that 1-bromopropane can induce morphological alterations in neurons, which may lead to motor and sensory deficits. Studies in animals show that 1-bromopropane can induce biochemical, morphological, electrophysiological, and neurobehavioral alterations by mechanisms yet to be elucidated.

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1. Due to unclear adversity of biochemical changes in the nervous system, these end points were not used as the basis of NOAEL/LOAEL determinations unless they were clearly associated with an apical end point (e.g., neurobehavioral change, histopathological lesion, etc.).

#### **3.2.1.5 Reproductive Effects**

Available information regarding reproductive effects of 1-bromopropane in humans is limited. In two NIOSH health hazard reports, no exposure-related reproductive effects were reported by workers exposed to 1-bromopropane in response to the questions regarding whether they had been diagnosed with a reproductive or fertility problem, had ever seen a doctor for reproductive or fertility problems, or had failed to have a child after attempting for a full year (NIOSH 2002, 2003a). The geometric means for 1-bromopropane exposure levels were 168.9 and 45.7 ppm for the 2002 and 2003 report, respectively. In the 2003 report, a limited number of individuals (three exposed males, nine unexposed males) were evaluated for sperm parameters (NIOSH 2003a). There was no evidence of exposure-related changes in sperm count, motility, or morphology. In preliminary health surveys, female workers from a Chinese 1-bromopropane factory (n=23) did not report more menstrual abnormalities than age-matched referents

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from a beer factory (Ichihara et al. 2004a, 2004b). The 8-hour shift TWA median exposure was 1.61 ppm 1-bromopropane. Survey results were not included in the more comprehensive health survey from this and two other factories in China (Li et al. 2010).

Animal studies that evaluated sperm/estrous cycle parameters, reproductive organ weight and histology, and reproductive hormone levels were available for review. While the available human data are inadequate to assess the reproductive toxicity of 1-bromopropane, animal data suggest that the reproductive system may be a potential target of concern for 1-bromopropane toxicity in humans.

Alterations in sperm parameters have been consistently reported in rats and mice following intermittent, intermediate-duration inhalation exposure to 1-bromopropane at concentrations as low as 250 and 50 ppm, respectively. Observed effects in F-344 rats exposed to  $\geq 250$  ppm and rats exposed to  $\geq 400$  ppm included a 25–70% decrease in sperm count, a 7–58% decrease in sperm motility, and a 7–98.5% increase in percent of abnormal sperm (including tailless sperm and banana-like sperm heads); no sperm alterations were observed in rats exposed to  $\leq 200$  ppm 1-bromopropane (Ichihara et al. 2000a; NTP 2011). In Wistar rats, exposure to 400 ppm 1-bromopropane for 6 weeks results in a 23% decrease in epididymal sperm count and exposure to 1,000 ppm significantly reduced sperm motility and sperm count even 14 weeks after the 6-week exposure period ceased (Banu et al. 2007). The investigators suggested that different mechanisms operate at different exposure concentrations based on the observed failure of spermiogenesis at 400 ppm 1-bromopropane and spermatogenic cell depletion at 1,000 ppm 1-bromopropane. In three mouse strains with different capacities to metabolize 1-bromopropane (C57Bl/6J, DBA/2J, and BALB/cA), the strain with the highest CYP2E1 protein level and lowest total GSH content and GST activity in the liver (BALB/cA) was the most susceptible, showing a 27–78% decrease in sperm count, a 24–39% decrease in percent of motile sperm, and a 15–24% increase in the percent of abnormal sperm (2-tail sperm, banana-like sperm) at concentrations  $\geq 50$  ppm 1-bromopropane (lowest concentration tested) (Liu et al. 2009). Garner et al. (2007) had earlier reported that CYP2E1-null mice exposed to 800 ppm for 6 hours had a lower reduction (12%) in sperm motility than similarly exposed wild mice (37%). In B6C3F1 mice, sperm count was decreased 28% and sperm motility was decreased 3% at 500 ppm 1-bromopropane; no sperm alterations were observed at concentrations  $\leq 250$  ppm (NTP 2011).

Multiple studies reported alterations in the estrous cycle in rats and mice intermittently exposed to 1-bromopropane vapors at concentrations  $\geq 250$  and 500 ppm, respectively, for 12–14 weeks. Observed alterations included an increase in the number of irregular cycles or lack of estrous cycling in rats exposed to  $\geq 400$  ppm (Yamada et al. 2003), extended estrus period and decreased diestrus period during normal-

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length estrous cycles in F-344 rats exposed to  $\geq 250$  ppm for 14 weeks (NTP 2011), and a 10% increase in estrous cycle length in mice exposed to 500 ppm 1-bromopropane for 14 weeks (NTP 2011). No significant changes in the estrous cycle were observed in rats at  $\leq 200$  ppm or mice at  $\leq 250$  ppm (NTP 2011; Yamada et al. 2003). In a shorter intermediate-duration study in rats exposed intermittently to up to 1,000 ppm 1-bromopropane for 20 days, there were no exposure-related changes in the number of estrous cycles per group, number of cycles per rat, cycle days, number of rats with cycles  $> 6$  days in duration, or number of ovulated ova in the oviduct at sacrifice (during estrous) (Sekiguchi et al. 2002).

An acute inhalation study in male rats did not reveal histological lesions in the testes following a 4-hour nose-only exposure to up to 8,500 ppm 1-bromopropane (Elf AtoChem S.A. 1997).

Histopathological lesions in the reproductive organs were infrequently reported in longer-term studies. One intermediate-duration study reported several alterations in reproductive organ histology in male Wistar rats following intermittent exposure to 800 ppm 1-bromopropane for 12 weeks (Ichihara et al. 2000a). Histological alterations were described qualitatively only, and included alterations in the testes (increased number of degenerated spermatocytes and retention of elongated spermatids in the seminiferous tubules), epididymides (decreased diameter of the epididymal duct cavity, increased interstitial space, increased height of the epithelial cells, and presence of neutrophil leukocytes or degenerated epithelial cell-like profiles in the epididymal duct), and the prostate and seminal vesicles (smaller alveoli and many degenerated cells in the vesicular cavity of the seminal vesicles). With the exception of retention of elongated spermatids in the seminiferous tubules at 400 ppm, no histopathological changes were observed at concentrations  $\leq 400$  ppm 1-bromopropane (Ichihara et al. 2000a). A more recent study from the same group of investigators reported degenerative changes in the reproductive organs of male Wistar rats exposed to 1,000 ppm 1-bromopropane for 6 weeks (Banu et al. 2007). Fourteen weeks after exposure ceased, the appearance of the prostate and seminal vesicles had returned to normal, but the testes and epididymides still showed histological alterations (Banu et al. 2007). In females, one intermediate-duration study reported follicular changes in the ovaries of rats intermittently exposed to concentrations  $\geq 200$  ppm 1-bromopropane for 12 weeks, including a significant 33–75% decrease in the number of antral and growing follicles (Yamada et al. 2003). In this study, no histological changes were observed in the uterus or vagina at exposures up to 800 ppm 1-bromopropane (Yamada et al. 2003). However, no significant histopathological changes were reported in the reproductive organs in intermediate-duration studies in rats or mice exposed to up to 1,800 or 500 ppm 1-bromopropane, respectively (Albemarle Corporation 1997; Kim et al. 1999; NTP 2011; Yu et al. 1998,

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2001), or in chronic duration studies in rats or mice at concentrations up to 1,000 or 500 ppm, respectively (Morgan et al. 2001; NTP 2011).

Reproductive organ weight changes have been inconsistently reported in intermediate-duration studies with intermittent exposure to 1-bromopropane. Testes weight was significantly decreased by 12.5% in mice exposed to 250 ppm, but not  $\leq 110$  ppm 1-bromopropane (Liu et al. 2009); however, no other intermediate-duration study reported decreased testicular weight in mice or rats exposed to concentrations up to 500 and 1,800 ppm, respectively (Albemarle Corporation 1997; Ichihara et al. 2000a; Kim et al. 1999; Liu et al. 2009; NTP 2011). A study aimed at determining an  $LC_{50}$  for 1-bromopropane in rats did not report altered testes weight after the 14-day observation period at up to 8,500 ppm (Elf AtoChem S.A. 1997). Epididymides weight was significantly reduced by 11–28% in rats exposed to  $\geq 400$  ppm 1-bromopropane (Ichihara et al. 2000a) and by 14–19% in rats exposed to 1,000 ppm (but not  $\leq 500$  ppm) (NTP 2011); however, no changes in epididymides weight were reported in mice exposed to concentrations up to 500 ppm (Liu et al. 2009; NTP 2011). Significant reductions of 18–47% in weight of the seminal vesicles have been reported in rats and C57Bl/6J mice at  $\geq 200$  and 250 ppm, respectively; however, seminal vesicle weights were not altered in DBA/2J or BALB/cA mice exposed to concentrations up to 250 ppm (Ichihara et al. 2000a; Liu et al. 2009). In addition, one study reported a 32% decreased in prostate weight in rats at 800 ppm, but not  $\leq 400$  ppm (Ichihara et al. 2000a). A study that examined the reversibility of the effects of 1-bromopropane reported significant reductions in absolute weight of the prostate (56%), seminal vesicles (56%), testes (33%), and epididymides (28%) after 6 weeks of exposure to 1,000 ppm 1-bromopropane; no significant changes occurred at 400 ppm 1-bromopropane (Banu et al. 2007). Fourteen weeks after exposure ceased, the weight of the testes and epididymides were still significantly reduced compared to controls (Banu et al. 2007). One intermediate-duration study reported a significant 27–30% increase in the relative weight of the right and left ovaries in rats exposed to 1,800 ppm 1-bromopropane for 8 weeks; no changes were observed at concentrations  $\leq 300$  ppm (Kim et al. 1999). In other intermediate-duration studies, no changes were observed in female reproductive organ weights in rats exposed to concentrations up to 1,000 ppm (Albemarle Corporation 1997; Sekiguchi et al. 2002; Yamada et al. 2003).

Three intermediate-duration studies evaluated reproductive hormones in animals exposed to 1-bromopropane. Plasma testosterone levels were significantly decreased by 36% in male rats exposed to 800 ppm for 12 weeks (Ichihara et al. 2000a). Exposure to 1,000 ppm 1-bromopropane for 6 weeks resulted in a 56% reduction in serum testosterone in male Wistar rats (Banu et al. 2007). After a 4-week recovery period, serum testosterone was reduced 27% relative to controls, and returned to control values



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after a 14-week recovery period; no significant changes were reported at 400 ppm 1-bromopropane. No changes were observed in testosterone levels at  $\leq 400$  ppm or in plasma luteinizing hormone (LH) or FSH at concentrations up to 800 ppm 1-bromopropane (Ichihara et al. 2000a). No changes were observed in serum LH or FSH in female rats following intermittent exposure at concentrations up to 800 ppm 1-bromopropane for 12 weeks (Yamada et al. 2003).

A comprehensive 2-generation reproductive study defined a NOAEL and LOAEL of 100 and 250 ppm 1-bromopropane, respectively, for reproductive effects in rats (BSOC 2001a). Exposure to 250 ppm 1-bromopropane resulted in a significant reduction (14%) in absolute prostate weight in F0 males and increased length of the estrous cycle (9%) in F1 females. Other reported effects included 48% reduction of fertility at 500 ppm and complete infertility at 750 ppm in the F0 generation. The mating index was also significantly reduced at 750 ppm, and time between pairing and coitus was increased in groups exposed to  $\geq 500$  ppm 1-bromopropane. Males in the F0 generation exposed to  $\geq 500$  ppm 1-bromopropane had significantly reduced sperm motility and reduced morphologically normal sperm; this was also observed in F1 males exposed to 500 ppm. The number of implantation sites was significantly reduced in F0 dams exposed to 500 ppm 1-bromopropane. Examination of the ovary of F0 females showed significantly decreased corpora lutea at 500 and 750 ppm and increased follicular cysts and interstitial cell hyperplasia at 750 ppm. Ovaries of 500 ppm-exposed F1 females also showed an increased incidence of cysts and interstitial cell hyperplasia. No significant histological alterations were reported in the testes from male rats in the F0 or F1 generation. It should be noted, however, that exposure of rats to  $\leq 996$  ppm 1-bromopropane (highest concentration tested) during GDs 6–19 did not significantly affect pregnancy rates (pregnancy at termination), uterus weight, mean number of corpora lutea, pre- and post-implantation loss, or mean number of early and late resorptions (BSOC 2001b).

Some of the reproductive effects in rats reported by Albermarle Corporation (2001) were also reported in a study in which pregnant female rats were exposed to 1-bromopropane from conception to the end of lactation (Furuhashi et al. 2006). In the latter study, male offspring from rats exposed to 400 ppm 1-bromopropane showed no exposure-related changes in the epididymal sperm count or the percent motile sperm at postnatal day (PND) 50, but the rate of sperm arrival at cauda epididymides (the tail or inferior portion leading into the ductus deferens) was significantly lower than in controls. At 100 ppm (lowest concentration tested) and 400 ppm, testes showed fewer cells in the seminiferous tubules and fewer cell layers at PND 21 and a delay in thickening and differentiation of seminiferous tubules at day 33 (no quantitative data reported). Evaluation of sexual maturation in female offspring showed no

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exposure-related changes, as assessed by the timing of the first diestrous. No changes were observed in male or female reproductive organ weights at PND 21, 33, or 50.

Overall, the available human data are inadequate to assess the reproductive toxicity of 1-bromopropane. However, the available animal data suggest that the reproductive system may be a potential target of concern for 1-bromopropane toxicity in humans.

**3.2.1.6 Developmental Effects**

No studies were located for developmental effects in humans after inhalation exposure to 1-bromopropane.

Limited information regarding developmental effects in animals indicate that perinatal exposure to 1-bromopropane can lead to altered growth in rats, but the relevance of this information to exposure of humans is unclear.

Reduced fetal weight was reported in a gestational intermittent exposure study in rats (BSOC 2001b). On GD 20, fetal body weights (male and female combined) from dams exposed to 100, 498, or 996 ppm 1-bromopropane were reduced 2.5, 4.9, and 7.4% relative to controls, respectively. Exposure to 1-bromopropane did not significantly affect the mean number of live fetuses per rat or sex ratio. Exposure to 1-bromopropane also did not induce external, visceral, or skeletal malformations. There was a significant increased dose-related incidence of delayed ossification in fetuses from the mid- and high-exposure concentration groups, which the investigators suggested was probably associated with maternal toxicity (reduced food consumption and body weight) and reduced fetal weight. Reduced body weight in the offspring was also reported in another study in which rats were exposed intermittently to 700 ppm 1-bromopropane (only exposure concentration tested) on GDs 1–20 (Fueta et al. 2015). Offspring body weight on PND 14 (only time measured) was reduced 7.5–9.5% compared to controls; no maternal toxicity was reported in this study. Fueta et al. (2015) also reported that maternal exposure to 1-bromopropane resulted in suppression of a shaking behavior in 14-day-old pups induced by injection of kainate, but not of a scratching behavior induced by kainate; the relevance of these findings to human health is unknown.

In the 2-generation study by BSOC (2001a) summarized above, the number of F1 and F2 pups born and litter size from the group exposed to 500 ppm 1-bromopropane were significantly reduced compared to

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controls; no significant differences were seen at 250 ppm 1-bromopropane. F1 and F2 viability during lactation was not significantly affected by exposure to 500 ppm. F1 male pups exposed to 500 ppm had significantly reduced weight (13.7%) on PND 28. Male and female F1 pups necropsied on PND 21 or 28 showed no significant gross alterations in tissues or organs or alterations in selected organ weights (brain, spleen, thymus). A significant delay in F1 preputial separation occurred at 500 ppm; this was attributed to reduced body weights. Vaginal patency was not affected in F1 females. F2 male and female pup weights on PNDs 14 and 21 were significantly reduced (14–18%) at 500 ppm. Gross necropsy of F2 on PND 21 did not show treatment-related gross alterations or alterations in the brain, spleen, or thymus.

In a study in which rats were exposed to 1-bromopropane from conception to the end of lactation, survival of offspring during lactation was decreased in a dose-dependent fashion by ~5, 30, and 70% at 100 (lowest concentration tested), 400, and 800 ppm, respectively (Furuhashi et al. 2006). Decreased survival, however, was only statistically significant at 800 ppm. In order to determine if decreased survival and body weight gain in offspring were due to gestational or lactational exposure, a cross-foster experiment was also conducted with 0 or 800 ppm 1-bromopropane. The results showed that gestation and lactation exposure had comparable effects on survival rate, but lactation exposure played a greater role on growth of the offspring. Additionally, F1 animals were assessed for their ability to produce F2 offspring. Mated offspring from the lactation-only exposure group produced a significantly greater number of dead F2 offspring, compared with control. However, no exposure-related effects were observed in the F2 litter for gestational-only exposure. This suggested that lactation exposure may have played a greater role in sexual maturation of the offspring.

No teratogenic effects were reported by either BSOC (2001a, 2001b) or Furuhashi et al. (2006).

#### **3.2.1.7 Cancer**

No studies of cancer in humans exposed to 1-bromopropane by the inhalation route were located in the literature.

The potential carcinogenicity of 1-bromopropane has been examined in bioassays in rats and mice (Morgan et al. 2011; NTP 2011). In both bioassays, animals were exposed 6 hours/day, 5 days/week for up to 105 weeks. Rats were exposed to 0, 125, 250, or 500 ppm 1-bromopropane vapors, while mice were exposed to 0, 62.5, 125, 250, or 500 ppm 1-bromopropane vapors. 1-Bromopropane was a multi-site carcinogen in rats, significantly increasing the incidence of large intestine adenomas in females

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(500 ppm), skin keratoacanthoma in males ( $\geq 250$  ppm), skin keratoacanthoma, basal cell adenoma, or squamous cell carcinoma in males ( $\geq 125$  ppm), malignant mesothelioma in males (500 ppm), and pancreatic islet adenoma in males ( $\geq 125$  ppm). In mice, exposure to 1-bromopropane significantly increased the incidence of combined alveolar/bronchiolar adenoma or carcinoma in females ( $\geq 62.5$  ppm).

Based on the information available, the Department of Health and Human Services (DHHS) has classified 1-bromopropane as “*reasonably anticipated to be a human carcinogen*” (NTP 2016). Based on the findings in animals, ACGIH has assigned 1-bromopropane a classification of “*A3 – Confirmed animal carcinogen with unknown relevance to humans*” (ACGIH 2104, 2016). The International Agency for Research on Cancer (IARC) and the EPA have not evaluated the carcinogenicity of 1-bromopropane (IARC 2014; IRIS 2014).

#### 3.2.2 Oral Exposure

##### 3.2.2.1 Death

No reports of death in humans due to oral exposure to 1-bromopropane were located in the available literature.

In male and female rats exposed once to concentrations of 2,000 mg 1-bromopropane/kg via gavage, 0/5 males and 1/5 females died during the 14-day observation period; the LD<sub>50</sub> was determined to be greater than 2,000 mg 1-bromopropane/kg (Elf Atochem S.A. 1993). Necropsy did not reveal gross alterations. Although there are no monitoring data for 1-bromopropane in water or soil, it is unlikely that humans would be orally exposed to these high levels of 1-bromopropane.

##### 3.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, renal, endocrine, dermal, ocular, or metabolic effects in humans or in animals following oral exposure to 1-bromopropane. In addition, no studies were located regarding hepatic and body weight effects in humans exposed orally to 1-bromopropane.

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

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Table 3-2 Levels of Significant Exposure to 1-Bromopropane - Oral

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
ACUTE EXPOSURE								
Systemic								
1	Rat (Sprague-Dawley)	once (G)	Bd Wt	2000			Elf Atochem S.A. 1993 1-Bromopropane	
2	Rat (Wistar)	12 d 1 x/d (GO)	Bd Wt	800 M			Guo et al. 2015 1-Bromopropane	
3	Rat (Wistar)	12 d 1 x/d (GO)	Bd Wt	400 M	800 M (13% decrease in final body weight)		Zhong et al. 2013 1-Bromopropane	
4	Mouse (BALB/c)	once (GO)	Hepatic	200 F	500 F (centrilobular hepatocyte swelling)		Lee et al. 2007 1-Bromopropane	Congestion, hemorrhage, cellular swelling and vacuolization of hepatocytes was observed at 1,000 ppm
			Bd Wt	1000 F				
5	Mouse (ICR)	10 d 1 x/d (GO)	Bd Wt	600 M			Yu et al. 2008 1-Bromopropane	
Immuno/ Lymphoret								
6	Mouse (BALB/c)	once (GO)			200 F (reduced antibody response to T-dependent antigen)		Lee et al. 2007 1-Bromopropane	

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Table 3-2 Levels of Significant Exposure to 1-Bromopropane - Oral

(continued)

Key to Figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
Neurological								
7	Rat (Sprague-Dawley)	once (G)				2000 (sedation)	Elf Atochem S.A. 1993 1-Bromopropane	
8	Rat (Wistar)	12 d 1 x/d (GO)		100 M	200 M (impaired spatial memory and learning ability)		Guo et al. 2015 1-Bromopropane	
9	Rat (Wistar)	12 d 1 x/d (GO)			200 <sup>b</sup> M (impaired spatial learning and memory)		Zhong et al. 2013 1-Bromopropane	
Reproductive								
10	Mouse (ICR)	10 d 1 x/d (GO)			600 M (degeneration of pachytene spermatocytes)		Yu et al. 2008 1-Bromopropane	

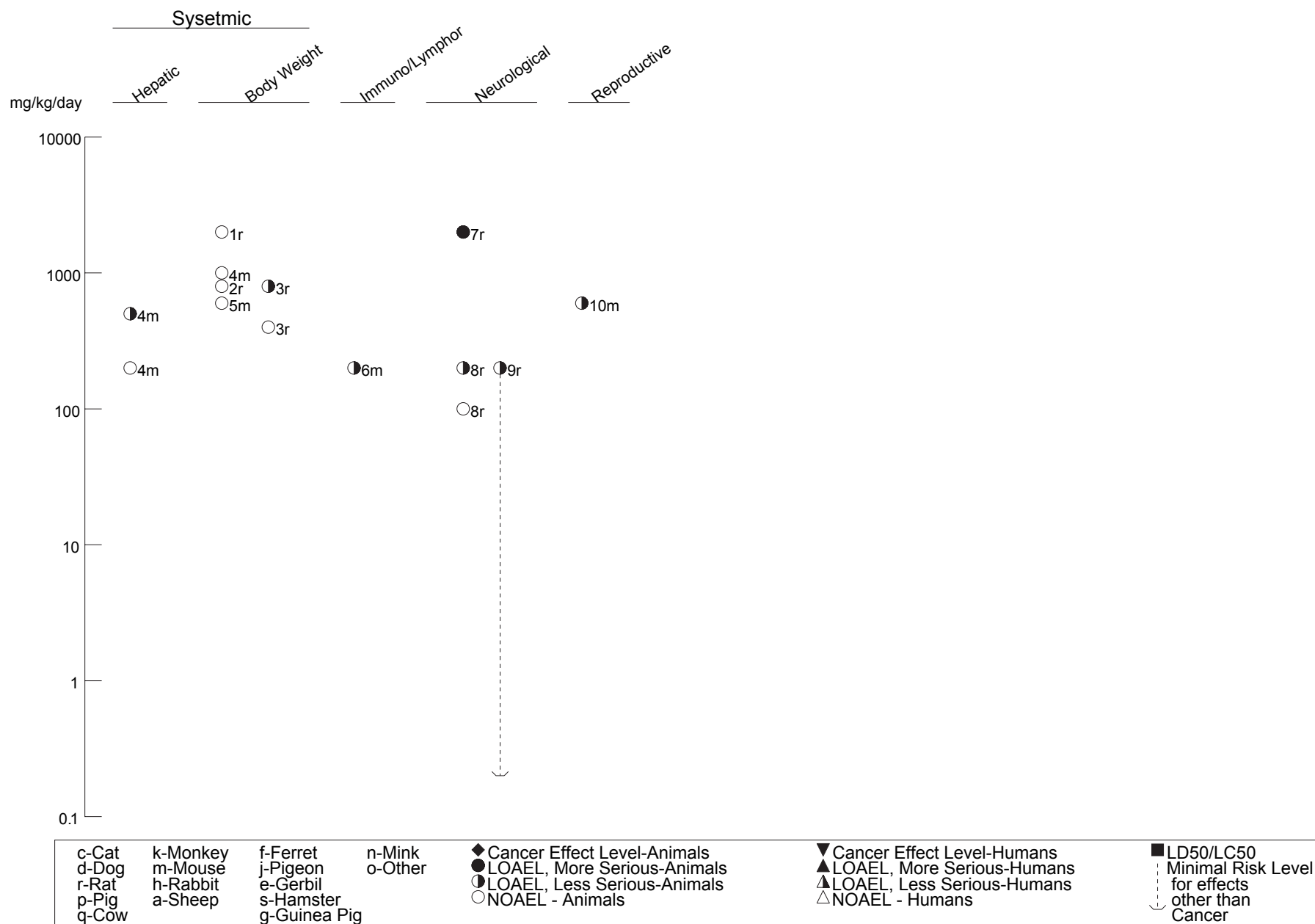
<sup>a</sup> The number corresponds to entries in Figure 3-2.

<sup>b</sup> Used to derive an acute-duration (14 days or less) oral minimal risk level (MRL) of 0.2 mg/kg/day for 1-BP. Using benchmark-dose modeling, a BMD1SD and BMDL1SD of 148.37 and 19.75 mg/kg/day, respectively, were calculated for decreased spatial memory in rats on Day 5 of the Morris water maze task from the selected model (Hill). The BMDL1SD was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) to derive the MRL of 0.2 mg/kg/day.

Bd Wt = body weight; d = day(s); F = Female; (G) = gavage; (GO) = gavage in oil; Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; x = time(s)

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Figure 3-2 Levels of Significant Exposure to 1-Bromopropane - Oral  
Acute ( $\leq 14$  days)



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**Hepatic Effects.** Data from a single acute-duration oral study in mice suggest that exposure to high oral doses of 1-bromopropane may induce severe liver effects, although further studies are needed to validate these data. Gavage administration of a single dose of 500 mg 1-bromopropane/kg to female mice induced centrilobular swelling of hepatocytes, and a single dose of 1,000 mg 1-bromopropane/kg induced liver congestion, hemorrhage, cellular swelling, and vacuolization assessed 12 hours after dosing and increasing in severity at later times (assessed up to 48 hours post-exposure) (Lee et al. 2007); no significant effects were reported in mice dosed with 200 mg 1-bromopropane/kg. These morphological changes were accompanied by increased serum ALT activity (maximally 380-fold 24 hours after dosing with 1,000 mg 1-bromopropane/kg). Biochemically, treatment with 1-bromopropane caused depletion of GSH and increased the formation of GSH conjugates, possibly leading to increased oxidative stress, as evidenced by increased levels of malondialdehyde and decreased catalase activity.

**Body Weight Effects.** Limited data in animals preclude drawing meaningful conclusions regarding effects from oral 1-bromopropane exposure on body weight. Body weight was not affected in male or female rats administered a single dose of 2,000 mg 1-bromopropane/kg and observed for up to 14 days (Elf Atochem S.A. 1993) or in female mice administered a single dose of 1,000 mg 1-bromopropane/kg and observed for up to 48 hours (Lee et al. 2007). In repeated-dose studies, administration of 800 mg 1-bromopropane/kg/day to male rats for 12 consecutive days resulted in a 13% decrease in terminal body weight; no significant effect was reported at 400 mg 1-bromopropane/kg/day (Zhong et al. 2013). No data on food consumption were provided in the latter study. In a similar study, 10 consecutive doses of up to 600 mg 1-bromopropane/kg/day did not significantly affect body weight in male mice (Yu et al. 2008).

### 3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans following oral exposure to 1-bromopropane.

A single mouse study provides relevant information, although it is insufficient to determine whether the immunological system might be a target for oral exposure to 1-bromopropane. Female mice dosed once by gavage with  $\geq 200$  mg 1-bromopropane/kg and immunized intraperitoneally with SRBC 30 minutes later showed a significant reduction in the antibody response to the T-dependent antigen of up to 60% 4 days later (Lee et al. 2007). It was also reported that  $\geq 200$  mg 1-bromopropane/kg/day significantly reduced the number of CD4<sup>+</sup>IL-2<sup>+</sup> cells in response to ConA by up to ~30%. Flow cytometry showed that



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1-bromopropane reduced the absolute number of all splenocyte subpopulations. The investigators also reported that exposure to 1-bromopropane decreased spleen GSH content while increasing a GSH conjugation product, and suggested that immunotoxicity might be related to increased oxidative stress.

**3.2.2.4 Neurological Effects**

No studies were located regarding neurological effects in humans following oral exposure to 1-bromopropane.

The limited number of studies in animals showed that high oral doses of 1-bromopropane can produce sedation, and repeated lower doses can affect learning and memory.

Clinical signs of neurotoxicity, including marked decrease in spontaneous activity (sedation), piloerection, and dyspnea, were observed in male and female rats within 4 hours of receiving a single gavage dose of 2,000 mg 1-bromopropane/kg (Elf Atochem S.A. 1993). Surviving animals (9/10) fully recovered by day 2 of the 14-day post-exposure observation period.

Limited data are available in a study that examined the effects of 1-bromopropane on cognitive function in male rats and the possible role of oxidative stress (Zhong et al. 2013). On days 8–12 of a 12-day treatment with 200, 400, or 800 mg 1-bromopropane/kg/day, cognitive function (spatial learning and memory) was assessed with the Morris water maze test. Some rats dosed with 400 and 800 mg 1-bromopropane/kg/day showed irritability at the start of dosing. After 1 week of dosing, rats in the 800 mg 1-bromopropane/kg/day group showed slow response and sluggishness. Dose-related impairments were observed in learning and memory measures in the Morris water maze task. During the 4-day learning phase, the escape latency was significantly increased in the 800 mg 1-bromopropane/kg/day group and the total swimming distance was increased at  $\geq 200$  mg 1-bromopropane/kg/day. Time spent in different swimming "search" patterns (direct finding, approaching target, random searching, and thigmotaxis) differed significantly in all exposed groups, compared with controls, with exposed animals showing increased thigmotaxis (time spent in periphery of tank). On day 5, when the escape platform was removed to assess memory, all exposure groups showed a significant decrease in the number of times that they crossed the former location of the target platform; rats exposed to 800 mg 1-bromopropane/kg/day also showed a significant decrease in time spent in the target quadrant. Assessment of biochemical indices in the brain showed an increase in oxidative stress (increased malondialdehyde and oxidized GSH, reduced GSH, and reduced GSH reductase activity) for the most part in the mid- and high-dose groups.

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Tests with specific monoclonal antibodies also showed increased total levels of reactive aldehyde modified proteins in the cerebral cortex. A more recent study by the same groups of investigators (Guo et al. 2015) confirmed the findings of Zhong et al. (2013) and proposed that 1-bromopropane-induced reduction of a novel neuroglobin (Ngb) with antioxidant properties might be involved in the neurotoxicity induced by 1-bromopropane. In another similar study, it was reported that melatonin, administered simultaneously with 1-bromopropane (600 mg/kg/day for 27 consecutive days) to rats, ameliorated the 1-bromopropane-induced impairment of learning and memory and loss of hippocampal neurons (Xu et al. 2016). The investigators suggested that melatonin acts by scavenging reactive oxygen species and reducing oxidative stress. Data from Zhong et al. (2013) were used to derive an acute-duration oral MRL for 1-bromopropane.

**3.2.2.5 Reproductive Effects**

No studies were located regarding reproductive effects in humans following oral exposure to 1-bromopropane.

Only one animal study with relevant information was identified; the results do not suggest that 1-bromopropane is a reproductive toxicant by the oral route.

