TOXICOLOGICAL PROFILE FOR CHLORINE DIOXIDE AND CHLORITE

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

September 2004

DISCLAIMER

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

UPDATE STATEMENT

Toxicological Profile for Chlorine Dioxide and Chlorite, Draft for Public Comment was released in September 2002. 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/Toxicology Information Branch
1600 Clifton Road NE,
Mailstop F-32
Atlanta, Georgia 30333

FOREWORD

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

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

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

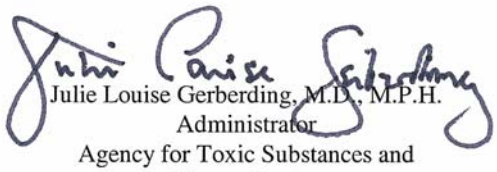
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

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

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

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

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



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

*Legislative Background

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

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

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

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

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

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

Other Sections of Interest:

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

ATSDR Information Center

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

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

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

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

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

Other Agencies and Organizations

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

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

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

Referrals

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

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

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHOR(S):

Jessilynn B. Taylor, M.S.
ATSDR, Division of Toxicology, Atlanta, GA

David W. Wohlers, Ph.D.
Richard Amata, M.S.
Syracuse Research Corporation, 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 Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

A peer review panel was assembled for chlorine dioxide and chlorite. The panel consisted of the following members:

1. Dr. Mohamed S. Abdel-Rahman, Professor of Pharmacology and Physiology, Director of Toxicology, New Jersey Medical School, Newark, New Jersey;

2. Dr. Syed M. GhiasUddin, Toxicologist and Section Chief, Environmental Toxicology and Chemistry Section, Indiana Department of Environmental Management, Indianapolis, Indiana; and

3. Dr. John S. Reif, Professor and Chairman, Department of Environmental Health, Colorado State University, Ft. Collins, Colorado.

These experts collectively have knowledge of chlorine dioxide's and chlorite's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

CONTENTS

APPENDICES

LIST OF FIGURES

LIST OF TABLES

1. PUBLIC HEALTH STATEMENT

This public health statement tells you about chlorine dioxide and chlorite and the effects of exposure to them.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Chlorine dioxide and chlorite have not been found in any of the 1,647 current or former NPL sites. Although the total number of NPL sites evaluated for these substances is not known, the possibility exists that chlorine dioxide and chlorite may be found in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to these substances may harm you.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to chlorine dioxide or chlorite, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with them. You must also consider any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT ARE CHLORINE DIOXIDE AND CHLORITE?

Chlorine dioxide is a yellow to reddish-yellow gas that can decompose rapidly in air. Because it is a hazardous gas, chlorine dioxide is always made at the location where it is used. Chlorine dioxide is used as a bleach at pulp mills, which make paper and paper products, and in public water-treatment facilities, to make water safe for drinking. It has also been used to decontaminate public buildings. Chlorine dioxide is soluble in water and will react rapidly with other compounds. When it reacts in water, chlorine dioxide forms chlorite ion, which is also a

very reactive chemical. Because chlorine dioxide is very reactive, it is able to kill bacteria and microorganisms in water. About 5% of large water-treatment facilities (serving more than 100,000 persons) in the United States use chlorine dioxide to treat drinking water. An estimated 12 million persons may be exposed in this way to chlorine dioxide and chlorite ions. In communities that use chlorine dioxide to treat drinking water, chlorine dioxide and its by-product, chlorite ions, may be present at low levels in tap water.

In this profile, the term "chlorite" will be used to refer to "chlorite ion," which is a water-soluble ion. Chlorite ion can combine with metal ions to form solid salts (e.g., sodium chlorite). Sodium chlorite dissolves in water and forms chlorite ions and sodium ions. More than 80% of all chlorite (present as sodium chlorite) is used to make chlorine dioxide to disinfect drinking water. Sodium chlorite is also used as a disinfectant to kill germs.

1.2 WHAT HAPPENS TO CHLORINE DIOXIDE AND CHLORITE WHEN THEY ENTER THE ENVIRONMENT?

Chlorine dioxide is a very reactive compound. In air, sunlight quickly breaks chlorine dioxide apart into chlorine gas and oxygen. In water, chlorine dioxide reacts quickly to form chlorite ions. When chlorine dioxide reacts with dissolved organic compounds in water-treatment systems, it forms disinfection by-products, such as chlorite and chlorate ions.

Like chlorine dioxide, chlorite is very reactive. Since chlorite is an ionic compound, it will exist primarily in water. Chlorite ions are mobile in water, and may move into groundwater. However, the reaction of chlorite ions with soils and sediments may reduce the concentration of chlorite ions capable of reaching groundwater. For additional information about what happens to chlorine dioxide and chlorite when they enter the environment, see Chapter 6.

1.3 HOW MIGHT I BE EXPOSED TO CHLORINE DIOXIDE AND CHLORITE?

Chlorine dioxide is added to drinking water to protect people from harmful bacteria and other microorganisms. Most people will be exposed to chlorine dioxide and its disinfection by-

product, chlorite ions, when they drink water that has been treated with chlorine dioxide. The EPA has set the maximum concentration in the drinking water at 0.8 milligrams per liter (mg/L) for chlorine dioxide and 1.0 mg/L for chlorite ion. The concentrations of chlorine dioxide and chlorite ion in your drinking water, however, may be lower or higher than these levels. For additional information about how you might be exposed to chlorine dioxide and chlorite, see Chapter 6.

1.4 HOW CAN CHLORINE DIOXIDE AND CHLORITE ENTER AND LEAVE MY BODY?

Chlorine dioxide and chlorite usually enter the body when people drink water that has been disinfected with chlorine dioxide. Because chlorine dioxide rapidly breaks down in air to chlorine gas and oxygen, you would not likely breathe air containing dangerous levels of chlorine dioxide, but if you did, it could be absorbed across your lungs. You are not likely to encounter chlorite in the air you breathe. Whether chlorine dioxide or chlorite on your skin would be absorbed to any great extent is not known.

Both chlorine dioxide and chlorite act quickly when they enter the body. Chlorine dioxide quickly changes to chlorite ions, which are broken down further into chloride ions. The body uses these ions for many normal purposes. Some chloride ions leave the body within hours or days, mainly in the urine. Most chlorite that is not broken down also leaves the body in the urine within a few days after exposure to chlorine dioxide or chlorite.

1.5 HOW CAN CHLORINE DIOXIDE AND CHLORITE AFFECT MY HEALTH?

Both chlorine dioxide and chlorite react quickly in water and moist body tissues. If you were to breathe air containing chlorine dioxide gas, you might experience irritation in your nose, throat, and lungs. If you were to eat or drink large amounts of chlorine dioxide or chlorite, you might experience irritation in the mouth, esophagus, or stomach. Most people will not be exposed to chlorine dioxide or chlorite in amounts large enough to damage other parts of the body, but if

you were, you might experience shortness of breath and other respiratory problems because of damage to the substances in blood that carry oxygen throughout the body.

Scientists use many tests to protect the public from harmful effects of toxic chemicals and to find ways for treating persons who have been harmed.

One way to learn whether a chemical will harm people is to determine how the body absorbs, uses, and releases the chemical. For some chemicals, animal testing may be necessary. Animal testing may also help identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method for getting information needed to make wise decisions that protect public health. Scientists have the responsibility to treat research animals with care and compassion. Scientists must comply with strict animal care guidelines because laws today protect the welfare of research animals.

Animal studies have shown effects of chlorine dioxide and chlorite that are similar to those seen in people exposed to very high amounts of these chemicals. In addition, exposure to high levels of chlorine dioxide and chlorite in animals both before birth and during early development after birth may cause delays in brain development. The levels to which the animals were exposed were much higher than levels that would likely be found in drinking water that has been disinfected with chlorine dioxide.

1.6 HOW CAN CHLORINE DIOXIDE AND CHLORITE AFFECT CHILDREN?

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

Children exposed to large amounts of chlorine dioxide or chlorite would likely be affected in the same manner as adults. Exposure to chlorine dioxide gas in young children, however, might more quickly reduce the ability of blood to carry oxygen than in adults, making breathing more difficult. If infants or babies still in their mother’s womb were exposed to large amounts of

chlorine dioxide, it might cause parts of their brains to develop more slowly. This has been seen in young animals, but has not actually been seen in humans.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO CHLORINE DIOXIDE AND CHLORITE

If your doctor finds that you have been exposed to substantial amounts of chlorine dioxide or chlorite, ask whether your children might also have been exposed. Your doctor might need to ask your state health department to investigate.

Families that drink water treated with chlorine dioxide may reduce the risk of exposure to chlorine dioxide and chlorite ions by drinking bottled water that has not been treated with chlorine dioxide or chlorite ions.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO CHLORINE DIOXIDE AND CHLORITE?

Although no medical tests are available to determine whether you have been exposed to chlorine dioxide or chlorite, exposure to very large amounts may result in damage to red blood cells that can be observed through routine blood tests.

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

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

and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

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 that is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

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 provides it. Some regulations and recommendations for chlorine dioxide and chlorite include the following:

OSHA regulates the level of chlorine dioxide in workplace air. The occupational exposure limit for an 8-hour workday, 40-hour workweek is 0.1 parts per million (0.28 milligrams per cubic meter [mg/m^3]). The EPA has set a maximum contaminant level of 1 mg/L for chlorite in drinking water and a goal of 0.8 mg/L for both the maximum residual disinfectant level for chlorine dioxide and the maximum contaminant level for chlorite in drinking water that has been treated with chlorine dioxide as a disinfectant.

For more information on regulations and guidelines, see Chapter 8.

1.10 WHERE CAN I GET MORE INFORMATION?

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

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

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

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE
Mailstop F-32
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

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

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO CHLORINE DIOXIDE AND CHLORITE IN THE UNITED STATES

Chlorine dioxide is a yellow to reddish-yellow gas that can decompose rapidly in air if it is present at high concentrations. Because it is a hazardous gas, chlorine dioxide is always made at the place where it is used. Chlorine dioxide is used as a bleach at pulp mills to make paper and paper products, and in publicly-owned treatment works (POTW) as a disinfectant for drinking water. In 2001, chlorine dioxide was used to decontaminate a number of public buildings following the release of anthrax spores in the United States. Chlorine dioxide is a very reactive compound and will not exist in the environment for long periods of time. In air, chlorine dioxide will dissociate in sunlight into chlorine gas and oxygen. Chlorine dioxide, a strong oxidizer, will react quickly in water to form by-products such as chlorite ions.

EPA has set the maximum concentration of chlorine dioxide and chlorite ion for drinking waters at 0.8 and 1.0 mg/L, respectively. However, the concentrations of chlorine dioxide and chlorite ion in drinking water may be higher or lower than these levels.

Human exposure to chlorine dioxide and its by-products (e.g., chlorite ion) occurs primarily by ingestion of drinking water. People who live in communities where chlorine dioxide is used in drinking water treatment have a greater probability of exposure to chlorine dioxide and chlorite ions than individuals who do not. About 5% of the water treatment facilities serving more than 100,000 people in the United States use chlorine dioxide to treat drinking water. This would translate to about 12 million people who may be exposed to chlorine dioxide and chlorite ions in the United States. However, the total number people exposed will be higher if smaller facilities (i.e., those serving less than 50,000 people) are also included in this value.

2.2 SUMMARY OF HEALTH EFFECTS

Available human and animal data indicate that airborne chlorine dioxide (ClO_2) primarily acts as a respiratory tract and ocular irritant. Chlorite (ClO_2^-) does not persist in the atmosphere either in ionic form or as chlorite salt, and is not likely to be inhaled. Potential for human exposure to chlorine dioxide or chlorite may be greatest via the oral exposure route because chlorine dioxide is sometimes used as a

disinfectant for drinking water. Available human and animal data indicate that oral exposure to relatively large amounts of chlorine dioxide or chlorite may result in irritation of the digestive tract, the severity of which is likely to be dose-dependent. In addition, high-level oral exposure results in increased levels of methemoglobin in the blood, which reduces the ability of oxygen to bind with hemoglobin.

Other hematological changes have been observed in animals exposed to chlorine dioxide and chlorite. However, the degree of reported changes does not appear to be dependent upon the amount of exposure, and the toxicological significance of such changes is not clear. Nor has the toxicological significance of changes in thyroid hormone levels in the blood been established.

Both chlorine dioxide and chlorite appear to induce delays in neurodevelopment, as evidenced by delayed brain growth, decreased locomotor and exploratory behavior, and altered auditory startle response in animals exposed during critical periods of neurodevelopment. It is not known whether similar chlorine dioxide- or chlorite-induced neurodevelopmental effects might occur in humans.

Limited carcinogenicity data for chlorine dioxide and chlorite do not indicate a particular cancer concern, but adequate animal cancer bioassays have not been performed. Genotoxicity testing has produced mixed results. Chlorine dioxide and chlorite do not appear to be reproductive toxicants.

Animal studies indicate that the lowest observed adverse-effect level (LOAEL) is approximately 5 mg/kg/day for repeated oral exposure to chlorite. Assuming that the average human male (70 kg reference bodyweight) drinks 2 liters of water per day, the dose of chlorite would be approximately 0.03 mg/kg/day from drinking water containing the maximum level of 1 mg chlorite/L that is allowed by EPA. It is not likely that humans would be exposed to levels of chlorine dioxide or chlorite in the drinking water that would approach adverse effect levels reported in animal studies.

Neurodevelopmental effects appear to be of greatest toxicological concern, particularly in light of the fact that chlorine dioxide and chlorite may be used as disinfectants for drinking water. Therefore, the following brief discussion includes only developmental effects. The reader is referred to Section 3.2, Discussion of Health Effects by Route of Exposure, for additional information regarding the potential for other chlorine dioxide- or chlorite-induced health effects.

Developmental Effects. Neurodevelopmental effects, such as decreases in brain weight, brain cell number, exploratory behavior, and locomotor activity, have been observed in rat pups whose mothers

were exposed to chlorine dioxide before mating and during gestation and lactation and other rat pups that were directly exposed via oral gavage only during postnatal development. Decreases in exploratory behavior and amplitude of auditory startle response have been reported in rat pups whose mothers were orally exposed to chlorite during gestation and lactation. Perinatal exposure to chlorine dioxide or chlorite has also resulted in altered serum thyroid hormone levels or activity. Although mechanisms of action responsible for mediating these chlorine dioxide- and chlorite-mediated thyroid hormone effects have not been identified, it is widely understood that the thyroid hormone, T3, is essential for normal development of the nervous system, and that T3 is synthesized from the deiodination of T4.

2.3 MINIMAL RISK LEVELS

Inhalation MRLs

An acute-duration inhalation MRL was not derived for chlorine dioxide because adequate human or animal data are not available.

No inhalation MRLs were derived for chlorite. The only available information regarding health effects following inhalation exposure to chlorite was limited to a single study of lethality in rats exposed to aerosols of sodium chlorite, an exposure scenario not likely to be encountered in environmental or occupational settings. Furthermore, lethality is a serious effect, and therefore cannot be used as the basis for deriving an MRL.

- An MRL of 0.001 ppm (0.003 mg/m^3) has been derived for intermediate-duration inhalation exposure (15–365 days) to chlorine dioxide.

This MRL is based on a lowest-observed-adverse-effect-level (LOAEL) of 1 ppm for respiratory effects in rats. Paulet and Desbrousses (1970) exposed groups of 10 rats/sex (strain not specified) to chlorine dioxide vapors at concentrations of 0 or 2.5 ppm, 7 hours/day for 30 days. Chlorine dioxide-exposed rats exhibited respiratory effects that included lymphocytic infiltration of the alveolar spaces, alveolar vascular congestion, hemorrhagic alveoli, epithelial erosions, and inflammatory infiltrations of the bronchi. The study authors also reported slightly decreased body weight gain, decreased erythrocyte levels, and increased leukocyte levels, relative to controls. Recovery from the pulmonary lesions was apparent in rats examined after a 15-day recovery period. In a follow-up study designed to examine a lower exposure level (Paulet and Desbrousses 1972), eight Wistar rats (sex not reported) were exposed to chlorine dioxide vapors at a concentration of 1 ppm, 5 hours/day, 5 days/week for 2 months. The authors

stated that weight gain and erythrocyte and leukocyte levels were not affected. Chlorine dioxide-induced respiratory effects included peribronchiolar edema and vascular congestion in the lungs. No alterations in epithelium or parenchyma were seen.

Collectively, these studies adequately identify a LOAEL for respiratory effects associated with intermediate-duration inhalation exposure to chlorine dioxide. The intermediate-duration inhalation MRL for chlorine dioxide was based on the LOAEL of 1 ppm identified in the Paulet and Desbrousses (1972) study, which was adjusted to 0.15 ppm ($LOAEL_{ADJ}$) to compensate for intermittent exposure, converted to the human equivalent concentration ($LOAEL_{HEC}$) of 0.3 ppm, and then divided by an uncertainty factor of 300 (3 for interspecies extrapolation using dosimetric adjustments, 10 for the use of a LOAEL, and 10 to account for sensitive populations).

A chronic-duration inhalation MRL was not derived for chlorine dioxide because chronic inhalation exposure studies in humans or animals are not available. An approach using an uncertainty factor for extrapolating from intermediate- to chronic-duration exposure was not used because it is not known whether respiratory irritation, observed during intermediate-duration inhalation exposure to chlorine dioxide, might result in more persistent effects in cases of chronic-duration exposure. Furthermore, it is not likely that humans would be chronically exposed to significant concentrations of chlorine dioxide vapors in environmental or occupational settings.

Oral MRLs

Acute-duration oral MRLs were not derived for chlorine dioxide or chlorite because adequate human or animal data are not available.

- An MRL of 0.1 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to chlorite.

This MRL is based on a no-observed-adverse-effect-level (NOAEL) of 2.9 mg chlorite/kg/day and a LOAEL of 5.7 mg chlorite/kg/day for neurodevelopmental effects (lowered auditory startle amplitude) in rat pups that had been exposed throughout gestation and lactation via their mothers (Gill et al. 2000). Groups of 30 male and 30 female Sprague-Dawley rats (F_0) received sodium chlorite in the drinking water at concentrations of 35, 70, or 300 mg/L (approximate chlorite doses of 3, 5.7, and 21 mg/kg/day for males and 3.9, 7.6, and 29 mg/kg/day for females) for 10 weeks prior to mating and during mating, after which exposure of females continued throughout gestation and lactation. Groups of F_1 pups were

continued on the same treatment regimen as their parents (chlorite doses of 2.9, 6, and 23 mg/kg/day and 3.9, 7.6, and 29 mg/kg/day for F_1 males and females, respectively). Low-dose female pups exhibited slight, but statistically significant differences in some hematological parameters, relative to controls. No other effects were seen in pups of this exposure level, and the hematological effects were not considered to be adverse. A significant decrease in maximum response to an auditory startle stimulus was noted in mid-dose pups on postnatal day 24, but not on postnatal day 60. Mid-dose F_1 pups also exhibited reduced liver weight. Significant effects at high dose included reduced absolute and relative liver weight in F_1 males and females, reduced pup survival, reduced body weight at birth and throughout lactation in F_1 and F_2 rats, lower thymus and spleen weight in both generations, lowered incidence of pups exhibiting normal righting reflex and with eyes open on postnatal day 15, decreased in absolute brain weight for F_1 males and F_2 females, delayed sexual development in F_1 and F_2 males (preputial separation) and F_1 and F_2 females (vaginal opening), and lowered red blood cell parameters in F_1 rats. The NOAEL of 2.9 mg/kg/day was divided by an uncertainty factor of 30 (10 for interspecies extrapolation and 3 to account for sensitive populations). An uncertainty factor of 3 rather than 10 was used for sensitive populations because the critical effect (neurodevelopmental delay) occurred in a sensitive population (perinatal rat pups).

Chlorine dioxide in drinking water rapidly degrades, predominately to chlorite (Michael et al. 1981). In laboratory animals, orally administered chlorine dioxide is rapidly converted to chlorite and chloride ion (Abdel-Rahman et al. 1980b). Being both a strong oxidizer and water soluble, chlorine dioxide is not likely absorbed in the gastrointestinal tract to any great extent. Chlorite is the most likely source of systemic toxicity resulting from oral exposure to either chlorine dioxide or chlorite. Therefore, the intermediate-duration oral MRL derived for chlorite should also be applicable to chlorine dioxide.

Chronic-duration oral MRLs were not derived for chlorine dioxide or chlorite. No human studies were available in which chronic oral exposure to chlorine dioxide or chlorite was evaluated, and available chronic-duration oral studies in animals identified LOAELs that were higher than those observed for developmental effects following exposures of significantly shorter duration.

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 chlorine dioxide and chlorite. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is

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

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

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

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

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

3.2.1 Inhalation Exposure

Available human and animal data indicate that airborne chlorine dioxide (ClO_2) primarily acts as a respiratory tract and ocular irritant. Chlorite (ClO_2^-) does not persist in the atmosphere either in ionic form or as chlorite salt. Available information concerning health effects associated with inhalation exposure is limited to chlorine dioxide.

3.2.1.1 Death

Information regarding death in humans exposed to atmospheres of chlorine dioxide is limited to a single case in which a bleach tank worker died after being exposed for an unspecified amount of time (Elkins 1959). A chlorine dioxide vapor concentration of 19 ppm (52.4 mg/m^3) was measured inside the tank.

Limited information is available regarding death in laboratory animals exposed to atmospheres of chlorine dioxide. Death resulted from the exposure of a single guinea pig for 44 minutes to an airborne chlorine dioxide concentration of 150 ppm (420 mg/m^3); at the same concentration, exposure for 5 or 15 minutes was not lethal (Haller and Northgraves 1955).

Dalhamn (1957) exposed four rats to approximately 260 ppm (728 mg/m^3) of chlorine dioxide for 2 hours. One of the rats died during exposure and the remaining three rats were sacrificed immediately following the 2-hour exposure period. Microscopic examination revealed pulmonary edema and circulatory engorgement. Dalhamn (1957) also reported death in three of five rats exposed to approximately 10 ppm (28 mg/m^3) of chlorine dioxide, 4 hours/day for up to nine exposures in a 13-day period; clinical signs of toxicity included rhinorrhea and altered respiration.

In another study, rats were repeatedly exposed for 1 month (15 minutes/exposure, 2 or 4 times/day) to atmospheres containing 15 ppm (42 mg/m^3) of chlorine dioxide (Paulet and Desbrousses 1974). Death was noted in 1/10 and 1/15 rats exposed 2 or 4 times/day, respectively. Histological examination of the exposed rats revealed nasal and ocular inflammation, bronchitis, and alveolar lesions. No deaths occurred in rats similarly exposed to 10 ppm (28 mg/m^3) of chlorine dioxide.

3.2.1.2 Systemic Effects

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

No reports were located in which gastrointestinal, musculoskeletal, endocrine, dermal, or metabolic effects were associated with inhalation exposure of humans or animals to chlorine dioxide or chlorite.

Respiratory Effects. Limited human data indicate that airborne chlorine dioxide is a primary respiratory tract irritant. In a case of accidental inhalation exposure to chlorine dioxide in the paper industry, exposure to 5 ppm (14 mg/m^3) for an unspecified amount of time was reported to be irritating (Elkins 1959). In another case report, a woman experienced coughing, pharyngeal irritation, and headache while mixing a bleach solution that was then used to bleach dried flowers (Exner-Freisfeld et al. 1986). The mixing process resulted in the release of chlorine dioxide. Increasing cough caused the woman to abandon the bleaching process. Seven hours later, the woman began experiencing intensified coughing and dyspnea that resulted in hospitalization (16 hours after the exposure) with clinical findings of cough, dyspnea, tachypnea, and rales. Pulmonary function tests revealed reduced VC (vital capacity) and FEV_1 (forced expiratory volume in 1 second) values and increased resistance. Blood gas analysis and blood chemistry revealed hypoxemia and leukocytosis, respectively. Corticosteroid treatment resulted in the alleviation of clinical signs and improved lung function, which was in the normal range at the 2-year follow-up examination.

Nasal abnormalities (including injection, telangectasia, paleness, cobblestoning, edema, and thick mucus) were observed in 13 individuals (1 man and 12 women) who had been accidentally exposed to chlorine dioxide from a leak in a water purification system pipe 5 years earlier (Meggs et al. 1996). These individuals also exhibited sensitivity to respiratory irritants. Nasal biopsies revealed chronic inflammation in the lamina propria of 11/13 chlorine dioxide-exposed individuals, compared with 1/3 control individuals. The severity of inflammation was significantly increased in the chlorine dioxide exposed group, compared to controls.

Several investigators examined the respiratory health of workers who had been occasionally exposed to increased levels of chlorine dioxide resulting from equipment failure (Ferris et al. 1967, 1979; Gloemme and Lundgren 1957; Kennedy et al. 1991). Since the results of these studies are confounded by concurrent exposure to chlorine gas and/or sulfur dioxide, the reported respiratory effects (such as

Table 3-1 Levels of Significant Exposure to Chlorine Dioxide And Chlorite - Inhalation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form
	ACUTE EXPOSURE								
	Death								
1	Rat	2 hr/d for 9 of 13 d					10	100% mortality by day 14	Dalhamn 1957 Chlorine Dioxide
	Systemic								
2	Rat	2 hr/d for 9 of 13 d	Resp		10	rhinorrhea and embarrased respiration			Dalhamn 1957 Chlorine Dioxide
	INTERMEDIATE EXPOSURE								
	Systemic								
3	Rat	3 min/d, 1d/wk, for 3 wk	Resp		760	bronchopneumonia			Dalhamn 1957 Chlorine Dioxide
4	Rat	5 hr/d for 10 wk	Resp	0.1					Dalhamn 1957 Chlorine Dioxide
5	Rat	2 hr/d for 30 d	Resp		10	bronchopneumonia			Paulet and Desbrousses 1970 Chlorine dioxide
			Hemato		10	increased RBC and WBC counts			
			Ocular		10	irritation			

Table 3-1 Levels of Significant Exposure to Chlorine Dioxide And Chlorite - Inhalation (continued)

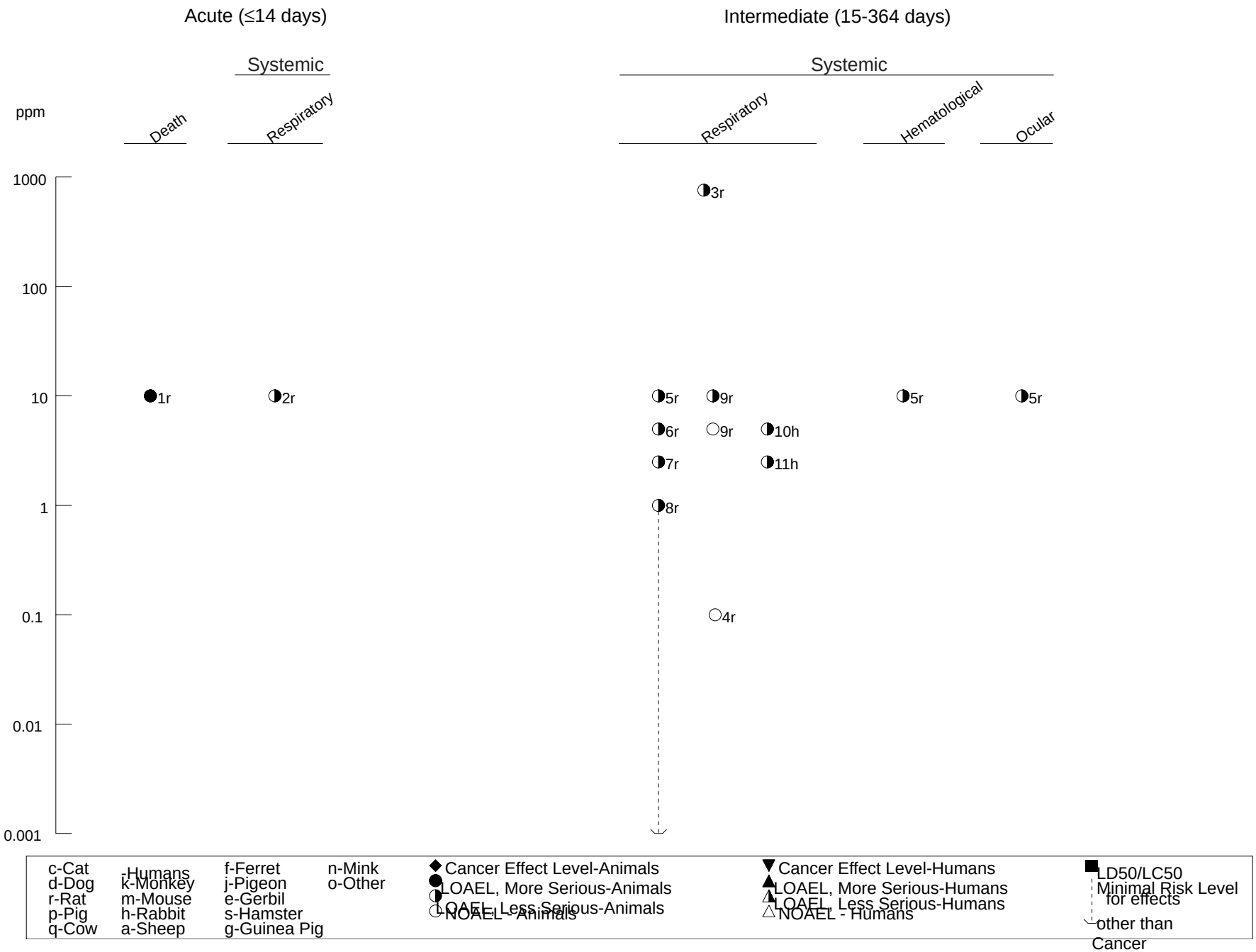
Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL			Reference Chemical Form
					Less Serious (ppm)		Serious (ppm)	
6	Rat	2 hr/d for 30 d	Resp		5	bronchopneumonia		Paulet and Desbrousses 1970 Chlorine dioxide
7	Rat	7 hr/d for 30 d	Resp		2.5	slight respiratory irritation		Paulet and Desbrousses 1970 Chlorine dioxide
8	Rat (Wistar)	5 hr/d 5 d/wk for 2 mo	Resp		1[b]	minimal peribronchiolar edema and vascular congestion in the lungs		Paulet and Desbrousses 1972 Chlorine dioxide
9	Rat	15 min 2 x/d (or 4 x/d) for 1 mo	Resp	5	10	alveolar irritation		Paulet and Desbrousses 1974 Chlorine dioxide
10	Rabbit	2 hr/d for 30 d	Resp		5	slight bronchopneumonia		Paulet and Desbrousses 1970 Chlorine dioxide
11	Rabbit	4 hr/d for 45 d	Resp		2.5	slight pulmonary irritation		Paulet and Desbrousses 1970 Chlorine dioxide

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

b An intermediate-duration inhalation MRL of 0.001 ppm was derived from a LOAEL of 1 ppm and adjusted to 0.15 ppm (LOAELADJ) to compensate for intermittent exposure, converted to the human equivalent concentration (LOAELHEC) of 0.3 ppm, and then divided by an uncertainty factor of 300 (3 for interspecies extrapolation using dosimetric adjustments, 10 for the use of a LOAEL, and 10 to account for sensitive populations).

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

Figure 3-1. Levels of Significant Exposure to Chlorine Dioxide And Chlorite- Inhalation



coughing, wheezing, shortness of breath, and excess phlegm) could not be specifically attributed to chlorine dioxide.

Animal studies also indicate that the respiratory system is a major target of toxicity following inhalation exposure to chlorine dioxide. Dalhamn (1957) reported the results of several inhalation studies in laboratory animals. In one study, a single 2-hour inhalation exposure of four rats to a chlorine dioxide concentration of 260 ppm (728 mg/m^3) resulted in pulmonary edema and nasal bleeding. Respiratory distress was reported in three other rats subjected to 3 weekly 3-minute exposures to decreasing concentrations of airborne chlorine dioxide from 3,400 to 800 ppm (from 9,520 to 2,240 mg/m^3); bronchopneumonia was observed in two of these rats. In a third rat study, repeated exposure to approximately 10 ppm (28 mg/m^3) of chlorine dioxide (4 hours/day for 9 days in a 13-day period) resulted in rhinorrhea, altered respiration, and respiratory infection. No indications of adverse effects were seen in rats exposed to approximately 0.1 ppm (0.28 mg/m^3) of chlorine dioxide 5 hours/day for 10 weeks.

Paulet and Desbrousses (1970, 1972, 1974) conducted a series of studies in which laboratory animals were exposed to atmospheres of chlorine dioxide. Nasal discharge and localized bronchopneumonia (with desquamation of alveolar epithelium) were noted in rats exposed to an airborne concentration of 10 ppm (28 mg/m^3), 2 hours/day for 30 days. Similar, but less severe, respiratory tract effects were observed in another group of rats exposed to a concentration of 5 ppm (14 mg/m^3), 2 hours/day for 10 days. Bronchial inflammation and alveolar congestion and hemorrhage were observed in rats exposed to 2.5 ppm (7 mg/m^3), 7 hours/day for 30 days. Alveolar congestion and hemorrhage were also seen in rabbits following inhalation exposure to 2.5 ppm (7 mg/m^3), 4 hours/day for 45 days. In a group of rats and rabbits sacrificed 15 days after exposure termination, recovery from the pulmonary lesions was apparent (Paulet and Desbrousses 1970). Vascular congestion and peribronchiolar edema were noted in the lungs of rats exposed to a concentration of 1 ppm (2.8 mg/m^3), 5 hours/day, 5 days/week for 2 months (Paulet and Desbrousses 1972). The LOAEL of 1 ppm for respiratory effects, identified in this study, served as the basis for the derivation of an intermediate-duration inhalation MRL for chlorine dioxide (see Section 2.3). In another rat study, exposure to concentrations of 10 or 15 ppm (28 or 42 mg/m^3) for periods as short as 15 minutes (2 or 4 times/day for 1 month) resulted in nasal, bronchial, and alveolar inflammation. These effects had subsided in a 15 ppm (42 mg/m^3) group of rats sacrificed 15 days following exposure termination. This study identified a NOAEL of 5 ppm (14 mg/m^3) for respiratory effects (Paulet and Desbrousses 1974).

Cardiovascular Effects. Information regarding cardiovascular effects in humans following inhalation exposure to chlorine dioxide is limited to a single account of tachycardia that developed in a woman several hours after having been exposed to an unknown concentration of chlorine dioxide that had triggered respiratory effects severe enough to force her to leave the area where she had been bleaching dried flowers (Exner-Freisfeld et al. 1986). The tachycardia was likely secondary to the primary respiratory effects.

Circulatory engorgement was observed in rats that had been exposed to atmospheres containing a chlorine dioxide concentration of approximately 260 ppm (728 mg/m^3) for 2 hours (Dalhamn 1957). This effect was likely secondary to respiratory distress.

Hematological Effects. Information regarding hematological effects in humans following inhalation exposure to chlorine dioxide is limited to a single account of marked leukocytosis diagnosed in a woman several hours after she had been exposed to an unknown concentration of chlorine dioxide that triggered respiratory effects severe enough to force her to leave the area where she had been bleaching dried flowers (Exner-Freisfeld et al. 1986).

Significantly increased blood erythrocyte and leukocyte levels were reported in rats exposed to atmospheres containing a chlorine dioxide level of approximately 10 ppm (28 mg/m^3), 2 hours/day for 30 days (Paulet and Desbrousses 1970). These effects were not seen in a group of rats exposed to 5 ppm (14 mg/m^3), 2 hours/day for 10 days.

Hepatic Effects. No information was located regarding hepatic effects in humans following inhalation exposure to chlorine dioxide.

Paulet and Desbrousses (1974) found no signs of liver effects in rats exposed to atmospheres containing chlorine dioxide levels as high as 10 ppm (28 mg/m^3), 2 hours/day for 30 days. On the other hand, Dalhamn (1957) reported acute liver congestion in rats that had been exposed to atmospheres of approximately 10 ppm of chlorine dioxide for 4 hours/day over 9 days in a 13-day period. However, the liver congestion may have been secondary to primary respiratory effects.

Renal Effects. No information was located regarding renal effects in humans following inhalation exposure to chlorine dioxide.

Evidence of renal effects in animals is limited to a single report of renal hyperemia in two of three rats subjected to 3 weekly 3-minute exposures to decreasing concentrations of airborne chlorine dioxide from 3,400 to 800 ppm (from 9,520 to 2,240 mg/m^3); however, two of three control rats similarly exhibited renal hyperemia (Dalhamn 1957).

Ocular Effects. Workers employed at a sulfite-cellulose production facility reported ocular discomfort that was associated with periods when equipment failure resulted in relatively high air concentrations of chlorine dioxide (Gloemme and Lundgren 1957). However, this finding was confounded by concurrent exposure to chlorine gas and sulfur dioxide.

Animal studies indicate that exposure to chlorine dioxide at airborne concentrations ≥10 ppm (28 mg/m^3) may result in ocular irritation (Dalhamn 1957; Paulet and Desbrousses 1970, 1974).

Body Weight Effects. No information was located regarding body weight effects in humans following inhalation exposure to chlorine dioxide.

Limited animal data indicate that repeated inhalation exposure to chlorine dioxide concentrations ≥10 ppm (28 mg/m^3) may result in depressed body weight gain (Dalhamn 1957; Paulet and Desbrousses 1970); however, this effect may be secondary to primary respiratory effects.

No reports were located in which the following health effects in humans or animals could be associated with inhalation exposure to chlorine dioxide:

3.2.1.3 Immunological and Lymphoreticular Effects

3.2.1.4 Neurological Effects

3.2.1.5 Reproductive Effects

3.2.1.6 Developmental Effects

3.2.1.7 Cancer

3.2.2 Oral Exposure

3.2.2.1 Death

No information was located regarding death in humans following oral exposure to chlorine dioxide or chlorite.

Shi and Xie (1999) indicated that an acute oral LD_{50} value (a dose expected to result in death of 50% of the dosed animals) for stable chlorine dioxide was >10,000 mg/kg in mice. In rats, acute oral LD_{50} values for sodium chlorite ($NaClO_2$) ranged from 105 to 177 mg/kg (equivalent to 79–133 mg chlorite/kg) (Musil et al. 1964; Seta et al. 1991; Sperling 1959).

No exposure-related deaths were observed in rats receiving chlorine dioxide in the drinking water for 90 days at concentrations that resulted in approximate doses as high as 11.5 mg/kg/day in males and 14.9 mg/kg/day in females (Daniel et al. 1990).

In a 14-day range-finding study of rats administered gavage doses of sodium chlorite in the range of 25–200 mg/kg/day (equivalent to 18.6–149.2 mg chlorite/kg/day), one exposure-related death was observed in each sex (Harrington et al. 1995a). The deaths occurred in the 200 mg/kg/day group on treatment days 2 and 3. No treatment-related deaths occurred in the groups receiving chlorite doses ≤56 mg/kg/day. In the 13-week main study performed by these investigators, treatment-related mortality was noted between exposure weeks 10 and 13 in 4/30 rats (3 males and 1 female) receiving sodium chlorite by gavage at a level resulting in a chlorite dose of 80 mg/kg/day. No treatment-related mortality was observed at chlorite dose levels 18.6 mg/kg/day. Death was noted in all four female rats that were administered sodium chlorite by gavage at a dose level of 200 mg/kg/day (equivalent to 150 mg chlorite/kg/day) on gestation days 8–10 (Couri et al. 1982b).

Haag (1949) exposed groups of rats to chlorine dioxide in the drinking water for 2 years at concentrations that resulted in estimated doses of 0.07, 0.13, 0.7, 1.3, or 13 mg/kg/day. The results did not indicate any significant differences in mortality between controls and treated groups up to the highest exposure level tested. Survival was not significantly decreased in groups of rats exposed to chlorite (as sodium chlorite) in the drinking water for 2 years at concentrations that resulted in estimated chlorite doses as high as 81 mg/kg/day (Haag 1949). In another chronic study (Kurokawa et al. 1986), survival was not adversely affected in rats given sodium chlorite in the drinking water at concentrations that resulted in estimated chlorite doses as high as 32.1 mg/kg/day in males and 40.9 mg/kg/day in females. This study was

terminated after 85 weeks of treatment, due to widespread Sendai viral infection in both treatment groups and controls. Exposure of mice to sodium chlorite for up to 85 weeks at concentrations resulting in estimated chlorite doses as high as 90 mg/kg/day did not appear to adversely affect survival. However, control males exhibited markedly reduced survival after 30 weeks of exposure, which was attributed to severe fighting (Kurokawa et al. 1986).

The only available LD_{50} value for chlorite is recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

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

No reports were located in which cardiovascular, musculoskeletal, dermal, ocular, or metabolic effects were associated with oral exposure of humans or animals to chlorine dioxide or chlorite.

Respiratory Effects. Extremely limited information is available regarding respiratory effects in humans following oral exposure to chlorine dioxide or chlorite. Respiratory distress was diagnosed in a patient who had ingested 10 g of sodium chlorite dissolved in 100 mL of water (Lin and Lim 1993). However, the respiratory distress was likely secondary to other effects such as severe methemoglobinemia. No adverse effects on respiration rate were seen in healthy adult males who ingested chlorine dioxide or chlorite every 3 days (for 16 days) at increasing doses of 0.1, 1, 5, 10, 18, and 24 mg/day or 0.01, 0.1, 0.5, 1.0, 1.8, and 2.4 mg/day, respectively (Lubbers et al. 1981). Assuming an average body weight of 70 kg, the individual doses were approximately 0.0014, 0.014, 0.070, 0.140, 0.26, and 0.34 mg/kg/day, respectively, for chlorine dioxide and a factor of 10 lower for respective chlorite doses. No adverse effects on respiration rate were observed in other healthy adult males who ingested chlorine dioxide or chlorite in daily amounts of 2.5 mg (0.04 mg/kg/day) for 12 weeks (Lubbers et al. 1981).

Information regarding respiratory effects in orally-exposed animals is limited to a report of a significantly increased incidence of nasal lesions (goblet cell hyperplasia and inflammation of nasal turbinates) following 90 days of exposure to chlorine dioxide in the drinking water at concentrations that resulted in estimated doses as low as 2 mg/kg/day in males and 8 mg/kg/day in females (Daniel et al. 1990). These

Table 3-2 Levels of Significant Exposure to Chlorine Dioxide And Chlorite - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat	1x (GW)				140 M (LD50)	Musil et al. 1964 Chlorite
	INTERMEDIATE EXPOSURE						
	Systemic						
2	Mouse A/J	12 hrs d 30 d (W)	Hemato	25			Moore and Calabrese 1982 Chlorine Dioxide
3	Mouse A/J	12 hrs/d 30 d (W)	Hemato		19 Increased average corpuscular volume and osmotic fragility		Moore and Calabrese 1982 Chlorite
4	Mouse C57L/J	12 hrs/d 30 d (W)	Hemato		19 Increased average corpuscular volume and osmotic fragility		Moore and Calabrese 1982 Sodium Chlorite
	Reproductive						
5	Rat (Long- Evans)	66-76 d (W)		0.9 M	9 M decreased progressive sperm movement		Carlton et al. 1987 Chlorite
6	Rat (Long- Evans)	1x/d for 9 wk (GW)		10			Carlton et al. 1991 Chlorine dioxide

Table 3-2 Levels of Significant Exposure to Chlorine Dioxide And Chlorite - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL: Less Serious (mg/kg/day)	LOAEL: Serious (mg/kg/day)	Reference Chemical Form
7	Rat (Sprague-Dawley)	16 wk (W)		29			Gill et al. 2000 Chlorite
8	Rat (Sprague-Dawley)	13 wk (W)		1.3		13 decreased number of implants	Suh et al. 1983 Chlorine dioxide
	Developmental						
9	Rat (Long- Evans)	8 wk (W)		0.9 M	9 M decreased serum T3 and T4 levels		Carlton et al. 1987 Chlorite
10	Rat (Sprague-Dawley)	16 wk (W)		2.9 M[b]	5.7 M lowered auditory startle response amplitude on postnatal day 24		Gill et al. 2000 Chlorite
11	Rat (Sprague-Dawley)	9 wk (W)			13 M decreased litter weight and exploratory activity		Mobley et al. 1990 Chlorine dioxide
12	Rat (Sprague-Dawley)	9 wk (W)		2.6 M	5.2 M decreased exploratory activity on postnatal days 36-39		Mobley et al. 1990 Chlorite

Table 3-2 Levels of Significant Exposure to Chlorine Dioxide And Chlorite - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
13	Rat (Sprague-Dawley)	8 wk (W)		2.6 F	13 F altered serum thyroid hormone levels		Orme et al. 1985 Chlorine dioxide
14	Rat (Sprague-Dawley)	ppd 5-20 (W)			14 decreased activity, decreased serum T4		Orme et al. 1985 Chlorine dioxide
15	Rat (Sprague-Dawley)	13 wk (W)		1.3		13 decreased number of live fetuses	Suh et al. 1983 Chlorine dioxide
16	Rat (Sprague-Dawley)	13 wk (W)		1.3			Suh et al. 1983 Chlorite
17	Rat (Sprague-Dawley)	8 wk (W)			13 M decreased activity, decreased brain weight and cell number		Taylor and Pfohl 1985 Chlorine dioxide
18	Rat (Sprague-Dawley)	ppd 5-20 (GW)			14 M decreased activity, decreased brain weight and DNA content		Taylor and Pfohl 1985 Chlorine dioxide
19	Rat (Long- Evans)	ppd 1-20 (GW)			14 decreased brain weight and protein content		Toth et al. 1990 Chlorine dioxide

Table 3-2 Levels of Significant Exposure to Chlorine Dioxide And Chlorite - Oral (continued)

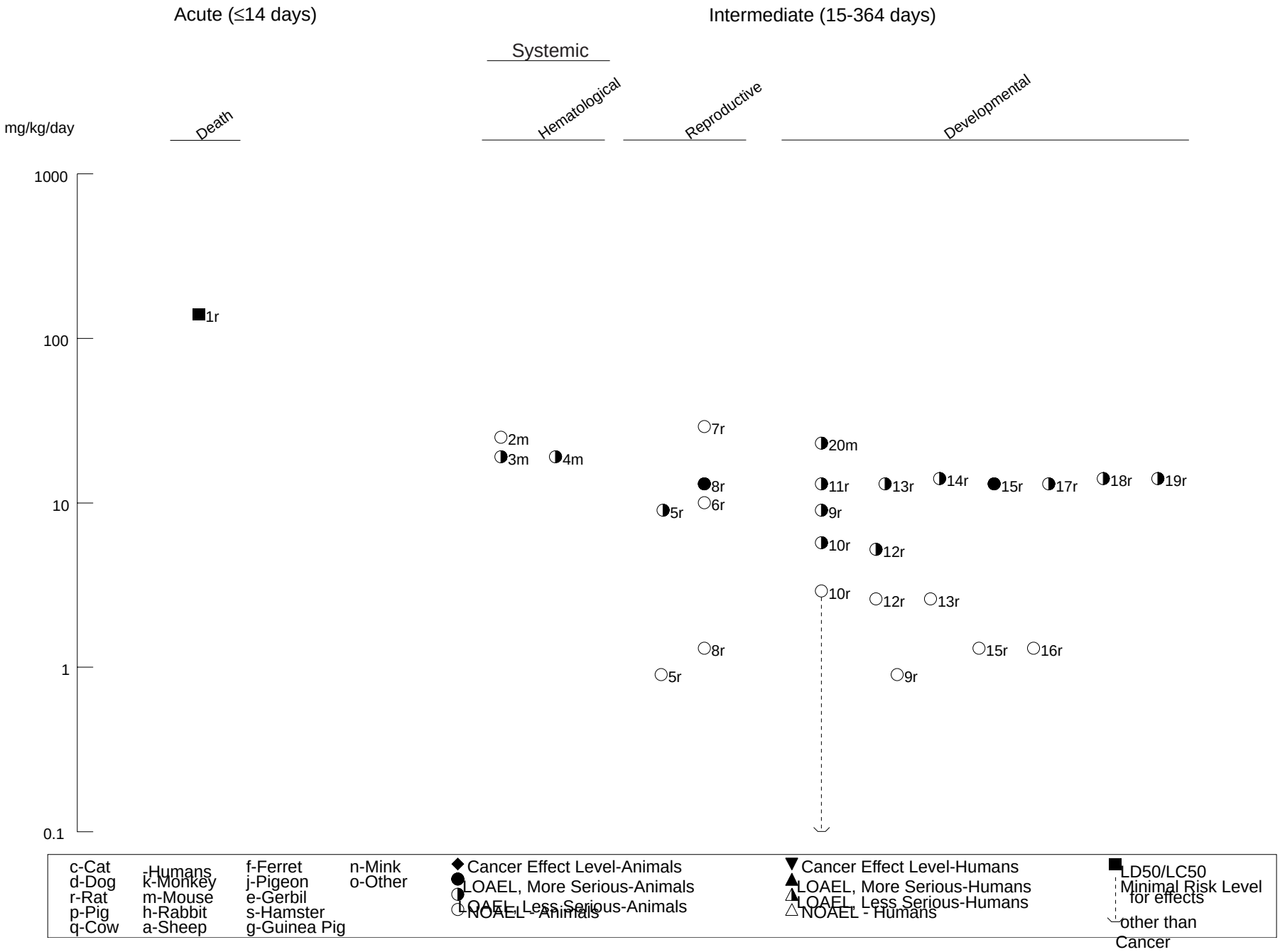
Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less Serious (mg/kg/day)		Serious (mg/kg/day)	
20	Mouse A/J	6 wk (W)			23	decreased average pupweaning weight and birth-to-weaning growth rate		Moore et al. 1980b Chlorite

aThe number corresponds to entries in Figure 3-2.

b An intermediate-duration oral MRL of 0.1 mg/kg/d was derived from a NOAEL of 2.9 mg/kg/day and divided by an uncertainty factor of 30 (10 for interspecies extrapolation and 3 to account for sensitive populations).

d = day(s); F = Female; G = gavage; hr = hour(s); GW = gavage in water; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; ppd = post parturition day; (W) = drinking water; wk = week(s)

Figure 3-2. Levels of Significant Exposure to Chlorine Dioxide And Chlorite- Oral



nasal effects were likely caused by inhalation of chlorine dioxide vapors released from the water rather than a systemic respiratory effect following oral exposure.

Gastrointestinal Effects. Information in humans is limited to a single account of abdominal cramps, nausea, and vomiting within a few minutes after a 25-year-old Chinese male had consumed 10 g of sodium chlorite dissolved in 100 mL of water in an apparent suicide attempt (Lin and Lim 1993).

Information regarding gastrointestinal effects in animals following oral exposure to chlorine dioxide or chlorite is also limited. Bercz et al. (1982) reported erythema and ulceration of the oral mucosa in adult African green monkeys exposed to chlorine dioxide in the drinking water for between 30 and 60 days at a concentration that resulted in a dose of approximately 9 mg/kg/day. Dose-related increased severity of salivation and histopathologic alterations in the stomach (including squamous epithelial hyperplasia, hyperkeratosis, ulceration, chronic inflammation, and edema) were observed in groups of rats administered sodium chlorite in gavage doses of 25 or 80 mg/kg/day (equivalent to 19 or 60 mg chlorite/kg/day, respectively) for 13 weeks; these effects were not seen at a dose level of 7.4 mg chlorite/kg/day (Harrington et al. 1995a).

Hematological Effects. Profound methemoglobinemia was diagnosed in a 25-year-old Chinese male after he had consumed 10 g of sodium chlorite dissolved in 100 mL of water in an apparent suicide attempt (Lin and Lim 1993). Other hematological effects, including ensuing intravascular coagulation, were likely secondary to the methemoglobinemia that persisted despite treatment with methylene blue. No indications of altered hematological parameters were seen in adult male subjects consuming chlorine dioxide in aqueous solution that resulted in a single dose of approximately 0.34 mg/kg of chlorine dioxide (Lubbers et al. 1981) or in other adult males consuming approximately 0.04 mg/kg/day for 12 weeks (Lubbers et al. 1981, 1984a). The same investigators tested chlorite for adverse effects in healthy adult males, and found no evidence of hematological effects after each subject consumed of a total of 1,000 mL of a solution containing 2.4 mg/L chlorite (approximately 0.068 mg/kg) in two doses (separated by 4 hours), or in other healthy normal or glucose-6-phosphate dehydrogenase (G6PD) deficient male subjects who consumed approximately 0.04 mg/kg/day for 12 weeks (Lubbers et al. 1981, 1984a, 1984b). No chlorine dioxide- or chlorite-induced hematological effects were seen among the inhabitants of a rural village who were exposed for 12 weeks via chlorine dioxide in the drinking water at weekly measured concentrations ranging from 0.25 to 1.11 mg/L (chlorine dioxide) or from 3.19 to 6.96 mg/L (chlorite) (Michael et al. 1981). In this epidemiological study, levels of chlorine dioxide in the drinking water before and after the treatment period were <0.05 mg/L. The chlorite level in the drinking water was

0.32 mg/L prior to chlorine dioxide treatment. At 1 and 2 weeks following cessation of treatment, chlorite levels dropped to 1.4 and 0.5 mg/L, respectively.

Some animal studies include reports of hematological effects following oral exposure to chlorine dioxide or chlorite. Abdel-Rahman and coworkers (Abdel-Rahman et al. 1984b; Couri and Abdel-Rahman 1980) exposed groups of male rats to chlorine dioxide in the drinking water, 20 hours/day for 11 or 12 months, at concentrations that resulted in estimated doses of 0.1, 1, 10, and 100 mg/kg/day. Abdel-Rahman et al. (1984b) noted that several hematological parameters were significantly altered in exposed rats, relative to controls, and included decreased osmotic fragility in the 10 and 100 mg/kg/day groups after 2, 4, 7, or 9 months of exposure, and in the 1 mg/kg/day group after 9 months of exposure; decreased erythrocyte counts in the 0.1 mg/kg/day and 100 mg/kg/day groups after 9 months of exposure, but not after 7 months; reduced hematocrit and hemoglobin levels in all groups at 9 months that did not exhibit clear dose-response patterns; increased hematocrit levels in the 10 and 100 mg/kg/day groups at 7 months; and increased mean corpuscular hemoglobin concentrations in the 10 and 100 mg/kg/day groups after 9 months. The study authors suggested that the decreased osmotic fragility may have been related to the disulfide bond between hemoglobin and the cell membrane as the result of oxidative stress. Couri and Abdel-Rahman (1980) found significant increases in blood glutathione reductase levels in rats of the 1, 10, and 100 mg/kg/day groups after 6 months of exposure. At 12 months of exposure, the blood glutathione reductase levels in all exposure groups were similar to those of controls, but the levels of blood glutathione peroxidase were significantly increased at 10 and 100 mg/kg/day. Blood catalase levels were increased in the 100 mg/kg/day group after 6 and 12 months of exposure and decreased in the 0.1 and 1 mg/kg/day groups after 6 months of exposure. The results of Couri and Abdel-Rahman (1980) generally indicate that chlorine dioxide and chlorite may induce increased blood glutathione oxidase activity and resulting decreased blood glutathione levels, which is consistent with the protective role of glutathione against oxidative cellular damage.

Abdel-Rahman and coworkers (Abdel-Rahman et al. 1984b; Couri and Abdel-Rahman 1980) also exposed male rats to sodium chlorite in the drinking water, 20 hours/day for up to 1 year, at concentrations that resulted in estimated doses of 1 or 10 mg/kg/day. Both dose levels resulted in increased mean corpuscular hemoglobin concentration (after 7, but not 9 months) and decreased osmotic fragility after 7–9 months). Erythrocyte glutathione levels were significantly decreased at dose levels 0.1 mg/kg/day by the end of the 1-year exposure period. No consistent treatment-related alterations in erythrocyte count, hematocrit, or hemoglobin levels were observed.

Harrington et al. (1995a) administered sodium chlorite to rats by gavage for 13 weeks, resulting in chlorite doses of 7.4, 19, or 60 mg/kg/day. Relative to controls, significant treatment-related hematological effects included decreased hematocrit and hemoglobin levels (high-dose males), increased methemoglobin and neutrophil levels (mid- and high-dose males), decreased lymphocyte count (mid-dose males), decreased mean erythrocyte count (high-dose males and females), morphological changes in erythrocytes (high-dose males and females), and increased spleen weights (high-dose males and mid- and high-dose females). An unexplained decrease in methemoglobin was observed in high-dose females.

No consistent alterations in hematological parameters (erythrocyte and total and differential leukocyte counts, hemoglobin levels, hematocrit, mean corpuscular volume) were observed in groups of male and female rats given chlorine dioxide in the drinking water for 90 days at concentrations that resulted in doses as high as 12 and 15 mg/kg/day for males and females, respectively (Daniel et al. 1990).

No significant alterations in hematological parameters were seen in adult African green monkeys given chlorine dioxide in the drinking water for up to 60 days at rising concentrations that resulted in estimated doses as high as 9 mg/kg/day (Bercz et al. 1982). Bercz and coworkers later exposed these same monkeys to sodium chlorite in the drinking water in rising concentrations that resulted in estimated chlorite doses as high as 58.4 mg/kg/day. Statistically significant dose-related hematological alterations in these monkeys included decreased erythrocyte levels and cell indices, decreased hemoglobin levels, and slight increases in reticulocyte and methemoglobin levels. However, the data were not presented in a manner that would allow identification of threshold doses for these effects.

Moore and Calabrese (1982) found no significant alterations in hematological parameters within groups of mice exposed to chlorine dioxide in the drinking water for 30 days, at a concentration that resulted in an estimated dose of 25 mg/kg/day. However, when similarly examining the hematotoxicity of chlorite, Moore and Calabrese (1982) found significant increases in mean corpuscular volume and osmotic fragility at a dose level of 19 mg/kg/day.

Heffernan et al. (1979b) observed significant methemoglobinemia within 1–2 hours in cats that had been administered chlorite in single doses of 20 or 64 mg/kg. These same investigators found no signs of methemoglobinemia in rats exposed to sodium chlorite in the drinking water for 30–90 days at concentrations that resulted in estimated chlorite doses as high as 50 mg/kg/day. Doses ≥10 mg/kg/day resulted in slight anemia at 30 days, but this condition appeared to improve at 60 and 90 days.

Hepatic Effects. No indications of adverse hepatic effects (assessed in tests of serum chemistry) were seen in adult male subjects consuming chlorine dioxide in aqueous solution that resulted in a dose of approximately 0.34 mg/kg (Lubbers et al. 1981) or in other adult males consuming approximately 0.04 mg/kg/day for 12 weeks (Lubbers et al. 1984a). The same investigators administered chlorite to healthy adult males, and found no evidence of adverse hepatic effects after each subject had consumed of a total of 1,000 mL of a solution containing 2.4 mg/L chlorite (approximately 0.068 mg/kg) in two doses (separated by 4 hours), or in other healthy normal or G6PD deficient male subjects who had consumed approximately 0.04 mg/kg/day for 12 weeks (Lubbers et al. 1984a, 1984b). No chlorine dioxide- or chlorite-induced signs of altered liver function were seen among the inhabitants of a rural village who were exposed for 12 weeks via chlorine dioxide in the drinking water at weekly measured concentrations ranging from 0.25 to 1.11 mg/L (chlorine dioxide) or from 3.19 to 6.96 mg/L (chlorite) (Michael et al. 1981). In this epidemiological study, levels of chlorine dioxide in the drinking water before and after the treatment period were <0.05 mg/L. The chlorite level in the drinking water was 0.32 mg/L prior to chlorine dioxide treatment. At 1 and 2 weeks following cessation of treatment, chlorite levels dropped to 1.4 and 0.5 mg/L, respectively.

Limited information is available regarding hepatic effects in animals following oral exposure to chlorine dioxide or chlorite. Daniel et al. (1990) exposed male and female rats to chlorine dioxide in the drinking water for 90 days at concentrations that resulted in estimated doses of 1.9, 3.6, 6.2, or 11.5 mg/kg/day for males and 2.4, 4.6, 8.2, or 14.9 mg/kg/day for females. Significantly depressed mean absolute liver weights were observed in males at doses ≥3.6 mg/kg/day and females of the 8.2 mg/kg/day dose group. However, these groups also exhibited decreased water consumption. Moore and Calabrese (1982) found significant increases in G6PD activity in mice receiving sodium chlorite in the drinking water for 30 days at a concentration that resulted in a chlorite dose of 19 mg/kg/day.

Renal Effects. No chlorine dioxide- or chlorite-induced signs of altered renal function were seen among the inhabitants of a rural village who were exposed for 12 weeks via chlorine dioxide in the drinking water at weekly measured concentrations ranging from 0.25 to 1.11 mg/L (chlorine dioxide) or from 3.19 to 6.96 mg/L (chlorite) (Michael et al. 1981). In this epidemiological study, levels of chlorine dioxide in the drinking water before and after the treatment period were <0.05 mg/L. The chlorite level in the drinking water was 0.32 mg/L prior to chlorine dioxide treatment. At 1 and 2 weeks following cessation of treatment, chlorite levels dropped to 1.4 and 0.5 mg/L, respectively. Acute renal failure developed in a 25-year-old Chinese male some days after he had consumed 10 g of sodium chlorite

dissolved in 100 mL of water in an apparent suicide attempt (Lin and Lim 1993), but this effect followed earlier signs of profound methemoglobinemia and respiratory distress.

Information regarding renal effects in animals is limited. Moore and Calabrese (1982) found no evidence of renal effects in mice exposed to sodium chlorite in the drinking water for up to 180 days at a concentration that resulted in an estimated chlorite dose of 25 mg/kg/day. Haag (1949) reported treatment-related pathological effects (distension of the glomerular capsule and appearance of a pale pinkish staining material in the renal tubules) in the kidneys of rats exposed to chlorite in the drinking water for 2 years at concentrations that resulted in estimated doses of 7 or 13 mg/kg/day. Increased relative kidney weights, in the absence histopathological renal effects, were observed in rats administered sodium chlorite in gavage doses of 80 mg/kg/day (equivalent to 60 mg chlorite/kg/day) for 13 weeks (Harrington et al. 1995a).

Endocrine Effects. No reports were located in which endocrine effects could be associated with oral exposure to chlorine dioxide or chlorite in humans.

Information from animal studies is limited to accounts of significantly reduced serum levels of the T4 thyroid hormone in African green monkeys consuming approximately 9 mg chlorine dioxide/kg/day from the drinking water for 6 weeks or approximately 58.4 mg chlorite/kg/day for 8 weeks (Bercz et al. 1982), and a single report of significantly increased adrenal weight in female rats administered sodium chlorite gavage doses ≥25 mg/kg/day (≥19 mg chlorite/kg/day) for 13 weeks (Harrington et al. 1995a). Refer to Section 3.2.2.6 for information regarding altered serum hormone levels in laboratory animals that had been exposed via their mothers during prenatal and postnatal development.

Body Weight Effects. No reports were located in which body weight effects could be associated with oral exposure to chlorine dioxide or chlorite in humans.

Abdel-Rahman et al. (1984b) reported significantly reduced body weight gain (up to 18% lower than controls) in male rats exposed to chlorine dioxide in the drinking water for 11 months at concentrations resulting in estimated doses ranging from 0.12 to 120 mg/kg/day. The same authors reported similar, but less pronounced, reduced body weight gain in rats exposed to sodium chlorite at concentrations that resulted in chlorite doses of approximately 1.2 and 12 mg/kg/day. Although this effect appeared earlier at the highest concentration, mean terminal body weight after 11 months of exposure was lower in low-dose rats than in high-dose rats. Furthermore, the authors did not provide information regarding water and

food consumption. Kurokawa et al. (1986) reported slightly decreased body weight gain (<10% lower than controls) in male and female rats exposed to sodium chlorite in the drinking water for up to 85 weeks at concentrations that resulted in estimated chlorite doses of 13.5 and 24 mg/kg/day in males and 21 and 31 mg/kg/day in females. The results of Kurokawa et al. (1986) are of questionable toxicological significance because water intake among sodium chloride treatment groups was lower than that of controls and the study had to be terminated early due to a Sendai virus infestation within all study groups.

Harrington et al. (1995a) found no significant adverse body weight effects in rats administered up to 60 mg chlorite/kg/day (via gavage) for 13 weeks. No treatment-related effects on body weight were seen in male rats that were administered chlorine dioxide in gavage doses of 2.5, 5, or 10 mg/kg/day for 56 days prior to mating and 10 more days during mating, or in female rats administered the same doses for 14 days prior to mating and throughout mating, gestation, and lactation (Carlton et al. 1991). No significant adverse body weight effects were seen in mice given sodium chlorite in the drinking water for up to 180 days at concentrations resulting in estimated chlorite doses as high as 25 mg/kg/day (Moore and Calabrese 1982) or in other mice exposed to sodium chlorite for 80 weeks at a concentration that resulted in an estimated chlorite dose of 90 mg/kg/day (Kurokawa et al. 1986).

3.2.2.3 Immunological and Lymphoreticular Effects

No reports were located in which immunological or lymphoreticular effects could be associated with oral exposure to chlorine dioxide or chlorite in humans.