The available study examined the effect of 1-bromopropane on dominant lethality in male mice (Yu et al. 2008) (see Section 3.3, Genotoxicity). Administration of 600 mg 1-bromopropane/kg/day (only dose level tested) for 10 consecutive days did not significantly affect serum testosterone levels, as assessed 5 weeks after treatment. At that time, microscopic examination of the testes showed degeneration of pachytene spermatocytes in the treated males. Evaluation of sperm parameters in cauda epididymides showed somewhat reduced motility in the treated group but the difference with controls was not statistically significant. All other sperm parameters in treated mice were comparable to controls (path velocity, straight line velocity, curvilinear velocity, lateral head displacement, and beat cross frequency). Further studies seem necessary to validate these findings.

No studies were located regarding the following effects in humans or animals following oral exposure to 1-bromopropane:

**3.2.2.6 Developmental Effects****3.2.2.7 Cancer**

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**3.2.3 Dermal Exposure**

Only one human study was located with relevant information. An occupational study reported that workers exposed to concentrations of 1-bromopropane in the air  $\geq 56.9$  ppm experienced symptoms of nose, eye, and throat irritation (Ichihara et al. 2004a). It is assumed that this occurred due to direct contact of vapors of the chemical with the tissues. It should be noted, however, that the measured concentrations included 1-bromopropane as well as 2-bromopropane, since the analytical method could not differentiate between the two compounds. In addition, no appropriate controls were used. Finally, given the nature of the complaints, it is reasonable to assume that no protective masks were used.

No animal studies were located with information that would support or refute the findings of the occupational study mentioned above. However, one animal study was located, in which application of 2,000 mg 1-bromopropane/kg to the skin of male and female rats under a semi-occlusive dressing for 24 hours did not induce mortalities, clinical signs of toxicity, cutaneous reactions, body weight effects, or gross abnormalities at necropsy during a 14-day post-exposure observation period. (Elf Atochem S.A. 1995).

**3.3 GENOTOXICITY**

Only one study was located regarding genotoxic effects in humans exposed to 1-bromopropane. The study was conducted in 63 workers at two facilities (facility A: 41 workers; facility B: 22 workers) where 1-bromopropane was used as a solvent for spray adhesives in foam cushions (Toraason et al. 2006). 1-Bromopropane TWA concentrations assessed from personal breathing zone samples ranged from 0.2 to 271 ppm at facility A and from 4 to 27 ppm at facility B. In general, exposures at facility A were estimated to be 4-fold higher than in facility B. Assessment of DNA damage in peripheral leukocytes from workers using the comet assay revealed no significant difference in DNA damage between sprayers and non-sprayers at either facility. However, results from multiple linear regression models that controlled for sex, age, smoking status, facility, and two glutathione *S*-transferase [GST] polymorphisms showed increased comet tail moment dispersion coefficients in sprayers at facility A at the end of the week. The covariates that had a significant effect in the models were GSTM1, facility, and sex. No conclusions can be drawn regarding the genotoxicity of 1-bromopropane in humans based on the results of a single study.

Results from *in vivo* and *in vitro* studies of 1-bromopropane genotoxicity are summarized in Tables 3-3 and 3-4, respectively. *In vivo* studies in animals have yielded negative results in tests for induction of

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**Table 3-3. Genotoxicity of 1-Bromopropane *In Vivo***

Species (test system)	End point	Results	Reference
Mammalian cells			
Human peripheral leukocytes	DNA damage and repair, strand breaks	(+)	Torasson et al. 2006
Mouse peripheral blood	Micronuclei	–	NTP 2011
Male rat	Dominant lethal	–	Saito-Suzuki et al. 1982
Male mouse	Dominant lethal	–	Yu et al. 2008

– = negative result; (+) = weak positive

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**Table 3-4. Genotoxicity of 1-Bromopropane *In Vitro***

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
<i>Salmonella typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538	Reverse mutation	– (open test system)	– (open test system)	Barber et al. 1980, 1981
<i>S. typhimurium</i> TA100, TA1535	Reverse mutation	+ (closed test system)	+ (closed test system)	Barber et al. 1980, 1981
<i>S. typhimurium</i> TA97, TA98, TA100, TA 1535	Reverse mutation	–	–	NTP 2011
<i>Escherichia coli</i> Wp2 <i>uvrA/pKM101</i>	Reverse mutation	–	–	NTP 2011
Mammalian cells:				
Peripheral leukocytes	DNA damage		+	Toraason et al. 2006
Human hepatoma cell-line (HepG2)	DNA damage and repair, single strand breaks		–	Hasspieler et al. 2006
Human hepatoma cell-line (HepG2)	DNA damage and repair, repair activity		–	Hasspieler et al. 2006

+ = positive results; – = negative results

### 3. HEALTH EFFECTS

micronuclei and dominant lethality. Exposure via inhalation to 62.5–500 ppm 1-bromopropane for 3 months did not increase the frequency of micronucleated normochromatic or polychromatic erythrocytes in the peripheral blood of male or female mice (NTP 2011). Gavage administration of 300 or 600 mg 1-bromopropane/kg to male ICR mice for 10 days before mating revealed no dominant lethal mutations in germ cells (Yu et al. 2008). In addition, no dominant lethal mutations were observed in male rats gavaged with 400 mg 1-bromopropane/kg for 5 days before mating (Saito-Suzuki et al. 1982).

Studies of the genotoxic potential of 1-bromopropane *in vitro* yielded mixed results. In two studies conducted by NTP (2011), 1-bromopropane did not induce mutations in *Salmonella typhimurium* or *Escherichia coli* with or without exogenous metabolic activation. However, when tested in a closed system to control for volatility, 1-bromopropane was mutagenic to *S. typhimurium* strains TA100 and TA1535 (Barber et al. 1980, 1981). In this same study, using a conventional (or open) test system yielded negative results for all tested *Salmonella* strains.

An *in vitro* study in peripheral leukocytes from unexposed volunteers yielded positive results for DNA damage at the highest concentration tested (1 mM) (Toraason et al. 2006). However, because lower concentrations ( $\geq 0.1$  mM) increased the incidence of apoptotic cells, the DNA damage may reflect general cell toxicity. In studies using the ethoxyresorufin O-deethylase (EROD) bioassay, 1-bromopropane did not induce DNA single-strand breaks or DNA repair in human hepatoma cell-line HepG2 at concentrations between 25 and 500 ppm. However, cytotoxicity was evident at 500 ppm (Hasspieler et al. 2006).

## 3.4 TOXICOKINETICS

### 3.4.1 Absorption

The detection of carbon-containing metabolites and elevated bromide ion concentrations in urine samples of workers exposed to 1-bromopropane by inhalation and dermal contact provides qualitative evidence that 1-bromopropane is absorbed by the respiratory tract and the skin in humans (Hanley et al. 2006, 2009, 2010; Valentine et al. 2007). In addition, reports of neurological and other effects in occupationally exposed subjects provide indirect evidence of absorption of 1-bromopropane (Ichihara et al. 2002; Majersik et al. 2007; MMWR 2008; NIOSH 2003a; Raymond and Ford 2007; Samukawa et al. 2012; Sclar 1999).

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Dermal absorption characteristics estimated in human epidermal membranes mounted on static diffusion cells included steady-state fluxes averaging 625–960  $\mu\text{g cm}^{-2} \text{ hour}^{-1}$  with pure 1-bromopropane and 441–722  $\mu\text{g cm}^{-2} \text{ hour}^{-1}$  with a commercial dry cleaning solvent, an average dermal penetration of about 0.2% from an applied dose of 13.5 mg/cm<sup>2</sup> under non-occluded conditions, and a dermal permeability coefficient for 1-bromopropane in water of 0.257 cm/hour (Frasch et al. 2011).

Qualitative evidence of absorption by the gastrointestinal and respiratory tracts comes from animal studies (Garner et al. 2006, 2015; Jones and Walsh 1979). <sup>13</sup>C-labeled metabolites were detected in urine collected from rats and mice exposed by inhalation to 800 ppm [1,2,3-<sup>13</sup>C]-1-bromopropane for 6 hours (Garner et al. 2006). Indicative of rapid and extensive absorption by the respiratory tract, rats placed in closed chambers with concentrations ranging from 70 to 2,700 ppm rapidly decreased the chamber concentrations within 2 hours, followed by a more gradual decrease in 2–8 hours (Garner et al. 2015). At the lower end of the initial chamber air concentration range, the decrease was almost complete within 3–6 hours (Garner et al. 2015). A number of mercapturic acid derivative metabolites were detected in pooled urine samples collected from rats given oral doses of 200 mg 1-bromopropane/kg/day in arachis oil for 5 days (Jones and Walsh 1979).

No other human or animal studies were located that determined the rate or extent of absorption of 1-bromopropane following inhalation, oral, or dermal exposure.

### 3.4.2 Distribution

Simulations with a preliminary human PBPK model for inhaled 1-bromopropane predicted some accumulation of the parent material in blood following exposure for 8 hours/day for 5 days (Garner et al. 2015; see Section 3.4.5 for more discussion of the development and limitations of this model).

Results from metabolic disposition studies with rats and mice exposed to 1-bromopropane by intravenous injection or inhalation indicate that 1-bromopropane is rapidly and widely distributed by the blood, especially to highly perfused tissues like the brain, followed by a rapid clearance mediated by exhalation of parent material or metabolically produced CO<sub>2</sub> and urinary excretions of oxygenated and conjugated metabolites (Garner and Yu 2014; Garner et al. 2006, 2007; Ishidao et al. 2002; Jones and Walsh 1979). For example, following intravenous injection of [1-<sup>14</sup>C]-1-bromopropane at nominal doses of 5, 20, or 100 mg/kg, radioactivity remaining in the carcass 48 hours after dose administration accounted for about 6, 6, and 2% of the administered dose in rats, and 4, 2, and 4% in mice (Garner et al. 2006). In these

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studies, most of the administered radioactivity was exhaled as parent material or metabolized CO<sub>2</sub> or excreted as metabolites in the urine. Distribution and accumulation of parent material in fatty tissue is limited with short-term exposure scenarios, but some accumulation with repeated exposures may occur (Garner and Yu 2014; Garner et al. 2006, 2015).

A cross-fostering study was conducted in rats to examine the disposition of bromine ion in the brain of rats and their offspring (Ishidao et al. 2016). Rats were exposed to 700 ppm 1-bromopropane 6 hours/day on GDs 1–20. On GD 20, bromine was significantly more concentrated (approximately 47% higher concentration) in the brain of exposed virgin rats than in the brain of exposed pregnant rats, which the investigators suggested could have been due to a dilution effect in the pregnant rats because of increasing body weight. On GD 20, brains from fetuses had significantly more bromine (approximately 68% higher concentration) than brains from the dams, indicating easy transfer of bromine to the fetus via the placenta. Analyses of the brains from pups from the different exposure groups showed that uptake of bromine via the milk was higher than through the placenta.

### 3.4.3 Metabolism

The metabolism of 1-bromopropane in mammals involves: (1) conjugation, principally with glutathione, leading to release of the bromide ion and formation of mercapturic acid derivatives and (2) oxidation (catalyzed by cytochrome P-450) of parent material and metabolites leading to metabolites with hydroxyl, carbonyl, and sulfoxide groups, and to CO<sub>2</sub>. These concepts are based on studies of urinary metabolites in workers exposed to 1-bromopropane (Hanley et al. 2006, 2009, 2010; Mathias et al. 2012; Valentine et al. 2007), *in vivo* metabolic disposition studies in rats and mice (Barnsley et al. 1966; Garner et al. 2006, 2007; Ishidao et al. 2002; Jones and Walsh 1979), and *in vitro* metabolism studies with rat liver preparations (Jones and Walsh 1979; Kaneko et al. 1997; Tachizawa et al. 1982). There is evidence that mice have a higher capacity for oxidative metabolism of 1-bromopropane than rats (Garner and Yu 2014; Garner et al. 2006, 2007).

Occupational studies have identified multiple urinary metabolites of 1-bromopropane. N-Acetyl-S-(n-propyl)-L-cysteine has been identified in urine samples from workers in a 1-bromopropane manufacturing plant (Valentine et al. 2007), in foam fabricating plants using spray adhesives containing 1-bromopropane (Hanley et al. 2006, 2009, 2010; Mathias et al. 2012), and in degreasing operations in plants using 1-bromopropane as a cleaning solvent in the manufacture of aerospace components, hydraulic equipment, optical glass, and printed electronic circuit assemblies (Hanley et al. 2010). Other



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urinary metabolites identified in 1-bromopropane workers are the bromide ion (Hanley et al. 2010) and three oxygenated metabolites present at lower urinary concentrations than N-acetyl-S-(n-propyl)-L-cysteine: N-acetyl-S-propylcysteine-S-oxide (also known as N-acetyl-3-(propylsulfinyl) alanine), N-acetyl-S-(2-carboxyethyl) cysteine, and N-acetyl-S-(3-hydroxy-propyl) cysteine (Cheever et al. 2009; Hanley et al. 2009). The correlations between time weighted average workplace air concentrations of 1-bromopropane and urinary levels of bromide and N-acetyl-S-(n-propyl)-L-cysteine (Hanley et al. 2006, 2009, 2010; Valentine et al. 2007) support the hypothesis that conjugation with glutathione is a quantitatively important pathway in humans (see Figure 3-3). The detection of oxygenated metabolites in urine samples indicates that oxidation pathways also exist in humans (see Figure 3-4 for structures of identified oxygenated metabolites).

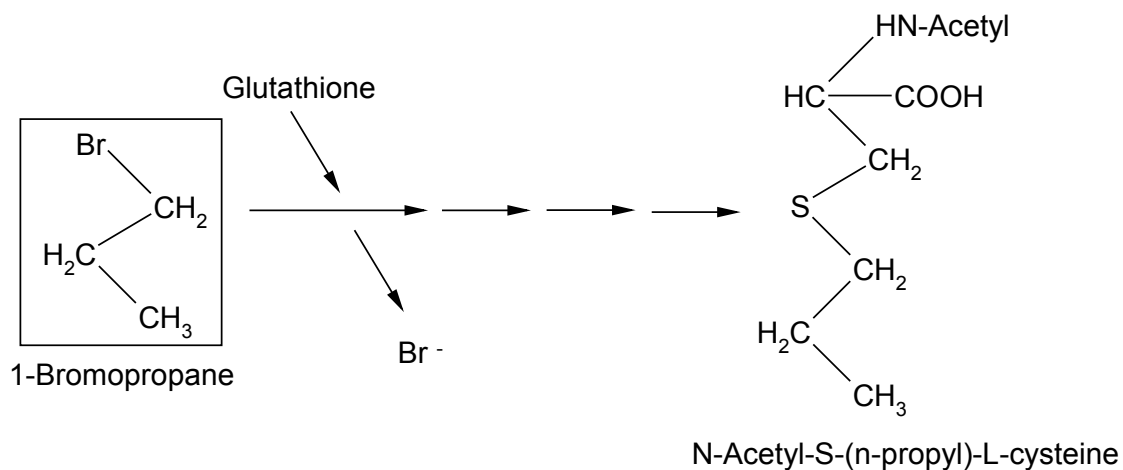
Results from metabolic disposition studies in rats and mice illustrate that the metabolism of 1-bromopropane in mammals is complex, involving initial competing conjugation or oxidation steps, followed by subsequent conjugation, oxidation, or rearrangement steps. Figure 3-5 presents proposed metabolic pathways based on results from studies of F-344 rats and B6C3F1 mice exposed to [1-<sup>14</sup>C]-1-bromopropane by intravenous injection or [1,2,3-<sup>13</sup>C]-1-bromopropane by inhalation or intravenous injection (Garner et al. 2006).

The metabolic scheme shows an oxidation path to CO<sub>2</sub> involving cytochrome P450 (CYP) oxidation steps to 1-bromo-2-propanol and bromoacetone. This path is proposed based on several findings:

1. Following intravenous injection of <sup>14</sup>C-1-bromopropane at nominal doses of 5, 20, or 100 mg/kg, radioactivity in CO<sub>2</sub> exhaled in 48 hours accounted for approximately 28, 31, and 10% of the administered dose in rats, and 22, 26, and 19% in mice (Garner et al. 2006). (These data also indicate that oxidative metabolism of 1-bromopropane in rats is more dependent on dose than oxidative metabolism in mice; the decrease in percentage dose exhaled as CO<sub>2</sub> at the highest dose is greater in rats than mice.)
2. Pretreatment of rats with 1-aminobenzotriazole (ABT) before administration of single intravenous doses of ~20 mg/kg <sup>14</sup>C-1-bromopropane or inhalation exposure to 800 ppm <sup>13</sup>C-1-bromopropane for 6 hours caused decreased exhalation of radioactivity as CO<sub>2</sub> and decreased formation of oxidative urinary metabolites (Garner et al. 2006). ABT is an inhibitor of a number of CYP enzymes (Emoto et al. 2003).

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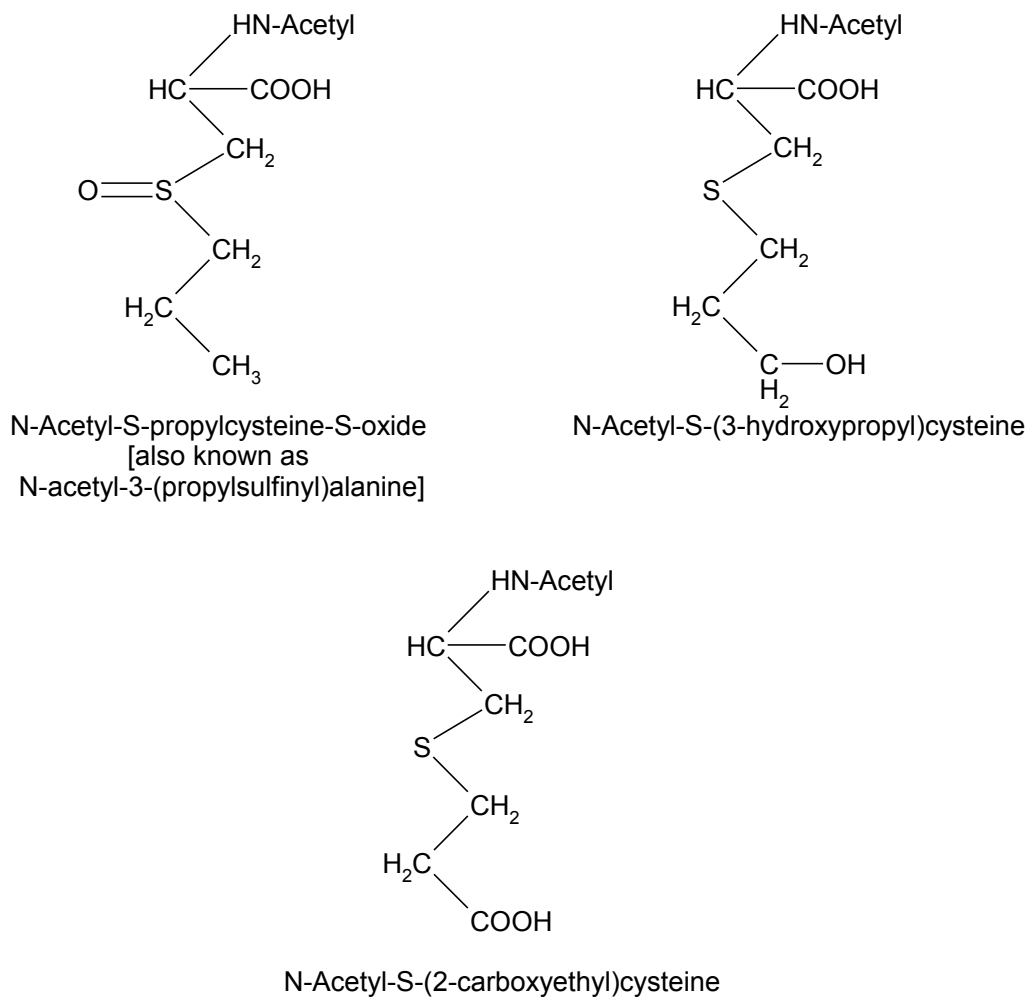
**Figure 3-3. Formation of N-Acetyl-S-(n-propyl)-L-cysteine from 1-Bromopropane via Conjugation with Reduced Glutathione (GSH)**



Sources: Hanley et al. 2009, 2010; Valentine et al. 2007

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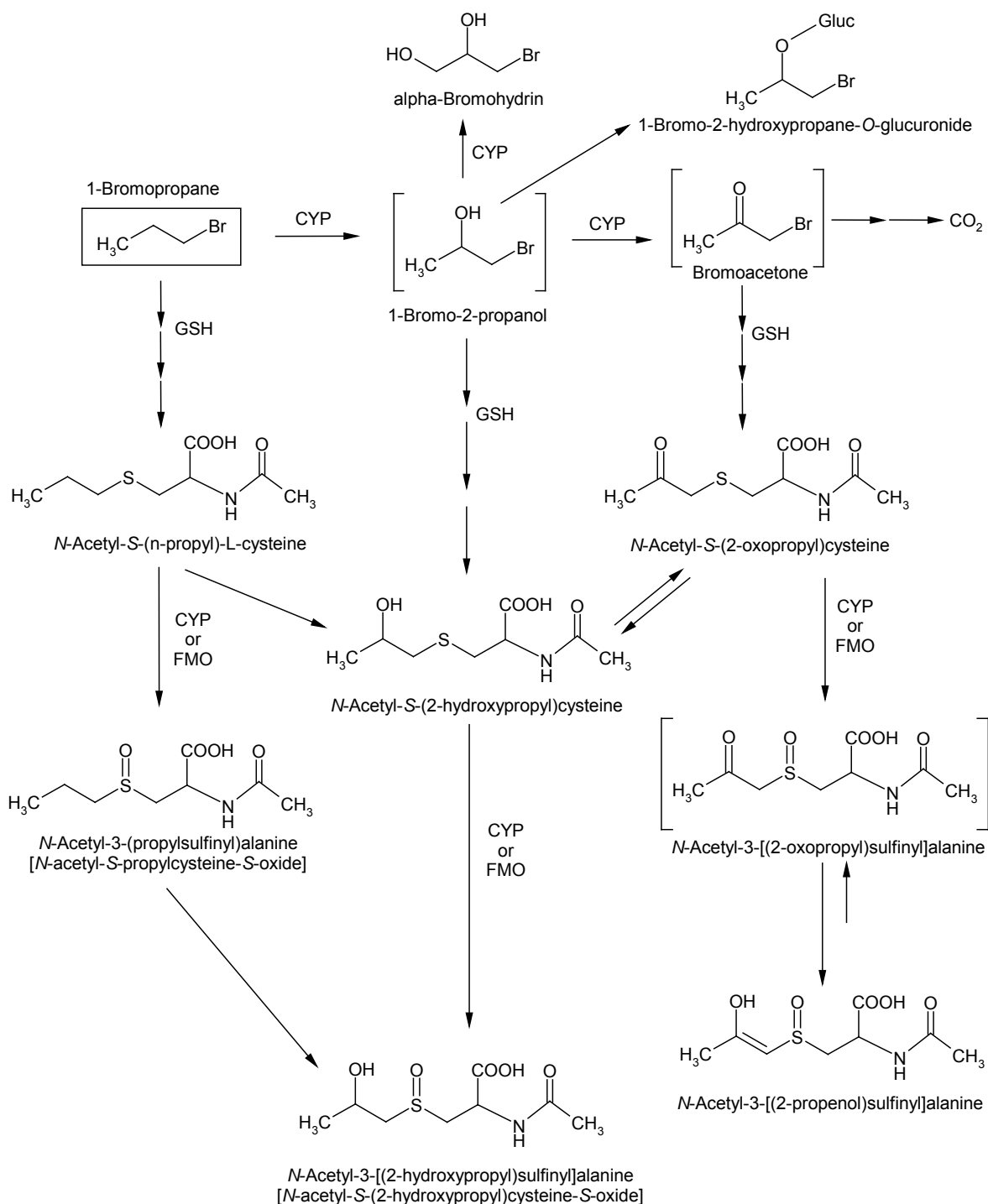
**Figure 3-4. Mercapturic Acid Metabolites with a Sulfoxide Group or a Hydroxyl or Carbonyl Group on the Propyl Residue Identified in Urine Samples of 1-Bromopropane-Exposed Workers**



Sources: Cheever et al. 2009; Hanley et al. 2009; Mathias et al. 2012

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**Figure 3-5. 1-Bromopropane Metabolism in Male F-344 Rats and B6C3F1 Mice Following Inhalation Exposure or Tail Vein Injection\***



\*Structures in brackets are proposed intermediates and were not isolated in urine.

CYP = cytochrome P450 monooxygenase; FMO = flavin-containing monooxygenase; GSH = glutathione

Sources: Garner et al. 2006, 2007; NTP 2013

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3. Urinary metabolites derived from 1-bromo-2-propanol accounted for over half of all carbon-containing urinary metabolites identified in rats and mice exposed by inhalation or intravenous injection of  $^{13}\text{C}$ -1-bromopropane. No 1-bromo-2-propanol-derived metabolites were found in urine of ABT-pretreated rats exposed to  $^{13}\text{C}$ -1-bromopropane (Garner et al. 2006). 1-Bromo-2-propanol and bromoacetone themselves were not detected in urine of 1-bromopropane-exposed rats, but their presence was detected in preparations of rat liver homogenates incubated with 1-bromopropane (Garner et al. 2006).
4. N-Acetyl-S-(2-hydroxypropyl) cysteine was identified in urine of rats given subcutaneous doses of 1-bromopropane (1 mL of a 40% solution of 1-bromopropane in arachis oil per rat) (Barnsley et al. 1966).

Based on urinary metabolites identified with nuclear magnetic resonance (NMR) spectroscopy, liquid chromatography-tandem mass spectrometry (LC-MS/MS), and high-performance liquid chromatography (HPLC) radiochromatography (Garner et al. 2006), the scheme in Figure 3-5 also shows an initial conjugation of 1-bromopropane with glutathione leading to N-acetyl-S-(n-propyl)-L-cysteine, an oxidation step from 1-bromo-2-propanol to alpha-bromohydrin, a glucuronic acid conjugation step from 1-bromo-2-propanol to 1-bromo-2-hydroxypropane-O-glucuronide, and glutathione conjugation of 1-bromo-2-propanol and bromoacetone followed by oxidation steps leading to metabolites with sulfoxide groups (e.g., N-acetyl-3-[(2-hydroxypropyl)sulfinyl] alanine). The steps involving oxidation of sulfur in the glutathione conjugate derivatives were proposed to be catalyzed by CYP oxygenases or flavin-containing monooxygenases (FMO) as suggested by Krause et al. (2002).

Catalysis of the oxidation steps by a number of CYP isozymes is supported by results from metabolic disposition studies in wild-type and *Cyp2e1*<sup>-/-</sup> knock-out mice (F1 hybrids of 129/Sv and C57BL/6N strains) exposed by inhalation to 800 ppm  $^{13}\text{C}$ -1-bromopropane for 6 hours (Garner et al. 2007). Three major metabolites were identified in urine collected from wild-type mice during exposure: N-acetyl-S-(2-hydroxypropyl) cysteine (34  $\mu\text{moles}$  in collected urine), 1-bromo-hydroxypropane-O-glucuronide (5  $\mu\text{moles}$ ), and N-acetyl-S-(n-propyl)-L-cysteine (8  $\mu\text{moles}$ ). In *Cyp2e1*<sup>-/-</sup> mice, the amounts of these metabolites in collected urine were changed to 21, 2, and 24  $\mu\text{moles}$ , respectively. The ratio of 2-hydroxylated metabolites to N-acetyl-S-(n-propyl)-L-cysteine was approximately 5:1 in wild-type and 1:1 *Cyp2e1*<sup>-/-</sup> mice. The results indicate that the deletion of CYP2E1 increased the relative importance of the glutathione conjugation pathway but did not eliminate the formation of oxygenated metabolites, suggesting the involvement of other CYP enzymes, in addition to CYP2E1, in oxidation steps as illustrated in Figure 3-5.

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Evidence for the initial conjugation of 1-bromopropane with glutathione leading to the formation of N-acetyl-S-(n-propyl)-L-cysteine comes from a number of studies in rats and mice (Garner et al. 2006, 2007; Jones and Walsh 1979; Khan and O'Brien 1991).

1. N-Acetyl-S-(n-propyl)-L-cysteine was detected in the urine of wild-type and *Cyp2e1*<sup>-/-</sup> mice exposed to 800 ppm 1-bromopropane for 6 hours, at molar ratios to hydroxylated metabolites of 5:1 and 1:1, respectively (Garner et al. 2007).
2. N-Acetyl-S-(n-propyl)-L-cysteine and N-acetyl-3-(propylsulfinyl) alanine (i.e., N-acetyl-S-propylcysteine-S-oxide) accounted for approximately 39 and 5% of excreted urinary metabolites, respectively, in urine collected for 24 hours after inhalation exposure of rats to 800 ppm 1-bromopropane for 6 hours (Garner et al. 2006).
3. N-Acetyl-S-(n-propyl)-L-cysteine was a relatively minor urinary metabolite in rats given single 5-mg 1-bromopropane/kg intravenous doses, but accounted for >80% of urinary metabolites following administration of 100 mg 1-bromopropane/kg (Garner et al. 2006).
4. N-Acetyl-S-(n-propyl)-L-cysteine and N-acetyl-S-propylcysteine-S-oxide were among the six mercapturic acid derivatives identified in urine from rats given 200 mg 1-bromopropane/kg by gavage (in arachis oil) for 5 days (Jones and Walsh 1979). The structures of the other four mercapturic acid derivatives identified were consistent with glutathione conjugation of oxygenated metabolites of 1-bromopropane, rather than 1-bromopropane itself. These included N-acetyl-S-(2-hydroxypropyl) cysteine, N-acetyl-S-(3-hydroxypropyl) cysteine, and N-acetyl-S-(2-carboxyethyl) cysteine (Jones and Walsh 1979). The techniques used in this study did not determine the relative amounts of the urinary mercapturic acid derivatives.
5. Isolated hepatocytes incubated for 60 minutes with 1-bromopropane showed a decrease in glutathione content (from 58.4 to 40.8 nmol/10<sup>6</sup> cells), consistent with the importance of glutathione conjugation in metabolic disposition of 1-bromopropane in mammals (Khan and O'Brien 1991).

Other studies have identified other metabolites, not included in Figure 3-5, in urine from rats and mice exposed to 1-bromopropane (Ishida et al. 2002; Jones and Walsh 1979) and in *in vitro* systems (Jones and Walsh 1979; Kaneko et al. 1997; Tachizawa et al. 1982). Jones and Walsh (1979) reported detecting metabolites in urine from rats orally exposed to 1-bromopropane that are consistent with the initial oxidation of the 3-C of 1-bromopropane: N-acetyl-S-(3-hydroxypropyl) cysteine, 3-bromopropionic acid, and N-acetyl-S-(2-carboxyethyl) cysteine. Garner et al. (2006) were not able to detect these metabolites in urine following administration of single intravenous doses up to 100 mg 1-bromopropane/kg in rats or exposure to 800 ppm for 6 hours in rats or mice. Garner et al. (2006) proposed that the apparent discrepancy may have been due to an amplification of minor metabolites from the pooling, concentration, and acid hydrolysis processes used in the earlier study. Glycidol (1,2-epoxy-3-propanol) was detected in urine of Wistar rats exposed by inhalation 6 hours/day to 700 ppm for 3 or 4 weeks or 1,500 ppm for 4 or

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12 weeks; however, no determination of the amount of this compound was made, and the report did not mention the detection of any other carbon-containing metabolites (Ishida et al. 2002). Kaneko et al. (1997) monitored the formation of n-propanol during incubation of rat liver microsomes with 1-bromopropane. 3-Bromopropanol and 3-bromopropionic acid were detected when 1-bromopropane was incubated in an *in vitro* oxidizing system, but 1-bromopropane metabolism with rat liver homogenates was not examined due to the low water solubility of 1-bromopropane (Jones and Walsh 1979). Propene, 1,2-epoxypropane, 1,2-propanediol, and propionic acid were detected when liver microsomes from phenobarbital-treated rats were incubated with 1-bromopropane, and the addition of glutathione to the reaction mixture led to formation of S-(1' propyl)glutathione and S-(2' hydroxyl-1'-propyl) glutathione (Tachizawa et al. 1982). Garner et al. (2006) reported that propene, propylene oxide, propanediol, and propionic acid were not detected in liver homogenate incubations with 1-bromopropane; they suggested that the use of phenobarbital as a CYP inducer may have resulted (in the Tachizawa et al. [1982] studies) in the formation of metabolites not generated by constitutive CYP enzymes.