Animal data are restricted to limited accounts of treatment-related altered thymus and spleen weights. Daniel et al. (1990) observed reduced spleen weights in female, but not male, rats exposed to chlorine dioxide in the drinking water for 90 days at concentrations that resulted in estimated doses ranging from 2 to 15 mg/kg/day, but the basis for this effect was not discussed. Harrington et al. (1995a) found significantly increased spleen weights in male rats administered sodium chlorite by gavage at a dose level of 80 mg/kg/day (60 mg chlorite/kg/day) for 13 weeks and in female rats similarly treated with 10 or 60 mg chlorite/kg/day. In this study, increased spleen weights were attributed to morphological changes in erythrocytes. Significantly lower spleen and thymus weights were seen in F_1 and F_2 rats that had been exposed to sodium chlorite via their mothers during gestation and lactation and via the drinking water after weaning (Gill et al. 2000).

3.2.2.4 Neurological Effects

No reports were located in which neurological effects could be associated with oral exposure to chlorine dioxide or chlorite in humans or animals. Refer to Section 3.2.2.6 for information regarding neurodevelopmental effects.

3.2.2.5 Reproductive Effects

No reports were located in which reproductive effects could be associated with oral exposure to chlorine dioxide or chlorite in humans.

A paucity of evidence exists for reproductive effects in animals following oral exposure to chlorine dioxide or chlorite. Slight, but significantly altered sperm morphology and motility were observed in male rats exposed to sodium chlorite in the drinking water for 66–76 days at concentrations that resulted in estimated chlorite doses of 9 and 37 mg/kg/day. No dose-related alterations in fertility rates or reproductive tissues (both gross and histopathological examination) were seen and no adverse effects were observed at a chlorite dose level of 0.9 mg/kg/day (Carlton and Smith 1985; Carlton et al. 1987).

Significantly decreased testicular deoxyribonucleic acid (DNA) synthesis was noted in male rats given chlorine dioxide or chlorite (as sodium salt) in the drinking water for 3 months at concentrations that resulted in estimated chlorine dioxide and chlorite doses ≥1.3 and 0.13 mg/kg/day, respectively (Abdel-Rahman et al. 1984b), and other male rats exposed for 3 weeks to a concentration that resulted in a chlorine dioxide dose of 13 mg/kg/day or a chlorite dose of 1.3 mg/kg/day (Suh et al. 1983). A treatment-related decreased number of implants was noted in untreated females that had been mated with chlorine dioxide-treated males of the 13 mg/kg/day level (Suh et al. 1983). No significant increases in abnormal sperm-head morphology were seen in mice given chlorine dioxide or chlorite in gavage doses as high as 16 and 40 mg/kg/day, respectively, for 5 days followed by 3 weeks without treatment prior to testing (Meier et al. 1985). Carlton et al. (1991) found no significant treatment-related effects on fertility rates or sperm parameters in rats following the administration of chlorine dioxide in gavage doses as high as 10 mg/kg/day for 56 days prior to mating and throughout a 10-day mating period (males) and 14 days prior to mating and throughout mating, gestation, and lactation (females).

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

3.2.2.6 Developmental Effects

Information regarding developmental effects in humans following oral exposure to chlorine dioxide or chlorite is limited.

Tuthill et al. (1982) retrospectively compared infant morbidity and mortality data for a community that had utilized chlorine dioxide as a drinking water disinfectant in the 1940s with data of a neighboring community that used conventional drinking water chlorination practices. Exposure to chlorine dioxide-treated water did not adversely affect fetal or perinatal mortality, or birth weight, maximum weight loss, weight loss at 6 days, sex ratio, or birth condition. The authors reported a significantly greater proportion of premature births in the community using chlorine dioxide, as judged by physician assessment. However, other measures of premature birth, such as birth weight and gestational age, did not support the results based on physician assessment. Infants from the community using chlorine dioxide exhibited statistically significantly greater maximum weight loss after birth and smaller weight gain in 6 days, although these effects appeared to be partially linked to the mode of feeding practiced by the mother.

Kanitz et al. (1996) followed 548 births at Galliera Hospital, Genoa, Italy, and 128 births at Chiavari Hospital, Chiavari, Italy, during 1988–1989. Data on infant birth weight, body length, cranial circumference, and neonatal jaundice and on maternal age, smoking, alcohol consumption, education, and preterm delivery were collected from hospital records. Women in Genoa were exposed to filtered water disinfected with chlorine dioxide, sodium hypochlorite, or both; trihalomethane levels varied from 8 to 16 ppb in sodium hypochlorite-treated water and from 1 to 3 ppb in chlorine dioxide-disinfected water. Levels of chlorine dioxide in the water immediately after treatment were <0.3 mg/L, while chlorine residue was <0.4 mg/L. Women residing in Chiavari used water pumped from wells, without any disinfection treatment, and served as the comparison group (controls). Odds ratios (ORs) were determined for the somatic parameters by comparison of groups exposed to chlorine dioxide, sodium hypochlorite, or both with controls and adjusted for maternal education level, income, maternal age, alcohol consumption, and smoking, as well as for sex of the child. Neonatal jaundice occurred more frequently (OR=1.7; 95% confidence interval [CI]=1.1–3.1) in infants whose mothers resided in the area where surface water was disinfected with chlorine dioxide, when compared with infants with mothers using nondisinfected well water. Infants born to mothers residing in areas where surface water was disinfected had smaller cranial circumference (≤35 cm) (OR=2.2, 95% CI=1.4–3.9 for chlorine dioxide; OR=3.5, 95% CI=2.1–8.5 for sodium hypochlorite vs. untreated well water; OR=2.4, 95% CI=1.6–5.3 for

both vs. untreated well water). In addition, these infants had a smaller body length (≤49.5 cm) (OR=2.0, 95% CI=1.2–3.3 for chlorine dioxide vs. untreated well water; OR=2.3, 95% CI=1.3–4.2 for sodium hypochlorite vs. untreated well water). Risks for low birth weight (≤2,500 g) were reported to be increased among mothers residing in areas using water disinfected with chlorine dioxide, but these associations were not statistically significant. For preterm delivery (≤37 weeks), small but not statistically significant increased risks were found among mothers residing in the area using chlorine dioxide. The study authors concluded that infants of women who consumed drinking water treated with chlorine compounds during pregnancy were at higher risk for neonatal jaundice, cranial circumference ≤35 cm, and body length ≤49.5 cm.

Interpretability of the results of Kanitz et al. (1996) is limited by lack of consideration of exposure and potential confounding variables such as lack of quantitative exposure information, exposure to other chemicals in the water, and nutritional habits of the women. In addition, baseline values for the infant sex ratio and percentage of low-weight births for the comparison group deviate from values presented by the World Health Organization for Italy. For example, the sex ratio (male/female live births x100) used in the study for the comparison group was 86, but most recent data (1996; as cited in WHO 2002) for Italy indicate a sex ratio value of 106. Although the percentage of low-weight births in the control group for the Kanitz et al. (1996) study was 0.8%, the percentage of low-weight births (<2,500 g) in Italy for 1994 was 6%. The quality of the untreated well water is not known (i.e., whether it contained any chemical or biological contaminants).

Källén and Robert (2000) found no adverse effects on congenital malformations, childhood cancer, infant mortality, low Apgar score, neonatal jaundice, or neonatal hypothyroidism among infants and children who lived in areas where drinking water was disinfected with chlorine dioxide, compared to controls living in areas where chlorination of drinking water was not practiced. This study is limited because levels of chlorination products and byproducts in the drinking water were not monitored.

Numerous animal studies are available in which developmental end points have been evaluated following oral exposure to chlorine dioxide or chlorite. Some studies cited effects such as decreases in brain weight, brain cell number, exploratory behavior, locomotor activity, and serum thyroxine levels in rat pups whose mothers were exposed to chlorine dioxide before mating and during gestation and lactation and other rat pups that were directly exposed via oral gavage only during postnatal development. Effects such as decreases in serum thyroxine levels, body weight and growth, exploratory behavior, and

amplitude of auditory startle response were reported in rat pups whose mothers were exposed to chlorite before mating and during gestation and lactation.

Chlorine Dioxide. Mobley et al. (1990) administered chlorine dioxide in the drinking water of female rats for 10 days prior to mating with unexposed males, and during gestation and lactation (until postconception days 35–42) at a concentration that resulted in an estimated dose of 13 mg/kg/day. No treatment-related effects were seen in litter size at birth, pup weight gain, or day of eye opening. Litter weight at birth was significantly lower (5%) than controls. At ages 36 through 39 days postconception, exploratory activity was significantly depressed, relative to controls, but not on day 40. On postconception days 37 and 38, no significant treatment-related effects were seen in serum T3 or T4 levels in male pups (serum thyroid hormone levels were not tested in female pups), but T3 uptake was significantly decreased. By postconception day 42, T3 uptake in the exposed male pups was no longer significantly different from controls. The authors suggested that reduced T3 uptake may be the source of delay in exploratory activity.

Orme et al. (1985) exposed rat dams to chlorine dioxide in the drinking water for 2 weeks prior to mating and throughout gestation and lactation at concentrations resulting in estimated doses of 0.26, 2.6, or 13 mg/kg/day. Maternal body weights were not significantly affected by treatment. No significant treatment-related effects were seen in pup body weights or age at eye opening. Consistent, but not significantly lower activity levels were observed in 13 mg/kg/day pups, relative to controls, on postpartum days 15–20. At 13 mg/kg/day, pups also exhibited significantly depressed serum T4 and elevated T3 levels, relative to controls, when tested on postpartum day 21. A significant correlation was noted between T4 levels and locomotor activity. In the same report, pups of unexposed rat dams were administered chlorine dioxide in a gavage dose of 14 mg/kg/day on postnatal days 5–20. Relative to controls, treated pups exhibited lower body weights at 14 and 21 days (17 and 33% lower, respectively), lower activity levels at days 18 and 19 (but not days 15–17 and 20), and lower serum T4 levels on postpartum day 21. Age at eye opening and serum T3 levels were not significantly different from controls. A significant correlation was noted between T4 levels and locomotor activity.

Taylor and Pfohl (1985) found no significant treatment-related effects on body weights of male rat pups whose mothers had been exposed to chlorine dioxide in the drinking water for 14 days prior to mating and throughout gestation and lactation at a concentration that resulted in an estimated dose of 13 mg/kg/day. Female rat pups were not assessed in this study. Compared with controls, the treated pups exhibited consistently (but not significantly) lower activity levels (assessed at 10–20 days of age), significantly

decreased whole brain weight (primarily because of a decrease in cerebellar weight) and cerebellar total DNA content (due to a decrease in total cell number) in 21-day-old pups, and decreased exploratory activity at 60 days of age. Other pups were exposed to chlorine dioxide only during postnatal days 5–20 at a daily gavage dose of 14 mg/kg. At 21 days of age, these pups exhibited significant decreases in body weight, absolute and relative whole brain and forebrain weights, and forebrain DNA content and total cell number, compared with controls. Decreased DNA content and total cell number were seen in the cerebellum and forebrain when tested at 11 days of age.

Toth et al. (1990) administered chlorine dioxide to male and female rat pups at a daily gavage dose of 14 mg/kg on postnatal days 1–20. Examinations were performed on selected pups at ages 11, 21, and 35 days, and results were compared to control pups. Significantly lower (5–7% lower) body weights and decreased ratio of forebrain content to cerebellum weight were noted at all three examination times. Significantly lower forebrain weights were seen on days 21 and 35, along with accompanying reductions in protein content (days 21 and 35) and reduced DNA content (day 35). Serum T3 and T4 levels were not affected by chlorine dioxide treatment. A slight, but statistically significant decrease in free T4 was reported at day 21, but the toxicological significance is not clear.

Suh et al. (1983) administered chlorine dioxide in the drinking water of female rats for 2.5 months prior to mating with unexposed males, and during gestation days 1–20 at levels that resulted in estimated doses of 0.13, 1.3, or 13 mg/kg/day. The only reported maternal effect was a slight (but not significantly) decreased maternal body weight gain in 1.3 and 13 mg/kg/day dams, relative to controls. Fetal effects included a significant dose-response trend for decreasing number of implants per litter and number of live fetuses per dam, and significantly increased total fetal weights and male fetal weights in the 13 mg/kg/day group, compared with controls. No significant effects were seen in crown-rump length or skeletal anomalies.

Carlton et al. (1991) administered chlorine dioxide to rats in gavage doses of 2.5, 5, or 10 mg/kg for 56 days prior to mating and during 10 days of mating (males) and 14 days prior to mating and throughout mating, gestation, and lactation (females). Relative to controls, pups in the exposure groups exhibited no significant differences in death before weaning, mean litter size, or mean body weight. Significantly lower absolute vaginal weight and vagina-to-body weight ratio were seen in F_1 females of the 10 mg/kg/day exposure group; no significant changes in reproductive organ weights were observed in F_1 males.

Chlorite. Gill et al. (2000; results previously published in CMA 1996) conducted a 2-generation study to examine reproductive, developmental, neurological, and hematological end points in rats exposed to sodium chlorite. Male and female rats (F_0) received sodium chlorite in the drinking water at concentrations that resulted in estimated chlorite doses of 3, 5.7, or 21 mg/kg/day for males and 3.9, 7.6, and 29 mg/kg/day for females. The treatment period lasted for 10 weeks prior to mating and during mating, after which males were sacrificed; exposure of females continued throughout gestation and lactation. Sodium chlorite concentrations were adjusted during lactation to maintain a constant intake during a period of increased water intake. F_1 generation pups were continued on the same treatment regimen as their parents (chlorite doses of 2.9, 6, or 23 mg/kg/day and 3.9, 8, or 29 mg/kg/day for F_1 males and females, respectively). Mating commenced at approximately 14 weeks of age to produce F_{2a} rats that were maintained through weaning on postnatal day 21. Due to a reduced number of litters in the mid-dose F_1-F_{2a} generation, the F_1 animals were remated following weaning of the F_{2a} rats to produce an F_{2b} generation. Significant alterations related to treatment at high-dose included reduced absolute and relative liver weight in F_1 males and females, reduced pup survival (increase in number of pups found dead and/or killed prematurely during lactation) and reduced body weight at birth and throughout lactation in F_1 and F_2 rats, lower thymus and spleen weight in both generations, decreased absolute brain weight for F_1 males and F_2 females, delayed sexual development in F_1 and F_2 males (preputial separation) and females (vaginal opening), and lowered red blood cell parameters and white blood cell counts in F_1 rats. In the mid-dose groups, reduced absolute and relative liver weight in F_1 males was observed. In addition, a significant decrease in maximum response to an auditory startle stimulus was noted in mid- and high-dose groups on postnatal day 24, but not on postnatal day 60. The NOAEL of 2.9 mg/kg/day, identified in this study, served as the basis for the derivation of an intermediate-duration oral MRL for chlorite. A LOAEL was 5.7 mg/kg/day for lowered auditory startle response amplitude and hematotoxicity on postnatal day 24.

Mobley et al. (1990) exposed female rats to chlorite in the drinking water for 10 days prior to mating with unexposed males and during gestation and lactation until postnatal days 42–53 at concentrations that resulted in estimated chlorite doses of 2.6 or 5.2 mg/kg/day. Chlorite exposure did not adversely affect litter size or pup weight gain. Significant, consistent decreases in exploratory activity were observed in the 5.2 mg/kg/day group on postnatal days 36–39, but not on days 39–41. In the 2.6 mg/kg/day group, there were significant decreases in activity on days 36 and 37, but not on days 38–40. No significant alterations in serum T3 or T4 levels or free T4 levels were observed in male pups (female pups were not assessed for thyroid hormone levels). The day of eye opening in the treatment groups was similar to that of controls.

Carlton et al. (1987) exposed groups of 12 male rats to sodium chlorite in the drinking water for 56 days prior to mating and throughout a 10-day mating period. Groups of 24 female rats were also exposed to sodium chlorite for 14 days prior to mating, during the mating period, and throughout gestation and lactation. Estimated chlorite doses were 0.09, 0.9, or 9 mg/kg/day for males and 0.1, 1, or 10 mg/kg/day for females. No significant alterations in litter survival rates, median day of eye opening, or median day of observed vaginal patency were observed. Significant decreases in serum T3 and T4 levels were consistently observed in high-dose groups of F_1 males and females at postnatal days 21 and 40.

Couri et al. (1982b) exposed pregnant rats to sodium chlorite in the drinking water during gestational days 8–15 at concentrations that resulted in estimated chlorite doses of 70, 440, or 610 mg/kg/day. The litters were either delivered at term or by cesarean section on gestational day 22. Significant decreases in crown-rump length were observed at all doses in term-delivered litters and in the 70 mg/kg/day group that was cesarean-delivered. Fetal weights were not adversely affected. An increase in the number of resorbed and dead fetuses was observed in cesarean-delivered litters of all exposure levels; two litters out of five were totally resorbed in the high-dose group. Postnatal growth and the incidences of soft tissue and skeletal malformations were not adversely affected.

Suh et al. (1983) administered chlorite in the drinking water of female rats for 2.5 months prior to mating with unexposed males and during gestational days 0–20 at chlorite concentrations that resulted in estimated doses of 0.13 or 1.3 mg/kg/day; the dams were killed on gestational day 20. No treatment-related effects were seen regarding resorptions, dead fetuses, or fetal body weights. Crown-rump length was significantly higher in the high-dose group compared with controls, but the difference was very small and is probably not biologically significant. Chlorite exposure did not significantly alter incidence of skeletal anomalies.

Moore and coworkers (Moore and Calabrese 1982; Moore et al. 1980b) exposed pregnant mice to sodium chlorite in the drinking water throughout gestation and lactation at a concentration that resulted in an estimated chlorite dose of 23 mg/kg/day. A decrease in the conception rate (number of females positive for vaginal plug/number of females producing litters; 39 vs. 56% in controls) was observed; the statistical significance was not reported. No significant alterations in gestation length, litter size, number of pups dead at birth, or number of pups alive at weaning were observed. Pup growth was adversely affected, as shown by significant decreases in average pup weaning weight and birth-to-weaning growth rate.

Harrington et al. (1995b) treated rabbits with sodium chlorite via their drinking water on gestation days 7–20 at levels that resulted in estimated chlorite doses of 10, 26, or 40 mg/kg/day. Dams were sacrificed on gestation day 28. Although the number and mean percentage of major external and visceral and skeletal abnormalities were increased in the 26 and 40 mg/kg/day groups (external/visceral: 6.6 and 2.9%, respectively, vs. 1.5% in controls; skeletal: 5.4 and 0%, respectively, vs. 0% in controls), the authors did not consider these to be treatment-related adverse effects. Mean fetal weights in the 26 and 40 mg/kg/day groups were slightly decreased (<9%, relative to controls). In the 26 and 40 mg/kg/day groups, the incidence of minor skeletal abnormalities (13.9 and 14.2% for the 26 and 40 mg/kg/day groups, respectively, vs. 7.7% in controls) and skeletal variants related to incomplete fetal bone ossification was higher than for controls. The authors state in their discussion that these alterations in fetal body weight and delayed ossification indicate embryonic growth retardation. Decreases in maternal food and water consumption and body weight gain may be responsible, at least in part, for some of the fetal effects.

Skowronski et al. (1985) administered Alcide (a liquid sterilizer consisting of sodium chlorite and lactic acid that form chlorine dioxide) to mice and rats in gavage doses of 1 and 0.1 mL, respectively, on gestation days 6–15. No signs of maternal toxicity were observed, and there were no statistically significant adverse fetal effects.

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

3.2.2.7 Cancer

No reports were located in which cancer could be associated with oral exposure to chlorine dioxide or chlorite in humans.

Kurokawa et al. (1986) performed a cancer bioassay on rats and mice that were exposed to sodium chlorite in the drinking water. Rats were exposed to concentrations that resulted in estimated chlorite doses of 13.5 or 24 mg/kg/day in males and 21 or 31 mg/kg/day in females. All groups of rats became infected with the Sendai virus, causing a premature termination of the study after 85 weeks of exposure. Mice were exposed for 80 weeks to concentrations that resulted in estimated doses of 45 or 90 mg/kg/day. Mice received distilled water only for an additional 5 weeks following the 80-week treatment period. Yokose et al. (1987) also published a report of the mouse data presented in Kurokawa et al. (1986). The

two accounts vary slightly in exposure duration information and in reported numbers of tumor-bearing mice at study end. Yokose et al. (1987) indicated that exposure of mice was terminated at 80 weeks according to a guideline for carcinogenicity studies from the Ministry of Health and Welfare of Japan.

No chlorite-related increased tumor incidences were observed in rats. Significant increases in liver and lung tumors were observed in the male mice. Incidence of hyperplastic nodules in the liver was significantly increased in the low- and high-dose groups relative to controls (3/35 [reported as 6/35 in Yokose et al. 1987], 14/47, and 11/43, in the control, low-, and high-dose groups, respectively) and combined incidence of liver hyperplastic nodules and hepatocellular carcinoma was increased in the low-dose group (7/35, 22/47, and 17/43, respectively). Incidence of lung adenoma (0/35, 2/47, and 5/43, respectively) and combined incidence for lung adenoma and adenocarcinoma (0/35, 3/47, and 7/43, respectively) were significantly increased in the high-dose group compared with controls. The study authors noted that incidences of liver hyperplastic nodules and lung adenomas in the treated animals were within the range of historical controls in their laboratory and in the National Toxicology Program laboratories. In addition, high mortality in the control males because of fighting reduced the sample size, making statistical comparisons between controls and treated animals difficult to interpret. In the female mice, the only significant alteration in tumor incidence was a significantly lower incidence of malignant lymphoma/leukemia in the high-dose group (7/47, 5/50, and 1/50, respectively). The exposure durations of both rat and mouse studies were considerably less-than-lifetime exposure guidelines for adequate carcinogenicity studies.

Using three short-term assays, Miller et al. (1986) found no evidence of carcinogenic potential of drinking water disinfected with chlorine dioxide. In an initiation-promotion assay, water was disinfected with chlorine dioxide, after which water samples containing chlorine dioxide residue were concentrated and administered orally to mice 3 times/week for 2 weeks. The mice were then exposed to 12-tetradecanyl-phorbal-13-acetate (a known cancer promoter) in acetone by dermal applications 3 times/week for 20 weeks. No significant increases in the number of skin tumors or the number of tumors per animal were observed, compared with vehicle controls. In a lung adenoma assay, groups of female Strain A mice received 0.25 mL gavage doses of the concentrated water samples 3 times/week for 8 weeks, followed by a 16-week observation period. The number of animals with lung adenomas and the number of adenomas per animal were not significantly altered compared with vehicle controls. In the third assay, partially hepatectomized rats were exposed to a single oral dose of the concentrated water samples followed 1 week later by administration of 500 mg/L sodium phenobarbital (a known cancer promoter) in drinking

water for 56 days. Examination of livers in the treated rats did not reveal significant treatment-induced increases in gamma glutamyl transpeptidase-positive foci (an indicator of preneoplastic liver changes).

3.2.3 Dermal Exposure

The database for health effects related to dermal exposure to chlorine dioxide or chlorite is extremely limited. No reports were located regarding adverse effects in humans following dermal exposure to chlorine dioxide or chlorite. Available information in animals is restricted to a report that a solution containing chlorine dioxide concentrations of approximately 9.7–11.4 mg/L was nonirritating to the skin of mice in a 48-hour test. Dermal exposure to high concentrations would be expected to result in irritation, due to the oxidizing properties of chlorine dioxide and chlorite. Sodium chlorite was not carcinogenic in mice treated dermally for 51 weeks. Nor did sodium chlorite appear to be a cancer promoter in mice initiated with a single dermal dose of dimethylbenzanthracene followed by 51 weeks of dermal exposure to sodium chlorite.

The toxicity of Alcide, an antimicrobial compound consisting of solutions of sodium chlorite and lactic acid that produce chlorine dioxide when mixed, was assessed in laboratory animals following repeated exposure and in fetuses of pregnant animals following *in utero* exposure during critical periods of organogenesis (Abdel-Rahman et al. 1987a, 1987b; Gerges et al. 1985). However, levels of exposure to sodium chlorite and chlorine dioxide were not known and uncertainty exists regarding the potential for the formation of other reactive substances that could trigger toxic responses.

3.2.3.1 Death

No reports were located regarding death in humans or animals following dermal exposure to chlorine dioxide or chlorite.

3.2.3.2 Systemic Effects

No reports were located in which respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, ocular, or body weight effects could be associated with dermal exposure to chlorine dioxide or chlorite in humans or animals.

Dermal Effects. No reports were located regarding dermal effects in humans following dermal exposure to chlorine dioxide or chlorite.

A solution containing chlorine dioxide concentrations of approximately 9.7–11.4 mg/L was nonirritating to the skin of mice in a 48-hour test (Shi and Xie 1999). Moderate to severe erythema was observed in rabbits following repeated daily applications of Alcide, an antimicrobial compound consisting of solutions of sodium chlorite and lactic acid that produce chlorine dioxide when mixed (Abdel-Rahman et al. 1987b). However, levels of exposure to sodium chlorite or chlorine dioxide could not be quantified.

No reports were located in which the following health effects in humans or animals could be associated with dermal exposure to chlorine dioxide or chlorite:

3.2.3.3 Immunological and Lymphoreticular Effects

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

No reports were located regarding developmental effects in humans following dermal exposure to chlorine dioxide or chlorite.

Animal data are limited to studies of laboratory rodents exposed to Alcide, an antimicrobial compound consisting of solutions of sodium chlorite and lactic acid that produce chlorine dioxide when mixed (Abdel-Rahman et al. 1987a; Gerges et al. 1985). No statistically significant treatment-related developmental effects were observed in the offspring of rats, mice, and rabbits treated daily with dermal applications of Alcide gel (as high as 2 g/kg) during the critical period of organogenesis. However, levels of exposure to sodium chlorite or chlorine dioxide could not be quantified.

3.2.3.7 Cancer

Kurokawa et al. (1984) conducted two dermal carcinogenicity assays on chlorite. In an assay designed to assess the ability of chlorite to act as a complete carcinogen, female mice were treated with dermal applications of sodium chlorite (in acetone) twice weekly for 51 weeks. Compared with controls, sodium

chlorite exposure did not result in increased tumor incidence. To test the ability of chlorite to act as a tumor promoter, a single initiating dose of dimethylbenzanthracene (DMBA) was applied to the skin of mice. The DMBA application was followed by dermal applications of sodium chlorite (in acetone) twice weekly for 51 weeks. Although incidences of tumors were higher in the chlorite/acetone-exposed mice than in those receiving acetone only, the differences were not statistically significant.

3.3 GENOTOXICITY

No reports were located regarding the genotoxicity of chlorine dioxide or chlorite in humans.
The genotoxic potential of chlorine dioxide and chlorite has been assessed in a number of standard genotoxicity test systems, resulting in both positive and negative results. Chlorine dioxide was not mutagenic (either with or without metabolic activation) in one Ames assay of *Salmonella typhimurium* strains TA 97, TA98, TA100, and TA102 (Wang et al. 2002a), but a weakly positive response (without metabolic activation) in strain TA100 was noted in another Ames assay (Ishdate et al. 1984). Chlorine dioxide did not increase chromosomal aberrations in Chinese hamster fibroblast cells (Ishidate et al. 1984). Samples of water that had been disinfected with chlorine dioxide did not induce reverse mutations in *S. typhimurium* with or without activation (Miller et al. 1986). Negative results were obtained from *in vivo* assays for micronuclei and bone marrow chromosomal aberrations in Swiss CD-1 mice, as well as sperm-head abnormalities in B6C3F1 mice, following gavage administration of chlorine dioxide doses ranging from 0.1 to 0.4 mg/mouse/day for 5 consecutive days (Meier et al. 1985). Chlorine dioxide did not induce micronuclei in the bone marrow of mice that had been exposed via the drinking water at a concentration of 624 mg/L (Wang et al. 2002b). Hayashi et al. (1988) reported positive results in the micronucleus assay in ddY mice following single intraperitoneal injection of chlorine dioxide at dose levels of 3.2–25 mg/kg.

Sodium chlorite induced reverse mutations in *S. typhimurium* (with activation) and chromosomal aberrations in Chinese hamster fibroblast cells (Ishidate et al. 1984). Negative results were obtained from *in vivo* assays for micronuclei and bone marrow chromosomal aberrations in Swiss CD-1 mice, as well as sperm-head abnormalities in B6C3F1 mice, following gavage administration of sodium chlorite at doses ranging from 0.25 to 1 mg/mouse/day for 5 consecutive days (Meier et al. 1985). Hayashi et al. (1988) reported negative results for induction of micronuclei in ddY mice that were administered sodium chlorite in single oral gavage doses ranging from 37.5 to 300 mg/kg, but positive results were obtained in mice subjected to single or multiple intraperitoneal injection of 7.5 to 60 mg sodium chlorite/kg.

3.4 TOXICOKINETICS

Although no data were located regarding absorption following inhalation exposure to chlorine dioxide, little absorption of parent compound across lung tissue would be expected due to the highly reactive nature of chlorine dioxide. The rapid appearance of ^{36}Cl in plasma following oral administration of chlorine dioxide ($^{36}ClO_2$) or chlorite ($^{36}ClO_2^-$) has been shown in laboratory animals. Using 72-hour urinary excretion rates for ^{36}Cl, absorption rates of 30–35% of intragastrically administered chlorine dioxide or chlorite have been estimated. Limited animal data indicate the presence of ^{36}Cl in plasma following dermal application of Alcide, an antimicrobial compound containing sodium chlorite and lactic acid that rapidly form chlorine dioxide when mixed together. In rats, absorbed ^{36}Cl (from $^{36}ClO_2$ or $^{36}ClO_2^-$ exposure sources) is slowly cleared from the blood and is widely distributed throughout the body. Chlorine dioxide rapidly dissociates, predominantly into chlorite (which itself is highly reactive) and chloride ion (Cl^-), ultimately the major metabolite of both chlorine dioxide and chlorite in biological systems. Urine is the primary route of ^{36}Cl elimination, predominantly in the form of chloride ion.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

No information was located regarding absorption following inhalation exposure to chlorine dioxide or chlorite in humans or animals.

3.4.1.2 Oral Exposure

No information was located regarding absorption following oral exposure to chlorine dioxide or chlorite in humans.

In rats, a single gavage dose of $^{36}ClO_2$ resulted in the rapid appearance of ^{36}Cl in the plasma, which peaked 1 hour after dosing (Abdel-Rahman et al. 1980a). Based on 72-hour urinary excretion of 30% of the ^{36}Cl in the administered dose, it can be assumed that absorption was at least 30%. The absorption rate constant and half-time were 3.77/hour and 0.18 hours, respectively (Abdel-Rahman et al. 1982). Similar results were reported following single gavage dosing of rats with $^{36}ClO_2^-$ (Abdel-Rahman et al. 1982). In

this study, peak plasma levels of ^{36}Cl were reached within 2 hours following dosing and 72-hour urinary excretion data indicated that at least 35% of the radiolabel had been absorbed. The absorption rate constant and half-time were 0.198/hour and 3.5 hours, respectively.

3.4.1.3 Dermal Exposure

No information was located regarding absorption following dermal exposure to chlorine dioxide or chlorite in humans.

Dermal absorption of ^{36}Cl was measured in rats following 10 daily applications of Alcide, an antimicrobial compound consisting of solutions of sodium chlorite and lactic acid that produce chlorine dioxide when mixed (Scatina et al. 1984). Maximal levels of plasma ^{36}Cl were reached after 72 hours. The absorption rate constant and half-life were 0.0314/hour and 22.1 hours, respectively.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

No information was located regarding distribution of chlorine dioxide, chlorite, or their metabolites following inhalation exposure in humans or animals.

3.4.2.2 Oral Exposure

No information was located regarding distribution of chlorine dioxide, chlorite, or their metabolites following oral exposure in humans.

Animal data indicate that ^{36}Cl, absorbed from the gastrointestinal tract following single oral (gavage) administration of $^{36}ClO_2$, is cleared from the blood with a half-time of elimination of 43.9 hours (Abdel-Rahman et al. 1982) and is widely distributed throughout the body (Abdel-Rahman et al. 1980a, 1980b, 1982, 1984a). At 72 hours following dosing, highest concentrations were found in the blood, stomach, and small intestines. Relatively high concentrations were also seen in the lung, kidney, liver, testes, spleen, thymus, and bone marrow. A shorter elimination half-time (31.0 hours) was noted in rats that had been exposed to chlorine dioxide in the drinking water for 2 weeks prior to receiving a single gavage dose

of $^{36}ClO_2$ (Abdel-Rahman et al. 1980a). Single oral (gavage) administration of chlorite ($^{36}ClO_2^-$) resulted in an elimination half-time of 35.2 hours from the blood and widespread distribution of ^{36}Cl (Abdel-Rahman et al. 1982, 1984a), similar to that observed following oral exposure to chlorine dioxide.