**3.4.4 Elimination and Excretion**

Results from animal metabolic disposition studies indicate that 1-bromopropane is eliminated from the body by exhalation of the parent material and metabolically derived CO<sub>2</sub> and by urinary excretion of metabolites (Garner et al. 2006; Jones and Walsh 1979). There is evidence that differences of relative importance of different excretion pathways between mice and rats may reflect higher capacity for oxidative metabolism of 1-bromopropane in mice than in rats (Garner and Yu 2014; Garner et al. 2006, 2007).

Following single intraperitoneal injections of 200 mg/kg doses of [1-<sup>14</sup>C]-1-bromopropane in rats, about 60% of the administered radioactivity was eliminated as unchanged 1-bromopropane in the expired air within 4–6 hours, about 1.4% of the administered radioactivity was exhaled as <sup>14</sup>CO<sub>2</sub> over 48 hours, and about 15% of the administered radioactivity was excreted in the urine within 48 hours. Following intravenous injection of [1-<sup>14</sup>C]-1-bromopropane at nominal doses of 5, 20, or 100 mg/kg, radioactivity in CO<sub>2</sub> exhaled in 48 hours accounted for about 28, 31, and 10% of the administered dose in rats, and 22, 26, and 19% in mice (Garner et al. 2006). Radioactivity in exhaled parent material accounted for about 25, 32, and 71% of the administered dose in rats, and 45, 39, and 48% in mice (Garner et al. 2006). Radioactivity in urine collected for 48 hours accounted for about 17, 19, and 13% of the administered

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dose in rats, and 23, 19, and 14% in mice (Garner et al. 2006). Radioactivity in feces accounted for <2% of administered doses, regardless of dose level, in both species (Garner et al. 2006).

Animal studies show that the elimination of 1-bromopropane from the body is rapid and only limited accumulation in the body is expected (Garner and Yu 2014; Garner et al. 2006; Ishida et al. 2002). Following intravenous injection of [ $^{14}\text{C}$ ]-1-bromopropane at nominal doses of 5, 20, or 100 mg/kg, radioactivity remaining in the carcass 48 hours after dose administration accounted for about 6, 6, and 2% of the administered dose in rats, and 4, 2, and 4% in mice (Garner et al. 2006). Garner et al. (2006) proposed that radioactivity remaining in the carcass could represent covalently bound residues from reactive metabolites or incorporation of  $^{14}\text{C}$  into cellular macromolecules from intermediate metabolic pathways. Following intravenous injection of 5 or 20 mg 1-bromopropane/kg doses into rats, the mean half-times of elimination of 1-bromopropane from the blood were 0.39 and 0.85 hours, respectively (Garner and Yu 2014). In gas uptake studies with male and female rats, calculated half-times of elimination for 1-bromopropane were rapid and increased with increasing air concentrations of 1-bromopropane (Garner and Yu 2014). Terminal elimination half-times were 0.5, 0.6, 1.1, and 2.4 hours for males, and 1.0, 1.0, 2.0, and 6.1 hours for females, exposed to initial air concentrations of 70, 240, 800, and 2,700 ppm, respectively. Pretreatment of female rats with ABT to inhibit CYP metabolism (intraperitoneal injection of 50 mg 1-bromopropane/kg 4 hours prior to gas uptake measurements) or buthionine sulfoxime, an inhibitor of glutathione synthesis (1,000 mg 1-bromopropane/kg/day orally for 3 days before gas uptake), resulted in longer elimination half-times: 9.6 hours with ABT and 4.1 hours with D,L-buthionine(S,R)-sulfoximine (BSO), compared with 2.0 hours in untreated females at 800 ppm 1-bromopropane in the gas uptake chamber (Garner and Yu 2014). The results with the inhibitors show that both CYP mediated oxidative metabolism and glutathione conjugation play important roles in the elimination of 1-bromopropane. Levels of 1-bromopropane in blood decreased rapidly to detection limits within 0.7 hours after exposure stopped in Wistar rats exposed to 700 or 1,500 ppm 1-bromopropane 6 hours/day for  $\geq 3$  weeks (Ishida et al. 2002). Clearance of the bromide ion from blood and urine, however, showed slower elimination kinetics: elimination half-times for bromide were 4.7–15.0 days in blood and 5.0–7.5 days in urine (Ishida et al. 2002).

### 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



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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 (Clewett 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 and Krishnan 1994; Andersen et al. 1987). 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 parameterization, (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. However, if the uptake and disposition of the chemical substance(s) are adequately described, 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.

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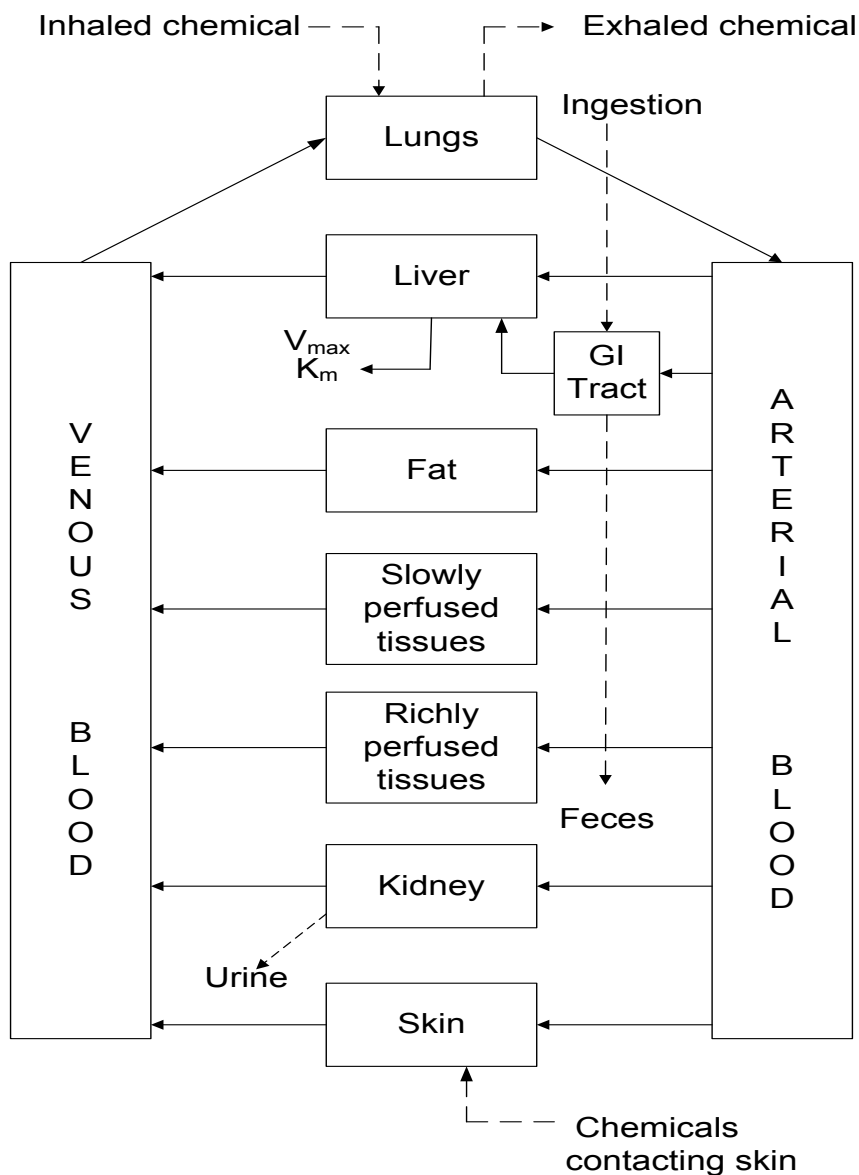
PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in 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 3-6 shows a conceptualized representation of a PBPK model.

If PBPK models for 1-bromopropane exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

Garner et al. (2015) developed male and female PBPK models for 1-bromopropane in F-344 rats, using data from gas uptake experiments at initial closed chamber concentrations of 70, 240, 800, and 2,700 ppm 1-bromopropane (Garner and Yu 2014). The models consisted of seven compartments: blood, lung, fat, rapidly perfused tissues, slowly perfused tissues, kidneys, and liver. The models assumed flow-limited distribution and metabolism in the liver via two competing initial steps: saturable CYP2E1-mediated oxidation (described by  $V_{\max}$  and  $K_m$  kinetic constants) and GSH conjugation (described by a  $K_{\text{gst}}$  kinetic constant). Values for blood flow and tissue volume parameters were based on those used by Brown et al. (1997) and tissue partition coefficients were based on those reported by Gargas et al. (1989). Metabolic kinetic constants for the male and female rat models were estimated through optimization procedures involving visual assessment of fits to time-course data for closed chamber concentrations of 1-bromopropane, while holding other model parameters constant. Further validations or calibrations of the rat models were not conducted (e.g., comparing simulated blood concentrations versus observed blood concentration time-course data). Model simulations of blood concentrations indicated rapid attainment of maximal concentration after the start of 8-hour exposure periods, and rapid decline (within 30 minutes) after cessation of exposure. Simulations for a repeated exposure scenario (8 hours/day for 5 days) indicated no accumulative increase in blood concentrations at exposure levels of 20 and 800 ppm 1-bromopropane. A human PBPK model was developed from a general human model for volatile chemicals developed by Anderson et al. (2008) and body weight scaling of the rat metabolic parameters. Simulations with the human model for the repeated exposure scenario at 200 ppm indicated that the blood concentration at the end of the fifth day of exposure was increased by about 25% above the concentration at the end of the first day. Garner et al. (2015) speculated that simulated results showing that humans (but not rats) have accumulative increases in blood concentrations after a 5-day exposure scenario might be due to species differences in fat tissue volume (rat 7% and human 21.4%). Further development of the rat

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**Figure 3-6. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance**



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.

Source: Krishnan and Andersen 1994

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and the human models are necessary before they can be used to reliably extrapolate doses between rats and humans in the development of MRLs. Garner et al. (2015) noted that further development of the model to include metabolite concentrations in the model would be particularly useful for cross-species dosimetry purposes.

### 3.5 MECHANISMS OF ACTION

#### 3.5.1 Pharmacokinetic Mechanisms

**Absorption.** As discussed in Section 3.1, 1-bromopropane is expected to be well absorbed by the gastrointestinal tract and the respiratory tract, but quantitative data on the extent of absorption are not available. *In vitro* studies with human epidermal explants have determined a dermal permeability coefficient of 0.25 cm/hour in water, dermal fluxes with pure compound and a commercial dry cleaning solvent ranging from 441 to 960  $\mu\text{g cm}^{-2} \text{ hour}^{-1}$ , and a low dermal penetration of about 0.2% under non-occluded conditions (Frasch et al. 2011). Results from gas uptake studies with rats in closed chambers indicated rapid and extensive absorption by the respiratory tract (Garner 2015). Like other volatile, lipophilic, noncharged gases, absorption of 1-bromopropane from the alveoli to the blood is thought to be mediated by passive diffusion (Lehman-McKeeman 2013).

**Distribution.** As discussed in Section 3.4.2, results from metabolic disposition studies with rats and mice exposed to 1-bromopropane by intravenous injection or inhalation indicate that 1-bromopropane is rapidly and widely distributed by the blood, especially to highly perfused tissues like the brain, followed by a rapid clearance mediated by exhalation of parent material or metabolically produced  $\text{CO}_2$  and urinary excretion of oxygenated and conjugated metabolites (Garner and Yu 2014; Garner et al. 2006, 2007; Ishida et al. 2002; Jones and Walsh 1979). Distribution and accumulation of parent material in blood or fatty tissue is limited with short-term exposure scenarios, but some accumulation with repeated exposures may occur (Garner et al. 2006; 2015; Garner and Yu 2014).

**Metabolism.** As discussed in Section 3.4.3, and illustrated in Figures 3-3, 3-4, and 3-5, the metabolism of 1-bromopropane in mammals is complex, involving initial competing conjugation or oxidation steps, followed by subsequent conjugation, oxidation, or rearrangement steps. The balance between oxidative and glutathione-mediated metabolic pathways will determine whether 1-bromopropane is activated to reactive metabolites or degradation products are conjugated and eliminated in the urine (Garner and Yu 2014; Garner et al. 2015; Lee et al. 2010; Liu et al. 2009; Zong et al. 2016). Most urinary and exhaled metabolic products are debrominated leading to elevated levels of bromide ion in blood and

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urine (Hanley et al. 2006, 2009, 2010; Garner and Yu 2014; Garner et al. 2006, 2007; Ishidao et al. 2002; Valentine et al. 2007). Oxidation steps are mediated by CYP2E1 and other, as yet unspecified CYP monooxygenases. Reduced glutathione is the principal conjugating molecule for the parent compound, as well as for proposed oxygenated brominated intermediate metabolites (Garner et al. 2006, 2007; Jones and Walsh 1979). The most recent metabolic disposition studies in rats and mice indicate that oxidation at the 2-C of 1-bromopropane is the principal oxygenation site (Garner et al. 2006, 2007), but oxygenation at the 3-C of 1-bromopropane may be possible based on the identification of urinary metabolites, N-acetyl-S-(2-carboxyethyl) cysteine and N-acetyl-S-(3-hydroxypropyl) cysteine, in an earlier rat study (Jones and Walsh 1979) and in human workers (Cheever et al. 2009; Hanley et al. 2006). Proposed reactive intermediate metabolites include bromoacetone and alpha-bromohydrin (Garner et al. 2006, 2007), glycidol (Ishidao et al. 2002), and propene and 1,2-epoxypropane (Tachizawa et al. 1982).

**Excretion.** Results from animal studies indicate that 1-bromopropane is rapidly eliminated from the body by exhalation of the parent material and metabolically derived CO<sub>2</sub> and by urinary excretion of bromide ion and carbon-containing metabolites (Garner and Yu 2014; Garner et al. 2006, 2007; Ishidao et al. 2002; Jones and Walsh 1979). Forty-eight hours after single intravenous injections of doses of radiolabeled 1-bromopropane to rats and mice, residual radioactivity in the body accounted for <7% of administered doses (Garner et al. 2006). Gas uptake studies indicated that whole-body elimination half-times in rats increased with increasing air concentration, and were 2.4 and 6.2 hours at the highest tested concentration of 2,700 ppm (Garner and Yu 2014). Pretreatment of rats with inhibitors of CYP monooxygenases or glutathione synthesis prolonged whole-body elimination half-times indicating the importance of metabolism to the clearance of 1-bromopropane (Garner and Yu 2014). Elimination half-times for the bromide ion from the blood (~5–15 days) and urine (~5–8 days) were considerably longer than clearance of 1-bromopropane from the blood of rats repeatedly exposed by inhalation to 700 or 15,000 ppm; blood levels of 1-bromopropane were below levels of detection within 0.7 hours of the end of exposure (Ishidao et al. 2002).

### 3.5.2 Mechanisms of Toxicity

**Overview.** As summarized in Section 2.2 (Summary of Health Effects) and detailed in Section 3.2.1.4, Neurological Effects, the main target of concern following 1-bromopropane exposure in humans is the nervous system. The mechanisms for neurotoxicity have not been elucidated; however, proposed mechanisms include changes in neurotransmitter systems, electrophysiological alterations, decreased neurogenesis, glial activation, alteration of hippocampal proteins, and oxidative stress. Other potential

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targets for 1-bromopropane toxicity include the respiratory, hepatic, renal, reproductive, immune, and hematological systems; however, evidence for these end points is limited. Likewise, mechanistic data for effects outside the nervous system are extremely limited. Available mechanistic data are summarized below.

***Mechanisms of Neurotoxicity.*** Neurotoxic effects observed in humans range from subtle neurological deficits, such as decreased vibration sense and paresthesia, to frank neurotoxic effects, including ataxia, spastic paraparesis, and symmetric demyelinating polyneuropathy (Ichihara et al. 2002; Li et al. 2010; Majersik et al. 2007; NIOSH 2002; Raymond and Ford 2007; Samukawa et al. 2012; Sclar 1999). Evidence from animal studies supports that exposure to 1-bromopropane can result in neurotoxicity (Fueta et al. 2002; Honma et al. 2003; Ichihara et al. 2000b; Kim et al. 1999; Mohideen et al. 2011, 2013; Subramanian et al. 2012; Wang et al. 2002, 2003; Yu et al. 2001; Zhong et al. 2013).

Observed neurological effects may result from alterations in the gabanergic system following exposure to 1-bromopropane. A series of studies reported a decrease in paired pulse inhibition (PPI) of pyramidal cells of CA1 and granule cells of the dentate gyrus (DG) in hippocampal slices harvested from rats exposed to 1-bromopropane at  $\geq 700$  ppm intermittently for 4–12 weeks (Fueta et al. 2002, 2004). Granule cells, but not pyramidal cells, also showed decreased PPI at 400 ppm for 8–12 weeks; no effect was observed in either cell type at 200 ppm (Fueta et al. 2007; Ueno et al. 2007). Since no changes were observed in excitatory field potentials, changes in the PPI are likely caused by a reduction of recurrent inhibition (disinhibition) rather than changes in excitatory drives of principal neurons. In support, application of a  $\gamma$ -aminobutyric acid (GABA) receptor agonist (pentobarbital), a selective inhibitor of GABA transporter GAT 1 (Tiagabine), or a NMDA receptor antagonist (DL-2-amino-5-phosphopentanoic acid) led to an increase in PPI in the DG, indicating that 1-bromopropane exposure may lead to reduced GABA inhibition of N-methyl-D-aspartate (NMDA) receptors; the disinhibition in the hippocampal CA1 region appeared to have been caused by a different (unknown) mechanism (Fueta et al. 2002, 2004). Ueno et al. (2007) also showed that exposure to 1-bromopropane decreased the expression of the GABA<sub>A</sub> receptor  $\beta 3$  and  $\delta$  subunit mRNA in the hippocampus from rats intermittently exposed to 400 ppm 1-bromopropane for 12 weeks. A significant reduction of mRNA expression of GABA<sub>A</sub> was also observed in the hippocampus of rats exposed to  $\geq 800$  ppm for 4 weeks; in the cortex, mRNA expression was significantly reduced after exposure to 800 ppm but not 1,000 ppm (Mohideen et al. 2009). In another study, a significant reduction in GABA neurotransmitter levels was reported in the hippocampus and cortex of rats intermittently exposed to 1,000 ppm 1-bromopropane for 3 weeks, compared with controls; no changes were observed at  $\leq 200$  ppm (Suda et al. 2008).

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Other neurotransmitter systems have also been evaluated in rats following inhalation exposure to 1-bromopropane. Changes in levels of neurotransmitters or their metabolites or precursors from the serotonergic (5HT), dopaminergic (DA), noradrenergic (NE), and glutamatergic systems have been reported in various brain regions in rat intermittently exposed to 50–1,000 ppm 1-bromopropane for 3 weeks, compared with controls, when examined 2 and 19 hours after the final exposure (Suda et al. 2008). At 2 hours, significant observations in the 1,000 ppm group included decreased 5-hydroxy-indoleacetic acid (5HIAA; 5HT metabolite) in the striatum, decreased 3,4-dihydroxyphenylacetic acid (DOPAC; DA metabolite) in the hippocampus, and increased glutamine (glutamate precursor) in the hippocampus, midbrain, and cerebellum. 5HIAA was also significantly decreased at 200 ppm; no changes were observed at 2 hours in the 50 ppm group except for a significant decrease in DA in the striatum and in 5HIAA in the frontal cortex. At 19 hours, significant changes included decreased homovanillic acid (HVA; DA metabolite) and HVA/DA ratio in the striatum; decreased 3-methoxy-4-hydroxyphenylglycol (MHPG, NE metabolite), decreased MHPG/NE ratio, and increased 5HT in the occipital cortex; increased 5HIAA in the medulla; and increased glutamine in the frontal cortex, occipital cortex, hippocampus, striatum, midbrain, hypothalamus, and cerebellum. Alterations in the NE, DA, and 5HT neurotransmitter and/or metabolite levels were also reported in rats exposed to  $\geq 200$  ppm for 1–4 weeks (Zhang et al. 2013). At 1 week, observed effects included decreased NE and DOPAC/DA ratio in the striatum and a decreased HVA/DA ratio in the prefrontal cortex. At 4 weeks, observed effects included decreased NE and DA and increased HVA, HVA/DA, DOPAC/DA and (DOPAC + HVA)/DA ratio in the hippocampus; decreased NE, 5HIAA, HVA, and HVA/DA in the prefrontal cortex; and decreased NE in the striatum. In another study, several changes in the expression of serotonergic and dopaminergic receptor mRNA were reported in various brain regions of rats intermittently exposed to  $\geq 400$  ppm for 4 weeks (Mohideen et al. 2009). Significant changes included decreased 5HT<sub>1a</sub> (cortex at 800 and 1,000 ppm, medulla at 400, 800, and 1,000 ppm), decreased 5HT<sub>2a</sub> (cortex at 800 ppm, hippocampus at 1,000 ppm), increased 5HT<sub>2c</sub> (cortex at 1,000 ppm), increased 5HT<sub>3a</sub> (amygdala at 400 and 1,000 ppm), decreased D<sub>1</sub>R (cerebellum and cortex at 800 ppm), decreased D<sub>2</sub>R (hippocampus at 400, 800, and 1,000 ppm), and decreased 5HT<sub>3a</sub> (pons/medulla at 400, 800, and 1,000 ppm). However, protein levels of D<sub>2</sub> and 5HT<sub>2a</sub> were not significantly altered in the cortex or hippocampus at up to 1,000 ppm; other receptor protein levels were not measured (Mohideen et al. 2009). Although the above studies show that exposure to 1-bromopropane can affect numerous neurotransmitter systems in various brain areas, these changes have not been associated with specific functional alterations; therefore, the biological significance of the changes is yet unknown.

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1-Bromopropane may also cause neurotoxicity by interfering with neurogenesis, as a decrease in the number of BrdU-positive cells in the dentate gyrus of the hippocampus was observed in rats exposed to  $\geq 800$  ppm for 4 weeks (Zhang et al. 2013). Observed downregulation of hippocampal brain-derived neurotrophic factor (BDNF) and glucocorticoid receptor (GR) mRNA levels and low hippocampal NE levels may contribute to the reduced neurogenesis. Significant reductions in BDNF mRNA expression have also been observed in the U251 human astrocytoma cell line and mouse primary astrocytes (Yoshida et al. 2009). Yoshida et al. (2009) also show that DNA-binding and specific reporter activity of cAMP response element-binding transcription factor (CREB) and protein kinase A (PKA) activity were reduced in U251 cells, suggesting that BDNF downregulation may result from suppression of PKA activity (and subsequent decreased phosphorylation of CREB). Results of experiments by Huang et al. (2015) showed that exposure of rats to 1-bromopropane induced up- and down-regulation of proteins in the hippocampus involved in response to stimuli, metabolic processes, and apoptosis signaling.

1-Bromopropane has also been shown to cause glial activation (Mohideen et al. 2013; Subramanian et al. 2012), which suggests that neuroinflammation may contribute to observed neurotoxic effects. Immunostaining showed that exposure to  $\geq 400$  ppm 1-bromopropane significantly increased the number of astrocytes in the middle cerebellar peduncle and induced significant elongation of processes in astrocytes in the cerebellum (Mohideen et al. 2013). In another study, cerebellar microglia cells appeared larger and had longer ramified processes in rats exposed to 1,000 ppm 1-bromopropane for 4 weeks, compared with controls; this effect was not observed at 800 ppm (Subramanian et al. 2012). Increased markers of oxidative stress (TBARs), as well as reactive oxygen species and nitric oxide (NO) content, were also observed in the cerebellum of rats exposed to 1,000 ppm, suggesting that oxidative stress may contribute to glial activation (and potential neuroinflammation) associated with 1-bromopropane exposure (Subramanian et al. 2012). Alterations in markers of oxidative stress (total and oxidized glutathione, glutathione reductase, thiol content, malondialdehyde, glutathione peroxidase) have also been reported in the brain and spinal cord of rats exposed to 200–1,000 ppm 1-bromopropane for 1–4 weeks (Guo et al. 2015; Huang et al. 2012; Wang et al. 2002, 2003; Zhong et al. 2013). Guo et al. proposed that 1-bromopropane-induced reduction of a neuroglobin with antioxidant properties might be involved in the neurotoxicity of 1-bromopropane. Additionally, studies in murine macrophages suggest that 1-bromopropane can cause dose-dependent induction of NO and proinflammatory proteins/genes, such as IL-1 $\beta$ , IL-6, TNF- $\alpha$ , COX-2, prostaglandin E<sub>2</sub>, through nuclear factor-kappaB (NF- $\kappa$ B) transactivation via the Akt/ERK and p38 MAP kinase pathways (Han et al. 2008, 2012).



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Human and animal studies have reported decreased nerve conduction velocities following 1-bromopropane exposure (Ichihara et al. 2000b; Li et al. 2010; Sclar 1999; Yu et al. 2001). Decreased nerve conduction velocity could be due to morphological changes such as swelling of the axons and alteration of the myelin sheath, which have been observed in rats exposed to  $\geq 800$  ppm for several weeks (Ichihara et al. 2000b; Wang et al. 2002; Yu et al. 2001). Mohideen et al. (2013) reported adverse effects on myelination in the cerebellum in rats exposed to 1,000 ppm 1-bromopropane for 4 weeks, including decreased levels of myelin basic protein (MBP) and decreased numbers of oligodendrocytes; however, the mechanisms underlying these changes have not been determined.

Protein expression studies have identified multiple systems/pathways in the brain that can be altered following 1-bromopropane exposure; however, strong conclusions regarding mechanisms of neurotoxicity from these studies cannot be made at this point. Decreased CK and isoenzyme (CK-B, CK-M) activity and increased heat-shock protein 27 levels were observed in the brain and/or spinal cord from rats exposed to  $\geq 200$  ppm 1-bromopropane for 1 or 12 weeks (Wang et al. 2002, 2003). These studies also indicated that modification of functional proteins containing a sulfhydryl base as a critical site might underlie mechanisms of neurotoxicity because 1-bromopropane exposure decreased levels of sulfhydryl bases of protein and nonprotein fractions in the cerebrum, cerebellum, and brain stem (Wang et al. 2002, 2003). Suda et al. (2008) reported a significant decrease in the level of the free amino acid taurine in several brain regions in rats exposed to  $\geq 50$  ppm 1-bromopropane for 3 weeks. Taurine is involved in many functions such as detoxification, cholesterol metabolism, neuromodulation, and transamination. Other amino acids involved in transamination were also altered, including cystathionine, serine, threonine, and  $\beta$ -alanine. In a proteomic analysis of hippocampal tissue obtained from rats intermittently exposed to 0, 400, or 1,000 ppm, 19 proteins were significantly altered after 1 and 4 weeks of exposure and 8 were altered in a dose-dependent fashion (Huang et al. 2011). Identified proteins were categorized into functional classes, including nucleocytoplasmic transport, immunity and defense, energy metabolism, ubiquitination-proteasome pathway, neurotransmitter, and purine metabolism, suggesting that hippocampal damage associated with 1-bromopropane exposure may involve oxidative stress, loss of ATP production, neurotransmitter dysfunction, and inhibition of the ubiquitination-proteasome system. Due to evidence of oxidative stress, another study by the same group of investigators specifically looked for proteins with increased carbonyl modification using the same protocol (Huang et al. 2012). Ten proteins with increased carbonyl modification were identified, including proteins involved in glycolysis, ATP production, tyrosine catabolism, GTP binding, guanine degradation, and neuronal metabolism of dopamine.

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As summarized above, 1-bromopropane can induce neurological alterations by acting at multiple levels in the nervous system. The identity of the neurotoxic moiety(s), however, remains unknown.

***Mechanisms of Hepatotoxicity.*** Hepatic effects have been observed in animal studies following inhalation exposure to 1-bromopropane, including histopathological changes (liver congestion, hemorrhage, cellular swelling, vacuolization of hepatocyte and/or degeneration) and increased liver weight (Albemarle Corporation 1997; Kim et al. 1999; Lee et al. 2007; Liu et al. 2010; NTP 2011; Yamada et al. 2003; Zong et al. 2016). Following exposure to  $\geq 100$  ppm for 28 days, *Nrf2*-null mice (lacking nuclear factor erythroid 2-related factor 2) showed significantly larger areas of hepatic necrosis relative to wild-type mice at the same exposure level (Liu et al. 2010). Since *Nrf2* is a transcription factor that upregulates a battery of cytoprotective genes in response to oxidative stress and/or chemical exposure, these findings suggest that oxidative stress may play a role in hepatotoxic effects of 1-bromopropane. In wild-type mice, 1-bromopropane exposure at 300 ppm increased the mRNA levels of several cytoprotective genes regulated by *Nrf2*, including heme oxygenase-1 (HO-1), glutamate-cysteine ligase modifier subunit (GcLM), glutamate-cysteine synthetase (GcLc), glutathione reductase, and NAD(P)H:quinone oxidoreductase 1 (NQO1); these genes were not upregulated in *Nrf2*-null mice. Additionally, *Nrf2*-null mice have constitutively low mRNA expression levels of antioxidant enzymes and high malondialdehyde levels (Liu et al. 2010). Khan and O'Brien (1991) also suggested that oxidative stress plays a role in hepatotoxic effects of 1-bromopropane, reporting time-dependent glutathione depletion in isolated rat hepatocytes exposed to 100  $\mu$ M 1-bromopropane. The role of oxidative stress in 1-bromopropane-induced liver toxicity is also suggested by the results of a study in three mouse strains with different capacities to metabolize 1-bromopropane (C57Bl/6J, DBA/2J, and BALB/cA) (Liu et al. 2009). Intermittent exposure of the mice induced concentration-related increases in hepatocellular degeneration and liver necrosis; the strain with the highest CYP2E1 protein level and lowest total GSH content and GST activity in the liver (BALB/cA) was the most susceptible to hepatic damage (Liu et al. 2009).

***Mechanisms of Testicular Toxicity.*** Testicular effects have been observed in animal studies following inhalation or oral exposure to 1-bromopropane, including alterations in sperm parameters and degeneration of spermatocytes (Banu et al. 2007; Ichihara et al. 2000a; Liu et al. 2009; NTP 2011; Yu et al. 2008). While oral exposure to 400 ppm 1-bromopropane caused failure of spermiation in male Wistar rats, exposure to 1,000 ppm caused spermatogenic cell depletion (Banu et al. 2007), suggesting that different mechanisms operate depending on the exposure levels. Similarly, decreased epididymal sperm count was observed in rats injected with intraperitoneal doses of 1,000 mg 1-bromopropane/kg/day for

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14 days (Xin et al. 2010). This finding was accompanied by a significant increase in the number of TUNEL-positive cells, indicating that increased apoptosis may be a mechanism of testicular toxicity. However, the apoptotic pathway is unclear because 1-bromopropane did not lead to significant changes in the expression of apoptosis-related genes and proteins (caspase-3, p53, Bax, Bcl-2, Fas, FasL). As with hepatotoxicity (see above), sperm toxicity appears to be, at least in part, caused by oxidative stress, based on findings of Garner et al. (2007) and Liu et al. (2009). The former showed that 1-bromopropane reduced sperm motility in CYP2E1-null mice to a much lesser extent than in wild type mice. Liu et al. (2009) exposed three mouse strains with different capacities to metabolize 1-bromopropane (C57Bl/6J, DBA/2J, and BALB/cA) and reported that the strain with the highest CYP2E1 protein level and lowest total GSH content and GST activity in the liver (BALB/cA) was the most susceptible to 1-bromopropane-induced alterations in sperm parameters.