3.4.2.3 Dermal Exposure

No information was located regarding distribution of chlorine dioxide, chlorite, or their metabolites following dermal exposure in humans or animals. However, ^{36}Cl has been measured in plasma of rats following 10 daily applications of Alcide, an antimicrobial compound consisting of solutions of sodium chlorite and lactic acid that produce chlorine dioxide when mixed (Scatina et al. 1984).

3.4.3 Metabolism

3.4.3.1 Inhalation Exposure

No information was located regarding metabolism of chlorine dioxide or chlorite following inhalation exposure in humans or animals.

3.4.3.2 Oral Exposure

Both chlorine dioxide and chlorite are primarily metabolized to chloride ion. At 72 hours following single oral (gavage) administration of radiolabeled chlorine dioxide in rats, chloride ion accounted for approximately 87% of the radioactivity that had been collected in the urine and 80% of the radioactivity in a plasma sample (Abdel-Rahman et al. 1980b). Chlorite was the other major metabolite, accounting for approximately 11 and 21% of the radioactivity in the urine and plasma samples, respectively. Chlorate was a minor component of the radioactivity in the urine. Similarly, chloride ion accounted for approximately 85% of the radioactivity in the 72-hour urine collection of rats that had been orally administered radiolabeled chlorite; the remainder in the form of chlorite (Abdel-Rahman et al. 1984a).

Both chlorine dioxide and chlorite, being strong oxidizing agents, are most likely rapidly reduced in biological systems mainly to chloride ion. Bercz et al. (1982) demonstrated this reduction for chlorine dioxide that was introduced into saliva obtained from anesthetized monkeys.

3.4.3.3 Dermal Exposure

No information was located regarding metabolism of chlorine dioxide or chlorite following dermal exposure in humans or animals.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

No information was located regarding elimination or excretion following inhalation exposure to chlorine dioxide or chlorite in humans or animals.

3.4.4.2 Oral Exposure

The urine is the primary route of excretion of orally administered radioactivity from radiolabeled chlorine dioxide or chlorite. In rats, 72 hours following single oral (gavage) administration of $^{36}ClO_2$, 31 and 4.5% of the radiolabel had been excreted in the urine and feces, respectively, mainly in the form of the chloride ion. The ratio of $^{36}Cl^-$ to $^{36}ClO_2^-$ was 4 to 1, and no parent compound was detected (Abdel-Rahman et al. 1980a, 1980b). In rats administered a single oral (gavage) dose of radiolabeled chlorite, 35 and 5% of the radiolabel were excreted in the urine and feces, respectively, in the first 72 hours after dosing. Approximately 90% of the urinary label was in the form of chloride ion (Abdel-Rahman et al. 1984a).

3.4.4.3 Dermal Exposure

Urinary excretion of ^{36}Cl was observed in rats that had been administered Alcide, an antimicrobial compound consisting of sodium chlorite and lactic acid that form chlorine dioxide when mixed (Scatina et al. 1984). The rats had received 10 daily dermal applications, followed by an application of radiolabeled Alcide. Urinary excretion was greatest in the first 24 hours post application; the half-time of urinary elimination was 64 hours. The excreted radioactivity consisted of approximately equal portions of chloride ion and chlorite. No radioactivity was detected in feces or expired air.

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

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

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

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

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for

many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-3 shows a conceptualized representation of a PBPK model.

No PBPK models for exposure to chlorine dioxide or chlorite were identified.

3.5 MECHANISMS OF ACTION

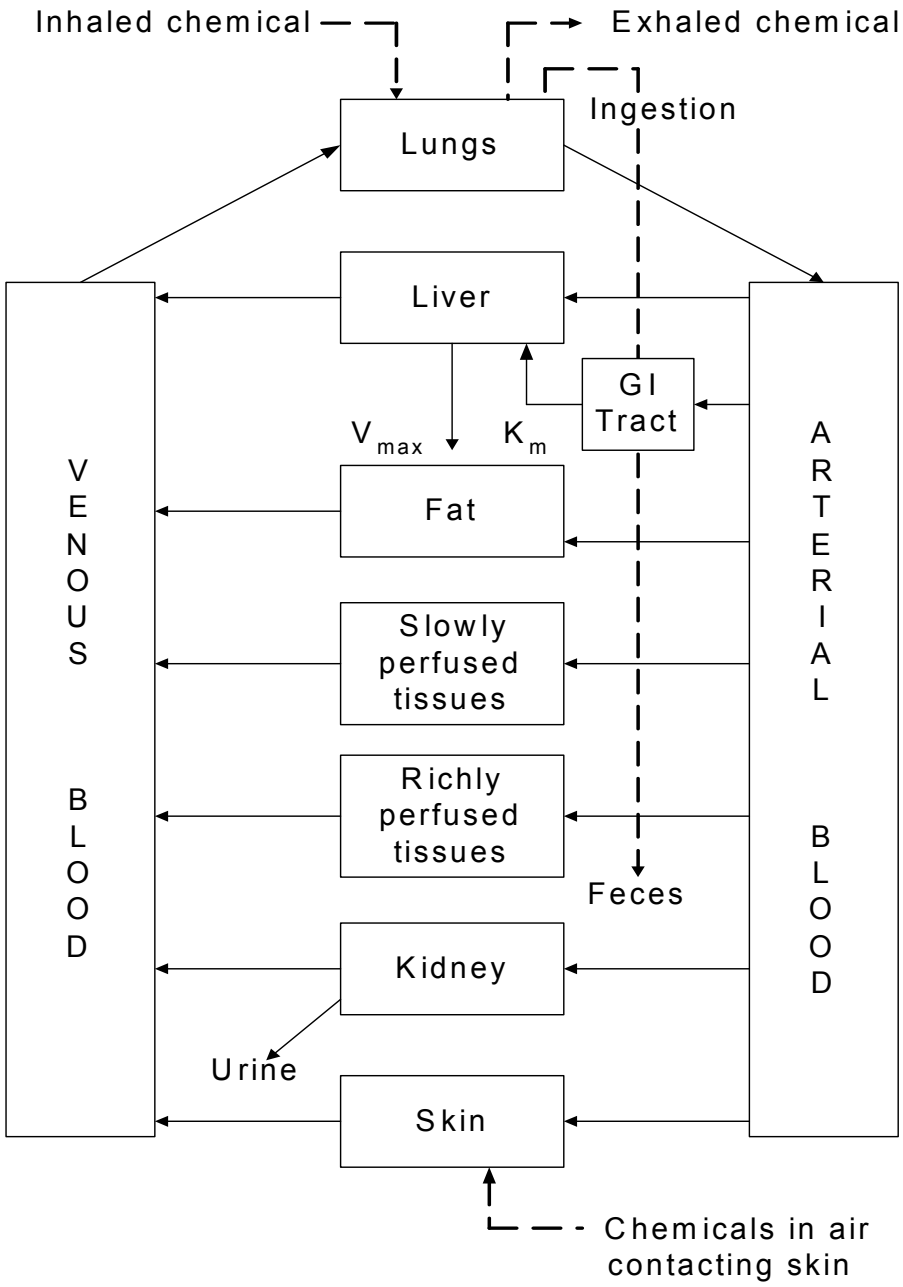
3.5.1 Pharmacokinetic Mechanisms

Absorption. No information was located regarding mechanisms of absorption of chlorine dioxide or chlorite. Being a strong oxidizer, chlorine dioxide is likely to undergo rapid redox reactions within biological tissues rather than to be absorbed as parent compound. Chlorite levels have been measured in urine following oral exposure to chlorine dioxide or chlorite, indicating that some degree of chlorite absorption occurs across the digestive tract. Due to the highly reactive nature of chlorite, itself a strong oxidizer, absorption would be expected to occur via passive diffusion rather than active transport mechanisms.

Distribution. No information was located regarding the transport of chlorine dioxide or chlorite in the blood. However, based on the fact that the strong oxidizing property of chlorine dioxide likely results in rapid conversion to chlorite (also a strong oxidizer) in biological systems, and ultimately to chloride ion, it would be expected that distribution would follow normal ionic distribution patterns.

Metabolism. Although no information was located regarding mechanisms of chlorine dioxide and chlorite metabolism, ultimate transformation to chloride ions is likely achieved via redox reactions with a variety of substances in biological systems that are readily oxidized.

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



Source: adapted from Krishnan et al. 1994

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

Excretion. No information was located regarding specific mechanisms of excretion of chlorine dioxide, chlorite, or their metabolites. However, since chloride ion is the primary excretory product of chlorine dioxide and chlorite, excretory mechanisms would be expected to be similar to those responsible for excretion of other ions.

3.5.2 Mechanisms of Toxicity

Chlorine dioxide and chlorite are strong oxidizing agents that readily react upon direct contact with biological tissues, resulting in local irritation. Mechanisms whereby chlorine dioxide and chlorite exert hematological effects such as methemoglobinemia in humans (Lin and Lim 1993; Michael et al. 1981) and animals (Bercz et al. 1982; Harrington et al. 1995a; Heffernan et al. 1979b) and alterations in other blood factors are not presently known, but may be related to their properties as oxidants. Due to its highly reactive nature, it is unlikely that chlorine dioxide would be absorbed in quantities large enough to produce systemic toxicity directly. Chlorite is produced and absorbed following oral exposure to chlorine dioxide in animals (Abdel-Rahman et al. 1980b), and may be more likely to be involved in observed hematological effects than chlorine dioxide itself. Chlorite has been shown to be more efficient than chlorine dioxide in the production of methemoglobin, in decreasing blood glutathione, and in alteration of erythrocytes (Abdel-Rahman et al. 1980a, 1984b; Couri and Abdel-Rahman 1980; Heffernan et al. 1979a, 1979b). *In vitro* studies have further shown that sufficient amounts of glutathione may prevent chlorine dioxide-induced osmotic fragility, presumably by the prevention of the formation of disulfide bonds between hemoglobin and components of the cell membrane (Abdel-Rahman et al. 1984b). A recent *in vitro* study demonstrated that sodium chlorite readily depleted glutathione in mammalian cells, but treatment of phospholipids with chlorite yielded only low levels of hydroperoxides (Ingram et al. 2003). These findings indicate that chlorite-induced cellular damage may be more likely due to interaction with thiol compounds than with cell membrane lipids.

Although changes in thyroid hormones have been reported in laboratory animals that were either directly exposed to chlorine dioxide or exposed to chlorine dioxide or chlorite via their mothers during pre and postpartum development (Bercz et al. 1982; Carlton and Smith 1985; Carlton et al. 1987, 1991; Mobley et al. 1990; Orme et al. 1985), possible mechanisms that might mediate such effects have not been elucidated. Increased levels of iodine have been noted in esophagus and small intestine of rats up to 24 hours after administration of gavage doses of radiolabeled iodine followed by chlorine dioxide (Harrington et al. 1985). However, no concurrent treatment-related alterations in blood or thyroid gland iodine level were seen. Because the extent of thyroid uptake of bioavailable iodine does not appear to

decrease following oral exposure to chlorine dioxide, Bercz et al. (1986) speculated that indications of altered hormonogenesis, such as altered serum thyroid hormone, could be the result of absorption of iodinated molecules having thyromimetic or thyroid inhibitory properties. These results, however, do not imply that the effect is mediated through a hormonal pathway.

Likewise, mechanisms responsible for the developmental effects observed in laboratory animals exposed to chlorine dioxide or chlorite are not known. They might be related to the oxidative properties of these chemicals. Although overt signs of neurodevelopmental effects (delays in exploratory activity and general locomotor activity) and altered serum thyroid hormone have been observed concurrently in animals that had been exposed via their mothers during pre and postpartum development, a mechanistic basis has not been investigated.

3.5.3 Animal-to-Human Extrapolations

Mechanisms involved in chlorine dioxide- and chlorite-induced oxidative stress, such as methemoglobinemia in humans and animals, would be expected to be similar across species. However, the database of pharmacokinetic and health effects information for chlorine dioxide or chlorite does not include studies in which interspecies comparisons were made.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the Environmental Protection Agency (EPA) to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), which in 1998 completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such

chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 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).

Treatment-related altered serum thyroid hormone levels indicate that chlorine dioxide and chlorite may exert toxic effects that are mediated through the neuroendocrine axis. Changes in thyroid hormones have been reported in laboratory animals that were either directly exposed to chlorine dioxide (repeated doses as low as 9 mg/kg/day), or exposed to chlorine dioxide or chlorite via their mothers (maternal doses of chlorine dioxide and chlorite as low as 13 and 9 mg/kg/day, respectively) during pre- and postpartum development (Bercz et al. 1982; Carlton and Smith 1985; Carlton et al. 1987, 1991; Mobley et al. 1990; Orme et al. 1985).

Altered sperm morphology has been associated with oral exposure of rats to sodium chlorite at doses as low as 9 mg chlorite/kg/day for 66–76 days of exposure (Carlton and Smith 1985; Carlton et al. 1987). However, available data do not indicate that the endocrine pathway might be involved in this effect.

3.7 CHILDREN'S SUSCEPTIBILITY

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

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

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per

kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Developmental effects have been observed in animals following exposure of their mothers to chlorine dioxide or chlorite during gestation and/or lactation (Gill et al. 2000; Harrington et al. 1995b; Mobley et al. 1990; Moore and Calabrese 1982; Orme et al. 1985; Taylor and Pfohl 1985; Toth et al. 1990). In the absence of apparent maternal toxicity, these findings suggest that parent compound or toxic metabolite can cross the placenta and that infants and children may be particularly vulnerable to chlorine dioxide- and chlorite-mediated toxic effects. It is well recognized that neurological development continues after birth and that gastrointestinal uptake of many nutrients and chemicals is greater in the neonate than in the adult.

Infants may exhibit a greater degree of methemoglobinemia than adults following oral exposure to chlorine dioxide or chlorite because infants form methemoglobin more readily than adults, due at least in part to the presence of hemoglobin F at birth, which is readily oxidized to methemoglobin. Additional indications that infants may exhibit increased susceptibility to chlorine dioxide- or chlorite-induced hematological effects include a lower capacity to enzymatically reduce methemoglobin and a characteristically lower level of vitamin E (an important antioxidant) at birth. However, actual data were not found to support such speculation.

No information was located regarding age-related differences in toxicokinetic parameters for chlorine dioxide or chlorite.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The

preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to chlorine dioxide and chlorite 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 chlorine dioxide and chlorite 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 Chlorine Dioxide and Chlorite

Chlorine dioxide is a strong oxidizing agent that is not likely to be widely distributed in biological systems or excreted as parent compound. Chlorite may be detected in tissues, blood, urine, and feces, which may serve as an indication of exposure to chlorine dioxide or chlorite. However, no information

was located regarding the quantification of exposure based on measured levels of chlorite in biological samples.

3.8.2 Biomarkers Used to Characterize Effects Caused by Chlorine Dioxide and Chlorite

Exposure to relatively high levels of chlorine dioxide or chlorite may result in increased methemoglobin levels. However, this effect is not unique to chlorine dioxide or chlorite. Presently, no chemical-specific biomarkers of effect are known to exist for chlorine dioxide or chlorite.

3.9 INTERACTIONS WITH OTHER CHEMICALS

No information was located regarding interactions of chlorine dioxide or chlorite with other chemicals that might impact toxicity.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency may be more sensitive to chlorine dioxide or chlorite (Michael et al. 1981) because of a reduced capacity for maintaining significant levels of glutathione, which can lead to destruction of red blood cells and hemolytic anemia. Approximately 10% of the African American population expresses G6PD deficiency. Moore and Calabrese (1980a) demonstrated that G6PD-deficient human red blood cells exposed to chlorite exhibited markedly greater decreased glutathione and G6PD activity and increased methemoglobin levels than red blood cells from humans with normal G6PD activity. Abdel-Rahman and coworkers (Abdel-Rahman et al. 1984b; Couri and Abdel-Rahman 1980) noted decreased glutathione levels in rats chronically exposed to chlorite in the drinking water. Additionally, individuals who are deficient in NADH-dependent

methemoglobin reductase, the principal means by which methemoglobin is reduced to hemoglobin, may exhibit a decreased ability to reduce methemoglobin.

Refer to Section 3.7 for information regarding age-related differences in susceptibility to chlorine dioxide and chlorite.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to chlorine dioxide and chlorite. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to chlorine dioxide and chlorite. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. No texts were located that provide specific information about treatment following exposures to chlorine dioxide or chlorite.

3.11.1 Reducing Peak Absorption Following Exposure

No information was located regarding methods to reduce peak absorption following exposure to potentially toxic levels of chlorine dioxide or chlorite.

3.11.2 Reducing Body Burden

No information was located regarding methods to reduce body burden following exposure to potentially toxic levels of chlorine dioxide or chlorite. Chlorine dioxide is rapidly converted to chlorite and chloride ion in biological systems. Chlorite is fairly rapidly excreted in the urine following exposure to chlorine dioxide or chlorite. Increasing urinary output might be an effective method for reducing body burden shortly following exposure.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Intravenous administration of methylene blue may be an effective method for reducing chlorine dioxide- or chlorite-induced increases in methemoglobin. However, this treatment is not effective in G6PD-deficient individuals.

3.12 ADEQUACY OF THE DATABASE

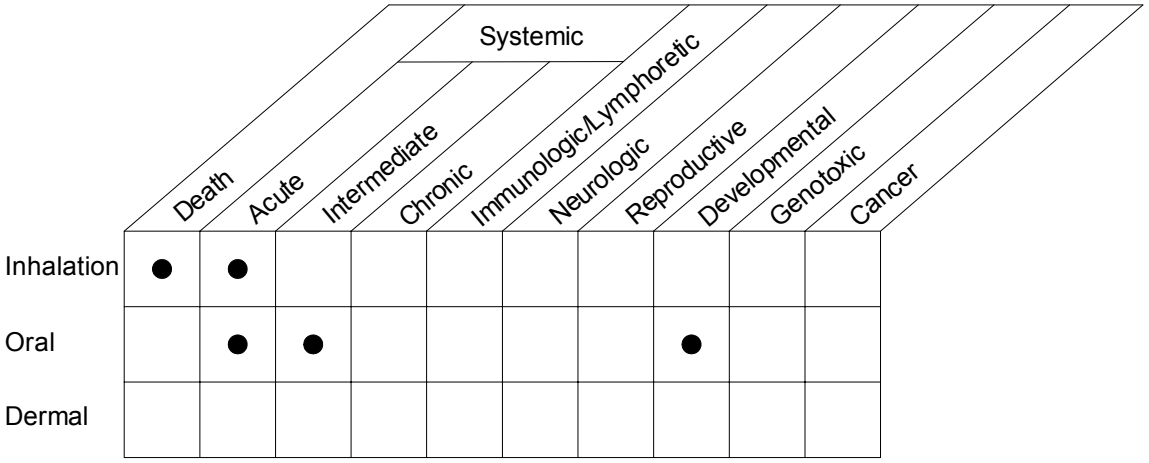
Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of chlorine dioxide and chlorite is available. Where adequate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

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.

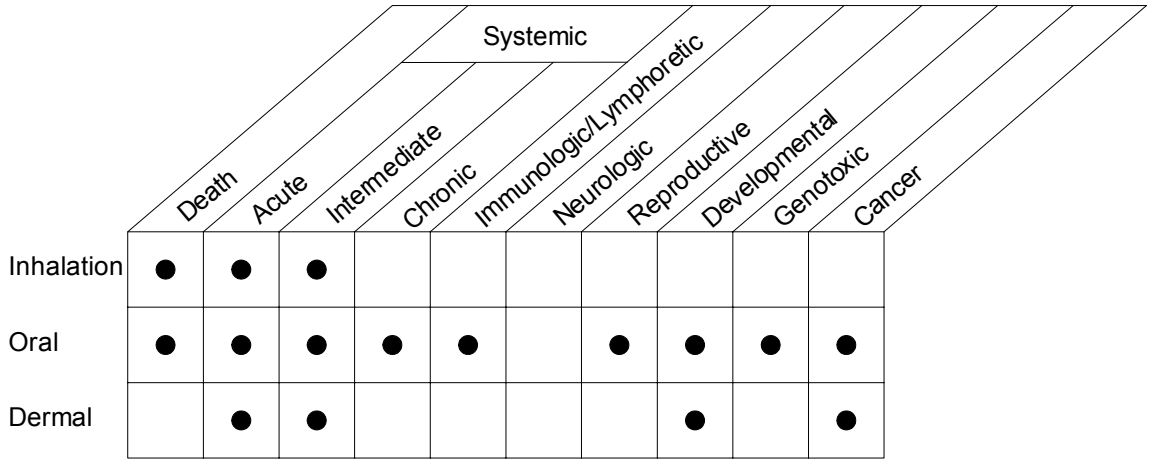
3.12.1 Existing Information on Health Effects of Chlorine Dioxide and Chlorite

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

Figure 3-4. Existing Information on Health Effects of Chlorine Dioxide and Chlorite



Human



Animal

● Existing Studies

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Chlorine dioxide and chlorite are strong oxidizing agents that readily react upon direct contact with biological tissues, resulting in local irritation. Information regarding health effects in acutely exposed humans is limited to cases of accidental exposure to concentrated chlorine dioxide vapors (Elkins 1959; Exner-Freisfeld et al. 1986; Meggs et al. 1996) and a single case of intentional ingestion of sodium chlorite in an apparent suicide attempt (Lin and Lim 1993). Reports of acute toxicity in animals primarily concern lethality following relatively high-level inhalation or oral exposure to chlorine dioxide or chlorite (Couri et al. 1982b; Dalhamn 1957; Haller and Northgraves 1955; Harrington et al. 1995a; Musil et al. 1964; Seta et al. 1991; Shi and Xie 1999; Sperling 1959). Additional acute toxicity studies should focus on oral and inhalation exposures that result in less serious critical effects. Results of such studies might serve as bases for establishing acute-duration oral and inhalation MRLs.

Intermediate-Duration Exposure. Information regarding chlorine dioxide- or chlorite-induced adverse health effects in humans following intermediate-duration exposure is restricted to a single report in which no adverse effects were seen in 198 persons of a rural village following 3 months of exposure to approximately 5 ppm of chlorite in drinking water that had been disinfected with chlorine dioxide (Michael et al. 1981). Animal studies indicate that the respiratory system is the major target of toxicity following inhalation exposure (Dalhamn 1957; Paulet and Desbrousses 1970, 1972, 1974). The studies of Paulet and Desbrousses served as the basis for an intermediate-duration inhalation MRL. Additional animal studies are needed to assess the effects of chlorine dioxide vapors on upper respiratory tissues, which may be more sensitive than pulmonary tissues. Intermediate-duration oral studies identified neurodevelopmental delay and thyroid hormone effects as the most sensitive chlorine dioxide- or chlorite-induced end points (Carlton and Smith 1985; Carlton et al. 1987; Gill et al. 2000; Mobley et al. 1990; Orme et al. 1985; Taylor and Pfohl 1985; Toth et al. 1990). Additional studies are needed to further assess these critical end points and to determine whether they might be interrelated. See Section 3.12.2 for additional information concerning potential for chlorine dioxide- or chlorite-induced neurodevelopmental effects following intermediate-duration oral exposure to chlorine dioxide or chlorite.

Chronic-Duration Exposure and Cancer. No information was located regarding health effects in humans following chronic-duration exposure to chlorine dioxide or chlorite; however, information is available from animal studies. Results of animal carcinogenicity testing are available for oral (Kurokawa

et al. 1986; Miller et al. 1986) and dermal exposure (Kurokawa et al. 1984). These results generally do not indicate a carcinogenic effect, with the exception of a report of significantly higher incidences of liver and lung tumors in male mice exposed to 250 and 500 ppm of chlorite, respectively, in the drinking water (Kurokawa et al. 1986). However, high mortality in the control males (due to fighting) reduced the sample size, making statistical comparisons between controls and treated animals difficult to interpret. A well-designed cancer bioassay that includes noncancer end points might provide valuable information concerning the effects of long-term exposure to chlorine dioxide or chlorite.

Genotoxicity. No reports were located regarding the genotoxicity of chlorine dioxide or chlorite in humans. Genotoxicity tests using standard *in vivo* and *in vitro* test systems have produced mixed results (Hayashi et al. 1988; Ishidate et al. 1984; Meier et al. 1985; Wang et al. 2002a, 2002b). Both chlorine dioxide and chlorite induced reverse mutations in *S. typhimurium* (with activation). Chlorite, but not chlorine dioxide, induced chromosomal aberrations in Chinese hamster fibroblast cells. Negative results were obtained in tests for micronuclei and chromosomal aberrations in bone marrow of mice orally administered chlorine dioxide or chlorite during a period of 5 days. However, both chlorine dioxide and chlorite produced positive results for micronuclei in mice following intraperitoneal injection. The database for chlorine dioxide and chlorite genotoxicity is not extensive and testing has produced mixed results; additional genotoxicity testing is not warranted.

Reproductive Toxicity. No information was located regarding chlorine dioxide- or chlorite-induced reproductive effects in humans. Slightly altered sperm morphology and motility were observed in rats administered sodium chlorite in the drinking water, but treatment did not result in significant alterations in fertility rates or reproductive tissues (Carlton and Smith 1985; Carlton et al. 1987). Repeated oral exposure of male rats to chlorine dioxide or chlorite resulted in significantly decreased testicular DNA synthesis (Abdel-Rahman et al. 1984b; Suh et al. 1983). No significant treatment-related effects on fertility rates or sperm parameters were seen in other rats following repeated oral exposure to chlorine dioxide (Carlton et al. 1991). Additional reproductive toxicity studies are needed to further investigate the potential for chlorine dioxide or chlorite to induce reproductive effects.

Developmental Toxicity. Epidemiological reports have focused on human populations exposed to chlorine dioxide-treated drinking water (Kanitz et al. 1996; Tuthill et al. 1982). However, study limitations preclude making definitive conclusions regarding the potential for chlorine dioxide- or chlorite-induced developmental toxicity in humans. Results from rat studies indicate that perinatal exposure to chlorine dioxide or chlorite may result in delayed neurodevelopment, observed as decreases

in brain size and exploratory and locomotor activities (Mobley et al. 1990; Orme et al. 1985; Taylor and Pfohl 1985; Toth et al. 1990) or decreased auditory startle response (Gill et al. 2000). In some studies, postnatal changes in serum thyroid hormone levels have also been observed (Carlton and Smith 1985; Carlton et al. 1987; Mobley et al. 1990; Orme et al. 1985). These effects have been observed at maternal doses of approximately 6–14 mg/kg/day. Neither chlorine dioxide nor chlorite appears to induce significant gross soft tissue or skeletal abnormalities (Couri et al. 1982b; Harrington et al. 1995b; Suh et al. 1983). Additional developmental toxicity studies in animals are needed, which include a mechanistic approach designed to investigate the basis of the observed neurodevelopmental delays and a possible relationship between thyroid hormone effects and neurodevelopmental delays.

Immunotoxicity. Reports of immunotoxicity are restricted to the findings of treatment-related altered thymus and spleen weights in animals exposed to chlorine dioxide or chlorite (Daniel et al. 1990; Gill et al. 2000; Harrington et al. 1995a). Neither chlorine dioxide nor chlorite appears to be of particular immunotoxicity concern. Additional immunotoxicity studies are not needed at this time.

Neurotoxicity. With the exception of neurodevelopmental effects, chlorine dioxide and chlorite do not appear to present a significant neurotoxicity concern. Additional studies should focus on neurodevelopmental end points (refer to Section 3.12.2).

Epidemiological and Human Dosimetry Studies. Limited information is available regarding health effects in humans following exposure to chlorine dioxide or chlorite. Respiratory effects were reported among individuals who were accidentally exposed to concentrated chlorine dioxide vapors (Elkins 1959; Exner-Freisfeld et al. 1986; Ferris et al. 1967, 1979; Gloemme and Lundgren 1957; Kennedy et al. 1991; Meggs et al. 1996). A single case report was located in which an individual ingested approximately 10 g of sodium chlorite in an apparent suicide attempt (Lin and Lim 1993). In a set of controlled studies, male volunteers consumed chlorine dioxide in aqueous solution and submitted blood samples for analysis (Lubbers et al. 1981, 1984a, 1984b). Three epidemiological studies were designed to investigate the potential for adverse effects in communities that utilized chlorine dioxide as a drinking water disinfectant (Kanitz et al. 1996; Michael et al. 1981; Tuthill et al. 1982). However, these studies had limitations in their designs that affect their interpretability. Well-designed epidemiological studies of populations orally exposed to chlorine dioxide in the drinking water could provide valuable information regarding safe levels.

Biomarkers of Exposure and Effect.

Exposure. No known biomarkers of exposure exist for chlorine dioxide. Being a water-soluble, strong oxidizing agent, chlorine dioxide is not likely to be absorbed as parent compound, but rather quickly reduced to chlorite and ultimately chloride ion. Chlorite levels can be measured in biological tissues and fluids, and may serve as an indication of recent exposure to chlorine dioxide or chlorite. Studies could be designed to quantify chlorite levels in various body tissues and fluids; however, it is not known whether such measurements could be used to quantify exposure levels.

Effect. No known chlorine dioxide- or chlorite-specific biomarkers of effect exist. Additional studies of mechanisms of toxicity might provide information that could aid in the search for biomarkers of effect. A human study of methemoglobinemia among persons (especially children and nursing infants) exposed to higher concentrations of chlorine dioxide and chlorite in the drinking water might be beneficial.

Absorption, Distribution, Metabolism, and Excretion. Information regarding the pharmacokinetics of chlorine dioxide and chlorite is predominantly derived from oral studies in laboratory animals. Chlorite (ClO_2^-) does not persist in the atmosphere either in ionic form or as chlorite salt. The rapid appearance of ^{36}Cl in plasma following oral administration of chlorine dioxide ($^{36}ClO_2$) or chlorite ($^{36}ClO_2^-$) has been shown in laboratory animals (Abdel-Rahman et al. 1980a, 1982, 1984a). Limited animal data indicate the presence of ^{36}Cl in plasma following dermal application of Alcide, an antimicrobial compound containing sodium chlorite and lactic acid which rapidly form chlorine dioxide when mixed together (Scatina et al. 1983). In rats, absorbed ^{36}Cl (from $^{36}ClO_2$ or $^{36}ClO_2^-$ sources) is slowly cleared from the blood and is widely distributed throughout the body (Abdel-Rahman et al. 1980a, 1980b, 1982, 1984a). Chlorine dioxide rapidly dissociates, predominantly into chlorite (which itself is highly reactive) and chloride ion (Cl^-), ultimately the major metabolite of both chlorine dioxide and chlorite in biological systems (Abdel-Rahman et al. 1980b, 1984a). Urine is the primary route of elimination, predominantly in the form of chloride ion (Abdel-Rahman et al. 1980a, 1980b, 1984a). Additional pharmacokinetic studies of chlorine dioxide and chlorite should be designed to examine mechanisms of absorption and metabolic changes that might account for observed neurodevelopmental effects. Such studies might also elucidate mechanisms underlying alterations in various hematological and thyroid hormone parameters of currently unknown significance.

Comparative Toxicokinetics. No studies were located in which toxicokinetics of chlorine dioxide or chlorite were examined in humans. Chlorine dioxide is used as a drinking water disinfectant and readily forms chlorite (ClO_2^-) in aqueous environments. Therefore, humans would be most likely to

encounter chlorine dioxide or chlorite via the oral exposure route. Currently, available toxicokinetic information is restricted to animal studies. Additional studies could be designed to examine toxicokinetics in humans orally exposed to chlorine dioxide or chlorite. Results of human and animal studies could then provide a basis for development of PBPK models for species extrapolation.

Methods for Reducing Toxic Effects. No information was located regarding methods for reducing the toxic effects of chlorine dioxide or chlorite. Increasing urinary output might be an effective method for reducing body burden shortly following exposure. Intravenous administration of methylene blue might reduce chlorine dioxide- or chlorite-induced increases in methemoglobin. Future studies should be designed to evaluate mechanisms of chlorine dioxide- and chlorite-mediated toxicity. Results of such mechanistic studies might elucidate methods to reduce the toxic effects.

Children's Susceptibility. Neurodevelopmental delays and postnatal changes in serum thyroid hormone levels have been observed in animals following exposure of their mothers to chlorine dioxide or chlorite during gestation and/or lactation (Carlton and Smith 1985; Carlton et al. 1987; Gill et al. 2000; Mobley et al. 1990; Orme et al. 1985; Taylor and Pfohl 1985; Toth et al. 1990). It is not known whether age-related differences in toxicokinetic parameters exist for chlorine dioxide or chlorite. Additional studies should be designed to further examine neurodevelopmental toxicity and underlying mechanisms.

A human study of methemoglobinemia among children and nursing infants exposed to higher concentrations of chlorine dioxide and chlorite in the drinking water might provide valuable information regarding age-related susceptibility.

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

3.12.3 Ongoing Studies

No ongoing studies pertaining to the toxicity or pharmacokinetics of chlorine dioxide or chlorite were located in a search of the Federal Research in Progress database (FEDRIP 2003).

4. CHEMICAL AND PHYSICAL INFORMATION

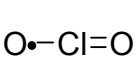
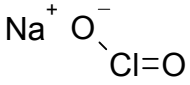
4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of chlorine dioxide and sodium chlorite is located in Table 4-1. Table 4-1 lists common synonyms, trade names, and other pertinent identification information for chlorine dioxide and sodium chlorite.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of chlorine dioxide and sodium chlorite is located in Table 4-2. Table 4-2 lists important physical and chemical properties of chlorine dioxide and sodium chlorite, but is not intended to be all inclusive.

Table 4-1. Chemical Identity of Chlorine Dioxide and Sodium Chlorite

Characteristic	Information	
Chemical name	Chlorine dioxide	Sodium chlorite
Synonym(s)	Alcide; Anthium dioxcide; Chlorine(IV) oxide; Chlorine oxide; Chlorine peroxide; Chloroperoxide; Chloriperoxyl; Chloryl radical; Dioxide de cloro [Spanish]; Dioxide de chlore [French]; Caswell No. 179A; Doxcide 50	Chlorous acid, sodium salt; Textone
Registered trade name(s)	No data	No data
Chemical formula	ClO_2	$NaClO_2$
Chemical structure		
Identification numbers:		
CAS Registry	10049-04-4	7758-19-2
NIOSH RTECS	FO3000000	VZ4800000
EPA Hazardous Waste	No data	No data
OHM/TADS	No data	No data
DOT/UN/NA/IMCO	NA 9191 (Frozen Solution)	UN 1496 (solid)/UN 1908 (solution)
HSDB	517	733
NCI	No data	No data

CAS = Chemical Abstracts Services; CIS = Chemical Information System; DOT/UN/NA/IMCO = 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

Table 4-2. Physical and Chemical Properties of Chlorine Dioxide and Sodium Chlorite

Property	Chlorine dioxide	Sodium chlorite
Molecular weight (g/mol)	67.452[a]	90.45[b]
Color	Yellow to reddish-yellow[c]	White[b]
Physical state	Gas[c]	Solid[c]
Melting point	-59 °C[c]	180–200° C (decomposes)[c]
Boiling point	11 °C[c]	Decomposes[c]
Density	1.640 g/mL (0 °C; liquid)[a] 1.614 g/mL (10 °C; liquid)[a]	2.468 g/mL (solid)[d]
Odor	Pungent, distinctive from chlorine[a]	No data
Odor threshold:		
Water	No data	No data
Air	No data	No data
Taste	No data	No data
Solubility:		
Water	3.01 g/L at 25 °C and 34.5 mm Hg[c]	390 g/L at 30 °C[c]
Other solvents	No data	No data
Partition coefficients:		
Log K_{ow}	No data	No data
Log K_{oc}	No data	No data
Vapor pressure at 25 °C	>1 atm (gas)[e]	No data
Photolysis	Unstable in light[e]	No data
Henry's law constant at 25 °C	No data	No data
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits at 25 °C	No data	No data
Incompatibilities	Organic materials, heat, phosphorus, potassium hydroxide, sulfur, mercury, carbon monoxide; unstable in light; a powerful oxidizer[e]	Organic matter, sulfur, powdered coal; a powerful oxidizer[b]
Conversion factors (25 °C and 1 atm)	1 ppm=2.76 mg/m^3[e]	No data

Table 4-2. Physical and Chemical Properties of Chlorine Dioxide and Sodium Chlorite

Property	Chlorine dioxide	Sodium chlorite
Explosive limits	Explosive at temperatures >-40 °C[a] and concentrations in excess of 10% v/v at 1 atm[f]	No data

[a]Kaczur and Cawfield 1993
[b]Vogt et al. 1986
[c]O'Neil 2001
[d]HSDB 2002
[e]NIOSH 2002
[f]Dobson and Cary 2002

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

5.1 PRODUCTION

Chlorine dioxide is always manufactured on site because of the risk of rapid decomposition. In all processes, chlorine dioxide is produced in strong acid solutions from either sodium chlorite or sodium chlorate. Small- and medium-scale industrial production of chlorine dioxide utilizes sodium chlorite as the raw material. This is typical of water treatment and disinfection applications that require high purity (i.e., chlorine-free) waters. Other applications not requiring high purity waters utilize sodium chlorate. This is typical of pulp bleaching where large quantities of chlorine dioxide are necessary. There are several processes used to generate chlorine dioxide from sodium chlorate. In the R2 process, chlorine dioxide is produced from sodium chlorate and sulfuric acid, with sodium chloride as the reducing agent. Chlorine dioxide is absorbed from the gas phase in packed towers in cold water, and chlorine leaves the system as a by-product. In the Mathieson process, a sulfur dioxide-air mixture is diffused into a solution of sodium chlorate and sulfuric acid. Sulfur dioxide is used as the reductant to produce chlorine dioxide with a much lower chlorine content. The process also produces sulfuric acid, reducing the overall acid requirement. Exit gases from the Mathieson process are passed through a scrubber to remove any unreacted sulfur dioxide. The Solvay process uses sodium chlorate and sulfuric acid, with methanol as the reducing agent. Products from this process are chlorine dioxide, formic acid, and carbon dioxide. In improved Solvay processes, sulfuric acid demand is reduced by crystallizing out the by-products sodium sulfate, sodium sesquisulfate, or sodium bisulfate (Kaczur and Cawlfield 1993; Vogt et al. 1986).

The production volume of chlorine dioxide can be accurately estimated from the total sodium chlorate consumption for chemical pulp bleaching because this accounts for >95% of all chlorine dioxide production. The annual production of chlorine dioxide in the United States was estimated to be 79, 81, 146, 226, and 361 kilotons for the years 1970, 1975, 1980, 1985, and 1990, respectively (Kaczur and Cawlfield 1993).

Table 5-1 lists the facilities in each state that manufacture or process chlorine dioxide, the intended use, and the range of maximum amounts of chlorine dioxide that are stored on-site. There are 118 facilities that produce or process chlorine dioxide in the United States. Current estimates for the amounts of chlorine dioxide stored on-site as a by-product or impurity range from 99 to 9,999,999 pounds/year (45–

Table 5-1. Facilities that Produce, Process, or Use Chlorine Dioxide

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	9	10,000	999,999	1, 3, 6, 10, 11, 12
AR	4	10,000	9,999,999	1, 3, 10, 11
CA	3	0	99,999	1, 3, 10, 12
CO	1	1,000	9,999	1, 3, 12
FL	7	0	9,999,999	1, 3, 10, 11, 12
GA	8	100	999,999	1, 3, 5, 10, 11, 12
ID	1	10,000	99,999	1, 3, 10
IL	1	0	99	1, 3, 12
KY	3	10,000	999,999	1, 3, 6, 12
LA	5	1,000	999,999	1, 3, 6, 10, 11
MA	1	0	99	1, 3, 12
MD	1	10,000	99,999	1, 3, 10
ME	6	10,000	9,999,999	1, 3, 6, 10, 11, 12
MI	3	10,000	99,999	1, 3, 7, 10, 11
MN	2	10,000	99,999	1, 3, 10
MS	4	10,000	999,999	1, 3, 8, 10
NC	8	0	9,999,999	1, 3, 5, 6, 10, 12
NY	2	1,000	99,999	1, 3, 10, 12
OH	1	10,000	99,999	1, 3, 10
OR	3	10,000	999,999	1, 3, 10
PA	6	1,000	999,999	1, 2, 3, 10, 11, 12
SC	6	0	99,999	1, 3, 6, 10, 11, 12
TN	2	10,000	99,999	1, 3, 6, 10
TX	4	1,000	99,999	1, 3, 5, 10, 11
VA	3	1,000	999,999	1, 3, 10, 12
VT	1	0	99	1, 3, 12
WA	7	0	99,999	1, 3, 6, 10, 11, 12
WI	3	100	99999	1, 3, 4, 10, 11, 12

Source: TRI01 2003

[a]Post office state abbreviations used
[b]Amounts on site reported by facilities in each state
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

4,500,000 kg/year) (TRI01 2003). The data from the Toxics Release Inventory (TRI) listed in Table 5-1 should be used with caution, however, since only certain types of facilities were required to report (EPA 1995). This is not an exhaustive list.

The commercial manufacture of sodium chlorite is based almost entirely on the reduction of chlorine dioxide gas in a sodium hydroxide solution containing hydrogen peroxide as the reducing agent. The chlorine dioxide is generated from the chemical or electrochemical reduction of sodium chlorate under acidic conditions. The product is a 33 weight percent solution of sodium chlorite, which is then converted to a dry solid containing approximately 80% of sodium chlorite with other added salts (e.g., sodium chloride), which act as diluents for increased safety in storage and handling (Kaczur and Cawlfield 1993; Vogt et al. 1986).

In 1991, the production capacity of sodium chlorite was 7,700 metric tons for 80% assay basis sodium chlorite (Kaczur and Cawlfield 1993). In the United States, sodium chlorite is produced by International Dioxcide, Inc. (North Kingstown, Rhode Island) and Vulcan Materials Co. (Wichita, Kansas) (SRI 2001).

5.2 IMPORT/EXPORT

In all cases, chlorine dioxide is produced at the point of use. No import or export of this chemical occurs (Kaczur and Cawlfield 1993; Vogt et al. 1986).

Import/export data on chlorites from the U.S. Department of Commerce are combined with data for hypochlorites and hypobromites (ITA 2002). Separate data on the import/export of chlorite were not located.

5.3 USE

Wood-pulp bleaching is the largest use of chlorine dioxide, which is a uniquely selective oxidizer for lignin. In general, the trend in the pulp industry has been to eliminate chlorine and hypochochlorite as bleaching agents and replace them with chlorine dioxide. Since chlorine dioxide functions via an oxidative reaction rather than a chlorinating reaction, the formation of chlorinated organic compounds is limited. Also, unlike other oxidizing agents, chlorine dioxide does not attack cellulose, and thus preserves the mechanical properties of bleached pulp. In the final stages of the pulp-bleaching processes,

chlorine dioxide is the most frequently used bleaching chemical. A unique whiteness can be achieved using chlorine dioxide in kraft pulp, sulfite pulp, and soda pulp processes. In the United States, the first-stage of the pulp-bleaching process makes use of mixtures of chlorine and chlorine dioxide to reduce the formation of organic chlorine compounds (EPA 2002c; Kaczur and Cawlfield 1993; Vogt et al. 1986).

In the textile industry, chlorine dioxide is used as a bleaching agent and produces high-quality textile fibers with additional qualities. For example, "shrinkproof" wool owes its qualities to the reaction of chlorine dioxide with the cross-linking sulfur atoms of the wool.

In industrial and municipal waste-water treatment, chlorine dioxide is more effective than chlorine as a biocide over a wide pH range. It is also less corrosive and more compatible with some construction materials. Some municipal water systems use chlorine dioxide to eliminate taste and odor problems from drinking waters (EPA 2002c; Kaczur and Cawlfield 1993; Vogt et al. 1986). The advantage of using chlorine dioxide, rather than chlorine or ozone, is that chlorine dioxide does not react with organic matter to form trihalomethanes (THMs); it also does not transform bromide into hypobromite (OBr^-), which could react with organic matter to form bromoform ($CHBr_3$) or bromate (BrO_3^-) (Aieta and Berg 1986; Stevens 1982; WHO 2000). As part of the EPA Information Collection Rule (ICR), 5.1% of the water treatment facilities serving more than 100,000 people in the United States reported that chlorine dioxide was used in 1995 (Hoehn et al. 2000). Table 5-2 summarizes the number of facilities utilizing chlorine dioxide for water treatment in each state. However, the percentage of facilities using chlorine dioxide would be higher if smaller facilities (i.e., those serving less than 50,000 people) were also included in this value.

Chlorine dioxide has been recognized for its disinfectant properties since the early 1900s. Chlorine dioxide kills microorganisms by disrupting the transport of nutrients across the cell wall. In 1967, EPA first registered the liquid form of chlorine dioxide for use as a disinfectant and sanitizer. Liquid formulations are used as disinfectants in a variety of applications (e.g., on pets and farm animals; in bottling plants; and in food processing [fruit and vegetable washing, meat and poultry disinfection, disinfection of food processing equipment], handling, and storage plants). In industrial processes, chlorine dioxide is used as a disinfectant in water treatment (cooling systems/towers), ammonia plants, pulp mills (slime control, paper machines), oil fields, scrubbing systems, odor-control systems, and the electronics industry. In 1988, EPA registered chlorine dioxide gas as a sterilant. Chlorine dioxide gas is

Table 5-2. Publicly Owned Treatment Works (POTW) Utilizing Chlorine Dioxide for Water Treatment in 1995

Number of facilities	States[a]
0	AK, DE, FL, HI, ID, MD, MN, MS, ND, NV, OR, UT, VT, WI, WV
1–5	AL, AR, AZ, CA, CO, CT, IN, KS, LA, ME, MI, MT, NE, NH, NJ, NM, NY, OK, PA, RI, SD, TN, WA, WY
6–10	IA, KY, MA, NC, VA
11–15	GA, MO, SC
21–25	OH
72	TX

Source: Hoehn et al. 2000

[a]Post office state abbreviations used

registered for sterilizing manufacturing and laboratory equipment, environmental surfaces, tools, and clean rooms. (EPA 2002c; Kaczur and Cawlfield 1993; Vogt et al. 1986).

Chlorine dioxide is one of many antimicrobial agents being considered for use in some anthrax decontamination efforts because of its effectiveness against spore-forming bacteria. Section 18 of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) authorizes EPA to allow certain state and federal agencies to use a pesticide for an unregistered use for a limited time if EPA determines that emergency conditions exist. On November 9, 2001, EPA issued a crisis exemption for the limited sale, distribution, and use of EPA-registered pesticide products containing aqueous chlorine dioxide for cleaning surfaces contaminated with anthrax. Under the crisis exemption, only registered stabilized chlorine dioxide products may be sold or distributed to employees of EPA, other federal, state, or local government agencies, and the U.S. Postal Service. Application of the pesticide products under crisis exemption are limited to specific buildings or treatment sites identified by EPA, other federal, state, or local government agencies, and the U.S. Postal Service (EPA 2002c).

More than 80% of all sodium chlorite produced is used for the generation of chlorine dioxide. Sodium chlorite is also used in disinfectant formulations and for sterilization. Like chlorine dioxide, it must be registered with EPA under FIFRA for each specific application use as a disinfectant. Sodium chlorite is used in other industrial settings (e.g., in scrubber systems used to remove NO_x and SO_x from combustion flue gas; in the treatment and removal of toxic and odorous gases such as hydrogen sulfide and mercaptans; and as an aqueous formulation used to oxidize copper surfaces in multilayer circuit boards) (Kaczur and Cawlfield 1993).

5.4 DISPOSAL

Chlorine dioxide is a strong oxidizer and will not persist in the open environment for long periods. At concentrations >10%, chlorine dioxide is easily detonated by sunlight (O'Neil et al. 2001). It can remain for short periods of time in clean distribution systems (Kaczur and Cawlfield 1993; NRC 1980; Vogt et al. 1986). No further information on the disposal of chlorine dioxide was located.

Chlorite ions and salts are strong oxidizers. Responsible care should be undertaken during disposal of chlorite ion solutions and salts. For example, solid sodium chlorite is unstable and can form explosive mixtures with oxidizable materials, such as organic compounds. Chlorite ion solutions should not be allowed to dry on textiles because this may result in a flammable combination (Kaczur and Cawlfield

1993; Vogt et al. 1986). No further information on the disposal of chlorite ions and chlorite salts were located.

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Chlorine dioxide and chlorite have not been identified in any of the 1,647 waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2004). However, the number of sites evaluated for chlorine dioxide and chlorite are not known. The frequency of these sites can be seen in Figure 6-1.

Chlorine dioxide is a highly reactive chemical (see Section 6.3.2) that will exist only in the immediate vicinity of where it is produced or used. In the United States, the primary route of exposure to chlorine dioxide and chlorite (ions and salts) is from the consumption of drinking water. Chlorine dioxide is added to drinking water as a disinfectant in some municipal water-treatment systems in the United States. In 1995, 5.1% of community water-treatment systems in the United States reported that chlorine dioxide was used (Hoehn et al. 2000). However, the total number people exposed will be higher if smaller facilities (i.e., those serving less than 50,000 people) are also included in this value (see Section 5.3). As regulated by EPA (as of January 1, 2002), the maximum residual disinfectant levels in drinking water for chlorine dioxide and chlorite ion are 0.8 and 1.0 mg/L, respectively (EPA 2002e, 2002g).

6.2 RELEASES TO THE ENVIRONMENT

Releases of chlorine dioxide are required to be reported under Superfund Amendment Reauthorization Act (SARA) Section 313; consequently, data are available for this compound in the Toxics Release Inventory (TRI) (EPA 1995). According to the TRI, a total of 582,315 pounds (264,134 kg) of chlorine dioxide was released to the environment in 2001 (TRI01 2003). The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

6.2.1 Air

The estimated release of 582,005 pounds (263,993 kg) of chlorine dioxide to the atmosphere from over 100 manufacturing, processing, and waste-disposal facilities in 2001 accounted for about 99.9% of the

Figure 6-1. Frequency of NPL Sites with Chlorine Dioxide and Chlorite Contamination

Derived from HazDat 2004

*No data are available in HazDat 2004

estimated total environmental releases (TRI01 2003). These releases are summarized in Table 6-1. The data from the TRI listed in Table 6-1 should be used with caution, however, since only certain types of facilities are required to report (EPA 1995). This is not a comprehensive list.

No other information was found in the literature about the releases of chlorine dioxide and chlorite (ions or salts) into air.

6.2.2 Water

The estimated release of 310 pounds (141 kg) of chlorine dioxide to water from one electric power facility in Florida accounted for <0.1% of the estimated total environmental releases in 2001 (TRI01 2003). No releases (0 pounds) of chlorine dioxide occurred via underground injection (TRI01 2003). These releases are summarized in Table 6-1. The data from the TRI listed in Table 6-1 should be used with caution, however, since only certain types of facilities are required to report (EPA 1995). This is not a comprehensive list.

No other information was found in the literature about the releases of chlorine dioxide and chlorite (ions or salts) into water.

6.2.3 Soil

One manufacturing facility reported releases of chlorine dioxide to the environment in 2001; no chlorine dioxide was reportedly released to land (TRI01 2003). Releases to the environment from facilities that produce, process, or use chlorine dioxide are summarized in Table 6-1. The data from the TRI should be used with caution since only certain types of facilities are required to report (EPA 1995). This is not a comprehensive list.

No other information was found in the literature about the releases of chlorine dioxide and chlorite (ions and salts) to soils and sediment.

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Chlorine Dioxide[a]

		Reported amounts released in pounds per year[b]						
State[c]	Number of facilities	Air[d]	Water	Under-ground injection	Land	Total on-site release[e]	Total off-site release[f]	Total on and off-site release
AL	9	53,789	0	0	0	53,789	0	53,789
AR	5	18,848	0	0	0	18,848	0	18,848
CA	3	3,391	0	0	0	3,391	0	3,391
CO	1	255	No data	0	0	255	0	255
FL	8	110,496	310	0	0	110,806	0	110,806
GA	8	6,924	0	0	0	6,924	0	6,924
ID	1	6,105	No data	0	0	6,105	0	6,105
IL	2	9,714	No data	0	0	9,714	0	9,714
KY	3	5,147	0	0	0	5,147	0	5,147
LA	6	19,861	0	0	0	19,861	0	19,861
MA	1	0	No data	0	0	0	0	0
MD	1	19,005	No data	0	0	19,005	0	19,005
ME	6	8,936	0	0	0	8,936	0	8,936
MI	3	1,563	0	0	0	1,563	0	1,563
MN	2	23,229	0	0	0	23,229	0	23,229
MS	4	35,758	0	0	0	35,758	0	35,758
NC	8	66,695	0	0	0	66,695	0	66,695
NY	2	6,560	0	0	0	6,560	0	6,560
OH	1	22,005	0	0	0	22,005	0	22,005
OR	3	15,295	No data	0	0	15,295	0	15,295
PA	6	34,555	0	0	0	34,555	0	34,555
SC	6	56,967	0	0	0	56,967	0	56,967
TN	2	13,403	No data	0	0	13,403	0	13,403
TX	4	6,259	0	0	0	6,259	0	6,259
VA	3	14,105	0	0	0	14,105	0	14,105
VT	1	0	0	0	0	0	0	0
WA	7	15,846	0	0	0	15,846	0	15,846
WI	5	7,294	No data	0	0	7,294	0	7,294
Total	111	582,005	310	0	0	582,315	0	582,315

Source: TRI01 2003

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]The sum of fugitive and stack releases are included in releases to air by a given facility.
[e]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[f]Total amount of chemical transferred off-site, including to publicly owned treatment works (POTW).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Chlorine dioxide is a very reactive compound and may exist in the environment for only short periods of time (see Section 6.3.2). Chlorine dioxide is readily soluble as a gas. However, chlorine dioxide can be easily driven out of aqueous solutions with a strong stream of air. The partition coefficient between water and $ClO_{2\,(g)}$ is about 21.5 at 35 °C and 70.0 at 0 °C (Aieta and Berg 1986; Kaczur and Cawlfield 1993; Stevens 1982). Transport and partition of chlorine dioxide in soils and sediments will not be significant. Chlorine dioxide is expected to be reduced to chlorite ions in aqueous systems (see Section 6.3.2.2).

Like chlorine dioxide, the chlorite ion is a strong oxidizer (Rav-Acha 1998). Since chlorite is an ionic species, it is not expected to volatilize and will not exist in the atmosphere in the vapor phase. Thus, volatilization of chlorite ions from moist soil and water surfaces or dry soil surfaces will not occur. Because chlorite is an anion, sorption of chlorite ions onto suspend particles, sediment, or clay surfaces is expected to be limited under environmental conditions. Thus, chlorite ions will be mobile in soils and leach into groundwater. However, chlorite (ions and salts) will undergo oxidation-reduction reactions with components in soils, suspend particles, and sediments (e.g., Fe^{2+}, Mn^{2+} ions; see Section 6.3.2.2). Thus, oxidation-reduction reactions may reduce the concentration of chlorite ions capable of leaching into groundwater.

No additional information was located in the literature on the transport and partitioning of chlorine dioxide and chlorite (ions and salts).

6.3.2 Transformation and Degradation

Chlorine dioxide is an unstable gas that rapidly decomposes in air. In water, chlorine dioxide is a strong oxidizer; 50–70% of the chlorine dioxide that reacts with organic and inorganic compounds will immediately appear as chlorite (ClO_2^-) and chloride (Cl^-) ions. Chlorine dioxide does not form trihalomethanes as disinfection by-products (DBPs). However, chlorine dioxide does result in the formation of other DBPs (e.g., lower chlorinated organics, chlorate, and chlorite) which may be found in drinking water treated with chlorine dioxide (Aieta and Berg 1986; Chang 1982; Stevens 1982). Suh and Abdel-

Rahman (1985) reported that the presence of ClO_2 and HOCl (Cl_2 dissolved in water) inhibit the formation of trihalomethanes, and the degree of inhibition depends on the ratio of ClO_2 to HOCl.

6.3.2.1 Air

Chlorine dioxide gas is unstable and can rapidly decompose at high concentrations (>40 kPa partial pressure). It also decomposes to chlorine and oxygen with exposure to mild heat, noise, flame, and a minor pressure wave at low concentrations (Dobson and Cary 2002). Chlorine dioxide will decompose upon exposure to sunlight (Vogt et al. 1986). The gas-phase absorption spectrum for chlorine dioxide is the same as in aqueous solution (Kaczur and Cawfield 1993). The primary photochemical reaction of ClO_2 in the gas phase corresponds to homolytic scission of one of the chlorine-oxygen bonds (i.e., $ClO_2$6ClO + O). Products of this initial reaction generate secondary products including doublet-state oxygen (O_2^*), chlorine (Cl_2), and chlorine trioxide (Cl_2O_3) (Griese et al. 1992; Zika et al. 1984). If chlorine dioxide gas is diluted in air to <15 volume percent, it can be relatively stable in darkness (Vogt et al. 1986).

6.3.2.2 Water

Chlorine dioxide is readily soluble in water, forming a greenish-yellow solution. It is not unusual to simultaneously have multiple chlorine species present in chlorine dioxide solutions originating from by-products or unreacted precursors. Table 6-2 lists the various chlorine species that might be present in solutions of chlorine dioxide (Gordon 2001).

Chlorine dioxide alone will not hydrolyze in solution to any appreciable extent between pH 2 and 10. Dilute neutral or acidic aqueous solutions of chlorine dioxide are stable if kept cool, well sealed, and protected from sunlight. In the absence of oxidizable substances and in the presence of hydroxyl ions, chlorine dioxide will dissolve in water and then decompose with the slow formation of chlorite and chlorate ions (e.g., $2ClO_2 + 2OH^- \rightarrow ClO_2^- + ClO_3^- + H_2O$). At chlorine dioxide concentrations in the 5–10 mg/L range at pH 12, the decomposition half-life of chlorine dioxide in solution ranges from 20 to 180 minutes (Aieta and Berg 1986; Stevens 1982; WHO 2000). Lee et al. (2004) found that the concentration of chlorate ions formed from chlorine dioxide were higher at low pHs. For example,

Table 6-2. Chlorine Speciation in Aqueous Solutions

Oxidation State	Species	Formula
+7	Perchlorate ion	ClO_4^-
+5	Chlorate ion	ClO_3^-
+4	Chlorine dioxide	ClO_2
+3	Chlorite ion	ClO_2^-
+3	Hypochlorous acid	$HClO_2$
+1	Hypochlorite ion	OCl^-
+1	Hypochlorous acid	HOCl
0	Chlorine	Cl_2
-1	Chloride ion	Cl^-

10 and 15% chlorate ions were formed from chlorine dioxide at pHs 4 and 7, respectively. At pH 10, chlorate ions were not formed at all.

Chlorine dioxide has a positive chlorine-oxidation state of four (+4), which is intermediate between chlorite (+3) and chlorate (+5) ions. Reduction of chlorine dioxide usually results in the formation of chlorite ions (e.g., $ClO_2 + e^- \rightleftharpoons ClO_2^-$; $E^{pH=7}$=0.95 volts). Chlorite ions (ClO_2^-) are also effective oxidizing agents, although they react much slower than chlorine dioxide. The reduction of chlorite results in the formation of chloride ions (e.g., $ClO_2^- + 4H^+ + 4e^- \rightleftharpoons Cl^- + 2H_2O$; $E^{pH=7}$=0.37 volts). The redox potential at pH 7 (i.e., $E^{pH=7}$) indicates that chlorine dioxide is a stronger oxidizer than chlorite ions (Rav-Acha 1998). During water-treatment, approximately 50–70% of the chlorine dioxide reacted will immediately appear as chlorite and chloride (Aieta and Berg 1986; Stevens 1982).

Chlorine dioxide, like other strong oxidants, will oxidize manganese (II), iron (II), iodide (I^-), and sulfide (S^{2-}), forming insoluble manganese dioxide (MnO_2), iron hydroxides precipitates, iodine (I_2), and sulfate (SO_4^{2-}), respectively (Dernat and Pouillot 1992). In the absence of sunlight, bromide (Br^-) is not oxidized by chlorine dioxide. Thus, chlorine dioxide will not transform bromide into hypobromite (OBr^-), which could react with organic matter to form bromoform ($CHBr_3$) or bromate (BrO_3^-). This is a significant difference between the use of chlorine dioxide as an oxidant and the use of chlorine or ozone as oxidants in water-treatment systems (Aieta and Berg 1986; Stevens 1982; WHO 2000).

Since chlorine dioxide reacts generally as an electron acceptor, hydrogen atoms present in activated organic CH or NH bonds do not react by electrophilic substitution with chlorine (Hoigne and Bader 1994). As a result, chlorine dioxide will form fewer chlorinated compounds compared to Cl_2 when it reacts with organic matter. In contrast, chlorine (Cl_2) reacts not only by oxidation, but also by electrophilic substitution, resulting in a variety of volatile and nonvolatile chlorinated organic products; for example, trihalomethanes (THMs). It has been well established that “chlorine-free” chlorine dioxide in reaction with both humic and fulvic acids does not form THMs. However, some other types of chlorinated organics may be formed from the reaction of chlorine dioxide with humic and fulvic acids (Aieta and Berg 1986; Stevens 1982). The reactions of chlorine dioxide with olefin compounds in waste-water are apparently very complex and produce a host of chlorinated and nonchlorinated products. No evidence exists that chlorine dioxide undergoes reactions with saturated aliphatic hydrocarbons under mild conditions. Chlorine dioxide does not seem to cause the formation of odorous compounds with phenol. Chlorine dioxide treatment of phenols can cause chlorine substitution, ring cleavage, or both, depending on the particular phenol reacted and the conditions of the reaction. Through complex

mechanisms, chlorine dioxide reacts rapidly with phenols and phenoxide anions to form quinones and chloroquinones, and when in excess, oxalic and maleic acids. Chlorine substitution in the products, however, is not entirely absent (Aieta and Berg 1986; Rav-Acha and Choshen 1987; Stevens 1982). Chlorine dioxide reacts with natural organic matter (NOM; i.e., humic and fulvic acids) mainly on the aromatic part. Formaldehyde and acetaldehyde are the main byproducts of oxidation of NOM by chlorine dioxide; pH does not have any significant influence on this reaction (Dąbrowska et al. 2003).

At a waste water-treatment pilot plant in Evansville, Indiana, which used chlorine dioxide as a primary disinfectant, more than 40 different organic disinfection by-products (DBPs) were identified at very low concentrations. Eleven of these DBPs are regulated chemicals by EPA (i.e., bromodichloromethane, carbon tetrachloride, dibromochloromethane, 1,1,1-trichloro-2-propanone, maleic anhydride, bromoform, 1,4-dichlorobenzene, benzyl cyanide, benzoic acid, naphthalene, and decylphenol) (Richardson et al. 1994). Chlorine dioxide will not react with ammonia and reacts only slowly with primary amines. In general, amines produce the respective aldehyde upon reaction with chlorine dioxide in the following order of reactivity: tertiary>seconary>primary (Aieta and Berg 1986; Stevens 1982).

Chlorine dioxide readily degrades in aqueous solutions under ultraviolet light. It has a broad UV absorption band with a maximum near 360 nm and a molar extinction coefficient of about 1,150 $(M \times cm)^{-1}$ (Aieta and Berg 1986). It is postulated that the reaction in solution proceeds as in the gas phase, to give ClO and O. The initial photodissociation reaction is followed by rapid dark and light reactions to produce chlorate (ClO_3^-), hypochlorite (OCl^-), and chloride (Cl^-) (Zika et al. 1984). Solution speciation can have a marked effect on the mechanism and products generated from photolysis of chlorine dioxide. In the absence of light, chlorine dioxide will not oxidize bromide ion into hypobromite (OBr^-) and will not form of bromoform ($CHBr_3$) or bromate (BrO_3^-). However, under sunlight, some photolysis intermediates of chlorine dioxide with long half-lives are capable of oxidizing bromide to hypobromite, which will result in the formation of bromate. Thus, if labile organic materials are present during illumination, bromoform may be generated by the reaction of organic matter with hypobromite formed by intermediates of chlorine dioxide photolysis (Aieta and Berg 1986; Bolyard et al. 1993; Griese et al. 1992; Stevens 1982; WHO 2000; Zika et al. 1984).

Chlorite and chlorate ions have been shown to undergo reduction by bacteria under anaerobic conditions. Anaerobic degradation is an important process in anoxic groundwater, sediments, and some soils. It has been known for over 40 years that chlorate ions can be reduced by mixed cultures under anaerobic conditions (Logan 1998). Chlorate-respiring bacteria are widely distributed in the environment and

utilize electron acceptors (e.g., chlorate ions) in lieu of oxygen to generate energy and produce carbon-based building blocks. The reduction of chlorate ions occurs in two steps; chlorate reduction with chlorate reductase enzyme followed by chlorite disproportionation catalyzed by chlorite dismutase (a non-respiratory enzyme). Oxygen and chloride are formed as the end products (Danielsson et al. 2003; Xu et al. 2004). Although oxygen is produced during reduction processes, it is rapidly consumed by the bacteria such that oxygen does not accumulate to high levels. Chlorate dismutase activity is unaffected by oxygen, but expression of this enzyme does not occur under aerobic conditions even in the presence of perchlorate or chlorate ion (Xu et al. 2004). Several dinitrifying bacteria reduce chlorate but, in general, this reduction is not coupled to microbial growth (Wolterink et al. 2002). Moreover, these organisms lack chlorite dismutase enzyme, which is required for reduction of chlorite. Thus, it is likely that the nitrate and chlorate pathways for chlorate-reduction are not necessarily related (Wolterink et al. 2002). No quantitative information was located on the biodegradation rate of chlorate or chlorite ions in the environment. However, the rate of chlorate ion degradation appears to be rapid under anaerobic conditions in waste-water treatment facilities (Logan 1998).