***Mechanisms of Respiratory Toxicity.*** Limited human data from case reports suggest that exposure to 1-bromopropane can cause respiratory tract irritation at concentrations >100 ppm (Ichihara et al. 2002; Raymond and Ford 2007), and lesions of both the upper and lower respiratory tracts have been observed in rats and mice exposed to 1-bromopropane for intermediate and chronic durations (Morgan et al. 2011; NTP 2011). While studies specifically evaluating mechanisms of toxicity in the respiratory system have not been identified, Morgan et al. (2011) suggested that these lesions likely reflect the local irritant activity of 1-bromopropane, consistent with observations of other inhaled hydrocarbons.

***Mechanisms of Carcinogenicity.*** 1-Bromopropane is a multisite carcinogen in rats and mice (Morgan et al. 2011; NTP 2011, 2013). While mechanisms of carcinogenicity for 1-bromopropane are unknown, Morgan et al. (2011) suggested possible mechanisms may include formation of reactive metabolites that can alkylate proteins or nucleic acids and/or oxidative stress due to glutathione depletion. *In vitro* incubation of 1-bromopropane with calf thymus DNA resulted in the formation of a *N*<sup>7</sup>-guanine adduct (Thapa et al. 2016). Available data are insufficient to determine if 1-bromopropane can act by a genotoxic mode-of-action; see Section 3.3, Genotoxicity, for more details.

### 3.5.3 Animal-to-Human Extrapolations

Studies in rodents have shown species, strain, and sex differences in sensitivity to some 1-bromopropane-induced effects that are related to differences in the metabolic disposition of the chemical (Garner and Yu 2014; Garner et al. 2007; Liu et al. 2009). Differences in some toxicities of 1-bromopropane, such as hepatotoxicity and sperm toxicity, between rats and mice and between mice strains are related to

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differences in oxidative capacity, specifically CYP2E1 protein levels, and differences in glutathione levels and GST activity in the liver. How the activities of the oxidative and conjugation pathways in humans compare to those in rats and mice in disposing of 1-bromopropane has not been determined. Therefore, the rodent model that is most appropriate to assess potential liver and sperm toxicity of 1-bromopropane in humans is unknown.

**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 Thomas and Colborn (1992), was also used in 1996 when Congress mandated the 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), and in 1998, the EDSTAC 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 isoflavonoid 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 1997). 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).

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Limited human data do not suggest that 1-bromopropane is an endocrine disruptor. In the study of workers exposed to 1-bromopropane conducted by Li et al. (2010) discussed in Section 3.2.1, Inhalation Exposure, a significant trend for increased serum TSH was reported in females. Regression analyses that included exposure level and duration showed significant trends for increased serum TSH and FSH in female workers. However, neither serum estradiol in females nor serum testosterone levels in males were significantly associated with exposure to 1-bromopropane. A critical review of this study noted that because several of the measures in females experience temporal fluctuations related to the menstrual cycle, lack of appropriate control for these variables could have led to misleading results (Smith et al. 2011). Raymond and Ford (2007) reported that a 41-year-old woman who experienced adverse neurological effects after 2 weeks of working with a glue formulation containing 1-bromopropane had normal thyroid function tests results; the tests were performed about 2 months after she became ill. No further relevant information is available for humans.

In general, acute-, intermediate-, and chronic-duration inhalation studies in animals did not report significant gross or microscopic alterations in endocrine glands with the exception of moderate to marked necrosis of the adrenal cortex of female mice exposed intermittently to 500 ppm 1-bromopropane for 14 weeks (NTP 2011); the NOAEL was 250 ppm.

Two intermediate-duration studies evaluated reproductive hormones in animals exposed to 1-bromopropane. Plasma testosterone levels were significantly decreased by 36% in male Wistar rats exposed to 800 ppm 1-bromopropane for 12 weeks (Ichihara et al. 2000a). No significant changes were observed in testosterone levels at  $\leq 400$  ppm or in plasma LH or FSH at concentrations up to 800 ppm 1-bromopropane (Ichihara et al. 2000a). No changes were observed in serum LH or FSH in female Wistar rats following intermittent exposure at concentrations up to 800 ppm 1-bromopropane for 12 weeks (Yamada et al. 2003).

No *in vitro* studies were located regarding endocrine disruption of 1-bromopropane.

### 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 most biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect

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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 adverse health effects from exposure to hazardous chemicals, but whether there is a difference depends on the chemical(s) (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to exposure-related 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 that are most sensitive to disruption from exposure to hazardous substances. Damage from exposure in one stage 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). Past literature has often described the fetus/infant as having an immature (developing) blood-brain barrier that is leaky and poorly intact (Costa et al. 2004). However, current evidence suggests that the blood-brain barrier is anatomically and physically intact at this stage of development, and the restrictive intracellular junctions that exist at the blood-CNS interface are fully formed, intact, and functionally effective (Saunders et al. 2008, 2012).

However, during development of the brain, there are differences between fetuses/infants and adults that are toxicologically important. These differences mainly involve variations in physiological transport systems that form during development (Ek et al. 2012). These transport mechanisms (influx and efflux) play an important role in the movement of amino acids and other vital substances across the blood-brain barrier in the developing brain; these transport mechanisms are far more active in the developing brain than in the adult. Because many drugs or potential toxins may be transported into the brain using these same transport mechanisms—the developing brain may be rendered more vulnerable than the adult.

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Thus, concern regarding possible involvement of the blood-brain barrier with enhanced susceptibility of the developing brain to toxins is valid. It is important to note however, that this potential selective vulnerability of the developing brain is associated with essential normal physiological mechanisms; and not because of an absence or deficiency of anatomical/physical barrier mechanisms.

The presence of these unique transport systems in the developing brain of the fetus/infant is intriguing; whether these mechanisms provide protection for the developing brain or render it more vulnerable to toxic injury is an important toxicological question. Chemical exposure should be assessed on a case-by-case basis. Research continues into the function and structure of the blood-brain barrier in early life (Kearns et al. 2003; Saunders et al. 2012; Scheuplein et al. 2002).

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 given their low glomerular filtration rate and not having 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).

No information was located regarding health effects in children following exposure to 1-bromopropane. Since exposure to 1-bromopropane occurs mainly in occupational settings, children are not expected to experience exposures to 1-bromopropane.

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No studies were located that exposed animals of different ages to 1-bromopropane to determine whether age might be a factor in the toxicity of 1-bromopropane. Therefore, it is not known whether younger animals are more susceptible to 1-bromopropane than older animals. However, because the nervous system is the main target for 1-bromopropane toxicity in humans and animals, it seems reasonable to suggest that younger organisms, in which the nervous system is still developing, might be more susceptible to 1-bromopropane toxicity than mature individuals, if such an exposure were to occur.

1-Bromopropane was a developmental toxicant in rats. Studies of rats exposed to  $\geq 400$  ppm 1-bromopropane during gestation and lactation reported decreased survival of offspring during lactation (Furuhashi et al. 2006). A cross-foster experiment actually showed that gestation and lactation exposure had comparable effects on survival rate of the neonates, but lactation exposure played a greater role on growth of the offspring. Additional experiments showed that mated F1 offspring from the lactation-only exposure group produced a significantly greater number of dead F2 offspring, compared with controls. However, no exposure-related effects were observed in the F2 litter for gestational exposure only. This suggested that lactation exposure played a greater role in growth and sexual maturation of the offspring. 1-Bromopropane has not shown teratogenicity in studies in animals (BSOC 2001a, 2001b).

#### 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).

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, 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



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(e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to 1-bromopropane 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 1-bromopropane 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 1-Bromopropane

Proposed biomarkers of exposure to 1-bromopropane include urinary levels of N-acetyl-S-(n-propyl)-L-cysteine (AcPrCys), bromide, and 1-bromopropane itself. Field studies indicated that urinary levels of N-acetyl-S-(n-propyl)-L-cysteine and bromide were significantly correlated with time-weighted-average breathing zone air concentrations of 1-bromopropane in several groups of workers (Hanley et al. 2006, 2009, 2010). Use of N-acetyl-S-(n-propyl)-L-cysteine is expected to be more specific to 1-bromopropane than bromide due to the presence of the bromide ion in foods. Mathias et al. (2012) also reported a significant increase in urinary N-acetyl-S-(n-propyl)-L-cysteine and bromide ion levels in workers exposed to 1-bromopropane in a foam cushion manufacturing plant, compared with controls. The suitability of urinary levels of the metabolites 3-bromopropionic acid, N-acetyl-S-(n-propyl)-L-cysteine-S-oxide, N-acetyl-S-2-hydroxypropylcysteine, and N-acetyl-S-2-carboxyethylcysteine was also investigated by Mathias et al. (2012). There was no significant difference between urinary 3-bromopropionic acid levels between exposed and control workers, indicating that it is a poor biomarker. The analysis of the mercapturic acid metabolites N-acetyl-S-(n-propyl)-L-cysteine-S-oxide, N-acetyl-S-2-hydroxypropylcysteine, and N-acetyl-S-2-carboxyethylcysteine was discontinued due to low levels of

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detection in urine samples (Mathias et al. 2012). In another study of workers involved in 1-bromopropane manufacturing, urinary 1-bromopropane concentrations were significantly correlated with TWA concentrations of 1-bromopropane in workplace air (Ichihara et al. 2004a). Valentine et al. (2007) studied blood and urine samples from workers and ambient air samples in a Chinese 1-bromopropane production plant in order to support the potential of urinary AcPrCys and globin S-propylcysteine (PrCys) adducts as biomarkers of exposure in humans. It was found that there was a significant increase in globulin PrCys adducts in exposed workers (1.52 pmol/mg globin) compared with that of control factory workers (0.11 pmol/mg globin). Also, an increase in urinary AcPrCys levels was directly related to an increase in ambient air exposure levels, which ranged from 0 to 170.54 ppm. In a study of Japanese workers exposed to 1-bromopropane in cleaning and painting workshops, urinary 1-bromopropane at the end of an 8-hour shift correlated closely with the exposure concentration (geometric mean 1.4 ppm) (Kawai et al. 2001). The investigators noted that an exposure concentration of 2 ppm could be readily biomonitoring. Urinary bromide also correlated with 1-bromopropane in air, but the correlation was not as good as with urinary 1-bromopropane.

The distribution of the proposed biomarker N-acetyl-S-(n-propyl)-L-cysteine was evaluated in the general population in the National Health and Nutrition Examination Survey (NHANES) 2011–2012 (Jain 2015a). The study examined the distribution of urinary metabolites of volatile compounds by age, gender, race/ethnicity, and smoking status among 2,328 NHANES participants  $\geq 20$  years of age. Adjusted urinary geometric means of N-acetyl-S-(n-propyl)-L-cysteine were the same in males and females (5.3 ng/mL). Nonsmokers did not have statistically significantly different urinary levels of N-acetyl-S-(n-propyl)-L-cysteine than smokers. Non-Hispanic white subjects (3.9 ng/mL) had significantly lower levels of N-acetyl-S-(n-propyl)-L-cysteine than non-Hispanic black subjects (4.1 ng/mL) and non-Hispanic Asians (7.7 ng/mL). Non-Hispanic black subjects (4.1 ng/mL) had significantly lower levels of urinary N-acetyl-S-(n-propyl)-L-cysteine than Hispanics (6.2 ng/mL) and non-Hispanic Asians (7.7 ng/mL). Evaluation of 417 children, 6–11 years of age, also participants in NHANES 2011–2012 showed no significant differences between genders (2.6 ng/mL in males and 3.3 ng/mL in females) (Jain 2015b). Non-Hispanic Asian children had the highest urinary levels of N-acetyl-S-(n-propyl)-L-cysteine (5.0 ng/mL) followed by non-Hispanic black children (3.4 ng/mL), non-Hispanic white children (2.4 ng/mL), and Hispanic children (2.1 ng/mL). Children had significantly lower levels of urinary N-acetyl-S-(n-propyl)-L-cysteine than nonsmoking adults (3.4 versus 5.7 ng/mL).

Values similar to those reported by Jain (2015a, 2015b) were reported in pregnant women participants in the National Children's Vanguard Study (Boyle et al. 2016). The study included 488 women enrolled

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from 2009 to 2010 from seven locations in the United States. N-Acetyl-S-(n-propyl)-L-cysteine was detected in urinary samples collected during the third trimester of pregnancy with a frequency of 99%; the median was 2.61 ng/mL and the 75<sup>th</sup> percentile value was 9.44 ng/mL.

The ubiquitous nature of N-acetyl-S-(n-propyl)-L-cysteine in the urine of the general population suggests that it may not be a specific biomarker for 1-bromopropane, as exposure to 1-bromopropane is expected to be primarily occupational with limited exposure in the general population (NTP 2011, 2016); see Section 6.5 for more details. It is unknown if other chemicals and/or endogenous metabolism contributed to the observed urinary levels of N-acetyl-S-(n-propyl)-L-cysteine in the studies by Jain (2015a) and Boyle et al. (2016). However, occupational studies indicate that N-acetyl-S-(n-propyl)-L-cysteine is likely to be the most predictive biomarker of exposure available at this time (Hanley et al. 2006, 2009, 2010; Mathias et al. 2012; Valentine et al. 2007).

#### 3.8.2 Biomarkers Used to Characterize Effects Caused by 1-Bromopropane

There are no specific biomarkers to characterize effects caused by 1-bromopropane in humans. As summarized in Section 3.2.1, Inhalation Exposure, the main target of 1-bromopropane toxicity in humans is the nervous system, as demonstrated in several cases of occupational exposure to 1-bromopropane. Symptoms commonly reported include, but are not limited to, headache, dizziness, numbness, pain, paresthesias and weakness of the lower extremities, and difficulty walking/poor balance (Majersik et al. 2007). Signs reported include spasticity and weakness of the lower extremities, difficulty with tandem gait, lower extremity hyperreflexia, decreased lower extremity sensation to vibration, proprioception, temperature, and light touch. Sclar (1999) noted that results from nerve conduction velocity studies were consistent with primary, symmetric demyelinating polyneuropathy. Symptoms suggesting involvement of mainly the central nervous system include anxiety, irritation, forgetfulness, difficulty in concentrating, and listlessness (Ichihara et al. 2002). Many of these signs and symptoms can occur in subjects overexposed to solvents in general, not even structurally-related to 1-bromopropane.

### 3.9 INTERACTIONS WITH OTHER CHEMICALS

The only information regarding interaction of 1-bromopropane with other chemicals is that pretreatment of rats with 1-aminobenzotriazole (an inhibitor of a number of CYP enzymes) before administration of single intravenous doses of ~20 mg/kg <sup>14</sup>C-1-bromopropane or inhalation exposure to 800 ppm <sup>13</sup>C-1-bromopropane for 6 hours caused decreased exhalation of radioactivity as CO<sub>2</sub> and decreased formation of oxidative urinary metabolites (Garner et al. 2006). In general, chemicals that interfere with

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CYP enzymes or glutathione are likely to affect the metabolism of 1-bromopropane and increase or decrease toxicity.

**3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE**

A susceptible population will exhibit a different or enhanced response to 1-bromopropane than will most persons exposed to the same level of 1-bromopropane in the environment. Factors involved with increased susceptibility 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 1-bromopropane, or compromised function of organs affected by 1-bromopropane. Populations who are at greater risk due to their unusually high exposure to 1-bromopropane are discussed in Section 6.7, Populations with Potentially High Exposures.

No information was located in the available literature regarding human populations that may be unusually susceptible to toxic effects from 1-bromopropane. As discussed in Section 3.7 (Children's Susceptibility), children are not expected to experience exposures to 1-bromopropane since exposure occurs mainly in occupational settings.

Genetic differences in the ability to metabolize 1-bromopropane may confer differential susceptibility to toxic effects of 1-bromopropane. Following intermittent exposure to 50–250 ppm 1-bromopropane for 4 weeks, three mouse strains with different capacities to metabolize 1-bromopropane (C57Bl/6J, DBA/2J, and BALB/cA) showed dose-related increases in hepatocellular degeneration and liver necrosis; however, the strain with the highest CYP2E1 protein level and lowest total GSH content and GST activity in the liver (BALB/cA) was the most susceptible to hepatic damage (Liu et al. 2009). Mice are considerably more susceptible to 1-bromopropane-induced hepatotoxicity and spermatotoxicity than rats (Liu et al. 2009, 2010; NTP 2011). The greater susceptibility of mice is likely due to higher CYP2E1-catalyzed production of cytotoxic metabolites. Lower reduced GSH levels in mice may also play a role in increased sensitivity to cellular injury.

Studies that evaluated more than one rat strain have not been identified; however, available single-strain studies suggest that Sprague-Dawley rats are less susceptible to neurotoxic effects of inhaled 1-bromopropane, compared with Wistar and F-344 rats (Albemarle Corporation 1997; Fueta et al. 2002; Honma et al. 2003; Ichihara et al. 2000b; Sohn et al. 2002; Yu et al. 2001). The mechanism(s) underlying the apparent strain differences are unknown.

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**3.11 METHODS FOR REDUCING TOXIC EFFECTS**

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to 1-bromopropane. Because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to 1-bromopropane. When specific exposures have occurred, poison control centers, board certified medical toxicologists, board-certified occupational medicine physicians and/or other medical specialists with expertise and experience treating patients overexposed to 1-bromopropane can be consulted for medical advice. No texts were located that provide specific information about treatment following exposure to 1-bromopropane; however, the following texts provide information about treatment following exposures to halogenated aliphatic hydrocarbons (or hydrocarbons in general):

Currance PL, Clements B, Bronstein, AC. 2007. Halogenated aliphatic hydrocarbons and related compounds. In: Currance PL, Clements B, Bronstein, AC, eds. Emergency care for hazardous materials exposure. 3<sup>rd</sup> edition. St. Louis, MO: Mosby, Inc., 216-223.

Gummin DD. 2015. Hydrocarbons. In: Hoffman RS, Lewin NA, Goldfrank LR, et al., eds. Goldfrank's toxicologic emergencies. 7th ed. New York, NY: McGraw-Hill Education, 1334-1345.

Thompson TM. 2014. Chapter 126: Hydrocarbons. In: Schafermeyer R, Tenenbein M, Macias CG, eds. Strange and Schafermeyer's pediatric emergency medicine. New York, NY: McGraw-Hill.

Additional relevant information can be found in the front section of this profile under QUICK REFERENCE FOR HEALTH CARE PROVIDERS.

**3.11.1 Reducing Peak Absorption Following Exposure**

1-Bromopropane is expected to be absorbed by the skin, gastrointestinal tract, and respiratory tract, but quantitative data on the extent of absorption are not available (Frasch et al. 2011; Garner et al. 2006; Hanley et al. 2006, 2009, 2010; Jones and Walsh 1979; Valentine et al. 2007). There are no known methods for reducing peak absorption following inhalation exposure. In cases of ingestion, the use of Activated charcoal has limited ability to reduce gastrointestinal absorption of hydrocarbons in general (Gummin 2015; Thompson 2014). Because it may also distend the stomach and predispose patients to vomiting and aspiration, the use of activated charcoal may be justified only in patients with mixed overdoses (Gummin 2015). Rapid rinsing of the skin with water or washing with soap and water will reduce the opportunity for dermal absorption. If the eyes are affected, proper rinsing procedures should be followed (Currance et al. 2007; HSBD 2013).

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**3.11.2 Reducing Body Burden**

Results from animal studies indicate that 1-bromopropane is rapidly eliminated from the body by exhalation of the parent material and metabolically derived CO<sub>2</sub> and by urinary excretion of bromide ion and carbon-containing metabolites (Garner and Yu 2014; Garner et al. 2006, 2007; Ishidao et al. 2002; Jones and Walsh 1979). Following inhalation exposure, oxygen therapy and positive-pressure ventilation may be useful following inhalation exposure to 1-bromopropane to promote the loss of unmetabolized 1-bromopropane from the lungs (Currance et al. 2007; HSBD 2013). There are no known methods for reducing body burdens following oral or dermal exposure.

**3.11.3 Interfering with the Mechanism of Action for Toxic Effects**

Since the mechanism(s) of toxicity for 1-bromopropane in humans is/are not yet elucidated, there are no known methods for interfering with the mechanism of action.

However, there is evidence that CYP2E1-catalyzed oxidation contributes to 1-bromopropane-induced spermatotoxicity and hepatotoxicity in mice (Garner et al. 2006, 2007; Liu et al. 2009; Zong et al. 2016). The putative cytotoxic oxidative metabolites have not been identified, but CYP2E1 inhibition should be protective. An alternative therapeutic approach would be to administer antioxidants to inhibit lipoperoxidation. N-Acetylcysteine or another agent that will significantly enhance levels of reduced glutathione may also be beneficial. Whether these treatments would be beneficial in humans exposed to 1-bromopropane is unknown.

**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 1-bromopropane 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 adverse health effects (and techniques for developing methods to determine such health effects) of 1-bromopropane.

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

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reduce the uncertainties of human health risk 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.

**3.12.1 Existing Information on Health Effects of 1-Bromopropane**

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to 1-bromopropane are summarized in Figure 3-7. The purpose of this figure is to illustrate the existing information concerning the health effects of 1-bromopropane. 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 3-7, there is a limited amount of data on the health effects of 1-bromopropane in humans following inhalation exposures. There are no oral or dermal data available for humans; however, these are not primary routes by which humans are exposed to 1-bromopropane. It should be noted that while exposure to 1-bromopropane occurred primarily via the inhalation route in the available human studies, dermal exposure may have also occurred. In most cases, it was not known whether or not the workers were using protective clothing and/or respirators, so the specific contribution of each route of exposure is not possible to determine. Figure 3-7 also shows that information on health effects of 1-bromopropane in animals is available for all effect categories, but is mainly limited to inhalation exposure studies in animals.

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**Figure 3-7. Existing Information on Health Effects of 1-Bromopropane**

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

**Human**

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

**Animal**

● Existing Studies



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**3.12.2 Identification of Data Needs**

**Acute-Duration Exposure.** The only acute-duration inhalation studies in humans were a few case studies reporting subjective symptoms in workers within 2 weeks of 1-bromopropane introduction into the workplace. Adverse effects included respiratory irritation, headache, nausea, and lower extremity numbness, pain, and weakness. The geometric mean air concentration was 107 ppm for glue sprayers (range 58–254 ppm) (Raymond and Ford 2007). Acute animal inhalation studies are limited to two single-exposure studies evaluating lethality (Elf AtoChem S.A. 1997; Kim et al. 1999) and one evaluating sperm motility (Garner et al. 2007), a 1-week study evaluating neurogenesis and endocrine end points (Zhang et al. 2013), and a 1-week study evaluating morphological and biochemical changes in the brain (Wang et al. 2002); all of these studies were conducted in rats.

The lowest LOAEL identified in these studies may have been lower than 800 ppm because in the Garner et al. (2007) study, sperm motility was significantly decreased in mice following a single 6-hour exposure to an initial concentration of 800 ppm 1-bromopropane, which decreased steadily during the exposure period. Wang et al. (2002) reported for morphological changes in the medulla oblongata and posterior tibial nerve in rats exposed to 800 ppm 1-bromopropane, but not  $\leq 400$  ppm, for 1 week (Wang et al. 2002). However, it should be noted that only 1 rat/group was assessed for morphological alterations. Wang et al. (2002) also reported several biochemical changes in the central nervous system following exposure to 1-bromopropane at  $\geq 200$  ppm. The adversity of these changes is unclear because there were no clear associations between biochemical and morphological changes. Other reported neurological effects included decreased activity and ataxia after single exposures to  $\geq 1,800$  ppm, but not 300 ppm (Kim et al. 1999). No exposure-related changes in hippocampal neurogenesis, adrenal weight, or plasma corticosterone levels were reported in male rats intermittently exposed to 1,000 ppm 1-bromopropane for 1 week (Zhang et al. 2013). A study that reported decreased grip strength in male rats exposed for 8 hours/day to 1,000 ppm 1-bromopropane for 14 days was used to derive an acute-duration inhalation MRL for 1-bromopropane (Honma et al. 2003). Yet, the acute database would benefit from studies examining a comprehensive set of neurotoxicological end points as well as developmental studies to adequately characterize the most sensitive adverse effects following acute exposure. Additionally, a morphological study with larger animal groups and/or a comprehensive neurological battery in animals would be useful.

Acute oral studies are limited to a single-dose lethality study in rats (Elf Atochem S.A. 1993), a single-exposure study evaluating hepatotoxicity and immunotoxicity in mice (Lee et al. 2007), a 10-day study

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evaluating male reproductive end points in rats (Yu et al. 2008), and two 12-day studies evaluating neurobehavioral end points (learning and memory) in rats (Guo et al. 2015; Zhong et al. 2013). The lowest LOAELs identified in these studies were 200 mg 1-bromopropane/kg/day for impaired spatial learning and memory during the Morris water maze test in rats (Guo et al. 2015; Zhong et al. 2013) and 200 mg/kg/day for reduced antibody responses to the T-dependent SRBC antigen (Lee et al. 2007). A NOAEL of 100 mg 1-bromopropane/kg/day was identified in the Guo et al. (2015) study. Other effects reported at higher doses in other studies include congestion, hemorrhage, cellular swelling, and vacuolization of hepatocytes in mouse liver at  $\geq 500$  mg 1-bromopropane/kg/day, but not 200 mg 1-bromopropane/kg/day (Lee et al. 2007); degeneration of spermatocytes in mouse testes at 600 mg 1-bromopropane/kg/day (only dose tested) (Yu et al. 2008); and a 13% decrease in body weight at 800 mg 1-bromopropane/kg/day, but not  $\leq 400$  mg 1-bromopropane/kg/day (Zhong et al. 2013). While the acute oral database is limited, observed neurological effects are consistent with neurological effects observed in the more comprehensive inhalation database. Therefore, the LOAEL of 200 mg 1-bromopropane/kg/day for impaired spatial learning and memory was selected as the basis for the acute-duration oral MRL (Zhong et al. 2013); the results of Guo et al. (2015) support the oral MRL. Additional studies examining a comprehensive set of systemic and neurological end points, as well as developmental studies, would be useful to reduce uncertainty in the identification of the most sensitive outcome following acute oral exposure.

The available data for dermal exposure are limited to a single dermal study that reported a lack of cutaneous effects and lethality at 2,000 mg 1-bromopropane/kg (Elf Atochem S.A. 1995); however, this is not a primary route by which humans are exposed to 1-bromopropane.

**Intermediate-Duration Exposure.** The only intermediate-duration inhalation studies in humans are case studies, most of them reporting neurological signs and symptoms in workers following exposure to  $>100$  ppm 1-bromopropane for a few weeks or months, including marked ataxia, impaired balance and coordination, sensory deficits, inability to walk, and damage to peripheral nerves (Ichihara et al. 2002; Majersick et al. 2007; MMWR 2008; Raymond and Ford 2007; Sclar 1999). Several intermediate-duration inhalation studies in animals are available. Similar to the human case studies, animal studies reported neurological effects following intermediate-duration inhalation exposure at concentrations ranging from 50 to 1,500 ppm (Banu et al. 2007; Fueta et al. 2002, 2004, 2007; Honma et al. 2003; Ichihara et al. 2000b; Mohideen et al. 2011, 2013; Subramanian et al. 2012; Ueno et al. 2007; Wang et al. 2003; Yu et al. 1998, 2001; Zhang et al. 2013); all these studies were conducted in rats. Other effects observed at similar exposure levels include altered sperm parameters and liver effects at  $\geq 50$  ppm in rats

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and mice (Kim et al. 1999; Liu et al. 2009). The study by Honma et al. (2003) identified a NOAEL and LOAEL of 10 ppm and 50 ppm, respectively, for neurological effects in rats and was used to derive an intermediate-duration inhalation MRL for 1-bromopropane.

No intermediate-duration oral or dermal studies were located for 1-bromopropane; however, these are not primary routes by which humans are exposed to 1-bromopropane.

**Chronic-Duration Exposure and Cancer.** An epidemiological study of 1-bromopropane production workers from three plants in China reported neurological effects in females exposed to median 1-bromopropane concentrations  $\geq 1.28$  ppm for ~40 months, including decreased vibration sense, electrophysiological changes, and impaired visual perception and memory (Li et al. 2010). Limitations of the study acknowledged by the investigators include: (1) lack of control of the temperature of the skin of the legs may have impacted measurements of nerve conduction velocity; (2) clinical assessment of vibration threshold using a tuning fork is inherently inaccurate due to examiner bias and subject characteristics (age, weight, height); and (3) uncertainty in the assessment of cumulative exposure (1–3-day measurements, presumed to be the same level for entire duration of employment). Criticisms from others (Smith et al. 2011) include lack of monitoring data for the controls and possible underestimation of exposure since masks were not used. However, findings from this study were determined to be adequate as the basis for a chronic inhalation MRL, although confidence in this MRL is low due to the acknowledged limitations. Further discussion regarding the rationale for selecting the human study to derive the chronic inhalation MRL of 0.02 ppm, as well as data from a supporting animal study that yielded a virtually identical MRL of 0.03 ppm, can be found in Appendix A. Additional epidemiological studies of neurological end points in workers with better study designs (preferably prospective, longitudinal studies), longer durations of employment, more diligent measurement and reporting of exposure levels, and standardized measurement methods (particularly a quantitative measure of vibration sense) would be useful to better characterize the neurotoxicity of 1-bromopropane and increase the confidence in the MRL.

A limited number of studies have assessed carcinogenic effects of 1-bromopropane in rodents. In rats exposed by inhalation to 1-bromopropane for 2 years, significantly increased incidences of tumors were found in multiple sites: large intestine adenomas in females and skin keratoacanthoma, basal cell adenoma or squamous cell carcinoma, malignant mesothelioma, and pancreatic islet adenoma in males (Morgan et al. 2011; NTP 2011). In mice, exposure to 1-bromopropane significantly increased the incidence of combined alveolar/bronchiolar adenoma or carcinoma in females (Morgan et al. 2011; NTP

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2011). No studies have evaluated cancer mortality or morbidity in groups of 1-bromopropane-exposed humans. The chronic or carcinogenic effects of 1-bromopropane have not been investigated in humans or animals following oral or dermal exposures; however, these are not considered major routes of 1-bromopropane exposure. Studies of cancer mortality or morbidity in cohorts of 1-bromopropane-exposed workers and mechanistic studies of interspecies differences in 1-bromopropane carcinogenicity may help to better determine the potential carcinogenicity of 1-bromopropane in humans.

**Genotoxicity.** Available studies do not clearly identify 1-bromopropane as a genotoxic agent, and only a limited number of end points have been evaluated. The only study located regarding genotoxic effects in humans exposed to 1-bromopropane reported a weak association between 1-bromopropane exposure and DNA damage in peripheral lymphocytes (Toraason et al. 2006). *In vivo* animal studies did not show micronuclei induction or dominant lethality (Chung et al. 2006; NTP 2011; Saito-Zuzuki et al. 1982; Yu et al. 2008). *In vitro* studies have reported mixed findings for reverse mutation and DNA damage (Barber et al. 1980, 1981; Hasspieler et al. 2006; NTP 2011; Torasson et al. 2006). Additional studies for various genotoxic end points, including clastogenicity, could be useful to determine the genotoxicity of 1-bromopropane. Due to the volatility of 1-bromopropane, *in vitro* studies utilizing closed test systems would be preferential.

**Reproductive Toxicity.** Limited information regarding reproductive effects of 1-bromopropane in humans is available from two NIOSH Health Hazard Evaluation reports and two preliminary health surveys in workers exposed to 1-bromopropane (Ichihara et al. 2004a, 2004b; NIOSH 2002, 2003a). In these studies, no self-reported effects on fertility or menstrual cycles were observed in 1-bromopropane exposed workers and there was no evidence of exposure-related changes in sperm count, motility, or morphology in a limited number of individuals (three exposed males, nine unexposed males). However, several studies in rats and mice suggest that repeated inhalation exposure to 1-bromopropane may adversely affect both the male (sperm effects, decreased testosterone) and female reproductive systems (altered estrous cycles) at concentrations as low as 50 and 250 ppm, respectively (Banu et al. 2007; Ichihara et al. 2000a; Liu et al. 2009; NTP 2011; Yamada et al. 2003). Results from a comprehensive 2-generation study in rats showed that exposure of males and females to 750 ppm 1-bromopropane for at least 70 days before mating resulted in complete infertility and exposure to 500 ppm reduced fertility by 48% (BSOC 2001a). Exposure to lower concentrations (250 ppm) reduced prostate weight in F0 males and increased estrous cycle length in F1 females. Alterations in sperm parameters were reported in rats at  $\geq 500$  ppm and in mice at  $\geq 250$  ppm in the 14-week NTP (2011) study. Because Liu et al. (2009) reported significant sperm alterations in three strains of mice exposed to 50 ppm 1-bromopropane for 4 weeks,

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studies trying to replicate the findings of Liu et al. (2009) may be warranted. In addition, measurements of hepatic levels of CYP2E1 and GST activities in the B6C3F1 strain of mice used in the NTP (2011) study would be useful to possibly explain the significantly lower sensitivity of that strain for sperm effects compared to the mice strains studied by Liu et al. (2009). Epidemiology studies with fewer limitations (greater number of subjects, longer exposure durations, and better control for confounding factors) would help characterize the reproductive toxicity of 1-bromopropane in humans. Additional studies in animals do not seem necessary at this time.

**Developmental Toxicity.** No studies were located for developmental effects in humans after exposure to 1-bromopropane, and available studies in animals are inadequate to determine if developmental toxicity is a concern following 1-bromopropane exposure in humans. Two studies in rats showed that maternal exposure to 1-bromopropane during gestation can induce reductions in fetal or neonate body weight (BSOC 2001b; Fueta et al. 2015). Data from a 2-generation reproductive study in rats showed that exposure to 500 ppm 1-bromopropane can affect growth in rat pups (Albemarle Corporation 2002). An additional study in rats showed that perinatal exposure to 800 ppm can drastically reduce viability during the first weeks of life (Furuhashi et al. 2006). No teratogenic effects were reported in developmental studies. Based on the fact that 1-bromopropane did not have significant effects on endocrine organs in animals, and the chemical structure of 1-bromopropane, it seems unlikely that 1-bromopropane could affect development by disrupting endocrine processes. Therefore, studies focused on this issue do not seem warranted at this time.

**Immunotoxicity.** No studies were located that evaluated immunological effects in humans after inhalation exposure to 1-bromopropane, and available studies in animals are insufficient to assess the immunotoxic potential of 1-bromopropane exposure in humans. In animals exposed to 1-bromopropane via inhalation for 4–10 weeks, suppression of the IgM plaque forming response to immunization with SRBCs was observed in splenocytes harvested from female rats and mice exposed to 1,000 and  $\geq 125$  ppm, respectively (Anderson et al. 2010). Other exposure-related changes observed included reduced spleen weight and cellularity and significant changes in spleen cell subpopulations. Immune responses to SRBC and ConA were also reduced in mice dosed once by gavage with  $\geq 200$  mg 1-bromopropane/kg (Lee et al. 2007). No other animal studies examining immune function were located. Epidemiology studies evaluating immune end points and immunotoxicity batteries in animals would be useful to better characterize the immunotoxicity of 1-bromopropane.

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**Neurotoxicity.** The main target of concern following 1-bromopropane exposure in humans is the nervous system because the available data clearly indicate that the nervous system is a target for 1-bromopropane toxicity in humans and animals. Observed effects in humans range from subtle neurological deficits at exposure levels as low as 1.28 ppm 1-bromopropane, such as decreased vibration sense and paresthesia, to frank neurotoxic effects at exposures to concentrations  $\geq 100$  ppm, including ataxia, spastic paraparesis, and symmetric demyelinating polyneuropathy (Ichihara et al. 2002, 2004b; Li et al. 2010; Majersik et al. 2007; NIOSH 2002; Raymond and Ford 2007; Samukawa et al. 2012; Sclar 1999; Wang et al. 2015). Evidence from animal studies supports the 1-bromopropane neurotoxicity findings in humans. Observed effects in acute and intermediate-duration inhalation studies in rats showed that concentrations as low as 50 ppm can induce changes in neurobehavior, muscle strength, electrophysiology, and morphology and biochemistry of neural tissues (Banu et al. 2007; Fueta et al. 2002; Guo et al. 2015; Honma et al. 2003; Ichihara et al. 2000b; Kim et al. 1999; Mohideen et al. 2011, 2013; Subramanian et al. 2012; Ueno et al. 2007; Wang et al. 2002, 2003; Yu et al. 1998, 2001). Impaired learning and memory, sedation, and biochemical changes were also reported at doses as low as 200 mg 1-bromopropane/kg/day in the only available oral studies in rats examining neurological end points (Elf Atochem S.A. 1993; Zhong et al. 2013). Additional studies may be conducted to try to identify an acute-duration oral NOAEL for neurotoxicity, but consideration should be given to the fact that the oral route of exposure is not a route of concern for the general public or for occupational exposure. Research aimed at identifying the moiety(s) responsible for 1-bromopropane-induced neurotoxicity would be valuable. Studies could be conducted to examine the influence of CYP or GSH inducers or inhibitors or null strains of rodents on neurotoxic potency. Additional epidemiological studies in workers, particularly prospective, longitudinal studies, would be useful to lend support to the findings reported in the cross-sectional study by Li et al. (2010), which included minor neurological impairments in female workers exposed to median 1-bromopropane concentrations reported to be as low as 1.28 ppm. The critical effect identified in this study was increased vibration sense threshold; however, the methods employed relied heavily on the neurologist administering the test. Therefore, studies including quantitative measures of vibration sense as well as other neurophysiological and neurobehavioral parameters would be of particular interest. Improved procedures for more reliable exposure assessment are also necessary.

**Epidemiological and Human Dosimetry Studies.** Epidemiological studies are limited to a cross-sectional study in Chinese 1-bromopropane production workers from three factories (Li et al. 2010), two preliminary health surveys in Chinese 1-bromopropane production workers from a single factory (Ichihara et al. 2004a, 2004b), and two NIOSH health surveys in 1-bromopropane glue sprayers (NIOSH 2002, 2003a). As discussed above in the Chronic Studies section, the Li et al. (2010) study was selected

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as the basis of the chronic-duration inhalation MRL. Additional epidemiological studies in 1-bromopropane-exposed workers, particularly prospective, longitudinal studies, may help to better characterize the potential neurotoxicity and carcinogenicity of 1-bromopropane in humans.

**Biomarkers of Exposure and Effect.**

**Exposure.** Proposed biomarkers of exposure to 1-bromopropane include urinary levels of N-acetyl-S-(n-propyl)-L-cysteine, bromide, and 1-bromopropane itself (Hanley et al. 2006, 2009, 2010; Ichihara et al. 2004a; Kawai et al. 2001; Mathias et al. 2012; Valentine et al. 2007), as well as globin S-propylcysteine adducts in blood (Valentine et al. 2007). Use of N-acetyl-S-(n-propyl)-L-cysteine is expected to be more specific to 1-bromopropane than bromide due to the presence of the bromide ion in foods, although in a study of workers involved in 1-bromopropane manufacture, urinary 1-bromopropane concentrations were significantly correlated with TWA concentrations of 1-bromopropane in workplace air (Ichihara et al. 2004a). Other compounds considered as potential biomarkers were determined to be uncorrelated with exposure (3-bromopropionic acid) or were excluded from analysis due to low concentrations in urine (N-acetyl-S-(n-propyl)-L-cysteine-S-oxide, N-acetyl-S-2-hydroxypropylcysteine, and N-acetyl-S-2-carboxyethylcysteine) (Mathias et al. 2012). Additional occupational studies may better determine the reliability of proposed biomarkers of exposure.

N-Acetyl-S-(n-propyl)-L-cysteine has been measured in the urine of children and adult members of the U.S. general population participants in NHANES 2011–2012 (Jain 2015a, 2015b). The results showed no significant differences between geometric means in males and females and significantly lower levels in children (3.4 ng/mL) than in adults (5.7 ng/mL). Differences between race/ethnicities were reported. N-Acetyl-S-(n-propyl)-L-cysteine also was measured in urine collected from pregnant women during the third trimester of pregnancy (median, 2.61 ng/mL) (Boyle et al. 2016). These studies suggest that urinary N-acetyl-S-(n-propyl)-L-cysteine is found ubiquitously in the general population. However, it is unclear how the general public was exposed to 1-bromopropane, as most exposure is expected to be occupational (NTP 2011; see Section 6.5 for more details). This suggests that exposure to other chemicals and/or endogenous metabolism may be additional sources of urinary N-acetyl-S-(n-propyl)-L-cysteine. Studies designed to identify other environmental or endogenous sources of N-acetyl-S-(n-propyl)-L-cysteine would help to clarify the specificity of N-acetyl-S-(n-propyl)-L-cysteine as a biomarker of 1-bromopropane exposure in non-occupational settings. If the specificity of N-acetyl-S-(n-propyl)-L-cysteine is quantified (or another more specific biomarker is identified), research could potentially be aimed at estimating biomonitoring equivalents for 1-bromopropane would be useful. Biomonitoring

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equivalents are defined as the concentration or range of concentrations of a chemical or its metabolites in a biological matrix (i.e., urine for N-acetyl-S-(n-propyl)-L-cysteine) that is consistent with an existing noncancer health-based exposure guidance value (i.e., reference dose [RfD] or reference concentration [RfC]) (Aylward et al. 2013). Comparing biomonitoring equivalents with guidance values helps determine whether exposure to a chemical is excessive. Biomonitoring equivalents have been derived for a number of chemicals (Aylward et al. 2013).

**Effect.** There are no specific biomarkers to characterize effects caused by 1-bromopropane. Additional information on the mechanism of neurotoxicity may suggest a useful biomarker of either exposure or effect. However, at this time, there is little to suggest that such biomarkers exist.

**Absorption, Distribution, Metabolism, and Excretion.** The detection of urinary metabolites in humans and animal exposed to 1-bromopropane provides qualitative evidence for absorption by the gastrointestinal tract and the respiratory tract, but quantitative data on the extent of absorption are not available (Garner and Yu 2014; Garner et al. 2006, 2007; Hanley et al. 2006, 2009, 2010; Ishidao et al. 2002; Jones and Walsh 1979; Valentine et al. 2007). *In vitro* dermal absorption characteristics have been measured in studies with human skin samples (Frasch et al. 2011). 1-Bromopropane is not expected to accumulate in tissues due to efficient processes leading to exhalation of parent material or metabolically produced CO<sub>2</sub> and urinary excretion of oxygenated and conjugated metabolites (Garner and Yu 2014; Garner et al. 2006, 2007; Ishidao et al. 2002; Jones and Walsh 1979). Metabolism of 1-bromopropane in mammals is complex, involving initial competing conjugation or oxidation steps, followed by subsequent conjugation, oxidation, or rearrangement steps. Most urinary and exhaled metabolic products are debrominated leading to elevated levels of bromide ion in blood and urine (Hanley et al. 2006, 2009, 2010; Garner and Yu 2014; Garner et al. 2006, 2007; Ishidao et al. 2002; Valentine et al. 2007). Oxidation steps are mediated by CYP2E1 and other, as yet unspecified, CYP oxygenases; reduced glutathione is the principal conjugating molecule for the parent compound, as well as for proposed oxygenated brominated intermediate metabolites (Garner et al. 2006, 2007; Jones and Walsh 1979).

**Comparative Toxicokinetics.** Metabolic disposition and toxicokinetic studies have found differences between mice and rats that reflect higher capacity for oxidative metabolism of 1-bromopropane in mice than rats (Garner and Yu 2014; Garner et al. 2006, 2007). In rats given nominal single intravenous doses of 5, 20, or 100 mg 1-bromopropane/kg, the percentage dose exhaled as metabolized CO<sub>2</sub> or excreted as oxygenated metabolites in urine decreased with increasing dose, whereas the percentage dose excreted in urine as metabolites from the glutathione conjugation pathway and the



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percentage dose exhaled as parent material increased with increasing dose (Garner et al. 2006). In mice, the percentage dose exhaled as metabolized CO<sub>2</sub> did not decrease with increasing dose to the same degree as in rats, and the percentage dose exhaled as parent material did not significantly change with increasing dose (Garner et al. 2006, 2007). Additional research may increase understanding of how these species differences in metabolism and toxicokinetics may be related to species differences in the sensitivity to 1-bromopropane-induced toxicity. A PBPK model for 1-bromopropane in F-344 rats was developed (Garner et al. 2015). The model examined two metabolic assumptions for gas uptake in inhalation studies. Experiments are being conducted to further develop the model by including the compartments of the metabolites of 1-bromopropane in order to help with quantitative extrapolation of animal studies to humans (Garner et al. 2015).

**Methods for Reducing Toxic Effects.** Oxygen therapy and positive-pressure ventilation may be useful following inhalation exposure to 1-bromopropane to promote the loss of unmetabolized 1-bromopropane from the lungs (Currance et al. 2007; HSBD 2014). Washing of 1-bromopropane from exposed body surfaces is beneficial. In cases of ingestion of isolated hydrocarbons, the use of activated charcoal to reduce gastrointestinal absorption is generally not recommended (Gummin 2015; Thompson 2014); however, its use may be justified in patients with mixed overdoses (Gummin 2015). Other than these general guidelines, there is very little information available on methods of mitigating the toxic effects of 1-bromopropane. Additional data on the outcome of emergency response procedures would be beneficial. Further research assessing the efficacy of antioxidants and compounds that increase glutathione levels, thus preventing the formation of hepatotoxic intermediates or metabolites that affect sperm parameters, would be valuable. Studies of the benefit of diet, ethanol absence, and controlled exposure to prescription or nonprescription drugs on blood levels of 1-bromopropane and its metabolites could provide information that would be helpful in understanding the impact of these factors on the risks from occupational exposure.

**Children's Susceptibility.** Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

The health effects of 1-bromopropane exposure in children are unknown; however, the nervous system is expected to be a target based on findings in adults. Because the nervous system is still developing in children, they might be more susceptible to 1-bromopropane toxicity than adults if exposure to 1-bromo-

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propane were to occur. However, since exposure to 1-bromopropane occurs mainly in occupational settings, children are not expected to experience exposures to 1-bromopropane.

Fetuses and infants may potentially be exposed to 1-bromopropane through their mothers; however, there are no human studies that evaluated effects in offspring of mothers exposed to 1-bromopropane during pregnancy and/or lactation. Studies evaluating placental or lactation transfer of 1-bromopropane would be useful for determining the potential risk to developing offspring. Limited information from a 1-generation study in rats indicates that there is a potential for alterations in growth and maturity of offspring following gestational and lactation exposure to 1-bromopropane vapors (Furuhashi et al. 2006). Guideline developmental toxicity studies would be useful to better characterize the potential developmental toxicity of 1-bromopropane.

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

#### **3.12.3 Ongoing Studies**

No ongoing studies pertaining to 1-bromopropane have been identified (RePORTER 2014).

## **4. CHEMICAL AND PHYSICAL INFORMATION**

### **4.1 CHEMICAL IDENTITY**

Information regarding the chemical identity of 1-bromopropane is provided in Table 4-1.

Commercial 1-bromopropane has been reported to be 99% pure (ACGIH 2014). 1-Bromopropane used as a commercial solvent blend is formulated to improve performance and inhibit decomposition, including stabilization to prevent hydrolysis (NTP 2011) and is between 85 and 99% pure (UNEP 2001).

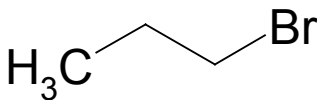
2-Bromopropane is present as a contaminant at 0.1–0.2% (OSHA 1999).

### **4.2 PHYSICAL AND CHEMICAL PROPERTIES**

Information regarding the physical and chemical properties of 1-bromopropane is provided in Table 4-2.

## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-1. Chemical Identity of 1-Bromopropane<sup>a</sup>**

Characteristic	Information
Chemical name	1-Bromopropane
Synonym(s)	Propane, 1-bromo-; propyl bromide; n-propyl bromide; 1-BP
Registered trade name(s)	Abzol; Ensolv; Solvon; Ensolv-NDI; Whisper Spray; Soft Seam <sup>b</sup>
Chemical formula	C <sub>3</sub> H <sub>7</sub> Br
Chemical structure	
Identification numbers:	
CAS Registry	106-94-5
NIOSH RTECS	TX4110000 <sup>c</sup>
EPA Hazardous Waste	No data
OHM/TADS	No data
DOT/UN/NA/IMDG	UN 2344; IMO 3
HSDB	1068
NCI	No data

<sup>a</sup>All information obtained from HSDB (2013), unless otherwise noted.<sup>b</sup>EPA 2007c.<sup>c</sup>RTECS 2009.

CAS = Chemical Abstracts Services; CIS = Chemical Information System; DOT/UN/NA/IMDG = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substance 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

## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-2. Physical and Chemical Properties of 1-Bromopropane<sup>a</sup>**

Property	
Molecular weight (g/mol)	122.99
Color	Colorless
Physical state	Liquid
Melting point	-110°C
Boiling point	71°C
Density: at 20°C/20°C	1.353
Odor	Sweet
Odor threshold:	
Water	No data
Air	No data
Taste	No data
Solubility:	
Water at 20°C	2.45x10 <sup>3</sup> mg/L
Other solvents	Soluble in acetone, ethanol, ether, benzene, chloroform, carbon tetrachloride
Partition coefficients:	
Log K <sub>ow</sub>	2.10
Log K <sub>oc</sub>	40 (estimated)
Vapor pressure at 20°C	110.8 mm Hg
OH radical rate constant at 25°C	1.18×10 <sup>-12</sup> cm <sup>3</sup> /molecules-second <sup>b</sup>
Henry's law constant at 20°C	7.3×10 <sup>-3</sup> atm-m <sup>3</sup> /mol (estimated)
Autoignition temperature	490°C
Flashpoint	21°C <sup>c</sup>
Flammability limits at 25°C	No data
Incompatibilities	Strong oxidants; strong bases
Conversion factors (25°C and 1 atm)	1 mg/L=198.8 ppm; 1 ppm=5.03 mg/m <sup>3</sup>
Explosive limits	LEL=4.6%

<sup>a</sup>All information obtained from HSDB (2013), unless otherwise noted.<sup>b</sup>Donaghy et al. (1993)<sup>c</sup>Alfa Aesar (2014)

## 4. CHEMICAL AND PHYSICAL INFORMATION

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

### 5.1 PRODUCTION

1-Bromopropane is primarily produced by reacting propanol with an excess of hydrogen bromide gas. Small amounts of 2-bromopropane are produced as a byproduct. There are various modifications to the production method that increase the purity of the 1-bromopropane product, as well as distillation procedures to remove byproducts (NTP 2011).

Another production method is dehydration of propanol with bromine or hydrogen bromide in the presence of a sulfur catalyst (NTP 2003).

In 2012, 1-bromopropane was reported to be manufactured by at least 21 companies globally, including at least 1 in the United States (NTP 2013).

Worldwide annual production capacity of 1-bromopropane was estimated to be >20,000 metric tons (mt) in 2006. The same year, U.S. production was estimated to be about 5,000 mt and growing by 15–20% per year (NTP 2011). The non-confidential 2012 Chemical Data Reporting (CDR) database listed the U.S. national production volume as 15,348,727 lb/year (6,962 mt/year) (HSDB 2013).

It was estimated that in 2000, 2001, and 2002, the global sales and emissions of 1-bromopropane for solvent and adhesive applications were 4,839, 3,152, and 3,736 mt, respectively. In 2003, the estimation of use and emissions was 5,000–10,000 mt (NTP 2003).

As of November 23, 2015, the EPA published a final rule adding 1-bromopropane to the TRI list of reportable chemicals (EPA 2015). Under this rule, facilities that manufacture or process 1-bromopropane are required to report release and waste management data under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 2005). This rule applies to the reporting year beginning January 1, 2016, and facility reports are due on July 1, 2017 (EPA 2015). It is estimated that 140 facilities will be required to report release and waste management data (EPA 2015).

Available data on the release and environmental fate of 1-bromopropane can be found in Sections 6.2 and 6.3.

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

**5.2 IMPORT/EXPORT**

It was reported that the U.S. imported 2.8 million pounds (1,270 mt) of 1-bromopropane in 2000 (NTP 2003). In 2007 and 2011, U.S. imports were reported as 10.9 and 10.3 million pounds (4,944 and 4,672 mt), respectively; however, this amount was for brominated derivatives of acyclic hydrocarbons and included other chemicals in addition to 1-bromopropane.

In 2007 and 2011, U.S. exports were reported as 8.8 and 15.1 million pounds (3,992 and 6,849 mt), respectively; however, this amount was for brominated derivatives of acyclic hydrocarbons and included other chemicals in addition to 1-bromopropane (NTP 2013).

**5.3 USE**

1-Bromopropane was originally used as an intermediate in the early to mid-1990s, primarily in the production of pesticides, flavors and fragrances, pharmaceuticals, and other chemicals. In the mid to late-1990s, methylene chloride, used in emissive applications such as degreasing operations and cleaning of electronics and metals, was determined to be toxic to workers, so 1-bromopropane was introduced as a less toxic replacement for these applications. 1-Bromopropane is often used as a vapor due to its relatively high vapor pressure. Aerosol-applied adhesives containing 1-bromopropane have been used extensively in the foam fabricating industry (NTP 2011).

In the last decade, the use of 1-bromopropane in industry has increased due to new applications as an alternative to ozone-depleting substances (ODS) and possible carcinogens. For example, the dry cleaning industry started using 1-bromopropane as a substitute for tetrachloroethylene, in response to states pursuing to ban the suspected carcinogen (NTP 2013). Also, 1-bromopropane was reviewed through the U.S. EPA's Significant New Alternatives Policy (SNAP) program that identifies substitutes for ODSs, such as hydrochlorofluorocarbons (EPA 2007c). Due to increased application of 1-bromopropane, exposure to workers has been increasing, which has caused some human health concern, such as neurological alterations and reproductive toxicity. Therefore, its use in certain industries is being reevaluated (NTP 2013). In 2007, the U.S. EPA proposed to allow the use of 1-bromopropane as an alternative to CFC-113, HCFC-141b, and methyl chloroform in some, but not all, end uses. The decision found 1-bromopropane to be an acceptable substitute in metals, electronics, and precision cleaning and acceptable subject to use conditions as a coating, but not as an aerosol solvent or adhesive carrier solvent due to the exposure potential and health risks to workers (EPA 2007c). It has also been reported that at least three manufacturers are limiting or eliminating use of 1-bromopropane for solvent applications (NTP



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

2003). In 2013, OSHA issued a hazard alert for 1-bromopropane suggesting that the most effective way to reduce worker exposure is by eliminating or substituting 1-bromopropane (OSHA 2014). In addition, in 2014, ACGIH significantly lowered the TLV-TWA for 1-bromopropane, from 10 to 0.1 ppm and also reclassified it as a confirmed animal carcinogen (USAPHC 2014). In 2016, EPA developed a Toxic Substances Control Act (TSCA) Work Plan Chemical risk assessment for 1-bromopropane in order to assess the uses with significant potential for exposure, and based on the findings, may bring about risk reduction actions (EPA 2016). Due to these new threshold values and hazard alerts, 1-bromopropane may no longer be a viable option for use in some industry applications, such as vapor degreasing, and therefore, the occupational use of 1-bromopropane may decrease in the future.

The EPA (2014e) indicated that some consumer products may contain 1-bromopropane, including aerosol cleaning products, spot cleaners, and arts and craft spray glues. However, no consumer products were identified as containing 1-bromopropane in the U.S. Department of Health and Human Services (DHHS) household database (DHHS 2016).

#### 5.4 DISPOSAL

Disposal of the chemical must take into consideration the material's impact on air quality, its potential migration to groundwater, its effect on biological species, and must follow disposal regulations (HSDB 2013). Because of its propensity to volatilize, most disposal is by release to the atmosphere. Disposal of liquid or solid wastes that contain 1-bromopropane is regulated by federal restrictions that apply to hazardous substances (see Chapter 8).

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

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## 6. POTENTIAL FOR HUMAN EXPOSURE

### 6.1 OVERVIEW

1-Bromopropane has not been identified in any of the 1,832 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2015).

1-Bromopropane is a solvent widely used in commercial applications, such as adhesive sprays, degreasing operations for cleaning metals, plastics, and electronic components, dry cleaning, asphalt production, aircraft maintenance, and synthetic fiber manufacturing (Chalupka 2014). Almost all of the potential exposure to 1-bromopropane is associated with its production and use. Individuals living in close proximity to facilities that use aerosol products containing 1-bromopropane may be exposed via inhalation of ambient air (Blando et al. 2010; NTP 2011, 2016).

The dominant process affecting the overall environmental fate and transport of 1-bromopropane is volatilization. In water, estimated volatilization half-lives for a model river and a model lake were reported as 1.2 hours and 4.4 days, respectively (EPIWIN 2012). 1-Bromopropane in air will be degraded by photochemically produced hydroxyl radicals, with a half-life of 14 days (Donaghy et al. 1993). Hydrolysis and biodegradation by microorganisms have also been shown to break down 1-bromopropane in aquatic and terrestrial environments (Janssen et al. 1987; Mabey and Mill 1978; NITE 2010). 1-Bromopropane is not expected to bioaccumulate in aquatic organisms (EPIWIN 2012).

### 6.2 RELEASES TO THE ENVIRONMENT

As of November 23, 2015, the EPA published a final rule adding 1-bromopropane to the TRI list of reportable chemicals (EPA 2015). Under this rule, facilities that manufacture or process 1-bromopropane are required to report release and waste management data under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 2005). This rule applies to the reporting year beginning January 1, 2016, and facility reports are due on July 1, 2017 (EPA 2015).

The use of 1-bromopropane in commercial and industrial applications, such as vapor and immersion degreasing, adhesive sprays, dry cleaning, and solvent sprays, may result in its release to the environment (Chalupka 2014).

## 6. POTENTIAL FOR HUMAN EXPOSURE

**6.2.1 Air**

Since 1-bromopropane is volatile and is used as a vapor in emissive applications (NTP 2011), most environmental releases are into the air. No data regarding the amount of 1-bromopropane released to air could be located in the available literature.

There is no information on releases of 1-bromopropane to the atmosphere from manufacturing and processing facilities at this time; however, facility reports are due July 1, 2017 (EPA 2015).

**6.2.2 Water**

Schwarzenbach et al. (1985) reported on the investigation of groundwater contamination caused by a leaking waste water tank at an alkyl halides chemical plant in Switzerland where 1-bromopropane was manufactured at >5 tons/year. No 1-bromopropane could be detected in groundwater 7 years after the termination of plant operations and an extensive area cleanup, most likely due to hydrolysis.

It was reported that 1-bromopropane may be transported from macroalgae that produce 1-bromopropane as a product of fatty acid hydrolysis to the marine environment (Gschwend et al. 1985).

No other data regarding the amount of 1-bromopropane released to water could be located in the available literature.

There is no information on releases of 1-bromopropane to the water from manufacturing and processing facilities at this time; however, facility reports are due July 1, 2017 (EPA 2015).

**6.2.3 Soil**

No data regarding the amount of 1-bromopropane released to soil could be located in the available literature.

There is no information on releases of 1-bromopropane to the soil from manufacturing and processing facilities at this time; however, facility reports are due July 1, 2017 (EPA 2015).

## 6. POTENTIAL FOR HUMAN EXPOSURE

**6.3 ENVIRONMENTAL FATE****6.3.1 Transport and Partitioning**

Due to its volatility, 1-bromopropane released to the environment is expected to partition mostly to air. Based on the vapor pressure of 1-bromopropane (see Table 4-2), when released to the atmosphere, it would be expected to exist in the vapor phase (Bidleman 1988).

1-Bromopropane released to water will primarily volatilize based on its estimated Henry's Law constant (see Table 4-2). Estimated volatilization half-lives for a model river and a model lake were reported as 1.2 hours and 4.4 days, respectively (EPIWIN 2012). It is not expected to adsorb to suspended soils or sediments based on its estimated organic carbon partition coefficient ( $K_{oc}$ ) of 40, and therefore, leaching to groundwater may occur (EPIWIN 2012).

1-Bromopropane is not expected to bioaccumulate in aquatic organisms. This is based on its estimated bioconcentration factor (BCF) of 11 (EPIWIN 2012). No experimental data on the bioaccumulation of 1-bromopropane in fish could be located in the available literature.

If released to soil, 1-bromopropane is expected to partition primarily to the atmosphere through volatilization based on its vapor pressure (see Table 4-2). It may also be transported to surface water via runoff and to groundwater as a result of leaching. 1-Bromopropane is expected to have very high mobility in soil based on its estimated  $K_{oc}$  (Swann et al. 1983).

**6.3.2 Transformation and Degradation**

1-Bromopropane is subject to a variety of abiotic and biotic degradation processes in all environmental compartments (Belkin 2002; Donaghy et al. 1993; ECHA 2014; Mabey and Mill 1978).

**6.3.2.1 Air**

1-Bromopropane in the atmosphere will be degraded by photochemically produced hydroxyl radicals at a rate that has been measured as  $1.18 \times 10^{-12}$  cm<sup>3</sup>/molecule-second at 25°C (Donaghy et al. 1993). This corresponds to a half-life of 14 days, assuming an atmosphere containing  $5 \times 10^5$  hydroxyl radicals/m<sup>3</sup> at 25°C (Meylan and Howard 1993). The atmospheric lifetime of 1-bromopropane is not largely affected by photolysis (Wuebbles et al. 1998).

## 6. POTENTIAL FOR HUMAN EXPOSURE

**6.3.2.2 Water**

1-Bromopropane released to water may be subject to both abiotic and biotic degradation by microorganisms (Belkin 2001; ECHA 2014; Mabey and Mill 1978).

1-Bromopropane will slowly hydrolyze in water. A neutral first-order hydrolysis rate constant of  $3.01 \times 10^{-7}$ /second was measured at 55°C, corresponding to an aqueous hydrolysis half-life of approximately 26 days (Mabey and Mill 1978). It should be noted that this hydrolysis half-life is longer than the estimated volatilization half-lives from a model river and a model pond (see Section 6.3.1), suggesting that most 1-bromopropane will volatilize before extensive hydrolysis can occur.

1-Bromopropane has been shown to degrade in activated sludge during ready biodegradation tests. At a concentration of 100 mg/L, it degraded 70% after 4 weeks using an activated sludge inoculum at 30 mg/L. However, it was noted that 1-bromopropane was hydrolyzed in the test solution to 1-propanol and bromide ion, and degradation of 1-propanol is what was measured (NITE 2010). In a closed bottle test, 5.6 mg/L of 1-bromopropane biodegraded 19.2% after 28 days using an activated sludge inoculum (ECHA 2014).

Pure culture microorganisms have also been shown to have the potential to biodegrade 1-bromopropane. Degradation of haloalkanes, such as 1-bromopropane, by microorganisms takes place primarily via hydrolytic dehalogenation by enzymes (Belkin 2002). 1-Bromopropane was hydrolytically dehalogenated by *Arthrobacter* HA1 with a specific growth rate of 0.12/hour, a growth yield of 4.0 g protein/molC, and producing 1-propanol as a product (Scholtz et al. 1987). *Acinetobacter* strain GJ70 had a generation time of 7.4 hours when utilizing 1-bromopropane as a carbon source (Janssen et al. 1987). 1-Bromopropane was completely dehalogenated within 6 days when added to a 32 mM culture medium, producing 2.2 mM of the halide. A crude cell extract of strain GJ70 degraded 1-bromopropane to reaction products, 1-propanol and bromide ion. The mechanism for this reaction was reported to be hydrolytic dehalogenation, considering that no aldehydes were produced and no oxygen was consumed (Janssen et al. 1987). *Pseudomonas* strain ES-2, isolated from organobromide-rich industrial wastewater, was shown to organically debrominate 1-bromopropane, but was unable to use it as a carbon source for growth (Shochat et al. 1993).