6.3.2.3 Sediment and Soil

No information was located in the literature on the transformation and degradation of chlorine dioxide or chlorite (ions and salts) in sediment and soils.

6.3.2.4 Other Media

No information was located in the literature on the transformation and degradation of chlorine dioxide or chlorite (ions and salts) in other environmental media.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

6.4.1 Air

Chlorine dioxide degrades rapidly in air (see Section 6.3.2.1) and should be measurable only near its source of production or use (e.g., pulp and paper-mill plants, water-treatment facilities). As part of an international study of workers in the pulp and paper industry, the concentration of chlorine dioxide was measured in the workplace air of pulp and paper mills in 19 countries. The concentration of chlorine dioxide was measured in the following work areas: steam and power generation (range, <1–60 ppb);

effluent water-treatment (range, not detected to 3 ppb); and maintenance (range, <detection limit to 5.8 ppb) (Kauppinen et al. 1997; Teschke et al. 1999). In another study, the concentration of chlorine dioxide was measured in the workplace air at a pulp mill in British Columbia, Canada between May and June, 1988. The concentration of chlorine dioxide was <10 ppb in area samples and personal full-shift samples. The exception was in the bleach/chemical preparation area sample in which the concentration of chlorine dioxide ranged from <10 to 300 ppb (Kennedy et al. 1991).

The formation of offensive odors in indoor air, such as “kerosene-like” and “cat-urine-like” odors, have been attributed to drinking water treated with chlorine dioxide. The “kerosene-like” and “cat-urine-like” odors are produced by reactions between chlorine dioxide escaping from water and volatile organic compounds found in homes, primarily from new carpeting. This has been ascribed to over-dosing drinking water with residual chlorine dioxide (or chlorite ions), which is used as a postdisinfectant to prevent microbial growth in water-distribution systems (Dluzniewski 2002; Hoehn et al. 1990, 2003).

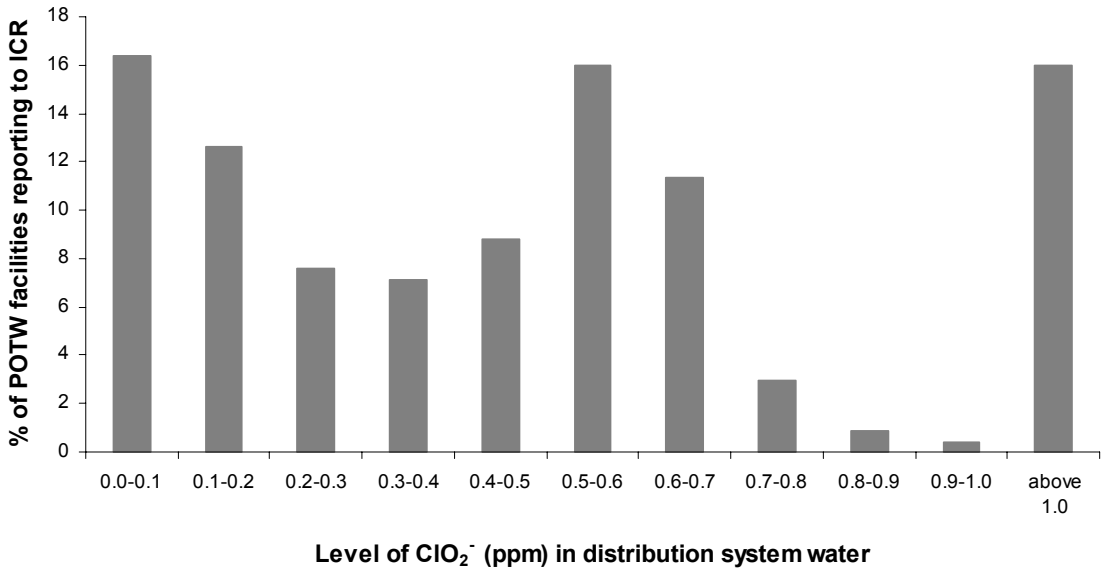
No other information was located in the literature on the concentrations of chlorine dioxide or chlorite (ions and salts) in air.

6.4.2 Water

Chlorine dioxide is added to drinking water as a disinfectant in some municipal water-treatment systems in the United States. In 1995, 5.1% of community water-treatment systems in the United States reported that chlorine dioxide was used (Hoehn et al. 2000). This would translate to about 12 million people who may be exposed to chlorine dioxide and chlorite ions in the United States. However, the total number of people exposed will be higher if smaller facilities (i.e., those serving <50,000 people) are also included in this value.

As regulated by EPA (as of January 1, 2002), the maximum residual-disinfectant level (MRDL) for chlorine dioxide is 0.8 mg/L (EPA 2002g); the maximum contaminant level (MCL) for its oxidation product, chlorite ion, in drinking water is 1.0 mg/L (EPA 2002e). The levels of chlorite ion in distribution system waters have been reported as part of the Information Collection Rule (ICR), a research project used to support the development of national drinking-water standards in the United States (EPA 2002d). Figure 6-2 illustrates the levels of chlorite ion in drinking waters sampled from distribution systems versus the percentage of publicly-owned treatment works (POTW) facilities in the United States

Figure 6-2. Percentage of POTW Facilities Reporting to ICR vs. Level of Chlorite in Distribution System Water*



Source: EPA 2002d

*Samples were taken from the distribution system of POTW facilities that utilized chlorine dioxide.

ClO_2^- = chlorite; ICR = Information Collection Rule; POTW = publicly owned treatment works

that reported as part of the ICR in 1998. Approximately 16% of this group had levels of chlorite ion over the MCL of 1 mg/L.

In a 12-week epidemiological study conducted in a small town in Ohio, the ranges of concentrations of chlorine dioxide, chlorite ion, and chlorate ion in drinking water were 0.3–1.1, 3.2–7.0, and 0.3–1.1 mg/L, respectively (Lykins et al. 1990; Michael et al. 1981). In one study using a sensitive analytical method, the average concentration of chlorine dioxide in tap water from the city of Brest, France was $1.8x10^{-7}$ mol/L (0.012 mg/L) (Quentel et al. 1994).

Bolyard et al. (1993) analyzed samples from four water-treatment facilities in the United States that use chlorine dioxide as a disinfectant. Source water samples were also analyzed from each facility and no chlorite or chlorate ions were detected. At these water-treatment facilities, additional gaseous Cl_2 was added to provide a residual disinfectant in the distribution systems. Water taken from these distribution systems (i.e., water sampled at water-treatment plant) had measurable concentrations of both chlorite and chlorate ions. The ranges of concentrations were 15–740 and 21–330 µg/L for chlorite and chlorate, respectively (Bolyard et al. 1993). In general, chlorite ion was the predominate disinfection by-product. However, at two sites where water was chlorinated prior to passing through secondary sedimentation basins containing activated carbon, concentrations of chlorate ion concentrations were higher than chlorite ions. At these sites, residual Cl_2 and activated carbon likely oxidized chlorite to chlorate, which resulted in elevated levels of chlorate in finish water samples (Bolyard et al. 1993).

No other information was located in the literature on the concentrations of chlorine dioxide or chlorite (ions and salts) in water.

6.4.3 Sediment and Soil

No information was located in the literature on the concentrations of chlorine dioxide or chlorite (ions and salts) in sediments and soil. Due to the high reactivity of chlorine dioxide and chlorite (ions and salts), however, concentrations of these compounds are expected to be small or nil.

6.4.4 Other Environmental Media

No information was located in the literature on the concentrations of chlorine dioxide or chlorite (ions and salts) in other environmental media.

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population may be exposed to chlorine dioxide and chlorite (ions or salts) by the ingestion of drinking water. As part of the ICR, 5.1% of the water-treatment facilities serving more than 100,000 people in the United States reported that chlorine dioxide was used in 1995 (Hoehn et al. 2000). However, the percentage of facilities using chlorine dioxide would be higher if smaller facilities (i.e., those serving <50,000 people) were also included in this value. Individuals who live in communities with water-treatment facilities using chlorine dioxide will have a higher exposure to chlorine dioxide and chlorite ions than other segments of the population.

For communities that utilize chlorine dioxide as a drinking-water disinfectant, an exposure estimate may be calculated based on the maximum residual-disinfectant levels for chlorine dioxide and chlorite ion. If the concentration of chlorine dioxide in U.S. drinking water is assumed to be 0.8 mg/L (the maximum residual disinfectant level [EPA 2002g]) and the consumption rate of drinking water by a normal adult is assumed to be 2 L/day, then the exposure to chlorine dioxide from drinking water would be 1.6 mg/day. Similarly, if the concentration of chlorite ion in U.S. drinking water is assumed to be 1.0 mg/L (the maximum contaminant level [EPA 2002e]), and the consumption rate of drinking water by a normal adult is assumed to be 2 L/day, then the exposure from drinking water would be 2.0 mg/day. However, the exposure to chlorine dioxide and chlorite ion may be much lower than these estimated levels depending on individual conditions for each community. Other sources of exposure to chlorine dioxide and chlorite (ions and salts) are not significant for the general population.

Occupational exposure to chlorine dioxide and chlorite may occur at facilities that utilize these chemicals as bleaching agents (e.g., pup and paper mills) or water disinfectants (e.g., water-treatment facilities). The primary route of occupational exposure will be by inhalation of these compounds in the immediate vicinity of their use. As part of an international study of workers in the pulp and paper industry, the concentration of chlorine dioxide was measured in the workplace air of pulp and paper mills from 19 countries. The concentration of chlorine dioxide was measured in the following work areas: steam and power generation (range, <1–60 ppb); effluent water-treatment (range, not detected to 3 ppb); and

maintenance (range, <detection limit to 5.8 ppb) (Kauppinen et al. 1997; Teschke et al. 1999). In another study, the concentration of chlorine dioxide was measured in the workplace air at a pulp mill in British Columbia, Canada between May and June in 1988. The concentration of chlorine dioxide was <10 ppb in area samples and personal full-shift samples. The exception was in the bleach/chemical preparation area sample, in which the concentration of chlorine dioxide ranged from <10 to 300 ppb (Kennedy et al. 1991).

6.6 EXPOSURES OF CHILDREN

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

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

Specific information on the exposure of children to chlorine dioxide and chlorite (ions and salts) was not located. Like adults, the primary route of exposure for children will be from drinking water. Water consumption among children is higher on a proportional body weight basis than for adults. Therefore, children may have a higher exposure to chlorine dioxide and chlorite (ions and salts). Other sources of exposure to chlorine dioxide and chlorite (ions and salts) will not be significant. Chlorine dioxide and chlorite (ions and salts) are reactive chemicals and will not be found in amniotic fluid, meconium, neonatal blood, or breast milk.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Individuals who are employed at pulp and paper mills, municipal water-treatment facilities, and other facilities that use chlorine dioxide as a disinfectant may have high exposures to chlorine dioxide and chlorite (ions and salts) (see Section 6.5).

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 chlorine dioxide and chlorite are available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of chlorine dioxide and chlorite.

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 relevant physical and chemical properties of chlorine dioxide and chlorite (ions and salts) are well known and permit estimation of its environmental fate. Physical and chemical properties are presented in Table 4-2 (Dobson and Cary 2002; HSDB 2002; Kaczur and Cawfield 1993; O'Neil 2001; NIOSH 2002; Vogt et al. 1986).

Production, Import/Export, Use, Release, and Disposal. Data regarding the production of chlorine dioxide and chlorite (ions and salts) are available, but are limited (Kaczur and Cawlfield 1993). Annual production of chlorine dioxide in the United States has increased from 79 to 361 kilotons between the years 1970 and 1990 (Kaczur and Cawlfield 1993). Additional production information for chlorite (ions and salts) specifically whether the production amount (7,700 metric tons in 1991; Kaczur and Cawlfield 1993) is larger or smaller than in the past would be useful. Information on future production of

chloride dioxide and chlorite (ions and salts) would also be helpful. Chlorine dioxide and chlorite (ions and salts) are not widely used in the home or environment. Some municipal waste water-treatment facilities use chlorine dioxide or chlorite (ions and salts) to disinfect drinking water (EPA 2002c; Kaczur and Cawlfield 1993; Vogt et al. 1986). Wood-pulp bleaching is the largest industrial use of chlorine dioxide (EPA 2002c; Kaczur and Cawlfield 1993; Vogt et al. 1986). Air is the medium most likely contaminated with chlorine dioxide near facilities where it is used (TRI01 2003). Additional information on disposal methods is not warranted since chlorine dioxide and chlorite (ions and salts) are reactive and will not exist for long periods of time in the environment (see Section 6.3).

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. TRI, which contains this information for 2001, became available in July of 2003. This database is updated yearly and should provide a list of industrial facilities and emissions.

Environmental Fate. Chlorine dioxide and chlorite (ions and salts) are strong oxidizers and will not exist in the environment for long periods of time (Dobson and Cary 2002); therefore, transport and partitioning of chlorine dioxide and chlorite (ions and salts) are not important. Chlorine dioxide reacts immediately in water to form chlorite and chlorate ions, and in air to form chlorine and oxygen (Dobson and Cary 2002). Information on the half-life of chlorite (ions and salts) in environmental media would be useful.

Bioavailability from Environmental Media. Chlorine dioxide and chlorite (ions and salts) are strong oxidizers. Chlorine dioxide is highly reactive and will not be bioavailable in environmental media. Additional information concerning the bioavailability of chlorite (ions and salts) would be helpful.

Food Chain Bioaccumulation. Chlorine dioxide and chlorite (ions and salts) are strong oxidizers and will not bioconcentrate or biomagnify in plants, aquatic organisms, or animals.

Exposure Levels in Environmental Media. Chlorine dioxide and chlorite (ions and salts) are strong oxidizers and react quickly in air, water, soil, plant material, and foodstuffs. No environmental monitoring studies are available. The general population may be exposed to chlorine dioxide and chlorite (ions and salts) by the ingestion of drinking water. As part of the ICR, 5.1% of the water-treatment facilities serving more than 100,000 people in the United States reported that chlorine dioxide was used in 1995 (Hoehn et al. 2000). Using the maximum contaminant level (EPA 2002e) for chlorine dioxide and

chlorite, exposure from drinking water for these populations would be 1.6 and 2.0 mg/day, respectively. Additional monitoring data are needed for populations exposed to chlorine dioxide and chlorite (ions and salts) from drinking water. Reliable monitoring data for the levels of chlorine dioxide and chlorite (ions and salts) in contaminated media at hazardous waste sites are needed so that the information obtained on levels chlorine dioxide and chlorite (ions and salts) in the environment can be used in combination with the known body burden of chlorine dioxide and chlorite (ions and salts) to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Exposure Levels in Humans. Chlorine dioxide and chlorite (ions and salts) are strong oxidizers and react quickly in water or moist body tissues to form chloride ions. Consequently, chlorine dioxide and chlorite (ions and salts) are not detected in human tissues (e.g., blood, urine, fat, or breast milk). Biological monitoring studies are not available for these compounds near hazardous waste sites. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. There are no unique exposure pathways for children. Children will be exposed to chlorine dioxide and chlorite (ions and salts) in the same manner as adults in the general population (i.e., ingestion of water). Studies focusing on the exposure of children to drinking waters containing chlorine dioxide and chlorite (ions and salts) would be useful. Additional information on whether children are different in their weight-adjusted intake of chlorine dioxide and chlorite (ions and salts) is needed. Data on childhood specific means to decrease exposure would also be useful. Chlorine dioxide and chlorite (ions and salts) are strong oxidizers and react quickly in water or moist body tissues to form chloride ions. Consequently, chlorine dioxide and chlorite (ions and salts) will not be detected in tissues of children (e.g., blood, urine, or fat).

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

Exposure Registries. No exposure registries for chlorine dioxide and chlorite (ions and salts) were located. These substances are not currently compounds for which a sub-registry has been established in the National Exposure Registry. These substances will be considered in the future when chemical selections are 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

The Federal Research in Progress (FEDRIP 2003) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1. A National Science Foundation study exploring the photochemistry of chlorine dioxide relevant to stratospheric ozone depletion is currently being conducted by Dr. Prezhdo at the University of Washington. No other studies on the environmental fate of chlorine dioxide or chlorite (ions and salts) are reported to be currently in progress (FEDRIP 2003).

7. ANALYTICAL METHODS

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

No methods for determining chlorine dioxide in biological materials were located. Most studies concerning human health effects measure the concentrations of chlorine dioxide in the air or in water. The measurement of chlorine dioxide in biological materials is not commonly used because of the rapid conversion of chlorine dioxide to chlorine-containing metabolites, such as chlorite and chloride ions.

Abdel-Rahman et al. (1980b) developed a method to quantitatively and qualitatively measure the metabolites of chlorine dioxide (e.g., ClO_2^-, and ClO^-) in biological fluids. These biomarkers can be used to indirectly measure chlorine dioxide exposure.

The concentration of residual chlorite ion in vegetables and eggs treated with sodium chlorite was determined by UV-ion chromatography (Suzuki et al. 1997). Sodium chlorite was extracted with water and cleaned-up using C18 cartridge. The detection limit of sodium chlorite in vegetables and eggs was 1 mg/kg with recoveries of 90–100%.

7.2 ENVIRONMENTAL SAMPLES

Chlorine dioxide has been measured in air and water. Methods for determining levels in the air include spectrophotometry and ion chromatography. Environmental analyses of chlorine dioxide in water are

performed using electrochemical, chromatographic, or spectrophotometric methods. Analytical methods for the determination of chlorine dioxide in environmental samples are given in Table 7-1. Ion chromatography may also be used to analyze the inorganic disinfection by-products of chlorine dioxide (i.e., chlorite ions) in an analogous manner using EPA Method 300.0 (Pfaff and Brockhoff 1990).

Atmospheric chlorine dioxide may be sampled by pulling a given volume of air through a toxic gas vapor detector tube. The tube contains chemicals that react only with chlorine dioxide. If chlorine dioxide is present, the indicator chemical in the tube will change color. The concentration of the gas or vapor may be estimated by either the length-of-stain compared to a calibration chart or the intensity of the color change compared to a set of standards (EMMI 1997). Diffusive samplers have been used to monitor chlorine dioxide and chlorine in workplace air. In this technique, workplace air is diffused into an absorbing solution of neutrally buffered potassium iodide. In the absorbing solution, chlorine dioxide and chlorine are reduced by iodide ions to chlorite and chloride ions, respectively. The formed ions are then separated and quantified by ion chromatography. The analytical detection limits have been found to be 0.02 and 0.07 ppm for chloride and chlorite ions, respectively (Björkholm et al. 1990).

Spectrophotometry (or colorimetry) has been used to measure chlorine dioxide in water using indicators that change colors when oxidized by chlorine dioxide. Spectrophotometric analyzers determine the concentration of chlorine dioxide by measuring the optical absorbance of the indicator in the sample solution. The absorbance is proportional to the concentration of the chlorine dioxide in water. Indicators used for this technique include *N,N*-diethyl-*p*-phenylenediamine, chlorophenol red, and methylene blue (APHA 1998; Fletcher and Hemming 1985; Quentel et al. 1994; Sweetin et al. 1996). For example, chlorophenol red selectively reacts with chlorine dioxide at pH 7 with a detection limit of 0.12 mg/L. The interferences from chlorine may be reduced by the addition of oxalic acid, sodium cyclamate, or thioacetamide (Sweetin et al. 1996).

APHA Method 4500-CLO2-B, iodometric titration analysis, measures the concentration of chlorine dioxide in water by titration with iodide, which is reduced to form iodine. Iodine is then measured colorimetrically when a blue color forms from the production of a starch-iodine complex. The detection limit for this method is 20 µg/L (APHA 1998).

Table 7-1. Analytical Methods for Determining Chlorine Dioxide and Chlorite in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	None.	Toxic gas vapor detector tube	0.05 ppm	No data	EPA 1997
Work-place air	Diffusion of air into potas-sium iodide solution at pH 7.	Ion chromato-graphy (of chlorite ion in solution)	0.02 ppm of chlorine dioxide	No data	Björkholm et al. 1990; Hekmat et al. 1994 (OSHA Method 202)
Water	None.	Ion chromato-graphy with conductivity detector	0.01 mg/L (as chlorite ion)	No data	Hoehn et al. 2000 (EPA Method 300.0)
			0.03 mg/L (as chlorite ion)		Pfaff and Brockhoff 1990
Water	To 100 mL sample, add 2 mL glycine solution and mix. In a separate flask, place 5 mL buffer reagent and N,N-diethyl-p-phenylene-diamine indicator solution and mix. Add 200 mg EDTA, disodium salt, and then add glycine-treated sample and mix.	UV/VIS spectrometry	>0.1 mg/L[a]	No data	APHA 1998 (Method 4500-CLO2-D)
Water	Add buffer and indicator.	UV/VIS spectrometry	Indicator (detection limit); acid chrome violet K (0.02 mg/L); amaranth (0.005 mg/L); lissamine green B (0.03 mg/L); methylene blue (0.02 mg/L); chlorophenol red (0.12 mg/L)	No data	Fletcher and Hemmings 1985; Hofmann et al. 1998; Hui et al. 1997; Sweetin et al. 1996
Water/ waste water	Measure initial temperature and pH and protect sample from light throughout the procedure. Phenylarsine oxide is used as standard titrant.	Amperometric titration	0.5 mg/L[a]	No data	APHA 1998 (Method 2350-C), (Method 4500-CLO2-C) (Method 4500-CLO2-E)
Water	None.	Flow injection using redox electrode detector	3.4 ppb (as chlorite ion)	No data	Ohura et al. 1999

Table 7-1. Analytical Methods for Determining Chlorine Dioxide and Chlorite in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Transfer 5 mL acetic acid, or enough to adjust sample pH between 3 and 4, and 1 g KI, and 1 mL starch solution; pour in sample and mix.	Iodometric titration	20 µg/L	No data	APHA 1998 (Method 4500-CLO2-B)
Water, drinking	Add sample to 1,2-di-hydroxy-anthra-quinone-3-sulphonic acid in phosphate buffer.	Polarographic analyser	2 µg/L	No data	Quentel et al. 1994

[a]Hofmann et al. (1998)

APHA = American Public Health Association; EDTA = ethylene diamine tetraacetic acid; EPA = Environmental Protection Agency; KI = potassium iodide; OSHA = Occupational Safety and Health Administration; UV/VIS = ultraviolet/visible light

For APHA Methods 2350-C and 4500-CLO2-E, amperometric analyzers are used to measure chlorine dioxide in water. Amperometric analyzers measure the current that is necessary to maintain a constant concentration of titrant as chlorine dioxide reduces the titrant (e.g., phenylarsine oxide). This method is limited by interference from compounds that might react with the titrant (e.g., chlorine and chloroamine) (APHA 1998).

Because of its sensitivity and precision, ion chromatography (EPA Method 300.0) is a good technique for analyzing chlorine dioxide in water. Ion chromatography utilizes the ability of certain ion exchange resins to separate a mixture of anionic species. A liquid mobile phase (e.g., eluant) is used to carry the sample through the system either by isocratic (using same eluant) or gradient (varying concentration or flow rate) elution. After separation is achieved, the separated anions are measured using a detector (e.g., conductometric, ultraviolet/visible, or fluorescence). Typically, chlorine dioxide is indirectly analyzed as chlorite ions (Hoehn et al. 2000). Detection limits for chlorite ions range from 0.01 to 0.03 mg/L (Hoehn et al. 2000; Pfaff and Brockhoff 1990). Other detection methods used with ion chromatography, such as ion-spray mass spectrometry, have been developed and offer greater ion selectivity and sensitivity (Charles and Pépin 1998). Precolumn sample treatments using tetraborate/boric acid to separate analytes from common interfering ions (e.g., chloride, carbonate, and nitrate) result in lower detection limits on the order of 10 µg/L for chlorite ions (Hautman and Bolyard 1992a). With postcolumn derivatization of chlorite ions to tribromate ions, detection limits on the order of 0.4 µg/L have been achieved for chlorite ions (Weinberg and Yamada 1998).

Gas-diffusion flow injection analysis is capable of detecting very low concentrations of chlorine dioxide in water (i.e., detection limit is 5 µg/L). A chemiluminescence flow-through detector cell is used to measure the concentration chlorine dioxide as a function of chemiluminescence intensity. A gas diffusion membrane separates the donor stream from the detecting stream and removes ionic interferences from iron and manganese compounds, as well as from other oxychlorinated compounds, such as chlorate and chlorite (Hollowell et al. 1986; Saksa and Smart 1985).

A rapid potentiometric flow inject technique for the simultaneous determination of oxychlorine species (e.g., ClO_2^-) was developed by Ohura et al. (1999). The analytical method is based on the detection of a large transient potential change of the redox electrode due to chlorine generated via the reaction of the oxychlorine species (e.g., ClO_2^-). The detection limit for ClO_2^- is 3.4 ppb.

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 chlorine dioxide and chlorite are available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of chlorine dioxide and chlorite.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Metabolites of chlorinated phenoloic compounds in fish bile have been found to be sensitive biomarkers of bleach pulp mill effluent exposure (Brumley et al. 1996). Analysis of metabolites of chlorinated syringaldehydyes in fish bile can provide a biomarker of effluent exposure that is sensitive to low levels of exposure and correlates well with exposure concentrations. Methods for determining biomarkers of exposure in human were not located. Abdel-Rahman et al. (1980b) developed a method to quantitatively and qualitatively measure the metabolites of chlorine dioxide (e.g., ClO_2^-, and ClO^-) in biological fluids. These biomarkers may be used to indirectly measure chlorine dioxide exposure. Methods for determining biomarkers of exposure in humans are needed to determine background levels in the population and levels at which biological effects occur.

Effect. Methods for determining biomarkers of effect in human were not located. Methods for determining biomarkers of effect in humans are needed to determine background levels in the population and levels at which biological effects occur.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods for determining chlorine dioxide and chlorite in air and water, the media of most concern for human exposure, are reliable, but may not be sensitive enough to measure background levels in the environment.

No data are available on methods for determining chlorine dioxide and chlorite in soil and other solid media. In addition, there is insufficient information on the methods for determining chlorine dioxide and chlorite in media such as shellfish, fish, and plants. Some exposure to chlorine dioxide and chlorite may occur via ingestion of food, and thus, standardized methods for foods are needed. Methods with sufficient sensitivity for measuring background levels in foods are needed as well.

7.3.2 Ongoing Studies

No ongoing studies were located as a result of a search of Federal Research in Progress (FEDRIP 2003).

8. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding chlorine dioxide and chlorite in air, water, and other media are summarized in Table 8-l.

ATSDR has derived an intermediate-duration inhalation MRL of 0.001 ppm (0.003 mg/m^3) for chlorine dioxide based on a LOAEL of 1 ppm for respiratory effects (peribronchiolar edema and vascular congestion in the lungs) in rats exposed to chlorine dioxide vapors 5 hours/day, 5 days/week for 2 months (Paulet and Desbrousses 1972). The LOAEL was converted to a $LOAEL_{HEC}$ of 0.3 ppm and divided by an uncertainty factor of 300 (3 for interspecies extrapolation using dosimetric adjustments, 10 for the use of a LOAEL, and 10 to account for sensitive populations).

ATSDR has derived an intermediate-duration oral MRL of 0.1 mg/kg/day for chlorite based on a NOAEL of 2.9 mg chlorite/kg/day and a LOAEL of 5.7 mg chlorite/kg/day for neurodevelopmental effects (lowered auditory startle amplitude) in rat pups that had been exposed throughout gestation and lactation via their mothers (CMA 1996; Gill et al. 2000). The NOAEL of 2.9 mg chlorite/kg/day was divided by an uncertainty factor of 30 (10 for interspecies extrapolation and 3 to account for sensitive populations).

ATSDR considered the intermediate-duration oral MRL for chlorite to be applicable to chlorine dioxide as well.

EPA (IRIS 2002) has derived an RfC of $2x10^{-4}$ mg/m^3 for chlorine dioxide based on a LOAEL of 2.76 mg/m^3 (1 ppm) for respiratory effects (peribronchiolar edema and vascular congestion in the lungs) in rats exposed to chlorine dioxide vapors 5 hours/day, 5 days/week for 2 months (Paulet and Desbrousses 1972). The LOAEL was converted to a $LOAEL_{HEC}$ of 0.64 mg/m^3 and divided by an uncertainty factor of 3,000 (10 for extrapolation of a chronic RfC from a subchronic study, 3 for interspecies extrapolation using dosimetric adjustments, 10 for intrahuman variability, and 10 to account for extrapolation from a LOAEL for mild effects and for the lack of inhalation developmental and reproductive toxicity studies).

EPA (IRIS 2002) has derived an RfD of $3x10^{-2}$ mg/kg/day for chlorite based on a NOAEL of 3 mg/kg/day for neurodevelopmental effects in rat pups that had been exposed throughout gestation and lactation via their mothers (CMA 1996; Gill et al. 2000). The NOAEL of 3 mg chlorite/kg/day was divided by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 to account for sensitive populations). EPA (IRIS 2002) considered the RfD for chlorite to be applicable to chlorine dioxide as well.

Table 8-1. Regulations and Guidelines Applicable to Chlorine Dioxide and Chlorite

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification		IARC 2002
	Sodium chlorite	Group 3[a]	
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	0.1 ppm	ACGIH 2001
	TLV-STEL (15-minute TWA)	0.3 ppm	
EPA	Chemical accident prevention		EPA 2002b 40CFR68, Appendix A
	Toxic end point	2.8×10^{-3} mg/L	
	Regulated toxic substance for accidental release prevention[b]		EPA 2002a 40CFR68.130, Table 1
	Threshold quantity	1,000 pounds	
NIOSH	TWA-REL (10-hour TWA)	0.1 ppm	NIOSH 2002
	STEL (15-minute TWA)	0.3 ppm	
	IDLH	5 ppm	
OSHA	PEL (8-hour TWA) for general industry	0.1 ppm	OSHA 2002b 29CFR1910.1000
	Highly hazardous chemical for general industry		OSHA 2002c 29CFR1910.119, Appendix A
	Threshold quantity	1,000 pounds	
	PEL (8-hour TWA) for construction industry	0.1 ppm	OSHA 2002a 29CFR1926.55
	Highly hazardous chemical for construction industry		OSHA 2002d 29CFR1926.64, Appendix A
	Threshold quantity	1,000 pounds	
b. Water			
EPA	Maximum contaminant level		EPA 2002e 40CFR141.64(a)
	Chlorite	1.0 mg/L	

Table 8-1. Regulations and Guidelines Applicable to Chlorine Dioxide and Chlorite

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Maximum contaminant level goal		EPA 2002f 40CFR141.53
	Chlorite	0.8 mg/L	
	Maximum residual disinfectant level	0.8 mg/L	EPA 2002g 40CFR141.65(a)
	Maximum residual disinfectant level goal	0.8 mg/L	EPA 2002h 40CFR141.54
c. Food			
EPA	Exemption from the requirement of a tolerance—sodium chlorite	For residues as a seed - soak treatment in growing Brassica (cole) leafy vegetables and radishes	EPA 2002j 40CFR180.1070
FDA	Direct food additive permitted in food for human consumption; used as an antimicrobial agent in water used in poultry processing and to wash fruits and vegetables	Not to exceed 3 ppm	FDA 2001e 21CFR173.300
	Direct food additive permitted in food for human consumption; used as an antimicrobial agent—acidified sodium chlorite	Used at levels from 50–1,500 ppm	FDA 2001d 21CFR173.325
	Indirect food additive; adjuvants, production aids, and sanitizers		FDA 2001b 21CFR178.1010
	Indirect food substance affirmed as generally recognized as safe; used as a slimicide in the manufacture of paper and paperboard that contact food—sodium chlorite	Used at levels from 125–250 ppm	FDA 2001c 21CFR186.1750
	Substance for use only as components of adhesives—sodium chlorite		FDA 2001a 21CFR175.105 (c)(5)
d. Other			
EPA	Chlorine dioxide		IRIS 2002
	Carcinogenicity classification	Group D[c]	
	RfC	$2x10^{-4}$ mg/m^3	
	RfD	$3x10^{-2}$ mg/kg/day	
	Chlorite		IRIS 2002
	Carcinogenicity classification	Group D[c]	
	RfC	No data	
	RfD	$3x10^{-2}$ mg/kg/day	

Table 8-1. Regulations and Guidelines Applicable to Chlorine Dioxide and Chlorite

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA			
	Toxic chemical release reporting; community right-to-know; effective date for reporting	01/01/87	EPA 2002k 40CFR372.65(a)
STATE			
Regulations and Guidelines:			
a. Air			
Louisiana	Toxic air pollutantd		BNA 2001
	Minimum emission rate	25 pounds/year	
New Mexico	Toxic air pollutant		BNA 2001
	OEL	0.3 mg/m^3	
	Emissions	0.02 pounds/hour	
Vermont	Hazardous air contaminant		BNA 2001
b. Water			
Maine	Drinking water guideline		HSDB 2002
	Chlorine dioxide	60 µg/L	
	Chlorite	7 µg/L	
c. Food	No data		
d. Other			
Florida	Toxic substance in the workplace		BNA 2001

[a]Group 3: not classifiable as to its carcinogenicity to humans
[b]Basis for listing: toxic gas
[c]Group D: not classifiable as to human carcinogenicity
[d]Class II: suspected human carcinogen and known or suspected human reproductive toxin

ACGIH = American Conference of Governmental Industrial Hygienists; BNA = Bureau of National Affairs; CFR = Code of Federal Regulations; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life and health; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; OEL = occupational exposure limit; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; ppm = parts per million; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; STEL = short-term exposure limit; TLV = threshold limit value; TWA = time-weighted average

9. REFERENCES

Abdel-Rahman MS, Scatina J. 1985. The effect of Alcide®, a new antimicrobial drug, on rat blood glutathione and erythrocyte osmotic fragility, in vitro. J Appl Toxicol 5(3):178-181.