## 6. POTENTIAL FOR HUMAN EXPOSURE

**6.3.2.3 Sediment and Soil**

Volatilization from moist and dry soil surfaces will be the predominant removal mechanism from these environmental compartments (Lyman et al. 1990). Ready biodegradation tests and pure culture studies (see Section 6.3.2.2) have shown that biodegradation may also be an important fate process for 1-bromopropane.

**6.3.2.4 Other Media**

Information on the transformation or degradation of 1-bromopropane in other media was not found in the available literature.

**6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT**

Reliable evaluation of the potential for human exposure to 1-bromopropane depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of 1-bromopropane in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on 1-bromopropane levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring 1-bromopropane in a variety of environmental media are detailed in Chapter 7.

There are very limited data on the detection of 1-bromopropane in the environment in the available literature.

**6.4.1 Air**

The Air Quality System (AQS) database is EPA's repository of criteria air pollutant and hazardous air pollutants monitoring data. In 2014, the AQS reported only positive detections of 1-bromopropane at one monitoring location. 1-Bromopropane was detected in ambient air of Philadelphia, Pennsylvania at levels of 0.14–0.16 ppb (0.047–0.053 ppbv) (EPA 2014b).

**6.4.2 Water**

No data on monitored levels of 1-bromopropane in water were found in the available literature.

## 6. POTENTIAL FOR HUMAN EXPOSURE

**6.4.3 Sediment and Soil**

No data on monitored levels of 1-bromopropane in soil or sediment were found in the available literature.

**6.4.4 Other Environmental Media**

The EPA (2014e) indicated that some consumer products may contain 1-bromopropane, including aerosol cleaning products, spot cleaners, and arts and craft spray glues, which could result in exposure to the general population; however, no consumer products were identified as containing 1-bromopropane in the U.S. Department of Health and Human Services household database (DHHS 2016). NTP (2016) indicated that no data are available on levels of 1-bromopropane in consumer products.

**6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE**

Exposure of 1-bromopropane to the general population may occur via inhalation of ambient air at locations in close proximity to the emissive use of 1-bromopropane due to potential vapor migration, such as degreasing operations or dry cleaners (Blando et al. 2010; NTP 2011, 2016). Vapor intrusion may also be a potential source of 1-bromopropane exposure, as vapor intrusion has been observed for several volatile organic chemicals (VOCs) with similar properties and overlapping usage (e.g., tetrachloroethylene and dry cleaning) (Blando et al. 2010). However, no information was located specifically evaluating vapor intrusion potential of 1-bromopropane. 1-Bromopropane has not been identified in consumer products (DHHS 2016; NTP 2016).

In NHANES 2011–2012, the distribution of the urinary metabolite of 1-bromopropane, N-acetyl-S-(n-propyl)-L-cysteine, by age, gender, race/ethnicity, and smoking status among 2,328 participants was examined; participants were  $\geq 20$  years of age. Adjusted urinary geometric means of N-acetyl-S-(n-propyl)-L-cysteine were the same in males and females (5.3 ng/mL). Nonsmokers did not have statistically significantly different urinary levels of N-acetyl-S-(n-propyl)-L-cysteine than smokers. Non-Hispanic white subjects (3.9 ng/mL) had significantly lower levels of N-acetyl-S-(n-propyl)-L-cysteine than non-Hispanic black subjects (4.1 ng/mL) and non-Hispanic Asians (7.7 ng/mL). Non-Hispanic black subjects (4.1 ng/mL) had significantly lower levels of urinary N-acetyl-S-(n-propyl)-L-cysteine than Hispanics (6.2 ng/mL) and non-Hispanic Asians (7.7 ng/mL).

In the National Children's Vanguard Study from 2009 to 2010 (Boyle et al. 2016), urinary samples collected from 488 pregnant women during the third trimester from seven locations in the United States



## 6. POTENTIAL FOR HUMAN EXPOSURE

contained N-acetyl-S-(n-propyl)-L-cysteine at a detection frequency of 99%; the median measured concentration was 2.61 ng/mL and the 75<sup>th</sup> percentile value was 9.44 ng/mL.

Biological exposure to the general population and workers can be assessed by measurement of bromide ion, 1-bromopropane, and its metabolite, N-acetyl-S-(n-propyl)-L-cysteine (AcPrCys) in urine or blood (NTP 2013). N-Acetyl-S-(n-propyl)-L-cysteine is expected to be more specific to 1-bromopropane than bromide due to the presence of the bromide ion in foods; however, there have also been concerns regarding the specificity of N-acetyl-S-(n-propyl)-L-cysteine. The ubiquitous nature of N-acetyl-S-(n-propyl)-L-cysteine in the urine of the general population suggests that it may not be a specific biomarker for 1-bromopropane, as general population exposure is expected to be limited. It is unknown if other chemicals and/or endogenous metabolism contributed to the observed urinary levels of N-acetyl-S-(n-propyl)-L-cysteine in biomonitoring studies.

Use of 1-bromopropane in emissive applications can lead to dermal and inhalation exposure of workers (NTP 2011). No data on the contribution of dermal exposure to body burdens could be located, but many studies have assessed personal breathing zone and indoor air concentrations.

Exposure to 24 female and 13 male workers in a 1-bromopropane factory in China was assessed through air, urine, and blood samples (Ichihara et al. 2004a). Mean ambient air concentrations of 1-bromopropane within the factory ranged from 2.1 to 79.7 ppm. Twelve-hour TWA 1-bromopropane breathing zone concentrations for workers ranged from 0.9 to 170.5 ppm. The study found that urinary 1-bromopropane levels directly correlated with individual exposure levels, but serum levels did not, suggesting urine samples may be a better biomarker for exposure. Valentine et al. (2007) studied blood and urine samples from workers and ambient air samples in a Chinese 1-bromopropane production plant in order to support the potential of urinary AcPrCys and globin S-propylcysteine (PrCys) adducts as biomarkers of exposure in humans. It was found that there was a significant increase in globin PrCys adducts on workers' globin (1.52 pmol/mg globin) compared with that of control factory workers (0.11 pmol/mg globin). Also, an increase in urinary AcPrCys levels was directly related to an increase in ambient air exposure levels, which ranged from 0 to 170.54 ppm (Valentine et al. 2007).

Air samples taken at the workplace where furniture foam cushions were manufactured during gluing operations had a mean 1-bromopropane concentration of 130 parts per million by volume (ppmv) (range, 91–176 ppmv) with a 7-hour TWA of 108 ppm (range, 92–127 ppm) (Majersik et al. 2007). Workers who complained of neurological symptoms had serum bromide levels of 44–170 mg/dL. Hanley et al.

## 6. POTENTIAL FOR HUMAN EXPOSURE

(2006) measured urinary bromide and personal breathing zone concentrations of 1-bromopropane during two full-shift days for 30 workers exposed to flexible foam spray adhesives used to construct foam seat cushions. Mean personal breathing zone concentrations were 92 ppm for adhesive sprayers and 11 ppm for other non-sprayer jobs, including glue line leads, sewing machine operators, wrappers, pillow stuffers, and foam and cloth cutters. Complete 48-hour urine samples for adhesive sprayers contained urinary bromide concentrations of 77–542 mg/g creatinine at work, 58–308 mg/g creatinine after work, and 46–672 mg/g creatinine in wake-up samples. Urinary bromide concentrations taken at the beginning of the week for sprayers were significantly higher than for non-spraying workers and unexposed controls, with measured means of 102, 31, and 3.8 mg/g creatinine, respectively (Hanley et al. 2006). In another study assessing the exposure of workers to 1-bromopropane in foam cushion spray adhesives used to construct foam seat cushions, personal breathing zone concentrations, as well as the metabolite, AcPrCys, in 48-hour urine samples from 30 workers and 21 unexposed controls were measured at two factories (Hanley et al. 2009). Full-shift geometric mean TWA personal breathing zone concentrations were reported as 92.4 and 10.5 ppm for sprayers and non-sprayers, respectively. Complete 48-hour urine samples for adhesive sprayers contained AcPrCys concentrations of 9.9–100 mg/g creatinine at work, 17.5–186 mg/g creatinine after work, and 15–184 mg/g creatinine in wake-up samples. Urinary AcPrCys concentrations taken at the beginning of the week for sprayers were significantly higher than for non-spraying workers and unexposed controls, with measured means of 3.2, 0.58, and 0.02 mg/g creatinine, respectively (Hanley et al. 2009).

In 1999 and 2001, NIOSH (2003a) evaluated exposure to 1-bromopropane at a facility that used a spray adhesive containing 1-bromopropane by measuring air and blood samples. The mean full shift personal breathing zone concentration for 16 samples collected in 1999 was 81.2 ppm (range, 18–254 ppm) and for 13 samples collected in 2001 was 45.7 ppm (range, 7–281 ppm). Unexposed workers full-shift personal breathing zone samples collected in 2001 had a mean 1-bromopropane concentration of 1.1 ppm (range, 0.1–4.9 ppm), which shows that 1-bromopropane vapors may migrate from spraying operations to other areas. Blood samples from all workers taken at the end of the week had a mean bromide concentration of 4.8 mg/dL (range, 1.7–43.5 mg/dL), of which exposed workers had a mean concentration of 14.9 mg/dL and unexposed workers had a mean concentration of 2.7 mg/dL. End of the week urine samples for all workers had a mean bromide concentration of 46.5 mg/dL (range, 15–595 mg/dL, of which exposed workers had a mean concentration of 151.8 mg/dL, and unexposed workers had a mean concentration of 28.5 mg/dL).

## 6. POTENTIAL FOR HUMAN EXPOSURE

Breathing zone samples taken at five facilities using 1-bromopropane solvents for vapor degreasing operations had mean full shift (8–10 hours) TWA 1-bromopropane concentrations of 2.6 and 0.31 ppm for workers near degreasers and those remote from degreasers, respectively (Hanley et al. 2010). Urinary metabolites for workers near degreasers were reported at mean bromide and AcPrCys concentrations of 8.9 and 1.3 mg/g creatinine, respectively, while workers remote from degreasers had mean bromide and AcPrCys concentrations of 3.7 and 0.12 mg/g creatinine, respectively (Hanley et al. 2010). In an assessment of a facility using 1-bromopropane in a cold vapor degreaser, the full shift time weighted average 1-bromopropane personal breathing zone concentrations for 20 remote workers ranged from 0.01 to 0.63 ppm, while two short-term task-based measurements from employees using the degreaser were 2.3 and 8.4 ppm (NIOSH 2001). The highest ambient air concentration in the facility collected during one area air sampling event was found in the degreaser room, which had 1-bromopropane concentrations of 4.42 ppm at the degreaser and 1.7 ppm at an area 5 feet from the degreaser.

In an investigation of potential exposure to 1-bromopropane among dry cleaners in New Jersey by measuring personal breathing zone and indoor air samples, the highest exposure measured for a dry cleaning machine operator was 54.55 ppmv as an 8-hour TWA, and the highest exposure for a clerk was 21.85 ppmv as an 8-hour TWA. Indoor air samples taken continuously for the time period dry cleaning work was being performed had measured average 1-bromopropane air concentrations ranging from not detected to 35.12 ppmv. This study found that the highest exposures to dry cleaning workers may occur during the addition of 1-bromopropane to the machines, during machine maintenance, unloading and sorting the cleaned clothes, when interrupting the wash cycle, and possible leaks from the machine (Blando et al. 2010). In 2008, NIOSH conducted an evaluation of the use of 1-bromopropane in four dry cleaning facilities in New Jersey (NIOSH 2010). Personal breathing zone air concentrations of 40 ppm for the machine operator and 17 ppm for the cashier during full shift sampling conducted at one of the facilities were reported. At the other three facilities, personal breathing zone concentrations in partial shift samples ranged from 1.5 to 160 ppm.

## 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 Section 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

## 6. POTENTIAL FOR HUMAN EXPOSURE

larger skin surface in proportion to their body volume than adults. 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 may spend more time outdoors. Children also are generally closer to the ground and have not yet developed the adult capacity to judge and take actions to avoid hazards (NRC 1993).

The general population may be exposed to 1-bromopropane in air when it is used during aerosol applications due to potential vapor migration, particularly at locations in close proximity to the emissive use of 1-bromopropane (NTP 2011). No studies on exposures specific to children could be located in the available literature.

Evaluation of 417 children, 6–11 years of age, also participants in the NHANES 2011–2012 study examining the distribution of the urinary metabolite of 1-bromopropane, N-acetyl-S-(n-propyl)-L-cysteine, among the general population, showed measured mean concentrations of 2.6 ng/mL in males and 3.3 ng/mL in females (Jain 2015b). Non-Hispanic Asian children had the highest urinary levels of N-acetyl-S-(n-propyl)-L-cysteine (5.0 ng/mL) followed by non-Hispanic black children (3.4 ng/mL), non-Hispanic white children (2.4 ng/mL), and Hispanic children (2.1 ng/mL). Children had significantly lower levels of urinary N-acetyl-S-(n-propyl)-L-cysteine than nonsmoking adults (3.4 versus 5.7 ng/mL).

## 6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Exposure to 1-bromopropane occurs mainly in occupational settings. Workers may be exposed by inhalation of vapors or spray mists or by dermal absorption. Workers involved in the production of 1-bromopropane, as well as those using it in commercial applications, such as adhesive sprays, degreasing operations for cleaning metals, plastics, and electronic components, dry cleaning, asphalt production, aircraft maintenance, and synthetic fiber manufacturing, have potential for high dose exposures (Chalupka 2014).

## 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 1-bromopropane is available. Where adequate information

## 6. POTENTIAL FOR HUMAN EXPOSURE

is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1-bromopropane.

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-chemical properties of 1-bromopropane are provided in Chapter 4. Important properties such as melting point, boiling point, vapor pressure, water solubility, and octanol/water partition coefficient are available. No data needs are identified.

**Production, Import/Export, Use, Release, and Disposal.** No information is available in the TRI database on facilities that manufacture or process 1-bromopropane because this chemical is not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 2005). However, as of November 23, 2015, the EPA published a final rule adding 1-bromopropane to the TRI list of reportable chemicals (EPA 2015). This rule applies to the reporting year beginning January 1, 2016, and facility reports are due on July 1, 2017 (EPA 2015). It is estimated that 140 facilities will be required to report release and waste management data (EPA 2015).

Production, use, and import/export data are available (NTP 2003, 2011, 2013). Continuously updated information regarding these quantities is necessary. Information regarding use in consumer products, if any, would be useful. The identification of stabilizers and additives used in commercial grades of 1-bromopropane would be useful in determining potential health effects.

**Environmental Fate.** The environmental fate and transport of 1-bromopropane is well understood. Volatilization is the dominant process affecting the overall fate and transport. Additional studies on the rate of volatilization, rate of hydrolysis, and bioaccumulation potential would be useful.

## 6. POTENTIAL FOR HUMAN EXPOSURE

**Bioavailability from Environmental Media.** 1-Bromopropane is expected to volatilize and hydrolyze in water and is not frequently detected in ambient air, so bioavailability from environmental media is expected to be low. No data needs are identified.

**Food Chain Bioaccumulation.** Due to the low bioavailability of 1-bromopropane, it is not expected to bioaccumulate. Measured BCF data would be useful in determining the actual bioaccumulation potential in the food chain.

**Exposure Levels in Environmental Media.** Reliable monitoring data for the levels of 1-bromopropane in contaminated media at hazardous waste sites are needed so that the information obtained on levels of 1-bromopropane in the environment can be used in combination with the known body burden of 1-bromopropane to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

**Exposure Levels in Humans.** Additional studies on levels of 1-bromopropane in the general environment would be useful in determining the exposure to the general public (NTP 2003). Environmental levels in indoor air due to use of consumer products containing 1-bromopropane would be particularly useful (EPA 2016). No measured data were located on levels of 1-bromopropane found in food, consumer products, or non-occupational exposures (NTP 2016). As there is potential for exposure to the general population through the use of at home consumer products, monitoring data on these products would be useful in determining exposure levels to the general public (EPA 2016).

Studies assessing the contribution of dermal contact to exposure of workers would be useful (NTP 2003). Additional research to better understand the potential exposure of the general public living or working in close proximity to dry cleaners that may vent 1-bromopropane vapors would be useful in assessing risk to these populations (Blando et al. 2010).

This information is necessary for assessing the need to conduct health studies on these populations.

**Exposures of Children.** Studies assessing the exposure of children due to their proximity to commercial uses of 1-bromopropane would be helpful in assessing their overall exposure risk. Specifically, monitoring data determining the exposure to children through the use of at home consumer products containing 1-bromopropane would be useful.

## 6. POTENTIAL FOR HUMAN EXPOSURE

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

**Exposure Registries.** No exposure registries for 1-bromopropane were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

### 6.8.2 Ongoing Studies

No ongoing studies were located for 1-bromopropane.

## 6. POTENTIAL FOR HUMAN EXPOSURE

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## 7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring 1-bromopropane, its metabolites, and other biomarkers of exposure and effect to 1-bromopropane. 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.

### 7.1 BIOLOGICAL MATERIALS

Table 7-1 lists the methods used for determining 1-bromopropane in biological materials. Biological exposure to the general population and workers can be assessed by measurement of bromide ion, 1-bromopropane, and its metabolite, N-acetyl-S-(n-propyl)-L-cysteine (AcPrCys), in urine or blood (NTP 2013). Direct analysis of 1-bromopropane in urine samples by gas chromatography (GC) equipped with an electron capture detector (ECD) was accomplished at a detection limit of 2 ng/mL (B'hymer and Cheever 2005).

The longer physiological half-lives of the metabolites of volatile organic compounds, such as those of 1-bromopropane, in urine compared to blood give monitoring urinary metabolites an advantage over blood sampling (Alwis et al. 2012). One method to measure the urinary metabolite of 1-bromopropane, AcPrCys, involves ultra-high performance liquid chromatography (UPLC) with electrospray ionization tandem mass spectrometry (ESI/MS/MS). Sample preparation involved collection of urine, where a 1.8 mL aliquot was stored at -70°C until the time of the assay. When assayed, the samples were diluted 1:10 with 425 µL of 15 mM ammonium acetate (pH 6.8), followed by washing with acetonitrile to obtain a mobile phase for detection. The limit of detection was reported to be 1.2 ng/mL (Alwis et al. 2012). Another method to measure the urinary metabolite, AcPrCys, involves solid-phase extraction (SPE) from urine samples by washing with a 40:60 solution of methanol and water followed by elution with acetone

## 7. ANALYTICAL METHODS

**Table 7-1. Analytical Methods for Determining 1-Bromopropane in Biological Samples**

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	50 µL urine diluted with 425 µL 15 mM ammonium acetate pH 6.8; washed with acetonitrile solvent to create mobile phase; analysis for AcPrCys	UPLC-ESI/MS/MS	1.2 ng/mL (AcPrCys)	95 (mean)	Alwis et al. 2012
Urine	Urine samples diluted with water (1:4) and fortification with 1-bromobutane, which was used as an internal standard; each sample then sealed in a headspace vial and placed in the analyzer	GC/ECD	2 ng/mL	104–121	B'hymer and Cheever 2005
Urine	Urine sample was extracted 4 times with 4.0 mL of ethyl acetate using a vortex mixer for 1 minute for each extraction; analysis for metabolite, 3-BPA	GC/MSD	0.01 µg/mL (3-BPA)	93–98	B'hymer and Cheever 2004
Urine	Urine sample extracted by SPE; washed with 40% methanol/60% water followed by elution with acetone; analysis for AcPrCys	HPLC/MS	0.01 µg/mL (AcPrCys)	96–103	Cheever et al. 2009
Urine	SPE of urine samples with addition of 1 mL ammonium formate buffer (50 mmol/L, pH 2.5) and 40 µL formic acid; sample vortex-mixed and centrifuged	LC/MS	2.0 µg/mL (PrMA)	99.5	Eckert and Goen 2014
Blood	Blood collected from laboratory animals by cardiac puncture using a heparinized syringe; plasma separated by centrifugation at 4°C and stored at -80°C until analysis	GC/MS	No data	No data	Ishidao et al. 2002

3-BPA = 3-bromopropionic acid; AcPrCys = N-acetyl-S-(n-propyl)L-cysteine; ECD = electron capture detector; ESI = electrospray ionization; GC = gas chromatography; HPLC = high-performance liquid chromatography; LC = liquid chromatography; MS = mass spectrometry; MSD = mass selective detector; PrMA = n-propyl mercapturic acid; SPE = solid phase extraction; UPLC = ultra high performance liquid chromatography

## 7. ANALYTICAL METHODS

and analysis using high performance liquid chromatography (HPLC) and mass spectrometry (MS) (Cheever et al. 2009). 3-Bromopropionic acid (3-BPA) is also a metabolic product of 1-bromopropane in human urine. B'hymer and Cheever (2004) discuss a GC method to quantify this metabolite in human urine. A method for the simultaneous determination of four short-chain alkyl mercapturic acids, including 1-bromopropane metabolite n-propyl mercapturic acid (PrMA), in human urine by SPE and detection by column-switching liquid chromatography and MS/MS has been discussed (Eckert and Goen 2014).

## 7.2 ENVIRONMENTAL SAMPLES

Table 7-2 lists the methods used for determining 1-bromopropane in environmental samples. Due to its volatility, 1-bromopropane released to the environment is expected to partition mostly to air (HSDB 2013).

The principal separation and detection methods for 1-bromopropane in air samples include GC in conjunction with flame ionization detection (FID). NIOSH Method 1025 and OSHA Method PV2061 have both been fully validated for use in occupational settings where regulatory exposure limits are of concern (NIOSH 2003b; OSHA 1999). Both of these methods draw air samples through a solid coconut shell charcoal (CSC) sorbent tube. The sample is then desorbed with carbon disulfide or a 99/1 (v/v) carbon disulfide/dimethylformamide mixture followed by GS/FID analysis. The limit of detection for NIOSH Method 1025 is 1.0 µg/sample, while the detection limit for OSHA Method PV2061 is reported as 0.007 ppm (0.037 mg/m<sup>3</sup>) at a 12-L air volume using a sampling rate of 0.1 L per minute.

## 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 1-bromopropane is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 1-bromopropane.

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

## 7. ANALYTICAL METHODS

**Table 7-2. Analytical Methods for Determining 1-Bromopropane in Environmental Samples**

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Air drawn through a solid sorbent tube lined with Anasorb CSC; desorbed with addition of 1.0 mL of carbon disulfide for 30 minutes	GC/FID (Method 1025)	1.0 µg/sample	96.8 (RSD= 0.015)	NIOSH 2003b
Air	Air drawn through CSC tube; desorbed with a mixture of 99/1 (v/v) carbon disulfide/dimethylformamide	GC/FID (Method PV2061)	0.007 ppm (0.037 mg/m <sup>3</sup> )	97.5	OSHA 1999
Air	Air sampled at 530 mL/minute to lithium ionization chamber	SCF/MS	52 pptv	No data	Fujii 1992

CSC = coconut shell charcoal; FID = flame ionization detector; GC = gas chromatography; MS = mass spectrometry; RSD = relative standard deviation; SCF = super critical fluid chromatography

## 7. ANALYTICAL METHODS

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.** Exposure to 1-bromopropane is typically assessed by measuring its metabolites such as AcPrCys, 1-bromopropionic acid, or released bromine in urine or blood (NTP 2013). Field studies indicated that urinary levels of N-acetyl-S-(n-propyl)-L-cysteine and bromide were significantly correlated with 8–12-hour TWA breathing zone air concentrations of 1-bromopropane in several groups of workers (Hanley et al. 2006, 2009, 2010). Methods of determining biomarkers of exposure are well characterized by urine analysis. Additional studies on the direct detection of 1-bromopropane biomarkers in human blood would be useful in determining exposure.

**Effect.** There are no specific biomarkers to characterize effects caused by 1-bromopropane. Nervous system effects caused by inhalation of 1-bromopropane can be caused by many other substances as well. See Section 3.8.2 for more details. Identification and additional studies of specific biomarkers would be useful in characterizing the effects caused by 1-bromopropane.

#### Methods for Determining Parent Compounds and Degradation Products in Environmental

**Media.** Human exposure to 1-bromopropane may occur through inhalation of ambient air and dermal uptake through occupational contact and consumer products containing 1-bromopropane. Methods have been reported for the detection of 1-bromopropane in air. The methods of NIOSH (2003b) (LOD 1.0 µg/sample) and OSHA (1999) (LOD 0.007 ppm [0.037 mg/m<sup>3</sup>]) are adequate for the determination of 1-bromopropane in air. Methods for detection of 1-bromopropane in other environmental media are not needed, as it is rarely found in environmental compartments other than air. Additional studies do not seem necessary at this time.

### 7.3.2 Ongoing Studies

No ongoing studies were located for 1-bromopropane.

## 7. ANALYTICAL METHODS

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## 8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance specific estimates that are intended to serve as screening levels. They are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

ATSDR has derived an acute-duration inhalation MRL of 1 ppm for 1-bromopropane based on a  $BMCL_{1SD}$  of 97.4 ppm for reduced forelimb strength in male rats exposed for 14 days (Honma et al. 2003). The  $BMCL_{1SD}$  was duration adjusted (8/24 hours) to a  $BMCL_{(HEC)}$  of 32.3 ppm and an uncertainty factor of 30 was used (3 for dosimetric adjustment and 10 for human variability).

ATSDR has derived an intermediate-duration inhalation MRL of 0.1 ppm for 1-bromopropane based on a NOAEL of 10 ppm for increased spontaneous locomotor activity in rats (Honma et al. 2003). The NOAEL was duration adjusted (8/24 hours) to a  $NOAEL_{(HEC)}$  of 3.33 ppm and an uncertainty factor of 30 was used (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

ATSDR has derived a chronic-duration inhalation MRL of 0.02 ppm for 1-bromopropane based on a minimal LOAEL of 1.28 ppm for a mild neurological impairment (decreased vibration sense as measured by increased vibration sense threshold) in female 1-bromopropane production workers (Li et al. 2010). The LOAEL was adjusted for continuous exposure (5/7 days x 12/24 hours) to a LOAEL of 0.46 ppm and an uncertainty factor of 30 was used (3 for use of a minimal LOAEL and 10 for human variability).

ATSDR has derived an acute oral MRL of 0.2 mg/kg/day for 1-bromopropane based on a  $BMDL_{1SD}$  of 19.75 mg 1-bromopropane/kg/day for impaired learning and memory in rats exposed via gavage for 12 days (Zhong et al. 2013). An uncertainty factor of 100 was used (10 for extrapolation from animals to humans and 10 for human variability).

IARC and the EPA have not evaluated the carcinogenicity of 1-bromopropane (IARC 2014; IRIS 2014). However, ACGIH has assigned 1-bromopropane a classification of “*A3 – Confirmed animal carcinogen with unknown relevance to humans*” (ACGIH 2014, 2016) and the Department of Health and Human Services has classified 1-bromopropane as “*reasonably anticipated to be a human carcinogen*” (NTP 2016).

## 8. REGULATIONS, ADVISORIES, AND GUIDELINES

OSHA has not set permissible exposure limits (PELs) to protect workers against adverse health effects resulting from exposure to 1-bromopropane (OSHA 2013a, 2013b). ACGIH has recommended a TLV-TWA of 0.1 ppm 1-bromopropane for workers (ACGIH 2014, 2016). No guidelines for worker exposure limits have been recommended by NIOSH (2014). The EPA has not derived RfDs or RfCs for 1-bromopropane.

The World Health Organization (WHO) has not established any air quality guidelines for 1-bromopropane (WHO 2010). 1-Bromopropane is not designated as a hazardous air pollutant, and no acute exposure guidelines (AEGLs) have been derived (EPA 2013a, 2014a). The Department of Energy (DOE) has established values for responding to potential releases of airborne 1-bromopropane for use in community emergency planning. The values established by the DOE (2012) are the Protective Action Criteria (PAC-1, -2, and -3). The PAC-1, -2, and -3 values are 18, 18, and 700 ppm, respectively, represent increasing severity of effects (mild, irreversible, and life threatening, respectively) for a 1-hour exposure (DOE 2012). The American Industrial Hygiene Association (AIHA) has not established Emergency Response Planning Guidelines (ERPGs-1, -2, -3) for 1-bromopropane (AIHA 2014).

WHO has not established any drinking water guidelines for 1-bromopropane (WHO 2011) and the EPA has not set drinking water standards for 1-bromopropane (EPA 2009a, 2009b, 2012, 2013c, 2013d, 2014c). The FDA has not set allowable levels for 1-bromopropane in bottled water (FDA 2013).

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



## 8. REGULATIONS, ADVISORIES, AND GUIDELINES

**Table 8-1. Regulations, Advisories, and Guidelines Applicable to 1-Bromopropane**

Agency	Description	Information	Reference
<u>INTERNATIONAL</u>			
Guidelines:			
IARC	Carcinogenicity classification	No data	IARC 2014
WHO	Air quality guidelines	No data	WHO 2010
	Drinking water quality guidelines	No data	WHO 2011
<u>NATIONAL</u>			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV-TWA	0.1 ppm	ACGIH 2014, 2016
AIHA	ERPGs	No data	AIHA 2014
DOE	PACs		DOE 2012
	PAC-1	18 ppm	
	PAC-2	18 ppm	
	PAC-3	700 ppm	
EPA	AEGLs	No data	EPA 2013a
	Regulated toxic and flammable substances under Section 112(r) of the Clean Air Act	No data	EPA 2013b 40 CFR 68.130
	Hazardous Air Pollutants	No data	EPA 2014a
	NAAQS	No data	EPA 2014b
	Protection of stratospheric ozone – listing of substitutes for ozone-depleting substances		
	In solvent cleaning	Acceptable (final rule)	EPA 2007a 72 FR 30142
	In adhesives and aerosols	Unacceptable (proposed rule)	EPA 2007b 72 FR 30168
	In coatings	Acceptable subject to use conditions (proposed rule)	
	REL	No data	NIOSH 2014
	IDLH	No data	
OSHA	PEL (8-hour TWA) for general industry	No data	OSHA 2013a 29 CFR 1910.1000, Table Z-1
	Highly hazardous chemicals	No data	OSHA 2013b 29 CFR 1910.119, Appendix A

## 8. REGULATIONS, ADVISORIES, AND GUIDELINES

**Table 8-1. Regulations, Advisories, and Guidelines Applicable to 1-Bromopropane**

Agency	Description	Information	Reference
NATIONAL (cont.)			
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	No data	EPA 2013c 40 CFR 116.4
	Drinking water contaminant candidate list	No data	EPA 2009a 74 FR 51850
	Drinking water standards and health advisories	No data	EPA 2012a
	National primary drinking water standards	No data	EPA 2009b
	National recommended water quality criteria	No data	EPA 2014c
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	No data	EPA 2013d 40 CFR 117.3
c. Food			
FDA	Allowable levels for contaminants in bottled water	No data	FDA 2013 21 CFR 165.110
	EAFUS <sup>a</sup>	No data	FDA 2014
d. Other			
ACGIH	Carcinogenicity classification	A3 <sup>b</sup>	ACGIH 2014, 2016
EPA	Carcinogenicity classification	No data	IRIS 2014
	RfC	No data	
	RfD	No data	
	Chemical substances subject to proposed or final TSCA rules or orders	No data	EPA 1998a
	TSCA Work Plan Chemical Risk Assessment	No data	EPA 2016
	Chemicals subject to EPCRA and Section 112(r) of the Clean Air Act	No data	EPA 2006
	Identification and listing of hazardous waste	No data	EPA 2013e 40 CFR 261, Appendix VIII
	Master Testing List	No data	EPA 2014d
	RCRA waste minimization PBT priority chemical list	No data	EPA 1998b 63 FR 60332
	Standards for owners and operators of hazardous waste TSD facilities; groundwater monitoring list	No data	EPA 2013f 40 CFR 264, Appendix IX
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance and reportable quantity	No data	EPA 2013g 40 CFR 302.4

## 8. REGULATIONS, ADVISORIES, AND GUIDELINES

**Table 8-1. Regulations, Advisories, and Guidelines Applicable to 1-Bromopropane**

Agency	Description	Information	Reference
NATIONAL (cont.)			
	Effective date of toxic chemical release reporting	July 1, 2017	EPA 2013h 40 CFR 372.65; EPA 2015
	Extremely hazardous substances and its threshold planning quantity	No data	EPA 2013i 40 CFR 355, Appendix A
DHHS	Carcinogenicity classification	Reasonably anticipated to be a human carcinogen	NTP 2016

<sup>a</sup>The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.

<sup>b</sup>A3: Confirmed animal carcinogen with unknown relevance to humans.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AEL = acceptable exposure limit; AIHA = American Industrial Hygiene Association; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DHHS = Department of Health and Human Services; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; EPCRA = Emergency Planning and Community Right-To-Know Act; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; FR = Federal Register; GRAS = generally recognized as safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; NAAQS = National Ambient Air Quality Standards; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PBT = persistent, bioaccumulative, and toxic; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral 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

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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 ( $K_d$ )**—The amount of a chemical adsorbed by 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 that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the 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.

## 10. GLOSSARY

**Ceiling Value**—A concentration that must not be exceeded.

**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 of people that 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 risk 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)**—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

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

## 10. GLOSSARY

**Immunological Effects**—Functional changes in the immune response.

**Incidence**—The ratio of new cases 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.

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

**In Vivo**—Occurring within the living organism.

**Lethal Concentration<sub>(LO)</sub> (LC<sub>LO</sub>)**—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

**Lethal Concentration<sub>(50)</sub> (LC<sub>50</sub>)**—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<sub>(LO)</sub> (LD<sub>LO</sub>)**—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<sub>(50)</sub> (LD<sub>50</sub>)**—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

**Lethal Time<sub>(50)</sub> (LT<sub>50</sub>)**—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.

## 10. GLOSSARY

**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 hazardous substance.

**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) that 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 OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

**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) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work 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 (insects or other organisms harmful to cultivated plants or animals).

**Pharmacokinetics**—The dynamic behavior of a material in the body, used to predict 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, whereas 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 that 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.



## 10. GLOSSARY

**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 blood:air 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<sub>1</sub>\***—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q<sub>1</sub>\* 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<sup>3</sup> for air).

**Recommended Exposure Limit (REL)**—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration 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<sup>3</sup> 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 hazardous substance. 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.

## 10. GLOSSARY

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

**Risk Factor**—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, 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 group.

**Short-Term Exposure Limit (STEL)**—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

**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 it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

**Time-Weighted Average (TWA)**—An average exposure within a given time period.

**Toxic Dose<sub>(50)</sub> (TD<sub>50</sub>)**—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 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 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

**Xenobiotic**—Any substance 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 route and 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 substance-induced endpoint 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

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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 100-fold 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 and Human Health Sciences, 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 and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30329-4027.

## APPENDIX A

**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical Name: 1-Bromopropane  
 CAS Numbers: 106-94-5  
 Date: August 2017  
 Profile Status: Final  
 Route: ☒ Inhalation ☐ Oral  
 Duration: ☒ Acute ☐ Intermediate ☐ Chronic  
 Graph Key: 10  
 Species: Rat

Minimal Risk Level: 1 ☐ mg/kg/day ☒ ppm

Reference: Honma T, Suda M, Miyagawa M. 2003. Inhalation of 1-bromopropane causes excitation in the central nervous system of male F344 rats. *Neurotoxicology* 24(4-5):563-575.

Experimental design: The study examined the effects of 1-bromopropane on several neurobehavioral tests conducted in male F-344 rats. Groups of rats were exposed whole-body to 0, 10, 50, 200, or 1,000 ppm 1-bromopropane vapors 8 hours/day, 7 days/week for 3 weeks. All tests were conducted at various times after the 3-week exposure period except for a traction test that was also conducted on exposure days 1, 7, and 14. In the traction test, rats are forced to hang from a horizontal bar with the forelimbs and the time until the rat falls from the bar is recorded. The traction test is used to measure forelimb grip strength. Five rats per group were used in this test.

Effect noted in study and corresponding doses: No statistically significant differences in grip strength were observed between exposed rats and controls on days 1 or 7. On day 14, however, rats exposed to 1,000 ppm 1-bromopropane showed a statistically significant decrease in grip strength compared to lower exposure groups and controls, thus defining NOAEL and LOAEL values of 200 and 1,000 ppm, respectively, for neurological effects in an acute-duration inhalation study. Because all data were presented graphically, the means and standard error (SDs were subsequently calculated) for traction time (assessed on day 14) were extracted digitally using GrabIt! Software (version XP2) (see Table A-1).

**Table A-1. Digitized Dataset for Traction Time in Male F-344 Rats Exposed to Vaporized 1-Bromopropane for 14 Days<sup>a</sup>**

Exposure concentration (ppm)	Number of rats	Traction time (seconds)	Standard deviation
0	5	15.158	9.644
10	5	13.433	6.339
50	5	11.338	3.582
200	5	8.627	5.787
1,000	5	3.204 <sup>b</sup>	2.480

<sup>a</sup>Data extracted from Figure 11 in Honma et al. (2003).

<sup>b</sup>p<0.05.

Dose and end point used for MRL derivation: BMCL<sub>1SD</sub> of 97.50 ppm for neurological effects in male rats.

☐ NOAEL ☐ LOAEL ☒ BMCL<sub>1SD</sub>

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The traction time data were fit to all available continuous models in EPA's Benchmark Dose Software (BMDS, version 2.4.0) using a benchmark response of 1 SD change from control. The following procedure for fitting continuous data was used. The simplest model (linear) was first applied to the data while assuming constant variance. If the data were consistent with the assumption of constant variance ( $p \geq 0.1$ ), then the fit of the linear model to the means was evaluated and the polynomial, power, exponential, and Hill models were fit to the data while assuming constant variance. Adequate model fit was judged by three criteria: goodness-of-fit p-value ( $p > 0.1$ ), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined benchmark response. Among all of the models providing adequate fit to the data, the lowest BMDL (95% lower confidence limit on the BMD) was selected as the POD when the difference between the BMCLs estimated from these models were  $>3$ -fold; otherwise, the BMDL from the model with the lowest Akaike's Information Criterion (AIC) was chosen. If the test for constant variance was negative, the linear model was run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provided an adequate fit ( $p \geq 0.1$ ) to the variance data, then the fit of the linear model to the means was evaluated and the polynomial, power, exponential, and Hill models were fit to the data and evaluated while the variance model was applied. Model fit and POD selection proceeded as described earlier. If the test for constant variance was negative and the nonhomogenous variance model did not provide an adequate fit to the variance data, then the data set was considered unsuitable for modeling.

All but two BMD models provided adequate and nearly equivalent fits (see Table A-2) by the various statistical criteria. Because the BMCL estimates are not sufficiently close, the model with the lowest BMCL (Exponential model 4) was selected. The Exponential model calculates  $BMC_{1SD}$  and  $BMCL_{1SD}$  values of 259.23 and 97.40 ppm, respectively, for decreased traction time (reduced grip strength) on day 14 (see Figure A-1).

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**Table A-2. Model Predictions for Traction Time in Male F-344 Rats Exposed to Vaporized 1-Bromopropane for 14 Days (Honma et al. 2003)**

Model	Test for significant difference p-value <sup>a</sup>	Variance p-value <sup>b</sup>	Means p-value <sup>b</sup>	Scaled residuals <sup>c</sup>			AIC	BMC <sub>1SD</sub> (ppm)	BMCL <sub>1SD</sub> (ppm)
				Dose below BMC	Dose above BMC	Overall largest			
Constant variance									
Linear <sup>d</sup>	0.01	0.04	0.59	-0.89	0.20	-0.89	117.70	ND	ND
Nonconstant variance									
Exponential (model 2) <sup>e</sup>	0.01	0.46	0.51	-0.54	0.17	0.64	112.84	452.29	211.80
Exponential (model 3) <sup>e</sup>	0.01	0.46	0.51	-0.54	0.17	0.64	112.84	452.29	211.80
Exponential (model 4) <sup>e,f</sup>	0.01	0.46	0.45	0.08	0.01	0.36	114.10	259.23	97.40
Exponential (model 5) <sup>e</sup>	0.01	0.46	0.45	0.08	0.01	0.36	114.10	259.22	97.40
Hill <sup>e</sup>									ND
Linear <sup>d</sup>									ND
Polynomial (2-degree) <sup>d</sup>	0.01	0.46	0.34	-0.86	0.06	-0.86	113.85	673.69	461.93
Polynomial (3-degree) <sup>d</sup>	0.01	0.46	0.34	-0.86	0.06	-0.86	113.85	673.69	461.93
Polynomial (4-degree) <sup>d</sup>	0.01	0.46	0.34	-0.86	0.06	-0.86	113.85	673.69	461.93
Power <sup>e</sup>	0.01	0.46	0.34	-0.86	0.06	-0.86	113.85	673.69	461.93

<sup>a</sup>Values >0.05 fail to meet conventional goodness-of-fit criteria.

<sup>b</sup>Values <0.10 fail to meet conventional goodness-of-fit criteria.

<sup>c</sup>Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.

<sup>d</sup>Coefficients restricted to be negative.

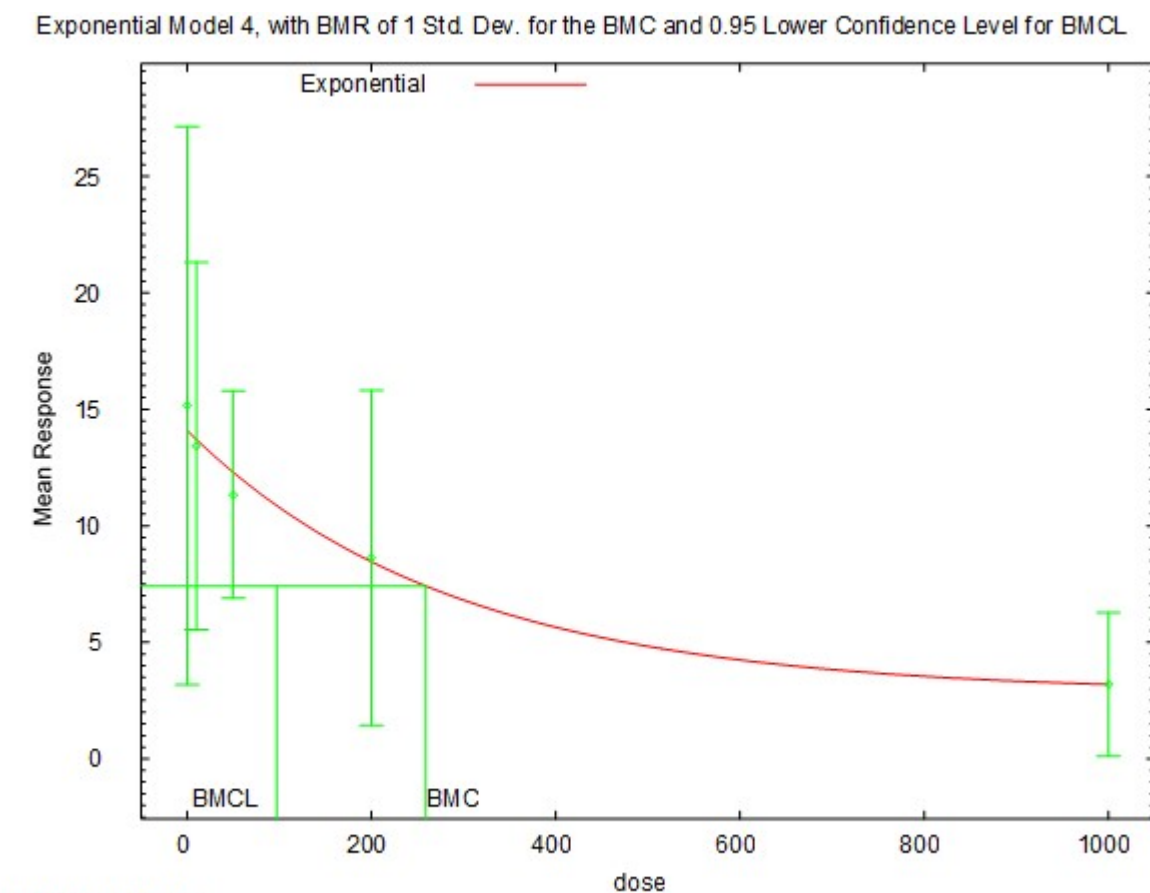
<sup>e</sup>Power restricted to  $\geq 1$ .

<sup>f</sup>Selected model. Constant variance model did not fit variance data, but non-constant variance model did. With non-constant variance model applied all models, except for the Hill and the Linear (BMCL computation failed), provided adequate fit to the variance data. BMCLs for models providing adequate fit were not sufficiently close (differed by >2–3-fold), so the model with the lowest BMCL was selected (Exponential 4 model; the Exponential 5 converged onto the Exponential 4).

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL<sub>1SD</sub> = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., 1SD = exposure concentration associated to a change in the mean response equal to one control standard deviation from the control mean); ND = not determined (BMCL computation failed or the BMC was higher than the highest dose tested)

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**Figure A-1. Selected Model (Exponential Model 4) for Decreased Grip Strength Following Exposure to 1-Bromopropane (Honma et al. 2003)**



Uncertainty Factors used in MRL derivation:

- ☐ 10 for use of a LOAEL
- ☒ 3 for extrapolation from animals to humans with dosimetric adjustment
- ☒ 10 for human variability

$$\text{MRL} = \text{BMCL}_{\text{HEC}} / 30 \text{ (UF)}$$

$$\text{MRL} = 32.3 \text{ ppm} / 30 = 1 \text{ ppm}$$

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

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

$$\text{BMCL}_{1\text{SD}[\text{HEC}]} = \text{BMCL}_{1\text{SD}[\text{ADJ}]} \times (\text{H}_{\text{b/gA}} / \text{H}_{\text{b/gH}})$$



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where:

$$\text{BMCL}_{\text{1SD[ADJ]}} = 97.40 \text{ ppm} \times 8 \text{ hours} / 24 \text{ hours} = 32.3 \text{ ppm}$$

$$H_{\text{b/gA}} = \text{animal blood:air partition coefficient} = 11.7 \text{ (NTP-CERHR 2004)}$$

$$H_{\text{b/gH}} = \text{human blood:air partition coefficient} = 7.08 \text{ (NTP-CERHR 2004)}$$

$$(H_{\text{b/gA}} / H_{\text{b/gH}}) = 11.7 / 7.08 = 1.653$$

Because the ratio of the partition coefficients is  $>1$ , a default value of 1 was used.

$$\text{BMCL}_{\text{[HEC]}} = 32.3 \text{ ppm} \times 1 = 32.3 \text{ ppm}$$

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

Other additional studies or pertinent information that lend support to this MRL: Limited information from a few case studies showed that workers exposed to 1-bromopropane for a few weeks reported subjective symptoms including respiratory irritation, headache, nausea, and lower extremity numbness, pain, and weakness; the geometric mean air concentration was 107 ppm for glue sprayers (range 58–254 ppm) (Raymond and Ford 2007). An acute-inhalation study in rats reported decreased activity and ataxia after single exposures to  $\geq 1,800$  ppm, but not 300 ppm; however, only qualitative data were provided (Kim et al. 1999). Intermediate-duration inhalation studies have shown that concentrations as low as 50 ppm can induce changes in neurobehavior, muscle strength, electrophysiology, morphology, and biochemistry (Fueta et al. 2002; Honma et al. 2003; Ichihara et al. 2000b; Kim et al. 1999; Mohideen et al. 2011, 2013; Subramanian et al. 2012; Ueno et al. 2007; Wang et al. 2002, 2003; Yu et al. 2001).

Agency Contact (Chemical Manager): Nickolette Roney

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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical Name: 1-Bromopropane  
CAS Numbers: 106-94-5  
Date: August 2017  
Profile Status: Final  
Route: ☒ Inhalation ☐ Oral  
Duration: ☐ Acute ☒ Intermediate ☐ Chronic  
Graph Key: 55  
Species: Rat

Minimal Risk Level: 0.1 ☐ mg/kg/day ☒ ppm

Reference: Honma T, Suda M, Miyagawa M. 2003. Inhalation of 1-bromopropane causes excitation in the central nervous system of male F344 rats. *Neurotoxicology* 24(4-5):563-575.

Experimental design: The study examined the effects of 1-bromopropane on several neurobehavioral tests conducted in rats. Tests included locomotor activity, open field behavior, passive avoidance test, water maze test, traction test and rota-rod tests. Body weight and temperature were also monitored. Groups of male F-344 rats (4 per group) were exposed whole-body to 0, 10, 50, 200, or 1,000 ppm 1-bromopropane vapors 8 hours/day, 7 days/week for 3 weeks. All tests were conducted at various times after a 3-week exposure period except for a traction test that was also conducted on exposure days 1, 7, and 14.

Effect noted in study and corresponding doses: Rats in the 1,000 ppm lost weight during the 3-week exposure period. At termination of exposure, body weight in the 1,000 ppm group was about 12% lower than in controls. However, it recovered over the next 25 days. Body temperature also was significantly reduced in 1,000 ppm group, especially during exposure days 1–7, but recovered when exposure ceased. Spontaneous locomotor activity was significantly increased in rats exposed to 50 ppm 1-bromopropane on post-exposure days 1, 2, and 3 and in the group exposed to 200 ppm on post-exposure days 1, 2, 3, and 4 (locomotor activity was not tested in rats exposed to 1,000 ppm 1-bromopropane). The open field test showed that exposure to 1-bromopropane reduced freezing time (all doses, but not significantly), significantly increased ambulation and rearing at 200 ppm, had no significant effect on preening, and significantly reduced defecation/urination at 1,000 ppm. Exposure to 1-bromopropane did not affect passive avoidance behavior. 1-Bromopropane increased latency time in the water maze test in the 1,000 ppm group. In addition, 1-bromopropane at 200 and 1,000 ppm decreased traction performance indicating decreased muscle strength. Performance in the rota-rod test (motor coordination) was not significantly affected. Of all the parameters examined, locomotor activity appeared to be the most sensitive and a NOAEL and LOAEL of 10 ppm and 50 ppm, respectively can be defined based on this test.

Dose and end point used for MRL derivation: NOAEL of 10 ppm for neurological effects in male rats.

☒ NOAEL ☐ LOAEL

The spontaneous locomotor activity results were presented graphically; however, the data were not amenable for extraction using GrabIt! Software (version XP2). Thus, the NOAEL/LOAEL approach was used to identify the POD for the MRL. The data (Figure 3 in the study) are presented as changes in spontaneous locomotor activity relative to pre-exposure levels (assigned as 100% activity) for each day post-exposure that the test was performed (up to 6 days post-exposure). The selection of which post-exposure day (1–6) to model to compare treated and controls would have been entirely arbitrary.

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Uncertainty Factors used in MRL derivation:

- [ ] 10 for use of a LOAEL
- [X] 3 for extrapolation from animals to humans with dosimetric adjustment
- [X] 10 for human variability

$$\text{MRL} = 3.33 \text{ ppm} / 30 (\text{UF}) = 0.1 \text{ ppm}$$

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

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

$$\text{NOAEL}_{[\text{HEC}]} = \text{NOAEL}_{[\text{ADJ}]} \times (\text{H}_{\text{b/gA}} / \text{H}_{\text{b/gH}})$$

where:

$$\text{NOAEL}_{[\text{ADJ}]} = 10 \text{ ppm} \times 8 \text{ hours} / 24 \text{ hours} = 3.33 \text{ ppm}$$

$$\text{H}_{\text{b/gA}} = \text{animal blood:air partition coefficient} = 11.7 \text{ (NTP-CERHR 2004)}$$

$$\text{H}_{\text{b/gH}} = \text{human blood:air partition coefficient} = 7.08 \text{ (NTP-CERHR 2004)}$$

$$(\text{H}_{\text{b/gA}} / \text{H}_{\text{b/gH}}) = 11.7 / 7.08 = 1.653$$

Because the ratio of the partition coefficients is >1, a default value of 1 was used.

$$\text{NOAEL}_{\text{HEC}} = 3.33 \text{ ppm} \times 1 = 3.33 \text{ ppm}$$

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

Other additional studies or pertinent information that lend support to this MRL: No human data suitable for MRL derivation. However, the human data available suggests that the nervous system is a target for 1-bromopropane toxicity. There are two publications of human cases exposed for intermediate durations (from weeks to months) that provide exposure levels. A case discussed by Ichihara et al. (2002) (case 3) was a woman who showed signs of staggering and numbness and paresthesias in the feet, thighs, lower back, and hips, and complained of headaches after 2 months of using 1-bromopropane as a solvent with a spray gun. Estimates of the exposure levels using a passive sampler indicated that the daily TWA concentration ranged from 60 to 261 ppm with an average of  $133 \pm 67$  ppm (SD). Raymond and Ford (2007) reported that four workers developed severe ataxia, sensory motor, and cognitive impairments soon after the introduction of 1-bromopropane into their workplace as a furniture adhesive. A survey conducted by NIOSH 9 months after the four workers became ill showed that the workers could have been exposed to a mean concentration of 1-bromopropane of 107 ppm (range 58–254 ppm).

Agency Contact (Chemical Manager): Nickolette Roney

## APPENDIX A

**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical Name: 1-Bromopropane  
CAS Numbers: 106-94-5  
Date: August 2017  
Profile Status: Final  
Route: ☒ Inhalation ☐ Oral  
Duration: ☐ Acute ☐ Intermediate ☒ Chronic  
Graph Key: 89  
Species: Human

Minimal Risk Level: 0.02 ☐ mg/kg/day ☒ ppm

Reference: Li W, Shibata, E, Zhou Z, et al. 2010. Dose-dependent neurologic abnormalities in workers exposed to 1-bromopropane. *J Occup Environ Med* 52(8):769-777.

Experimental design: The study examined the exposure-dependent effects of 1-bromopropane in a population of workers and age-, sex-, and region-matched controls in three 1-bromopropane production plants in China. The purity of the 1-bromopropane manufactured was >96% in one factory and ≥99% in the other two factories. The factories were evaluated at different times, but within the 2001–2005 year period. The final analysis comprised 120 women (60 exposed, 60 referents) and 52 men (26 exposed, 26 referents). The referents were randomly recruited from various factories not involved with 1-bromopropane; however, no monitoring data were available in the control factories. Workers from 1-bromopropane production plants could potentially be exposed to 1-bromopropane during: adding the chemical into the reaction pots; sitting close to the reaction pots to observe and record the temperature; taking out the crude product; adding hydroxy carbonate and stirring; or pouring the product into drums. No protective masks were worn in any of the factories studied, but in one of the factories investigated in 2001, the workers wore plastic gloves. The exposure periods ranged from 35.9 to 47.0 months. Workers were asked to fill out a questionnaire that included age, sex, smoking or drinking habits, education, past or present illnesses, and previous exposure to other chemicals and duration of exposure to 1-bromopropane. Electrophysiological studies measured motor nerve conduction velocity, distal latency, F-wave conduction velocity in the tibial nerve, sensory nerve conduction velocity in the sural nerve, and amplitude of the electromyography (EMG) elicited by stimulation of the motor nerve, and F-wave and potential of sensory nerve. Vibration sense was measured in the big toe, and reflexes and muscle strength were scored in four limbs. Various neurobehavioral tests, including Santa Ana, simple reaction time, digit symbol, Benton test, digit span, and pursuit aiming tests, were conducted. The report, however, does not indicate how often the tests were conducted. Comprehensive hematological and clinical tests were also conducted in addition to measuring serum TSH, LH, FSH, estradiol (females), and testosterone (males). Assessment of individual exposure to 1- and 2-bromopropane was done by analyzing the content of passive samplers attached to each worker during one 8- or 12-hour shift. This was done twice for two shifts and the average exposure level was used as the representative exposure level. Individual TWA exposure to 1-bromopropane ranged from 0.07 to 106.4 (median ± interquartile range, 6.6±16.3) ppm for females and from 0.06 to 114.8 (median ± interquartile range, 4.6±11.6) ppm for males. Females were classified into low-, mid-, and high-exposure groups (median exposures of 1.28, 6.6, and 22.58 ppm, respectively) and males into low- and high-exposure groups (median exposures of 1.05 and 12.5 ppm, respectively). Data were analyzed in three different ways. Continuous variables were analyzed with ANOVA followed by Dunnett's multiple comparison and scores of reflex and muscle strength were compared using nonparametric Wilcoxon test. Linear regression analysis was performed to confirm the trend with the exposure level or the product of exposure level and period of exposure (cumulative exposure). The median value of each exposure group (rather than individual exposures) was used for regression analysis or analysis of covariance (ANCOVA) on the exposure level.

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Effect noted in study and corresponding doses: Dunnett's multiple comparison following ANOVA showed significant differences between controls and exposed female groups for tibial distal latency (increase), sural sensory nerve conduction velocity (decrease), vibration sense threshold (increase), fatigue, serum LDH (increase), serum TSH (increase), serum FSH (increase), estradiol (decrease), white blood cell (decrease), red blood cells (decrease), and hemoglobin and hematocrit (decrease). The most sensitive effect was increased vibration sense threshold, which showed significant effects in all exposure groups. No differences between controls and exposed men were seen except for increased BUN in exposed men. Regression analysis adjusting for alcohol exposure and pair-matching for age, sex, and region in selecting controls showed significant trends in tibial distal latency, vibration sense in toes, Benton test (test for visual perception and memory), BUN, LDH, TSH, red blood cells, hematocrit, and platelets in females. In males, only BUN showed a significant trend. The same regression analysis on the product of exposure levels and duration of exposure (cumulative exposure) showed significant increases in tibial distal latency, vibration sense threshold, BUN, LDH, CK, TSH, MCV, MCH, red blood cells, and hematocrit in female workers and in BUN and Santa Ana non-preferred hand in male workers. Because estimation of vibration loss is influenced by the examining neurologist and body weight, which were not controlled for in the regression analysis, an ANCOVA analysis on 1-bromopropane exposure level (or 1-bromopropane cumulative exposure level), neurologist, age, height, body weight, and alcohol consumption was conducted in female workers (n=60/group; body weight data was unavailable for five age-matched pairs, so these pairs were assigned the average body weight of the group). The results showed that the effect of 1-bromopropane and cumulative 1-bromopropane were significant; however, the effect of examining neurologist was also significant.

This study has a number of limitations, some of which were identified by the investigators or pointed out by others (Smith et al. 2011). Of particular concern for the chronic inhalation MRL derivation are the following limitations: (1) the cross-sectional study design; (2) potential selection bias for the control group; (3) potential underestimation of 1-bromopropane exposure levels; (4) lack of biomonitoring data for controls; and (5) concerns regarding the vibration sense measurement method utilized in the study.

1. ATSDR acknowledges that use of a cross-sectional study design limits the ability to identify a cause-effect relationship between 1-bromopropane and observed effects. However, supporting evidence from two other cross-sectional studies and several case-reports supported an association between neurotoxic effects and exposure to 1-bromopropane (Ichihara et al. 2002; Majersik et al. 2007; NIOSH 2002, 2003a; Raymond and Ford 2007; Samukawa et al. 2012; Sclar 1999; Wang et al. 2015).
2. ATSDR acknowledges that there may be selection bias in the identification of the age-, sex-, and region-matched controls. While the investigators stated that controls were "randomly" selected from adjacent factories, it is unclear what methods were used to randomly select controls.
3. ATSDR acknowledges that estimated 1-bromopropane exposures provided by the study investigators may be lower than actual exposures. The study authors indicated that windows and doors were wide open during the working hours, but it is reasonable to assume that windows and/or doors may have been closed during rainy or cold weather. If monitoring was conducted with windows and doors open, the exposure levels would be greater if windows and doors were closed. Study authors also indicate uncertainties in the cumulative exposure assessment, as measurements were taken over a 1–3-day period and presumed to be the same level for entire duration of employment. Additionally, no details for the sampling rate on personal monitors was provided and indoor air temperature during monitoring was not reported (temperature is essential to convert the mass concentration in mg/m<sup>3</sup> to ppm). Furthermore, exposure levels were not reported by factory or job description, which would have led to a more meaningful evaluation of

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results. Also, potential dermal exposure from lack of wearing gloves and oral exposure if hands were not properly washed prior to eating may have contributed to exposure levels beyond measured air levels (Smith et al. 2011). In response, the study investigators clarified that plastic gloves were worn in at least one of the factories, decreasing the potential for dermal/oral exposure (Ichihara et al. 2011), but it does not appear that gloves were worn in other factories.

4. Smith et al. (2011) raised concerns regarding lack of biomonitoring data for controls from nearby factories not using 1-bromopropane, particularly the lack of exposure data for other potentially neurotoxic chemicals. However, ATSDR agrees with the study investigators, who proposed that if neurotoxic chemical exposure did occur at control factories it would only serve to underestimate the neurotoxic effects in the bromopropane-exposed group of workers (Ichihara et al. 2011).
5. ATSDR acknowledges that the 128 Hz tuning fork is not the best choice for quantitative analysis of vibration sense between individuals, as more specialized equipment is available that would have produced more quantitatively accurate results (such as the quantitative Rydel-Seiffer 64 Hz tuning fork, bio/neurothesiometer, or Computer Assisted Sensation Examination IV [CASE IV]) (Burns et al. 2002; Levy 2010; Nizar et al. 2014; Pestronk et al. 2004; Willits et al. 2015). Identification of clinical vibration impairment using a tuning fork has been shown to overestimate the quantitative vibration threshold (identified by the CASE IV system), and the discordance was associated with age, height, and body surface area of the subject (Burns et al. 2002). However, the study authors acknowledged that clinical assessment of vibration threshold using a tuning fork is inherently inaccurate due to examiner bias and subject characteristics (age, weight, height), and reported that findings remained significant after statistical adjustment for examiner and subject characteristics. A follow-up letter to the editor by the study investigators clarified that examiners were blinded to the exposure group (Ichihara et al. 2011), which was an initial concern raised by Smith et al. (2011). Other studies evaluating the 128 Hz tuning fork for the ability to accurately detect loss of vibration sense in patients with diabetic neuropathy reported a sensitivity (ability to diagnose condition if present) of 40–69% and a specificity (ability to diagnose lack of condition) of 90–100%, compared with detection using the neurothesiometer (which is considered the diagnostic tool of choice) (Nizar et al. 2014; Willits et al. 2015). These values indicate that use of a 128 Hz tuning fork to clinically identify loss of vibration sense will most likely underestimate (rather than overestimate) the presence of dysfunction. Additionally, by placing the tuning fork on the examiner's foot (once subjects indicated they could no longer feel vibration), the study investigators deviated from the standard protocol (as described by Gilman 2002), which involves removing the tuning fork from the subject and placing it on the examiner's fingers (which are much more sensitive). This deviation would also most likely underestimate (rather than overestimate) the presence of dysfunction. Taking into consideration all available evidence, while the 128 Hz tuning fork is not the most sensitive or quantitative assessment tool, it was able to detect statistically significant differences between control and exposed groups after adjusting for examiner and subject characteristics (age, weight, height). Therefore, ATSDR considered data obtained using this method adequate for the derivation of the chronic inhalation MRL.

Other limitations of the study identified by Smith et al. (2011) or the study authors include: (1) lack of control of the temperature of the skin of the legs may have impacted measurements of nerve conduction velocity; (2) abnormally high control values for tibial nerve distal latency; (3) co-exposure to low levels of 2-bromopropane in the exposed group of workers (which has been shown to have reproductive and hematopoietic effects on workers and animals); and (4) no data on menstrual cycle of females (which could have influenced some hematology and some clinical chemistry results). While these limitations are acknowledged by ATSDR, they do not directly impact end points used in the MRL derivation because

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they relate either to neurological end points not selected as the basis for the MRL (limitations 1 and 2) or to non-neurological end points (limitations 3 and 4).