*Abdel-Rahman MS, Couri D, Bull RJ. 1980a. Kinetics of ClO_2 and effects of ClO_2, ClO_2^-, and ClO_3^- in drinking water on blood glutathione and hemolysis in rat and chicken. J Environ Pathol Toxicol 3:431-449.

*Abdel-Rahman MS, Couri D, Bull RJ. 1982. Metabolism and pharmacokinetics of alternate drinking water disinfectants. Environ Health Perspect 46:19-23.

*Abdel-Rahman MS, Couri D, Bull RJ. 1984a. The kinetics of chlorite and chlorate in the rat. J Am Coll Toxicol 3(4):261-267.

*Abdel-Rahman MS, Couri D, Bull RJ. 1984b. Toxicity of chlorine dioxide in drinking water. J Am Coll Toxicol 3(4):277-284.

Abdel-Rahman MS, Couri D, Bull RJ. 1985a. The kinetics of chlorite and chlorate in rats. J Environ Pathol Toxicol Oncol 6(1):97-103.

Abdel-Rahman MS, Couri D, Bull RJ. 1985b. Toxicity of chlorine dioxide in drinking water. J Environ Pathol Toxicol Oncol 6(1):105-113.

*Abdel-Rahman MS, Couri D, Jones JD. 1980b. Chlorine dioxide metabolism in rat. J Environ Pathol Toxicol 3:421-430.

*Abdel-Rahman MS, Skowronski GA, Gerges SE, et al. 1987a. Teratologic studies on Alcide Allay® gel in rabbits. J Appl Toxicol 7(3):161-165.

*Abdel-Rahman MS, Skowronski GA, Turkall RM, et al. 1987b. Subchronic dermal toxicity studies of Alcide Allay® gel and liquid in rabbits. J Appl Toxicol 7(5):327-333.

Abdel-Rahman MS, Skowronski GA, Turkall RM. 1987c. Subchronic vaginal toxicity studies of Alcide Allay® gel and liquid in guinea pigs. Drug Chem Toxicol 10(3-4):257-274.

*ACGIH. 2001. Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists. http://www.osha.gov/comp-links.html. May 9, 2002.

*Adinolfi M. 1985. The development of the human blood-CSF-brain barrier. Dev Med Child Neurol 27:532-537.

---

* Cited in text

9. REFERENCES

*Adlercreutz H. 1995. Phytoestrogens: Epidemiology and a possible role in cancer protection. Environ Health Perspect Suppl 103(7):103-112.

*Agency for Toxic Substances and Disease Registry. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles; Notice. Fed Regist 54(174):37618-37634.

*Agency for Toxic Substances and Disease Registry. 1990. Biomarkers of organ damage or dysfunction for the renal, hepatobiliary, and immune systems. Atlanta, GA: Subcommittee on Biomarkers of Organ Damage and Dysfunction.

*Aieta EM, Berg JD. 1986. A review of chlorine dioxide in drinking water treatment. J Am Water Works Assoc 78(6):62-72.

Aieta EM, Roberts PV. 1985. The chemistry of oxo-chlorine compounds relevant to chlorine dioxide generation. In: Jolley RL, Bull RJ, Davis WP, et al., eds. Water chlorination - Chemistry, environmental impact and health effects. Vol. 5. Williamsburg, VA: Lewis Publishers, Inc., 783-784.

Aieta EM, Berg JD, Roberts PV, et al. 1980. Comparison of chlorine dioxide and chlorine in wastewater disinfection. J Water Pollut Control Fed 52(4):810-824.

Akin EW, Hoff JC, Lippy EC. 1982. Waterborne outbreak control: which disinfectant? Environ Health Perspect 46:7-12.

Alliger H, Roozdar H. 1997. Chlorine dioxide skin medicating compositions for preventing irritation. U.S. Patent No. 5,616,347. April 1, 1997.

*Altman PL, Dittmer DS. 1974. Biological handbooks: Biology data book. Vol. III. 2nd ed. Bethesda, MD: Federation of American Societies for Experimental Biology, 1987-2008, 2041.

*Andersen ME, Krishnan K. 1994. Relating *in vitro* to *in vivo* exposures with physiologically based tissue dosimetry and tissue response models. In: Salem H, ed. Animal test alternatives: Refinement, reduction, replacement. New York: Marcel Dekker, Inc., 9-25.

*Andersen ME, Clewell HJ III, Gargas ML, et al. 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol Appl Pharmacol 87:185-205.

Anderson AC, Reimers RS, DeKernion P. 1982. A brief review of the current status of alternatives to chlorine disinfection of water. Am J Public Health 72(11):1290-1293.

Andrews RC, Ferguson MJ. 1996. Minimizing disinfection by-product formation while ensuring *Giardia* control. In: Minear RA, Amy GL, eds. Disinfection by-products in water treatment. Chelsea, MI: Lewis Publishers, Inc., 17-55.

*APHA. 1998. Standard methods for the examination of water and wastewater. 20th ed. Baltimore, MD: United Book Press, Inc., 2-39 to 2-42, 4-73 to 4-78.

Astrakianakis G, Svirchev L, Tang C, et al. 1998. Industrial hygiene aspects of a sampling survey at a bleached-kraft pulp mill in British Columbia. Am Ind Hyg Assoc J 59(10):694-705.

Band PR, Le ND, Fang R, et al. 1997. Cohort mortality study of pulp and paper mill workers in British Columbia, Canada. Am J Epidemiol 146(2):186-194.

9. REFERENCES

Baribwau H, Prevost M, Desjardins R, et al. 2002. Chlorite and chlorate ion variability in distribution systems. J Am Water Works Assoc 94(7):96-105.

*Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8:471-486.

Bathija AT. 2003. Health Risk to Fetuses, infants and children from stage 1 disinfectants and disinfectant by-products (D/DBPs). Toxicologist 72(S-1):28.

Beitler MK, Chin HB. 1995. Improved determination of chlorite and chlorate in rinse water from carrots and green beans by liquid chromatography and amperometric and conductivity detection. J AOAC Int 78(3):878-883.

Benarde MA, Israel BM, Olivieri VP, et al. 1965. Efficiency of chlorine dioxide as a bactericide. Appl Microbiol 18(5):776-780.

*Bercz JP, Jones L, Garner L, et al. 1982. Subchronic toxicity of chlorine dioxide and related compounds in drinking water in the nonhuman primate. Environ Health Perspect 46:47-55.

*Bercz JP, Jones L, Harrington RM, et al. 1986. Mechanistic aspects of ingested chlorine dioxide on thyroid function: impact of oxidants on iodide metabolism. Environ Health Perspect 69:249-255.

*Berger GS. 1994. Epidemiology of endometriosis. In: Berger GS, ed. Endometriosis: Advanced management and surgical techniques. New York, NY: Springer-Verlag.

*Björkholm E, Hultman A, Rudling J. 1988. Determination of chlorine and chlorine dioxide in workplace air by impinger collection and ion-chromatographic analysis. J Chromatogr 457:409-414.

*Björkholm E, Hultman A, Rudling J. 1990. Evaluation of two diffusive samplers for monitoring chlorine and chlorine dioxide in workplace air. Appl Occup Environ Hyg 5(11):767-770.

*BNA. 2001. Environment and Safety Library on the Web. States and territories. Washington, DC: Bureau of National Affairs, Inc. http//www.esweb.bna.com. June 7, 2001.

*Bolyard M, Fair PS, Hautman DP. 1993. Sources of chlorate ion in US drinking water. J Am Water Works Assoc 85(9):81-88.

Bright DA, McKague B, Hodson PV, et al. 1998. Use of chlorine dioxide for the bleaching of pulp: a re-evaluation of ecological risks based on scientific progress since 1993. International Environmental Conference & Exhibit Bk. Atlanta, GA: Tappi Press, 3:1051-1054.

*Brumley CM, Haritos VS, Ahokas JT, et al. 1996. Metabolites of chlorinated syringaldehydes in fish bile as biomarkers of exposure to bleached eucalypt pulp effluents. Ecotoxicol Environ Saf 33:253-260.

*Carlton BD, Smith MK. 1985. Reproductive effects of alternate disinfectants and their by-products. Water chlorination: chemistry, environmental impact and health effects. In: Proceedings of the fifth conference on water chlorination- environmental impact and health effects, Williamsburg, Virginia, June 3-8, 1984. Chelsea, MI: Lewis Publishers, Inc., 295-305.

9. REFERENCES

*Carlton BD, Basaran AH, Mezza LE, et al. 1991. Reproductive effects in Long-Evans rats exposed to chlorine dioxide. Environ Res 56:170-177.

*Carlton BD, Habash DL, Basaran AH, et al. 1987. Sodium chlorite administration in Long-Evans rats: reproductive and endocrine effects. Environ Res 42:238-245.

Chang CY, Hsieh YH, Hsu SS, et al. 2000a. The formation of disinfection by-products in water treated with chlorine dioxide. J Hazard Mater B79:89-102.

Chang CY, Hsieh YH, Lin YM, et al. 2001. The organic precursors affecting the formation of disinfection by-products with chlorine dioxide. Chemosphere 44:1153-1158.

Chang CY, Hsieh YH, Shih IC, et al. 2000b. The formation and control of disinfection by-products using chlorine dioxide. Chemosphere 41:1181-1186.

*Chang SL. 1982. The safety of water disinfection. Annu Rev Public Health 3:393-418.

*Charles L, Pépin D. 1998. Analysis of oxyhalides in water by ion chromatography-ionspray mass spectrometry. J Chromatogr A 804:105-111.

Chien TW, Chu H. 2000. Removal of SO2 and NO from flue gas by wet scrubbing using an aqueous NaClO2 solution. J Hazard Mater B80:43-57.

Chow BM, Roberts PV. 1981. Halogenated byproduct formation by ClO_2 and Cl_2. J Environ Eng 107(EE4):609-618.

*Clewell HJ III, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1(4):111-131.

CMA. 1991. Initial submission: Letter submitting preliminary information from an acute inhalation study in rats on sodium chlorite with attachment. Chemical Manufacturers Association. CMA/88-920000094.

*CMA. 1996. Sodium chlorite: drinking water rat two-generation reproductive toxicity study. Chemical Manufacturers Association. Quintiles Report Ref. CMA/17/96.

*Colborn T, Clement C, eds. 1992. Chemically-induced alterations in sexual and functional development: The wildlife-human connection. In: Advances in modern environmental toxicology, Vol. XXI, Princeton, NJ: Princeton Scientific Publishing.

Colclough CA, Johnson JD, Christman RF, et al. 1985. Organic reaction products of chlorine dioxide and natural aquatic fulvic acids. In: Jolley RL, Bull RJ, Davis WP, et al., eds. Water chlorination-Environmental impact and health effects. Vol. 4. Pacific Grove, CA: Ann Arbor Science, IV-IX.

Condie LW. 1986. Toxicological problems associated with chlorine dioxide. J Am Water Works Assoc 78(6):73-78.

Condie LW. 1990. Toxicological effects associated with drinking water disinfectants and their by-products. In: Jolley RL, Johnson JD, et al., eds. Water chlorination. Chemistry, environmental impact and health effects. Oak Ridge, Tennessee: Lewis Publishers, 281-292.

9. REFERENCES

Connor PM, Moore GS, Calabrese EJ, et al. 1985. The renal effects of sodium chlorite in the drinking water of C57L/J male mice. J Environ Pathol Toxicol Oncol 6(2):253-260.

*Couri D, Abdel-Rahman MS. 1980. Effect of chlorine dioxide and metabolites on glutathione dependent system in rat, mouse and chicken blood. J Environ Pathol Toxicol 3:451-460.

Couri D, Abdel-Rahman MS, Bull RJ. 1982a. Toxicological effects of chlorine dioxide, chlorite and chlorate. Environ Health Perspect 46:13-17.

*Couri D, Miller CH, Bull RJ, et al. 1982b. Assessment of maternal toxicity, embryotoxicity and teratogenic potential of sodium chlorite in Sprague-Dawley rats. Environ Health Perspect 46:25-29.

Cowley G. 2000. Disinfection with chlorine dioxide. J New Engl Water Works Assoc 114(4):264-270.

*Dabrowska A, Swietlik J, Nawrocki J. 2003. Formation of aldehydes upon ClO2 disinfection. Water Res 37(5):1161-1169.

*Dalhamn T. 1957. Chlorine dioxide. AMA Arch Ind Health 15(2):101-107.

*Daniel FB, Condie LW, Robinson M, et al. 1990. Comparative subchronic toxicity studies of three disinfectants. J Am Water Works Assoc, 61-69.

Delves HT, Sieniawska CE, Fell GS, et al. 1997. Determination of antimony in urine, blood and serum and in liver and lung tissues of infants by inductively coupled plasma mass spectrometry. Analyst 122:1323-1329.

Denis M, Minon G, Masschelein WJ. 1989. Continuous determination of residual chlorite in water. Anal Chim Acta 226(1):121-128.

Dennison S, Bonnick DM. 1995. Stopped-flow thin-layer coulometric method for the determination of disinfectants in water. Anal Proc 32(1):13-15.

*Dernat M, Pouillot M. 1992. Theoretical and practical approach to the disinfection of municipal waste water using chlorine dioxide. Water Sci Technol 25(12):145-154.

Dietrich AM, Ledder TD, Gallagher DL, et al. 1992. Determination of chlorite and chlorate in chlorinated and chloraminated drinking water by flow injection analysis and ion chromatography. Anal Chem 64:498-502.

Dillner B, Larsson LO, Tibbling P. 1990. Nonchlorine bleaching of pulp produced by the modified continuous cooking process. TAPPI J 73(8):167-172.

*Dluzniewski TJ. 2002. Investigation into carpet odours with ClO2. Chlorine dioxide: The state of science, regulatory, environmental issues, and case histories. Las Vegas, NV: American Water Works Association, 105-130.

*Dobson A, Richard C. 2002. Concise international chemical assessment document 37. Chlorine dioxide (gas). Geneva, Switzerland: World Health Organization, 1-32.

Dreux M, Lafosse M, Gilbert M, et al. 1985. Analytical determination of inorganic chlorination products in water treatment by an HPLC method. In: Jolley RL, Bull RJ, Davis WP, et al., eds. Water

chlorination- Chemistry, environmental impact and health effects. Vol. 5. Williamsburg, VA: Lewis Publishers, Inc., 1065-1072.

*Elkins HB. 1959. The chemistry of industrial toxicology. 2nd ed. New York: John Wiley and Sons, 89-90.

*EMMI. 1997. Environmental Monitoring Methods Index. Version 1.1. PC# 4082. U.S. Environmental Protection Agency. Rockville, MD: Government Institutes.

*EPA. 1981. Study of chlorine dioxide and its metabolites in man. Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development. EPA600181068.

*EPA. 1988. Recommendations for and documentation of biological values for use in risk assessment Cincinnati, OH: U.S. Environmental Protection Agency. PB88179874.

*EPA. 1990. Interim methods for development of inhalation reference concentrations. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Office of Research and Development, Environmental Criteria and Assessment Office. EPA600890066A.

*EPA. 1994. Final draft for the drinking water criteria document on chlorine dioxide, chlorite and chlorate. Washington, DC: U.S. Environmental Protection Agency, Office of Science and Technology, Office of Water. EPA68C20139.

*EPA. 1995. Toxic chemical release inventory. Reporting form R and instructions. Washington DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. EPA745K95051.

*EPA. 1997a. Automated Form R for Windows: User's guide (RY97). Washington, DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics.

*EPA. 1997b. Special report on environmental endocrine disruption: An effects assessment and analysis. Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. EPA630R96012.

EPA. 1998. Health risk assessment/characterization of the drinking water disinfection by-products chlorine dioxide and chlorite. Washington, DC: U.S. Environmental Protection Agency, Office of Science and Technology, Office of Water. PB99111361.

*EPA. 2002a. Chemical accident prevention provisions. List of substances. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 68.130. Table 1. http://ecfr.access.gpo.gov/. April 24, 2002.

*EPA. 2002b. Chemical accident prevention provisions. Table of toxic endpoints. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 68. Appendix A. http://ecfrback.access. gpo.gov. April 24, 2002.

*EPA. 2002c. Chlorine dioxide. U.S. Environmental Protection Agency. Office of Pesticide Programs. http://www.epa.gov/pesticides/factsheets/chlorinedioxidefactsheet.htm. April 24, 2002.

*EPA. 2002d. Information collection rule- ICR query form. U.S. Environmental Protection Agency. http://www.epa.gov/enviro/html/icr/icr-query.html. April 24, 2002.

9. REFERENCES

*EPA. 2002e. National primary drinking water regulations. Maximum contaminant levels for disinfection byproducts. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.64(a). http://ecfrback.access.gpo.gov. April 24, 2002.

*EPA. 2002f. National primary drinking water regulations. Maximum contaminant level goals for disinfection byproducts. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.53. http://ecfrback.access.gpo.gov. April 24, 2002.

*EPA. 2002g. National primary drinking water regulations. Maximum residual disinfectant levels. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.65(a). http://ecfrback.access.gpo.gov. April 24, 2002.

*EPA. 2002h. National primary drinking water regulations. Maximum residual disinfectant level goals for disinfectants. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141.54. http://ecfrback.access.gpo.gov. April 24, 2002.

*EPA. 2002i. Standards for owners and operators of hazardous waste treatment, storage, and disposal facilities. Examples of potentially incompatible waste. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 264, Appendix V. http://ecfr.access.gpo.gov. April 24, 2002.

*EPA. 2002j. Tolerances and exemptions from tolerances for pesticide chemicals in food. Sodium chlorite; exemption from the requirement of a tolerance. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 180.1070. http://ecfrback.access.gpo.gov. April 24, 2002.

*EPA. 2002k. Toxic chemical release reporting: Community right-to-know. Chemicals and chemical categories to which this part applies. 40 CFR 372.65(a). http://ecfr.access.gpo.gov. April 24, 2002.

*Exner-Freisfeld H, Kronenberger H, Meier-Sydow J, et al. 1986. Intoxication from bleaching with sodium chlorite. The toxicology and clinical course. DTW Dtsch Tierarztl Wochenschr 111:1927-1930. (German with English abstract)

*FDA. 2001a. Indirect food additives: Adhesives and components of coatings. Adhesives. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 175.105. http://www.accessdata.fda.gov. April 24, 2002.

*FDA. 2001b. Indirect food additives: Adjuvants, production aids, and sanitizers. Sanitizing solutions. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 178.1010. http://frwebgate.access.gpo.gov. April 24, 2002.

*FDA. 2001c. Indirect food substances affirmed as generally recognized as safe. Sodium chlorite. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 186.1750. http://frwebgate.access.gpo.gov. April 24, 2002.

*FDA. 2001d. Secondary direct food additives permitted in food for human consumption. Acidified sodium chlorite solutions. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 173.325. http://frwebgate.access.gpo.gov. April 24, 2002.

*FDA. 2001e. Secondary direct food additives permitted in food for human consumption. Chlorine dioxide. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 173.300. http://frwebgate.access.gpo.gov. April 24, 2002.

9. REFERENCES

*FEDRIP. 2003. Federal Research in Progress: Chlorine dioxide. Dialog Information Service, Inc.

*Ferris BG, Burgess WA, Worcester J. 1967. Prevalence of chronic respiratory disease in a pulp mill and a paper mill in the United States. Br J Ind Med 24:26-37.

*Ferris BG, Puleo S, Chen HY. 1979. Mortality and morbidity in a pulp and a paper mill in the United States: a ten-year follow-up. Br J Ind Med 36:127-134.

Fleischaker SJ, Randtke SJ. 1983. Formation of organic chlorine in public water supplies. J Am Water Works Assoc 75(3):132-138.

*Fletcher IJ, Hemmings P. 1985. Determination of chlorine dioxide in potable waters using chlorophenol red. Analyst 110(6):695-699.

*Fomon SJ. 1966. Body composition of the infant: Part I: The male "reference infant." In: Falkner F, ed. Human development. Philadelphia, PA: WB Saunders, 239-246.

*Fomon SJ, Haschke F, Ziegler EE, et al. 1982. Body composition of reference children from birth to age 10 years. Am J Clin Nutr 35:1169-1175.

Fujie K, Aoki T. 1988. Acute cytogenic effect of alternative disinfectants on rat bone marrow cells *in vivo*. Chem Express 3(11):655-658.

Gates D. 1999a. A balanced view of chlorine dioxide. J Am Water Works Assoc 90(4):8,10.

Gates D. 1999b. Practical suggestions for meeting USEPA compliance monitoring requirements and in-plant operational control of chlorine dioxide in drinking water. Ozone Sci Eng 21:433-445.

Gates D, Harrington R. 1993. Drinking water disinfection practices: Chlorine dioxide in the nineties. In: Disinfection dilemma: Microbiological control versus by-products. Proceedings of the National Conference on Drinking Water, 339-363.

Gates DJ, Harrington RM. 1996. Neuro-reproductive toxicity issues concerning chlorine dioxide and the chlorite ion in public drinking water supplies. In: Proceedings 1995 water quality technology conference, Part I, University of California Berkeley, November 12-16, 1995. Denver, CO: American Water Works Association, 813-830.

*Gerges SE, Abdel-Rahman MS, Skowronski GA, et al. 1985. Effects of Alcide® Gel on fetal development in rats and mice. II. J Appl Toxicol 5(2):104-109.

*Gill MW, Swanson MS, Murphy SR, et al. 2000. Two-generation reproduction and developmental neurotoxicity study with sodium chlorite in the rat. J Appl Toxicol 20:291-303.

*Giwercman A, Carlsen E, Keiding N, et al. 1993. Evidence for increasing incidence of abnormalities of the human testis: A review. Environ Health Perspect Suppl 101(2):65-71.

*Gloemme J, Lundgren KD. 1957. Health hazards from chlorine dioxide. AMA Arch Ind Health 16:169-176.

Gordon G. 2000. Chemistry detail of ClO_2 generation: Impurities and by-products. In: Water quality technology conference proceedings. Oxford, OH: American Water Works Association, 754-762.

9. REFERENCES

*Gordon G. 2001. Is all chlorine dioxide created equal? J Am Water Works Assoc 93(4):163-174.

Gordon G, Tachiyashik S. 1991. Kinetics and mechanisms of formation of chlorate ion from the hypochlorous acid/chlorite ion reaction at pH 6-10. Environ Sci Technol 25:468-474.

Gordon G, Adam L, Bubnis B. 1995. Minimizing chlorate ion formation. J Am Water Works Assoc 87(6):97-106.

*Griese MH, Kaczur JJ, Gordon G. 1992. Combining methods for the reduction of oxychlorine residuals in drinking water. J Am Water Works Assoc 84(11):69-77.

*Guzelian PS, Henry CJ, Olin SS, eds. 1992. Similarities and differences between children and adults: Implications for risk assessment. Washington, DC: International Life Sciences Institute Press, VI-XI.

*Haag HB. 1949. The effect on rats of chronic administration of sodium chlorite and chlorine dioxide in the drinking water. Report to the Mathieson Alkali Works from H.B. Haag of the Medical College of Virginia. http://www.epa.gov/iris/subst/0496.htm.

*Haller JF, Northgraves WW. 1955. Chlorine dioxide and safety. TAPPI 38:199-202.

*Harrington RM, Romano RR, Gates D, et al. 1995a. Subchronic toxicity of sodium chlorite in the rat. J Am Coll Toxicol 14(1):21-33.

*Harrington RM, Romano RR, Irvine L. 1995b. Developmental toxicity of sodium chlorite in the rabbit. J Am Coll Toxicol 14(2):108-118.

*Harrington RM, Shertzer HG, Bercz JP. 1985. Effects of ClO_2 on the absorption and distribution of dietary iodide in the rat. Fundam Appl Toxicol 5:672-678.

*Hautman DP, Bolyard M. 1992a. Analysis of oxyhalide disinfection by-products and other anions of interest in drinking water by ion chromatography. J Chromatogr 602(1-2):65-74.

Hautman DP, Bolyard M. 1992b. Using ion chromatography to analyze inorganic disinfection by-products. J Am Water Works Assoc 84(11):88-93.

*Hayashi M, Kishi M, Sofuni T, et al. 1988. Micronucleus tests in mice on 39 food additives and eight miscellaneous chemicals. Food Chem Toxicol 26(6):487-500.

*HazDat. 2004. Agency for Toxic Substances and Disease Registry. http://toxnet.nlm.nih.gov. June 20, 2004.

*Heffernan WP, Guion C, Bull RJ. 1979a. Oxidative damage to the erythrocyte induced by sodium chlorite, *in vitro*. J Environ Pathol Toxicol 2(6):1501-1510.

*Heffernan WP, Guion C, Bull RJ. 1979b. Oxidative damage to the erythrocyte induced by sodium chlorite, *in vivo*. J Environ Pathol Toxicol 2:1478-1499.

*Hekmat M, Smith R, Fung P. 1994. An evaluation of the occupational health and safety administration method for the "determination of chlorine dioxide in workplace atmosphere." Am Ind Hyg Assoc J 55(11):1087-1089.

9. REFERENCES

Heller-Grossman L, Idin A, Limoni-Relis B, et al. 1999. Formation of cyanogen bromide and other volatile DBPs in the disinfection of bromide-rich lake water. Environ Sci Technol 33(6):932-937.

*Hoehn RC, Dietrich AM, Farmer WS, et al. 1990. Household odors associated with the use of chlorine dioxide. J Am Water Works Assoc 82(4):166-172.

Hoehn RC, Ellenberger CS, Gallagher DL, et al. 2003. ClO2 and by-product persistence in a drinking water system. J Am Water Works Assoc 95(4):141-150.

*Hoehn RC, Long BW, Gates DJ. 2000. Status of chlorine dioxide disinfection technologies. Blacksburg, VA. American Water Works Association, 1888-1906.

*Hoel DG, Davis DL, Miller AB, et al. 1992. Trends in cancer mortality in 15 industrialized countries, 1969-1986. J Natl Cancer Inst 84(5):313-320.

*Hofmann R, Andrews RC, Ye Q. 1998. Comparison of spectrophotometric methods for measuring chlorine dioxide in drinking water. Environ Technol 19:761-773.

*Hoigne J, Bader H. 1994. Kinetics of reactions of chlorine dioxide (OClO) in water--I. Rate constants for inorganic and organic compounds. Water Res 28(1):45-55.

*Hollowell DA, Gord JR, Gordon G, et al. 1986. Selective chlorine dioxide determination using gas-diffusion flow injection analysis with chemiluminescent detection. Anal Chem 58:1524-1527.

Hollowell DA, Pacey GE, Gordon G. 1985. Selective determination of chlorine dioxide using gas diffusion flow injection analysis. Anal Chem 57:2851-2854.

*HSDB. 2002. Chlorine Dioxide. Hazardous Substances Data Bank. National Library of Medicine. http://toxnet.nlm.nih.gov. June 3, 2004.

*Hui C, Gaizhen W, Li Y. 1997. Extraction spectrophotometric determination of trace chlorine dioxide with methylene blue. Anal Lett 30(7):1415-1421.

*IARC. 2002. Sodium chlorite. IARC monographs programme on the evaluation of carcinogenic risks to humans. International Agency for Research on Cancer. http://193.51.164.11/htdocs/Monographs/Vol52/02-Sodium%20chlorite.HTM. April 11, 2002.

*Ingram PR, Homer NZ, Smith RA, et al. 2003. The interaction of effects in vitro, in mammalian and in microbial cells. Arch Biochem 410(1):121-133.

*IRIS. 2002. Integrated Risk Information System. http://www.epa.gov/iris. April 11, 2002.

*Ishidate M, Sofuni T, Yoshikawa K, et al. 1984. Primary mutagenicity screening of food additives currently used in Japan. Food Chem Toxicol 22(8):623-636.

*ITA. 2002. U.S. Imports, December 2001, HS 282890. International Trade Administration, U.S. Department of Commerce. http://ita.doc.gov. May 16, 2002.

*Johanson CE. 1980. Permeability and vascularity of the developing brain: Cerebellum vs cerebral cortex. Brain Res 190:3-16.

9. REFERENCES

Junli H, Li W, Nanqi R, et al. 1997a. Disinfection effect of chlorine dioxide on bacteria in water. Water Res 31:607-613.

Junli H, Li W, Nanqi R, et al. 1997b. Disinfection effect of chlorine dioxide on viruses, algae and animal planktons in water. Water Res 31(3):455-460.

*Kaczur JJ, Cawlfield DW. 1993. Chlorine oxygen acids and salts (ClO_2, $HClO_2$). In: Kroschwitz JI, ed. Kirk-Othmer encyclopedia of chemical technology. Vol. 5. New York, NY: John Wiley & Sons, Inc., 969-991.

*Källén BAJ, Robert E. 2000. Drinking water chlorination and delivery outcome—a registry-based study in Sweden. Reprod Toxicol 14:303-309.

*Kanitz S, Franco Y, Patrone V, et al. 1996. Association between drinking water disinfection and somatic parameters at birth. Environ Health Perspect 104(5):516-520.

Karpel Vel Leitner N, De Laat J, Dore M. 1992. Photodecomposition of chlorine dioxide and chlorite by UV-irradiation- part II. Kinetic study. Water Res 26(12):1665-1672.

Karpel Vel Leitner N, De Laat J, Suty EH. 1991. [Kinetics of the reaction between chlorine and chlorite in dilute aqueous solution]. Environ Technol 12:477-487. (French)

*Kauppinen T, Teschke K, Savela A, et al. 1997. International data base of exposure measurements in the pulp, paper and paper product industries. Int Arch Occup Environ Health 70(2):119-127.

Kengen SWM, Rikken GB, Hagen WR, et al. 1999. Purification and characterization of (per)chlorate reductase from the chlorate-respiring strain GR-1. J Bacteriol 181(21):6706-6711.

*Kennedy SM, Enarson DA, Janssen RG, et al. 1991. Lung health consequences of reported accidental chlorine gas exposure among pulp mill workers. Am Rev Respir Dis 143(1):74-79.

Kim J, Marshall MR, Du WX, et al. 1999. Determination of chlorate and chlorite and mutagenicity of seafood treated with aqueous chlorine dioxide. J Agric Food Chem 47:3586-3591.

*Komori M, Nishio K, Kitada M, et al. 1990. Fetus-specific expression of a form of cytochrome P-450 in human livers. Biochemistry 29:4430-4433.

*Krishnan K, Andersen ME. 1994. Physiologically based pharmacokinetic modeling in toxicology. In: Hayes AW, ed. Principles and methods of toxicology. 3rd ed. New York, NY: Raven Press, Ltd., 149-188.

*Krishnan K, Andersen ME, Clewell HJ III, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang RSH, ed. Toxicology of chemical mixtures: Case studies, mechanisms, and novel approaches. San Diego, CA: Academic Press, 399-437.

Kross RD. 1997. Method and composition for prevention and treatment of female lower genital tract microbial infections. U.S. Patent No. 5,667.817. September 16, 1997.

Kun Z, Hui C, Guanghe L, et al. 1998. *In situ* remediation of petroleum compounds in groundwater aquifer with chlorine dioxide. Water Res 32(5):1471-1480.

9. REFERENCES

*Kurokawa Y, Takamura N, Matsushima Y, et al. 1984. Studies on the promoting and complete carcinogenic activities of some oxidizing chemicals in skin carcinogenesis. Cancer Lett 24:299-304.