Despite the limitations of this study, ATSDR still considers the study by Li et al. (2010) as the most appropriate study for deriving the chronic inhalation MRL (see further discussion in *Other additional studies or pertinent information that lend support to this MRL* section below). However, it is noted that the confidence in this MRL is low due to the acknowledged limitations.

The results of the study by Li et al. (2010) suggest a minimal LOAEL of 1.28 ppm based on a statistically significant increase in the vibration sense threshold in female workers. Women in this exposure group also showed significantly slower sural nerve conduction velocity; however, this effect was not selected as the critical effect as it was not observed consistently in higher exposure groups and was not significant based on regression analysis. Other neurological effects observed in this study at higher exposures ( $\geq 6.6$  ppm) in female workers included increased tibial nerve distal latency. Effects observed in hematology and clinical chemistry are not considered by ATSDR to be biologically relevant because they were small in magnitude and were generally within human reference ranges. No NOAEL was identified for this study.

Dose and end point used for MRL derivation: 1.28 ppm

[ ] NOAEL [X] LOAEL

A minimal LOAEL of 1.28 ppm was identified for mild neurological impairment in females (increased vibration sense threshold). No NOAEL was identified. BMD modeling was conducted on this end point; however, no models provided an adequate fit.

Uncertainty Factors used in MRL derivation:

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

$MRL = 1.28 \times 5 \text{ days}/7 \text{ days} \times 12 \text{ hours}/24 \text{ hours} = 0.46 \text{ ppm}$

$MRL = 0.46 \text{ ppm} / 30 \text{ (UF)} = 0.02 \text{ ppm}$

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? The exposure concentration was adjusted to continuous exposure basis as shown above. Although Li et al. (2010) report median exposure levels based on TWA concentrations for 8- or 12-hour work shifts, the majority of workers (65%) had 12-hour work shifts.

Other additional studies or pertinent information that lend support to this MRL: Candidate principal studies considered for deriving the chronic inhalation MRL are shown in Table A-3. Of the candidate human studies, only the Li et al. (2010) study was adequate for consideration. The NIOSH occupational health surveys (2002, 2003a) did not contain a reference group. Among the candidate animal studies, the lowest LOAEL was for various histological alterations in the respiratory tract of mice (Morgan et al. 2011; NTP 2011); LOAELs from other available studies occur at much higher concentrations. Therefore,

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both the Li et al. (2010) study in humans and the Morgan et al. (2011) study in mice were further evaluated as potential principal studies. The critical effects, PODs, uncertainty factors, and candidate MRL for each option are presented in Table A-4. Candidate MRLs based on the key human and animal studies are almost the same (0.02 and 0.03 ppm, respectively); rationale for selection of the human study over the animal study as the critical study is discussed below.

**Table A-3. Studies Considered for Deriving the Chronic-Duration Inhalation MRL**

Study	End point(s) evaluated	Significant effects at LOAEL	NOAEL (ppm)	LOAEL (ppm)
<b>Human studies</b>				
Li et al. (2010) Cross-sectional occupational exposure study; average exposure duration ~40 months	Hematology, clinical chemistry (including thyroid and reproductive hormones), neurological evaluation (nerve conduction velocity, vibration sense, neurobehavioral testing)	Increased vibration threshold	ND	1.28
NIOSH (2003a) Cross-sectional occupational health survey; average exposure duration ~29 months	Hematology, clinical chemistry, questionnaire for neurological deficits, nerve conduction velocity	Subjective complaints of neurotoxicity	ND	45.7
NIOSH (2002) Cross-sectional occupational health survey; exposure duration 4–9 years	Hematology, questionnaire for neurological and reproductive deficits	Subjective complaints of neurotoxicity	ND	117.1
<b>Animal studies</b>				
Morgan et al. (2011); NTP (2011) B6C3F1 mice, 105 weeks	Comprehensive 2-year bioassay; neurological function not assessed	Various histological alterations in the nasal respiratory epithelium, larynx, trachea, and bronchioles	ND	62.5
Morgan et al. (2011); NTP (2011) F-344 rats, 105 weeks	Comprehensive 2-year bioassay; neurological function not assessed	Glandular hyperplasia in the nose (both sexes), chronic active nasal inflammation (females)	ND	125
BSOC (2001a) Sprague-Dawley rats, 2 generations (~16–18 weeks per generation)	Comprehensive 2-generation reproductive toxicity study; neurological function not assessed	Hepatocellular vacuolization in F0 and F1 males, reduced prostate weight in F0 males	100	250

LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; ND = not determined; NOAEL = no-observed-adverse-effect level



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**Table A-4. Options for Derivation of Chronic-Duration Inhalation MRL Based on Principal Chronic Human and Animal Studies**

Study	Critical effect	POD (ppm)	UF	MRL (ppm)
Human study Li et al. (2010)	Decreased vibration sense	0.46 ppm (LOAEL <sub>CONV</sub> )	30  10 for human variability; 3 for use of minimal LOAEL	0.02
Mouse study Morgan et al. (2011); NTP (2011)	Respiratory lesions	0.78 (BMCL <sub>10HEC</sub> )	30  10 for human variability; 3 for dosimetric adjustment	0.03

BMCL = lower limit on the benchmark concentration; CONV = converted to continuous exposure; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; POD = point of departure; UF = uncertainty factor

Decreased vibration sense was identified as the most sensitive effect in the human occupational study by Li et al. (2010). As discussed above, there are numerous limitations to this study; however, the identification of neurological impairment as the critical effect is supported by the NIOSH occupational surveys and several human case reports of workers exposed to 1-bromopropane at workplace air concentrations >45 ppm for weeks to years. No other available study evaluated the reportedly low exposure levels (median exposures of 4.6 ppm in men and 6.6 ppm in women) reported in the Li et al. (2010) study. Reported neurological effects in workers in these other studies ranged from mild neurological impairments and complaints, such as numbness and tremors, to frank neurotoxic effects requiring hospitalization, such as ataxia, spastic paraparesis, and symmetric demyelinating polyneuropathy (Ichihara et al. 2002; Majersik et al. 2007; NIOSH 2002, 2003a; Raymond and Ford 2007; Samukawa et al. 2012; Sclar 1999; Wang et al. 2015). Several of the case studies reported decreased vibration sense, particularly in the lower extremities (Ichihara et al. 2002; Majersik et al. 2007; Raymond and Ford 2007; Samukawa et al. 2012; Sclar 1999), supporting the selection of increased vibration sense threshold in the toe from the Li et al. (2010) study as the critical effect.

Animal studies provide supporting evidence that exposure to 1-bromopropane can result in neurotoxicity. Although neurological function has not been evaluated in animals following chronic exposure, observed effects in acute- and intermediate-duration inhalation rat studies at concentrations as low as 50 ppm included changes in neurobehavior, muscle strength, electrophysiology, morphology, and biochemistry (Fueta et al. 2002; Honma et al. 2003; Ichihara et al. 2000b; Kim et al. 1999; Mohideen et al. 2011, 2013; Subramanian et al. 2012; Ueno et al. 2007; Wang et al. 2002, 2003; Yu et al. 2001).

In the chronic mouse study, lesions in the lung and nasal epithelium were the most sensitive effects occurring at the lowest tested concentration, 62.5 ppm (Morgan et al. 2011; NTP 2011). Lesions in the lung and nasal epithelium were also found in F-344 rats at the lowest tested concentration, 125 ppm (Morgan et al. 2011; NTP 2011). In intermediate-duration animal studies, respiratory tract lesions were found in mice exposed to concentrations as low as 125 ppm for 2–14 weeks (NTP 2011), but were not found in F-344 rats at concentrations up to 1000 ppm for 14 weeks (NTP 2011), Sprague-Dawley rats at concentrations up to 1,800 ppm for 8–13 weeks (Albamarle Corporation 1997; Kim et al. 1999), or Wistar rats at concentrations up to 800 ppm for 12 weeks (Ichihara et al. 2000a). These results suggest that mice are more sensitive to respiratory effects than rats following intermediate-duration inhalation exposure. Several acute and intermediate-duration rat studies found neurological effects at concentrations lower

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than those causing respiratory effects (as low as 50 ppm, see previous paragraph), providing support for neurological effects as the critical effects following acute and intermediate-duration exposure. In humans, the only evidence for respiratory effects was mild respiratory irritation reported in case studies of workers experiencing frank neurotoxicity following exposure to >100 ppm 1-bromopropane (Ichihara et al. 2002; Raymond and Ford 2007). The relative severities of the respiratory and neurotoxic effects in these cases suggest that humans are more susceptible to neurotoxic effects from 1-bromopropane than respiratory effects.

Based on available data, neurological effects appear to be the most sensitive effect for workers repeatedly exposed to 1-bromopropane and in animals exposed to 1-bromopropane for acute and intermediate durations. Neurological effects in chronically exposed animals, however, have not been adequately studied to characterize the relative sensitivity of neurological effects versus respiratory effects. In the absence of this information, a comparison was made of MRLs based on the minimal LOAEL for neurological effects in workers in the Li et al. (2010) study and the LOAEL for respiratory tract lesions in mice exposed for 2 years (Morgan et al. 2011; NTP 2011). The resultant MRLs were numerically equivalent (Table 3). Despite the limitations in the principal human study, ATSDR still considers Li et al. (2010) the best available study on which to base the MRL, principally because it is based on human data. ACGIH (2014) also used the same study to recommend a TLV-TWA of 0.1 ppm based on the LOAEL of 1.28 ppm for decreased vibration sense in toes from female workers in the Li et al. (2010) study. The TLV-TWA is TWA concentration for a conventional 8-hour workday and a 40-hour workweek, to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect (ACGIH 2016). Confidence in the chronic MRL is low because of the limitations of the principal study, but could be improved with additional and better-designed neurological evaluations (cross-sectional or prospective) of workers exposed to 1-bromopropane in workplace air.

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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical Name: 1-Bromopropane  
CAS Numbers: 106-94-5  
Date: August 2017  
Profile Status: Final  
Route: ☐ Inhalation ☒ Oral  
Duration: ☒ Acute ☐ Intermediate ☐ Chronic  
Graph Key: 7  
Species: Rat

Minimal Risk Level: 0.2 ☒ mg/kg/day ☐ ppm

Reference: Zhong Z, Zeng T, Xie K, et al. 2013. Elevation of 4-hydroxynonenal and malondialdehyde modified protein levels in cerebral cortex with cognitive dysfunction in rats exposed to 1-bromopropane. Toxicology 306:16-23.

Experimental design: The study examined the effects of 1-bromopropane on cognitive function in male Wistar rats and the possible role of oxidative stress. Groups of rats (10/group) were administered 0, 200, 400, or 800 mg 1-bromopropane/kg/day by gavage in corn oil for 12 consecutive days. On days 8–12, cognitive function (spatial learning and memory) was assessed with the Morris water maze test. Twenty-four hours after the last dose, the rats were killed, and the cerebral cortex was removed. The following were measured in cerebral cortex homogenates: GSH, oxidized glutathione (GSSG), total thiol (total -SH) content, GSH reductase and GSH peroxide (GSH-Px) activities, and MDA level, as well as 4-HNE and MDA modified proteins.

Effect noted in study and corresponding doses: Some rats in the 400 and 800 mg 1-bromopropane/kg/day groups showed irritability at the start of dosing. After 1 week of dosing, rats in the 800 mg 1-bromopropane/kg/day group showed slow response and sluggishness. Final body weight was reduced about 13% in the high-dose group; no data on food consumption were provided. Dose-related impairments were observed in learning and memory measures of the Morris water maze. During the 4-day learning phase, the escape latency was significantly increased in the 800 mg 1-bromopropane/kg/day group and the total swimming distance was increased at  $\geq 200$  mg 1-bromopropane/kg/day. Time spent in different swimming “search” patterns (direct finding, approaching target, random searching, and thigmotaxis) differed significantly in all exposed groups, compared with controls, with exposed animals showing increased thigmotaxis (time spent in periphery of tank). On day 5, when the escape platform was removed to assess memory, all exposure groups showed a significant decrease in the number of times they crossed the former location of the target platform; rats exposed to 800 mg 1-bromopropane/kg/day also showed a significant decrease in time spent in the target quadrant. Assessment of biochemical indices showed an increase in oxidative stress (increased MDA and GSSG, decreased GSH, and decreased GSH reductase activities), mostly observed in the mid- and high-dose groups. Tests with specific monoclonal antibodies also showed increased total levels of reactive aldehyde modified proteins in the cerebral cortex.

A LOAEL of 200 mg/kg/day was identified for this study based on impaired spatial learning and memory (increased swimming distance, altered search pattern, decreased number of crossings of the escape platform); no NOAEL was identified. All data were presented graphically. The SDs could not be extracted from day 1–4 figures either because they overlapped between dose-groups (total swimming distance) or they were not reported (distribution of search patterns); therefore, these data could not be used for BMD analysis. However, the means and SDs for the number of crossing of the escape platform

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(assessed on day 5) were extracted digitally using GrabIt! software (version XP2) for BMD analysis (Table A-5). Alternate data extraction of the means and SDs using DigitizeIt software resulted in BMDLs that differed by <17% on average, which would yield the same MRL.

**Table A-5. Digitized Dataset for Number of Crossings of Escape Platform Location on Day 5<sup>a</sup>**

Dose (mg/kg/day)	Animal number	Mean (number)	Standard deviation
0	10	7.2	2.8
200	10	4.3 <sup>b</sup>	2.6
400	10	3.7 <sup>c</sup>	2
800	10	2.4 <sup>c</sup>	2

<sup>a</sup>Data extracted from Figure 3B in Zhong et al. (2013).

<sup>b</sup>p<0.05.

<sup>c</sup>p<0.01.

Dose and end point used for MRL derivation: 19.75 mg/kg/day

[ ] NOAEL [ ] LOAEL [X] BMDL<sub>1SD</sub>

All models provided an adequate and nearly equivalent fits (see Table A-6) by the various statistical criteria, but the BMDLs had a 15.4-fold range, indicating some model dependence of the BMDL estimates. The range of results is judged to be reasonable, because the range of the absolute differences between the individual BMDs and their corresponding BMDLs was comparable, ranging from about 111 to 130 mg/kg/day. Because the BMDL estimates are not sufficiently close, selecting the model with the lowest BMDL is recommended (EPA 2012b). Thus, the BMDL of 19.75 mg/kg/day from the Hill model is a reasonable conservative estimate. The Hill model calculates BMD<sub>1SD</sub> and BMDL<sub>1SD</sub> values of 148.37 and 19.75 mg/kg/day, respectively, for decreased spatial memory in rats on day 5 of the Morris water test (see Figure A-2).

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**Table A-6. Model Predictions for Effects of 1-Bromopropane on the Spatial Memory Ability of Rats**

Model	Test for significant difference p-value <sup>a</sup>	Variance p-value <sup>b</sup>	Means p-value <sup>b</sup>	Scaled residuals <sup>c</sup>			AIC	BMD <sub>1SD</sub> (mg/kg/day)	BMDL <sub>1SD</sub> (mg/kg/day)
				Dose below BMD	Dose above BMD	Overall largest			
All doses									
Constant variance									
Exponential (model 2) <sup>d</sup>	0.002	0.61	0.45	-0.9692	0.0365	0.579	112.63	266.03	154.01
Exponential (model 3) <sup>d</sup>	0.002	0.61	0.45	-0.9692	0.0365	0.579	112.63	266.04	154.01
Exponential (model 4) <sup>d</sup>	0.002	0.61	0.52	0.0777	-0.3698	0.4757	113.46	165.96	55.12
Exponential (model 5) <sup>d</sup>	0.002	0.61	0.52	0.0777	-0.3698	0.4757	113.46	165.96	55.12
<b>Hill<sup>d,e</sup></b>	<b>0.002</b>	<b>0.61</b>	<b>0.63</b>	<b>0.0291</b>	<b>-0.247</b>	<b>0.384</b>	<b>113.29</b>	<b>148.37</b>	<b>19.75</b>
Linear <sup>f</sup>	0.002	0.61	0.15	-1.22	-0.573	1.2	114.85	435.59	305.49
Polynomial (2-degree) <sup>f</sup>	0.002	0.61	0.15	-1.22	-0.573	1.2	114.85	435.59	305.49
Polynomial (3-degree) <sup>f</sup>	0.002	0.61	0.15	-1.22	-0.573	1.2	114.85	435.59	305.49
Power <sup>d</sup>	0.002	0.61	0.15	-1.22	-0.573	1.2	114.85	435.59	305.49

<sup>a</sup>Values >0.05 fail to meet conventional goodness-of-fit criteria.

<sup>b</sup>Values <0.10 fail to meet conventional goodness-of-fit criteria.

<sup>c</sup>Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.

<sup>d</sup>Power restricted to  $\geq 1$ .

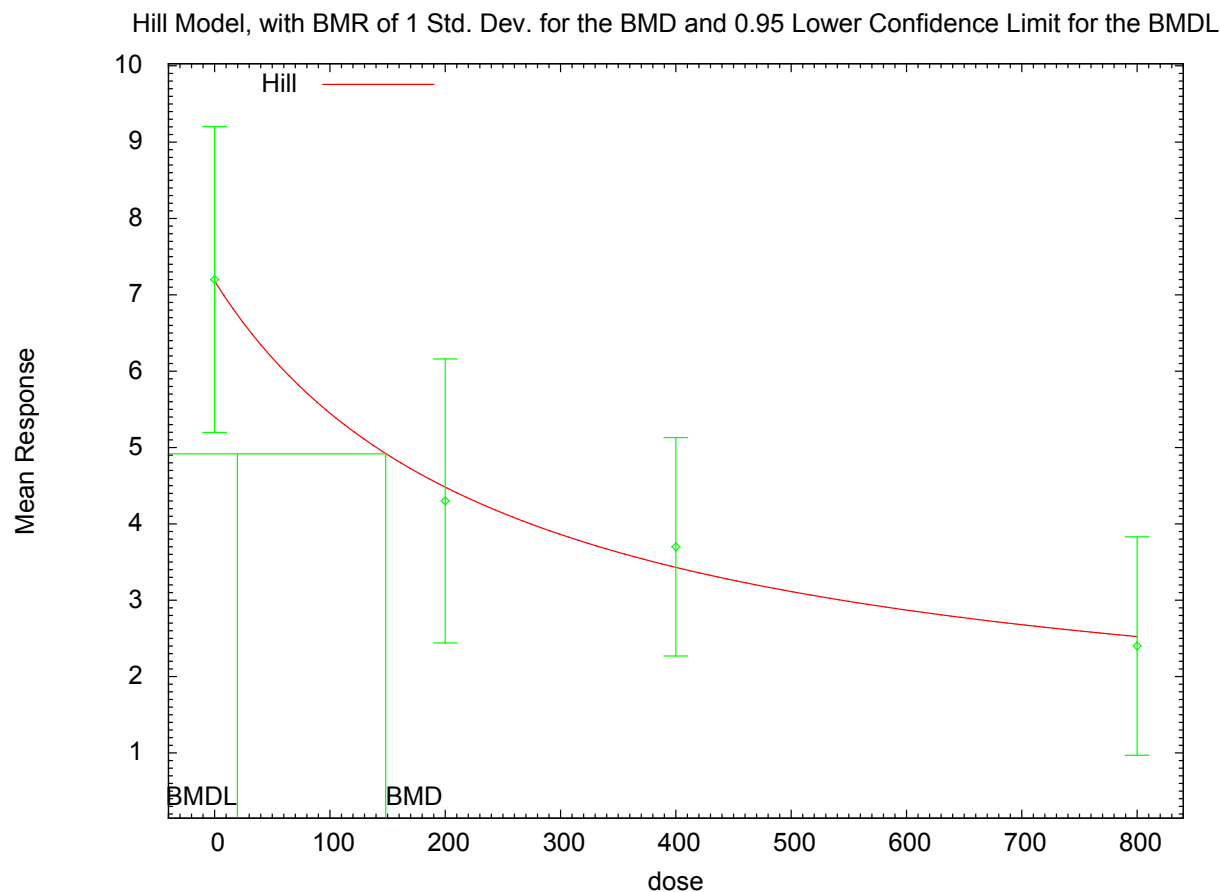
<sup>e</sup>Selected model. With constant variance applied, all the models provided an adequate fit to means. BMDLs for models providing adequate fit differed by >threefold, so the model with the lowest BMDL (Hill) was selected. The Hill model also provided the best fit in the low-dose range (based on scaled residuals).

<sup>f</sup>Coefficients restricted to be negative.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., <sub>1SD</sub> = exposure concentration associated to a change in the mean response equal to one control standard deviation from the control mean)

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**Figure A-2. Selected Model (Hill) for Impaired Spatial Memory Following Exposure to 1-Bromopropane (Zhong et al. 2013)**



Uncertainty Factors used in MRL derivation:

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

$$\text{MRL} = 19.75 \text{ mg/kg/day} \div 100 = 0.2 \text{ mg/kg/day}$$

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:  
Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Marked decreases in spontaneous activity (sedation), piloerection, and dyspnea were reported in rats exposed once to 2,000 mg 1-bromopropane/kg in a lethality study by Elf Atochem S.A. (1993). Clinical signs were observed within 4 hours of dosing; surviving animals (9/10) fully recovered by day 2 of the 14-day observation period. Of

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direct relevance to the results of Zhong et al. (2013) are the results of a recent study by the same groups of investigators, which confirmed the previous results and reported that treatment of male Wistar rats with  $\geq 200$  mg 1-bromopropane/kg/day for 12 days impaired spatial memory and spatial learning ability (Guo et al. 2015). In this study, rats exposed to  $\geq 200$  mg 1-bromopropane/kg/day tested in the Morris Water Maze showed a significantly dose-related decreased percent of time at the target platform; the NOAEL was 100 mg 1-bromopropane/kg/day. Modeling these data yielded a BMDL<sub>1SD</sub> (POD) of 77.94 mg 1-bromopropane/kg/day, which is higher than the BMDL<sub>1SD</sub> of 19.75 mg 1-bromopropane/kg/day used to derive the current MRL. Therefore, it is still more appropriate (more protective) to use data from Zhong et al. (2013) to derive an acute-duration oral MRL for 1-bromopropane. Also relevant is another study from the same group of investigators that reported motor abnormalities in rats administered  $\geq 200$  mg 1-bromopropane/kg/day for up to 16 weeks (Wang et al. 2012). Only limited data from this study were available for review.

While evidence for neurotoxicity following oral exposure is limited, human and animal evidence from inhalation studies indicate that the nervous system is a target for 1-bromopropane toxicity. Mild neurological symptoms have been reported in humans at median TWA workplace air levels as low as 1.28 ppm (Li et al. 2010), and two NIOSH health surveys and several case reports of workers exposed for months to years indicate that higher exposure levels ( $>45$  ppm) can lead to more severe, even permanent, effects (Ichihara et al. 2002; Majersik et al. 2007; NIOSH 2002; Raymond and Ford 2007; Samukawa et al. 2012; Sclar 1999). Neurological effects ranged from mild neurological impairments and complaints with acute exposure, such as headache, numbness and weakness, to frank neurotoxic effects requiring hospitalization following exposure for months or years, such as ataxia, spastic paraparesis, and symmetric demyelinating polyneuropathy. Evidence from animal studies supports that exposure to 1-bromopropane can result in neurotoxic effects. Observed effects in acute and intermediate-duration inhalation studies at concentrations as low as 50 ppm included changes in neurobehavior, muscle strength, electrophysiology, morphology, and biochemistry (Fueta et al. 2002; Honma et al. 2003; Ichihara et al. 2002; Kim et al. 1999; Mohideen et al. 2011, 2013; Subramanian et al. 2012; Suda et al. 2008; Ueno et al. 2007; Wang et al. 2002, 2003; Yu et al. 2001; Zhang et al. 2013).

All other effects observed in acute studies occurred at or above the LOAEL of 200 mg 1-bromopropane/kg/day identified in the neurobehavioral study by Zhong et al. (2013). Observed effects included reduced antibody responses to the T-dependent SRBC antigen at  $\geq 200$  mg 1-bromopropane/kg/day (Lee et al. 2007); congestion, hemorrhage, cellular swelling and vacuolization of hepatocytes in mouse liver at  $\geq 500$  mg 1-bromopropane/kg/day, but not 200 mg 1-bromopropane/kg/day (Lee et al. 2007); degeneration of spermatocytes in mouse testes at 600 mg 1-bromopropane/kg/day (only dose tested) (Yu et al. 2008); and a 13% decrease in body weight at 800 mg 1-bromopropane/kg/day, but not  $\leq 400$  mg 1-bromopropane/kg/day (Zhong et al. 2013). While the LOAEL of 200 mg 1-bromopropane/kg/day for immune effects was considered as the basis of the MRL, the evidence supporting that 1-bromopropane is an immunosuppressant (Anderson et al. 2010; Lee et al. 2007) is far less than the evidence indicating that 1-bromopropane is a neurotoxicant (discussed above).

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## 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 that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and 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.

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, ATSDR has derived 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.

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MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance 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 that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential 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 no-observed-adverse-effect level (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 levels of significant exposure (LSE) tables.

## **Chapter 3**

### **Health Effects**

#### **Tables and Figures for Levels of Significant Exposure (LSE)**

Tables and figures 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, 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 NOAELs, 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.

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**LEGEND****See Sample LSE Table 3-1 (page B-6)**

- (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. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 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 (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—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 include 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 two "18r" data points in sample 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 regimens 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 "Chemical x" via inhalation for 6 hours/day, 5 days/week, for 13 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, one systemic effect (respiratory) was investigated.
- (8) NOAEL. A NOAEL is the highest exposure level at which no adverse 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").

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- (9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse 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 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 that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

**LEGEND****See Sample Figure 3-1 (page B-7)**

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 acute and intermediate 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<sup>3</sup> 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 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

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

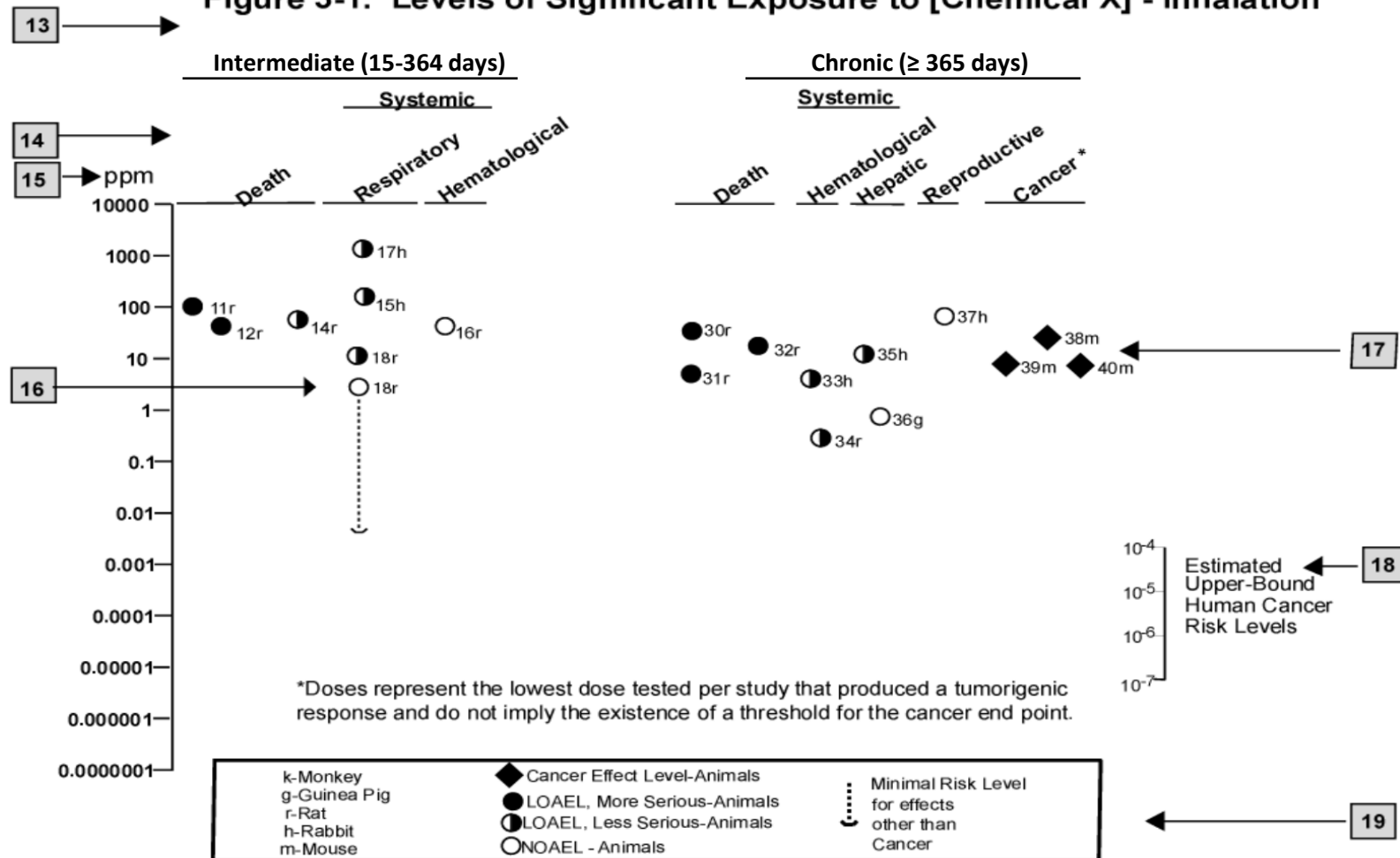
						LOAEL (effect)		
	Key to figure <sup>a</sup>	Species	Exposure frequency/ duration	System	NOAEL (ppm)	Less serious (ppm)	Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3 <sup>b</sup>	10 (hyperplasia)		Nitschke et al. 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 →

<sup>a</sup> The number corresponds to entries in Figure 3-1.<sup>b</sup> Used to derive an intermediate inhalation Minimal Risk Level (MRL) of  $5 \times 10^{-3}$  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



## APPENDIX B

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**APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS**

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
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
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
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
BMD/C	benchmark dose or benchmark concentration
BMD <sub>x</sub>	dose that produces a X% change in response rate of an adverse effect
BMDL <sub>x</sub>	95% lower confidence limit on the BMD <sub>x</sub>
BMDS	Benchmark Dose Software
BMR	benchmark response
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
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

## APPENDIX C

DOT/UN/	Department of Transportation/United Nations/
NA/IMDG	North America/Intergovernmental 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 <sub>1</sub>	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
K <sub>d</sub>	adsorption ratio
kg	kilogram
kgg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K <sub>oc</sub>	organic carbon partition coefficient
K <sub>ow</sub>	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC <sub>50</sub>	lethal concentration, 50% kill
LC <sub>Lo</sub>	lethal concentration, low
LD <sub>50</sub>	lethal dose, 50% kill
LD <sub>Lo</sub>	lethal dose, low
LDH	lactic dehydrogenase
LH	lutinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT <sub>50</sub>	lethal time, 50% kill
m	meter
MA	<i>trans,trans</i> -muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

## APPENDIX C

MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
mt	metric ton
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
NHANES	National Health and Nutrition Examination Survey
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
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
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

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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
PEL-C	permissible exposure limit-ceiling value
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
REL-C	recommended exposure level-ceiling value
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
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 <sub>50</sub>	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TLV-C	threshold limit value-ceiling 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

## APPENDIX C

WHO            World Health Organization

$>$	greater than
$\geq$	greater than or equal to
$=$	equal to
$<$	less than
$\leq$	less than or equal to
$\%$	percent
$\alpha$	alpha
$\beta$	beta
$\gamma$	gamma
$\delta$	delta
$\mu\text{m}$	micrometer
$\mu\text{g}$	microgram
$q_1^*$	cancer slope factor
$-$	negative
$+$	positive
$(+)$	weakly positive result
$(-)$	weakly negative result