*Kurokawa Y, Takayama S, Konishi Y, et al. 1986. Long-term *in vivo* carcinogenicity tests of potassium bromate, sodium hypochlorite, and sodium chlorite conducted in Japan. Environ Health Perspect 69:221-235.

*Lee Y, Kim H, Lee U. 2004. Formation of chlorite and chlorate from chlorine dioxide with Han River Water. Korean J Chem Eng 21(3):647-653.

*Leeder JS, Kearns GL. 1997. Pharmcogenetics in pediatrics: Implications for practice. Pediatr Clin North Am 44(1):55-77.

Leitner NKV, De Laat J, Dore M, et al. 1994. Inorganic and organic byproducts of the reactions between chlorite, activated carbon, and phenolic compounds. Environ Sci Technol 28(2):222-230.

Leitner NKV, Laat JD, Dore M, et al. 1992. [Comparison of activated carbons for the removal of chlorite.] Environ Technol 13:621-633. (French)

*Leung H-W. 1993. Physiologically-based pharmacokinetic modeling. In: Ballentine B, Marro T, Turner P, eds. General and applied toxicology. Vol. 1. New York, NY: Stockton Press, 153-164.

Limoni B, Choshen E, Rav-Acha C. 1984. Determination of oxidants formed upon the disinfection of drinking water with chlorine dioxide. J Environ Sci Health Part A 19(8):943-957.

*Lin JL, Lim PS. 1993. Acute sodium chlorite poisoning associated with renal failure. Ren Fail 15(4):645-648.

*Livingston, AL. 1978. Forage plant estrogens. J Toxicol Environ Health 4:301-324.

*Logan BE. 1998. A review of chlorate- and perchlorate-respiring microorganisms. Biorem J 2(2):69-79.

Lubbers JR, Bianchine JR. 1984. Effects of the acute rising dose administration of chlorine dioxide, chlorate and chlorite to normal healthy adult male volunteers. J Environ Pathol Toxicol 5(4-5):215-228.

*Lubbers JR, Chauhan S, Bianchine JR. 1981. Controlled clinical evaluations of chlorine dioxide, chlorite and chlorate in man. Fundam Appl Toxicol 1:334-338.

*Lubbers JR, Chauhan S, Miller JK, et al. 1984a. The effects of chronic administration of chlorine dioxide, chlorite and chlorate to normal healthy adult male volunteers. J Environ Pathol Toxicol Oncol 5-4(5):229-238.

*Lubbers JR, Chauhan S, Miller JK, et al. 1984b. The effects of chronic administration of chlorite to glucose-6-phosphate dehydrogenase deficient healthy adult male volunteers. J Environ Pathol Toxicol Oncol 5-4(5):239-242.

Luo J, Christensen PK. 1992. Sodium chlorite as an alternative for chlorine dioxide in pulp bleaching. Appita 45(1):38-40.

9. REFERENCES

*Lykins BW, Goodrich JA, Hoff JC. 1990. Concerns with using chlorine-dioxide disinfection in the USA. Aqua 39(6):376-386.

Malmqvist A, Welander T. 1992. Anaerobic removal of chlorate from bleach effluents. Water Sci Technol 25:237-242.

Marabini L, Fumagalli R, Radice S, et al. 2002. Toxicity evaluation or various drinking water disinfectants in HEPG2 cells. Toxicol Lett 135:S55.

*Mayr U, Butsch A, Schneider S. 1992. Validation of two *in vitro* test systems for estrogenic activities with zearalenone, phytoestrogens and cereal extracts. Toxicology 74:135-149.

*Meggs WJ, Elsheik T, Metzger WJ, et al. 1996. Nasal pathology and ultrastructure in patients with chronic airway inflammation (RADS and RUDS) following an irritant exposure. Clin Toxicol 34(4):383-396.

*Meier JR, Bull RJ, Stober JA, et al. 1985. Evaluation of chemicals used for drinking water disinfection for production of chromosomal damage and sperm-head abnormalities in mice. Environ Mutagen 7:201-211.

*Michael GE, Miday RK, Bercz JP, et al. 1981. Chlorine dioxide water disinfection: A prospective epidemiology study. Arch Environ Health 36:20-27.

*Miller RG, Kopfler FC, Condie LW, et al. 1986. Results of toxicological testing of Jefferson Parish Pilot plant samples. Environ Health Perspect 69:129-139.

*Mobley SA, Taylor DH, Laurie RD, et al. 1990. Chlorine dioxide depresses T3 uptake and delays development of locomotor activity in young rats. In: Jolley RL, Bull RJ, Davis WP, et al., eds. Water chlorination: chemistry, environmental impact and health effects. Vol. 6. Chelsea, MI: Lewis Publications, 347-358.

Monarca S, Feretti D, Collivignarelli C, et al. 2000. The influence of different disinfectants on mutagenicity and toxicity of urban wastewater. Water Res 34(17):4261-4269.

*Moore GS, Calabrese EJ. 1980a. G6PD: a potential high-risk group to copper and chlorite ingestion. J Environ Pathol Toxicol 4:271-279.

*Moore GS, Calabrese EJ. 1980b. The effects of chlorine dioxide and sodium chlorite on erythrocytes of A/J and C57L/J mice. J Environ Pathol Toxicol 4(2-3):513-524.

*Moore GS, Calabrese EJ. 1982. Toxicological effects of chlorite in the mouse. Environ Health Perspect 46:31-37.

Moore GS, Calabrese EJ, DiNardi SR, et al. 1978. Potential health effects of chlorine dioxide as a disinfectant in potable water supplies. Med Hypotheses 4(5):481-496.

Moore GS, Calabrese EJ, Forti A. 1984. The lack of nephrotoxicity in the rat by sodium chlorite, a possible byproduct of chlorine dioxide disinfection in drinking water. J Environ Sci Health Part A 19(6):643-661.

9. REFERENCES

Moore GS, Calabrese EJ, Ho SC. 1980a. Groups at potentially high risk from chlorine dioxide treated water. J Environ Pathol Toxicol 4(2-3):465-470.

*Moore GS, Calabrese EJ, Leonard DA. 1980b. Effects of chlorite exposure on conception rate and litters of A/J strain mice. Bull Environ Contam Toxicol 25:689-696.

*Morselli PL, Franco-Morselli R, Bossi L. 1980. Clinical pharmacokinetics in newborns and infants: Age-related differences and therapeutic implications. Clin Pharmacokin 5:485-527.

*Musil J, Knotek Z, Chalupa J, et al. 1964. Toxicologic aspects of chlorine dioxide application for the treatment of water containing phenols. Sb Vys Sk Chem Technol Praze Oddil Fak Technol Paliv Vody 8:327-345.

*NAS/NRC. 1989. Report of the oversight committee. In: Biologic markers in reproductive toxicology. Washington, DC: National Academy of Sciences, National Research Council, National Academy Press.

NASA-JPL. 1999. Public health assessment for jet propulsion laboratory (NASA), Pasadena, Los Angeles County, California. Region 9, CERCLIS no. CA9800013030. Atlanta, GA: Agency for Toxic Substances and Disease Registry, Division of Health Assessment and Consultation. PB99167470.

Nicoson JS, Margerum DW. 2002. Kinetics and mechanisms of aqueous chlorine reactions with chlorite ion in the presence of chloride ion and acetic acid/acetate buffer. Inorg Chem 41(2):342-347.

*NIOSH. 2002. Chlorine dioxide. NIOSH pocket guide to chemical hazards. National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/npg/npgd0116.html. April 11, 2002.

Nowack B, Buchs U, Kaiser H-P, et al. 1999. New methods for the determination of chlorine dioxide species in drinking water. Dübendorf, Switzerland: Swiss Federal Institute for Environmental Science and Technology, 1145-1161.

*NRC. 1980. National Research Council. Drinking water and health. Vol. 3. Washington, DC: National Academy of Sciences, National Research Council, National Academy Press, 199.

*NRC. 1993. National Research Council. Pesticides in the diets of infants and children. Washington, DC: National Academy of Sciences, National Research Council, National Academy Press.

*Ohura H, Imato T, Yamasaki S. 1999. Simultaneous potentiometric determination of ClO3--ClO2- and ClO3--HClO by flow injection analysis using Fe(III)-Fe(II) potential buffer. Talanta 49:1003-1015.

*O'Neil MJ, Smith A, Heckelman PE, et al, eds. 2001. The Merck index. 13th ed. Whitehouse Station, NJ: Merck & Co., Inc., 2213, 8869.

*Orme J, Taylor DH, Laurie RD, et al. 1985. Effects of chlorine dioxide on thyroid function in neonatal rats. J Toxicol Environ Health 15:315-322.

*OSHA. 2002a. Gases, vapors, fumes, dusts, and mists. Safety and health regulations for construction. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.55. http://www.osha.gov. May 19, 2002.

9. REFERENCES

*OSHA. 2002b. Limits for air contaminants. Occupational safety and health standards. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000. http://www.osha.gov. May 19, 2002.

*OSHA. 2002c. List of highly hazardous chemicals, toxics and reactives. Occupational safety and health standards. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.119. http://www.osha.gov. May 19, 2002.

*OSHA. 2002d. List of highly hazardous chemicals, toxics and reactives. Safety and health regulations for construction. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.64. http://www.osha.gov. May 19, 2002.

*Owen GM, Brozek J. 1966. Influence of age, sex and nutrition on body composition during childhood and adolescence. In: Falkner F, ed. Human development. Philadelphia, PA: WB Saunders, 222-238.

Owens JW, Swanson SM, Birkholz DA. 1994. Environmental monitoring of bleached kraft pulp mill chlorophenolic compounds in a Northern Canadian river system. Chemosphere 29(1):89-109.

Pantsar-Kallio M, Manninen PKG. 1998. Speciation of halogenides and oxyhalogens by ion chromatography-inductively coupled plasma mass spectrometry. Anal Chim Acta 360:161-166.

*Paulet G, Desbrousses S. 1970. On the action of ClO_2 at low concentrations on laboratory animals. Arch Mal Prof 31:97-106.

*Paulet G, Desbrousses S. 1972. On the toxicology of chlorine dioxide. Arch Mal Prof 33:59-61.

*Paulet G, Desbrousses S. 1974. Action of a discontinuous exposure to chlorine dioxide (ClO_2) on the rat. Arch Mal Prof 35:797-804.

*Pfaff JD, Brockhoff CA. 1990. Determining inorganic disinfection by-products by ion chromatography. J Am Water Works Assoc 82(4):192-195.

Pfohl B, Taylor D. 1983. Effect of chlorine dioxide on glucose uptake by developing rat brains. Am Zool 23(4):990.

Piccardi G, Barbolani E, Pantani F. 1980. Comparison between colorimetric and electrometric methods for chlorine and its derivative compounds. Water Air Soil Pollut 13:197-205.

Poovey HG, Rando RJ. 1995. Determination of chlorine and chlorine dioxide by non-suppressed ion chromatography and application to exposure assessment in the paper industry. J Liquid Chromatogr 18(2):261-275.

*Quentel F, Elleouet C, Madec C. 1994. Electrochemical determination of low levels of residual chlorine dioxide in tap water. Anal Chim Acta 295:85-91.

Rapson WH, Nazar MA, Butsky VV. 1980. Mutagenicity produced by aqueous chlorination of organic compounds. Bull Environ Contam Toxicol 24:590-596.

Ratcliff PA. 2000. Composition for treating abnormal conditions of the epithelium of bodily orifices. U.S. Patent No. 6, 017, 554. January 25, 2000.

9. REFERENCES

Ratcliff PA. 2001. Method for treating itching of the vagina. U.S. Patent No. 6,280,716 B1. August 28, 2001.

Rav-Acha C. 1984. The reactions of chlorine dioxide with aquatic organic materials and their health effects. Water Res 18(11):1329-1342.

*Rav-Acha C. 1998. Transformation of aqueous pollutants by chlorine dioxide: Reaction, mechanisms and products. In: Handbook of environmental chemistry. Vol. 5. 143-175.

*Rav-Acha C, Choshen E. 1987. Aqueous reactions of chlorine dioxide with hydrocarbons. Environ Sci Technol 21:1069-1074.

Rav-Acha C, Blits R, Choshen E, et al. 1983. The action of chlorine dioxide on aquatic organic materials during the disinfection of drinking water. J Environ Sci Health A18(5):651-671.

Richardson SD. 2002. The role of GC-MS in the discovery of drinking water disinfection by-products. Environ Monit Assess 4(1):1-9.

*Richardson SD, Thruston AD, Collette TW, et al. 1994. Multispectral identification of chlorine dioxide disinfection byproducts in drinking water. Environ Sci Technol 28(4):592-599.

Rubin ES. 1999. Toxic releases from power plants. Environ Sci Technol 33:3062-3067.

Sakemi K, Usami M, Kurebayashi H, et al. 1999. [Teratogenicity study of sodium chlorite in rats by oral administration.] Kokuritsu Iyakuhin Shokuhin Eisei Kenkyusho Hokoku 117:99-103. (Japanese)

*Saksa DJ, Smart RB. 1985. Chemiluminescent analysis of chlorine dioxide with a membrane flow cell. Environ Sci Technol 19:450-454.

*Scatina J, Abdel-Rahman MS, Gerges SE, et al. 1983. Pharmacokinetics of Alcide®, a germicidal compound in rat. J Appl Toxicol 3(3):150-153.

*Scatina J, Abdel-Rahman MS, Gerges SE, et al. 1984. Pharmacodynamics of Alcide, a new antimicrobial compound, in rat and rabbit. Fundam Appl Toxicol 4:479-484.

*Seta S, Miyake B, Sato H, et al. 1991. [Acute oral toxicity and acute irritation test to skin and eye of sodium chlorite.] Kagaku Keisatsu Kenkyusho Hokoku Hokagaku Hen 44(1):7-22. (Japanese)

*Setchell BP, Waites GMH. 1975. The blood-testis barrier. In: Creep RO, Astwood EB, Geiger SR, eds. Handbook of physiology: Endocrinology V. Washington, DC: American Physiological Society, 143-172.

Shaw JW. 1986. Indoor air quality of swimming pool enclosures. Managing Indoor Air for Health and Energy Conservation: Montreal, CA: Proceedings of the ASHRAE Conference. IAQ '86, 83-87.

*Shi L, Xie C. 1999. [Experimental observation on acute toxicity and irritative effect of stable chlorine dioxide.] Zhongguo Xiaoduxue Zazhi 16(1):39-40. (Chinese)

Shimoyama T, Hiasa Y, Kitahori Y, et al. 1985. [Absence of carcinogenic effect of sodium chlorite in rats.] Nara Igaku Zasshi 36(6):710-718. (Japanese)

9. REFERENCES

Siddiqui MS. 1996. Chlorine-ozone interactions: formation of chlorate. Water Res 30(9):2160-2170.

*Skowronski GA, Abdel-Rahman MS, Gerges SE, et al. 1985. Teratologic evaluation of Alcide® Liquid in rats and mice. I. J Appl Toxicol 5(2):97-103.

Smart RB. 1981. Measurement of chlorine dioxide with a membrane chemiluminescence cell. Anal Lett 14(A3):189-195.

Smart RB, Freese JW. 1982. Measuring chlorine dioxide with a rotating voltammetric membrane electrode. J Am Water Works Assoc 74(10):530-531.

Smith RP, Willhite CC. 1990. Chlorine dioxide and hemodialysis. Regul Toxicol Pharmacol 11(1):42-62.

Sofos JN, Smith GC. 1998. Nonacid meat decontamination technologies: Model studies and commercial applications. Int J Food Microbiol 44:171-188.

Solomon S, Sanders RW, Garcia RR, et al. 1993. Increased chlorine dioxide over Antarctica caused by volcanic aerosols from Mount Pinatubo. Nature 363:245-248.

*Sperling F. 1959. Oral LD_{50}-fasted male Winstar rats, sodium chlorite. Sperling Laboratories' report to Olin Mathieson Chemical Corp. Dated Oct. 8, 1959.

*SRI. 2001. 2001 Directory of chemical producers. United States. Menlo Park, CA: SRI International, 874-875.

*Stevens AA. 1982. Reaction products of chlorine dioxide. Environ Health Perspect 46:101-110.

Stevens AA, Moore L, Dressman RC, et al. 1985. Disinfectant chemistry in drinking water-overview of impacts on drinking water quality. In: Rice RG, ed. Safe drinking water: The impact of chemicals on a limited resource. Chelsea, MI: Lewis Publishers, Inc.

Strähle J, Schwenk M, Gabrio T, et al. 1998. [Determination of inorganic disinfection byproducts oxohalides in the water of indoor and outdoor swimming pools.] Zentralbl Hyg Umweltmed 201(1):96-97. (German)

*Suh DH, Abdel-Rahman MS. 1985. Mechanism of chloroform formation by chlorine and its inhibition by chlorine dioxide. Fundam Appl Toxicol 5:305-313.

*Suh DH, Abdel-Rahman MS, Bull RJ. 1983. Effect of chlorine dioxide and its metabolites in drinking water on fetal development in rats. J Appl Toxicol 3(2):75-79.

Suh DH, Abdel-Rahman MS, Bull RJ. 1984. Biochemical interactions of chlorine dioxide and its metabolites in rats. Arch Environ Contam Toxicol 13(2):163-169.

*Suzuki J, Okumoto C, Katsuki Y, et al. 1997. Determination of residual chlorite in vegetables and eggs treated with sodium chlorite by UV-ion chromatography and effect of soaking in water. J Food Hyg Soc Jpn 38(1):22-26.

*Sweetin DL, Sullivan E, Gordon G. 1996. The use of chlorophenol red for the selective determination of chlorine dioxide in drinking water. Talanta 43:103-108.

Tanner RS. 1989. Comparative testing and evaluation of hard-surface disinfectants. J Ind Microbiol 4:145-154.

*Taylor DH, Pfohl RJ. 1985. Effects of chlorine dioxide on the neurobehavioral development of rats. In: Jolley RL, Bull RJ, Davis WP, et al., eds. Water chlorination: chemistry, environmental impact and health effects. Vol. 6. Chelsea, MI: Lewis Publications, 355-364.

*Teschke K, Ahrens W, Andersen A, et al. 1999. Occupational exposure to chemical and biological agents in the nonproduction departments of pulp, paper, and paper product mills: an international study. Am Ind Hyg Assoc J 60:73-83.

*Thorell HD, Stenklo K, Karlsson J, et al. 2003. A gene cluster for chlorate metabolism in *Ideonella dechloratans*. Appl Environ Microbiol 69(9):5585-5592.

*Toth GP, Long RE, Mills TS, et al. 1990. Effects of chlorine dioxide on the developing rat brain. J Toxicol Environ Health 31:29-44.

Tratnyek PG, Hoigne J. 1994. Kinetics of reactions of chlorine dioxide (OClO) in water--II. Quantitative structure-activity relationships for phenolic compounds. Water Res 28(1):57-66.

*TRI01. 2003. TRI explorer: Providing access to EPA's toxics release inventory data. Washington, DC: Office of Information Analysis and Access, Offices of Environmental Information, U.S. Environmental Protection Agency. Toxic Release Inventory. http://www.epa.gov/triexplorer/. March 12, 2003.

Tsai LS, Higby R, Schade J. 1995. Disinfection of poultry chiller water with chlorine dioxide: consumption and byproduct formation. J Agric Food Chem 43:2768-2773.

*Tuthill RW, Giusti RA, Moore GS, et al. 1982. Health effects among newborns after prenatal exposure to ClO2-disinfected drinking water. Environ Health Perspect 46:39-45.

*Vieira I, Sonnier M, Cresteil T. 1996. Developmental expression of CYP2E1 in the human liver: Hypermethylation control of gene expression during the neonatal period. Eur J Biochem 238:476-483.

*Vogt H, Balej J, Bennett JE, et al. 1986. Chlorine oxides and chlorine oxygen acids. In: Gerhartz W, Yamamoto YS, Campbell FT, et al., eds. Ullman's encyclopedia of industrial chemistry. Vol. A6. New York, NY: Wiley-VCH, 483-500.

*Wang L, Huang J-L, Li B-X. 2002a. [Mutagenic effect of chlorine dioxide, chlorite and chlorate aqueous solutions.] Huanjing Huaxue 21(4):412-414. (Chinese)

*Wang L, Huang J-L, Li B-X. 2002b. [Micronucleus test of chlorine dioxide and by-products chlorite and chlorate in water.] Harbin Jianzhu Daxue Xuebao 35(1):58-60. (Chinese)

*Weinberg HS, Yamada H. 1998. Post-ion-chromatography derivatization for the determination of oxyhalides at sub-ppb levels in drinking water. Anal Chem 70:1-6.

*West JR, Smith HW, Chasis H. 1948. Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy. J Pediatr 32:10-18.

9. REFERENCES

Wheeler GL, Lott PF. 1978. A rapid microdetermination of chlorine dioxide in the presence of active chlorine compounds. Microchem J 23:160-164.

*WHO. 2000. Disinfectants and disinfectant by-products. World Health Organization. http://www.inchem.org. April 24, 2000.

*WHO. 2002. Health for All Statistical Database. European Public Health Information Network for Eastern Europe. World Health Organization. http://www.euphin.dk/hfa/Phfa.asp. April 24, 2002.

*Widdowson EM, Dickerson JWT. 1964. Chemical composition of the body. In: Comar CL, Bronner F, eds. Mineral metabolism: An advanced treatise. Volume II: The elements Part A. New York: Academic Press.

*Wolterink AFWM, Jonker AB, Kengen SWM, et al. 2002. *Pseudomonas chloritidismutans* sp. nov., a non-denityifying, chlorate-reducing bacterium. Int J Syst Evol Microbiol 52:2183-2190.

Wondergem E, Van Dijk-Looijaard AM. 1991. Chlorine dioxide as a post-disinfectant for Dutch drinking water. Sci Total Environ 102:101-112.

*Xu J, Trimble JJ, Steinberg L, et al. 2004. Chlorate and nitrate reduction pathways are separately induced in the perchlorate-respiring bacterium *Dechlorosoma* sp. KJ and the chlorate-respiring bacterium *Pseudomonas* sp. PDA. Water Res 38:673-680.

*Yokose Y, Uchida K, Nakae D, et al. 1987. Studies of carcinogenicity of sodium chlorite in B6C3F1 mice. Environ Health Perspect 76:205-210.

Zhang X, Echigo S, Minear RA, et al. 1999. Characterization and comparison of disinfection by-products from using four major disinfectants. Am Chem Soc Abstr Pap 39:251-254.

*Ziegler EE, Edwards BB, Jensen RL, et al. 1978. Absorption and retention of lead by infants. Pediatr Res 12:29-34.

*Zika RG, Moore CA, Gidel LT, et al. 1984. Sunlight-induced photodecomposition of chlorine dioxide. In: Jolley RL, Bull RJ, Davis WP, et al. eds., Water chlorination-Chemistry, environmental impact and health effects. Vol. 5. Williamsburg, VA: Lewis Publishers, Inc., 1041-1063.

Zoeteman BCJ, Hrubec J, de Greef E, et al. 1982. Mutagenic activity associated with by-products of drinking water disinfection by chlorine, chlorine dioxide, ozone and UV-irradiation. Environ Health Perspect 46:197-205.

10. GLOSSARY

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

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

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

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

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by 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 BMD10 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-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

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

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

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

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

Cross-sectional Study—A type of epidemiological study of a group or groups 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 assessment.

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

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

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

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

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

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

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

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

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

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

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

Immunological Effects—Functional changes in the immune response.

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

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

Lethal Concentration(Lo) (LC_{Lo})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

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

Lethal Dose(Lo) (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed 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) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

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

Pharmacokinetics—The 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.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

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

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

q1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

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

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

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL-from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

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

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

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

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

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

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

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

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

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

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

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

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

Toxic Dose(50) (TD50)—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 chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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

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

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

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

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 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, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Chlorine dioxide
CAS Number: 10049-04-4
Date: July 2, 2004
Profile Status: Final Post Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 8
Species: Rat

Minimal Risk Level: 0.001 [ ] mg/kg/day [X] ppm

Reference: Paulet G, Desbrousses S. 1972. On the toxicology of chlorine dioxide. Arch Mal Prof 33(1-2):59-61.

Experimental design and effects noted: The intermediate-duration inhalation MRL is based on results of a study in which the most significant finding was respiratory effects in adult rats exposed to chlorine dioxide vapors. Groups of eight Wistar rats (sex not reported) were exposed to chlorine dioxide vapors at a concentration of 1 ppm (2.8 mg/m^3), 5 hours/day, 5 days/week for 2 months. The authors stated that weight gain and erythrocyte and leukocyte levels were not affected, but concurrent control data were not presented. Chlorine dioxide-induced respiratory effects included peribronchiolar edema and vascular congestion in the lungs. No alterations in epithelium or parenchyma were seen. This study identified a LOAEL of 1 ppm (2.8 mg/m^3) for mild respiratory effects.

Dose and end point used for MRL derivation: 1 ppm; respiratory effects.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for use of a LOAEL
[X] 3 for interspecies extrapolation since the exposure concentration was dosimetrically adjusted
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? NA

Was a conversion used from intermittent to continuous exposure? Yes

$LOAEL_{ADJ}$ = LOAEL (1 ppm) x 5 hours/24 hours x 5 days/7 days = 0.15 ppm

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

The human equivalent concentration (HEC) for the LOAEL ($LOAEL_{HEC}$) was calculated by multiplying the $LOAEL_{ADJ}$ by the regional gas ratio for the pulmonary region of the respiratory tract ($RGDR_{PU}$) according to the equation:

$$RGDR_{PU} = \frac{\left(RGD_{PU}\right)_A}{\left(RGD_{PU}\right)_H} = \frac{\left[\frac{\dot{Q}_{alv}}{SA_{PU}}\right]_A}{\left[\frac{\dot{Q}_{alv}}{SA_{PU}}\right]_H} \cdot \left[\frac{\left[e^{-\frac{SA_{TB}}{\dot{V}_E}}\right]_A}{\left[e^{-\frac{SA_{TB}}{\dot{V}_E}}\right]_H}\right]^{K_{gTB}} \cdot \left[\frac{\left[e^{-\frac{SA_{ET}}{\dot{V}_E}}\right]_A}{\left[e^{-\frac{SA_{ET}}{\dot{V}_E}}\right]_H}\right]^{K_{gET}}$$

(EPA 1994, Equation 4-28 to be used for pulmonary effects of a Category 1 gas)

RGD = Regional Gas Dose
RGDR = Regional Gas Dose Ratio

Q_{alv} = alveolar ventilation rate (cm^3/minute)
SA = surface area (cm^2)
V_E = minute volume (cm^3/minute)
K_g = overall mass transport coefficient (cm/minute)

ET = extrathoracic (nose and mouth)
TB = tracheobronchial (trachea, bronchi, bronchioles to terminal bronchioles)
PU = pulmonary (respiratory bronchioles, alveolar region)
A = animal
H = human

The following values were used for respiratory parameters in the equation above:

	Surface area (SA) (EPA 1994, Table 4-4)		
Species	ET (cm^2)	TB (cm^2)	PU (cm^2)
Rat	15.0	22.5	3,400
Human	200	3,200	540,000

Species	Alveolar ventilation rate (Q_{alv}, in cm^3/minute)	Minute volume (VE, in cm^3/minute)
Rat	111 (67% of VE per EPA 1988)	165* (Equation 4-4, EPA 1994)
Human	9,250 (67% of VE per EPA 1988)	13,800 (EPA 1994)

* Average body weight of the treated rats in the critical study (Paulet and Desbrousses 1972) was 0.225 kg.

Since the overall mass transport coefficient (K_g) is not available, the value has been assumed to equal 1.

Therefore:

$$RGDR_{PU} = \frac{\left[\frac{111cm^3/\min}{3400cm^2}\right]_{rat}}{\left[\frac{9250cm^3/\min}{540{,}000cm^2}\right]_H} \cdot \left[\frac{\left[e^{-\frac{22.5cm^2}{165cm^3/\min}}\right]_{rat}}{\left[e^{-\frac{3200cm^2}{13800cm^3/\min}}\right]_H}\right]^1 \cdot \left[\frac{\left[e^{-\frac{15cm^2}{165cm^3/\min}}\right]_{rat}}{\left[e^{-\frac{200cm^2}{13800cm^3/\min}}\right]_H}\right]^1$$

$$RGDR_{PU} = \frac{[0.03265]_{rat}}{[0.01713]_H} \cdot \left[\frac{\left[e^{-0.1364}\right]_{rat}}{\left[e^{-0.2319}\right]_H}\right]^1 \cdot \left[\frac{\left[e^{-0.09091}\right]_{rat}}{\left[e^{-0.01449}\right]_H}\right]^1$$

$$RGDR_{PU} = 1.9060 \cdot \left[\frac{[0.8725]_{rat}}{[0.7930]_H}\right]^1 \cdot \left[\frac{[0.9131]_{rat}}{[0.9856]_H}\right]^1$$

$RGDR_{PU}$ = 1.9060x1.1003x0.9093=1.9070

Therefore: $LOAEL_{HEC}$ = 0.15 ppm x1.9=0.3 ppm

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

Paulet and Desbrousses (1970) exposed groups of 10 rats/sex (strain not specified) to chlorine dioxide vapors at a concentrations of 0 or 2.5 ppm (6.9 mg/m^3), 7 hours/day for 30 days. The weekly exposure frequency was not reported. Chlorine dioxide-exposed rats exhibited respiratory effects that included lymphocytic infiltration of the alveolar spaces, alveolar vascular congestion, hemorrhagic alveoli, epithelial erosions, and inflammatory infiltrations of the bronchi. The study authors also reported slightly decreased body weight gain and decreased erythrocyte and increased leukocyte levels, relative to controls. Recovery from the pulmonary lesions was apparent in rats examined after a 15-day recovery period.

A set of other inhalation studies supports the finding of the respiratory system as a major target of toxicity following exposure to chlorine dioxide vapors, although these studies are limited in design (Dalhamn 1957). A single 2-hour inhalation exposure of four rats to a chlorine dioxide concentration of 260 ppm (728 mg/m^3) resulted in pulmonary edema and nasal bleeding. Respiratory distress was reported in three other rats subjected to 3 weekly 3-minute exposures to decreasing concentrations of airborne chlorine dioxide from 3,400 to 800 ppm (from 9,520 to 2,240 mg/m^3); bronchopneumonia was observed in two of these rats. In a third rat study, repeated exposure to approximately 10 ppm (28 mg/m^3) of chlorine dioxide (4 hours/day for 9 days in a 13-day period) resulted in rhinorrhea, altered respiration, and respiratory infection. No indications of adverse effects were seen in rats exposed to approximately 0.1 ppm (0.28 mg/m^3) of chlorine dioxide 5 hours/day for 10 weeks.

Human data support the animal findings. In a case of accidental inhalation exposure to chlorine dioxide in the paper industry, exposure to 5 ppm (14 mg/m^3) for an unspecified amount of time resulted in signs of respiratory irritation (Elkins 1959). In another case report, a woman experienced coughing, pharyngeal irritation, and headache while mixing a bleach solution that was then used to bleach dried flowers (Exner-Freisfeld et al. 1986). Nasal abnormalities (including injection, telangectasia, paleness, cobblestoning, edema, and thick mucus) were observed in 13 individuals (1 man and 12 women) who had been accidentally exposed to chlorine dioxide from a leak in a water purification system pipe 5 years earlier (Meggs et al. 1996).

Agency Contact (Chemical Manager): Jessilynn B. Taylor, M.S.

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical Name: Chlorite (as sodium salt)
CAS Number: 7758-19-2
Date: July 2, 2004
Profile Status: Final Post Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 10
Species: Rat

Minimal Risk Level: 0.1 [X] mg/kg/day [ ] ppm

Reference: Gill MW, Swanson MS, Murphy SR, et al. 2000. Two-generation reproduction and developmental neurotoxicity study with sodium chlorite in the rat. J Appl Toxicol 20:291-303.

Experimental design and effects noted: The intermediate-duration oral MRL is based on results of a study in which the most significant finding was neurodevelopmental delays (lowered auditory startle amplitude, decreased brain weight) in rat pups that had been exposed throughout gestation and lactation via their mothers. Groups of 30 male and 30 female Sprague-Dawley rats (F_0) received sodium chlorite in the drinking water at concentrations of 35, 70, or 300 mg/L (approximate chlorite doses of 3, 5.7, and 21 mg/kg/day and 3.9, 7.6, and 29 mg/kg/day for males and females, respectively) for 10 weeks prior to mating and during mating; exposure of females continued throughout gestation and lactation. Groups of F_1 pups were continued on the same treatment regimen as their parents (chlorite doses of 2.9, 6.0, and 23 mg/kg/day and 3.9, 8.0, and 29 mg/kg/day for F_1 males and females, respectively). Low-dose female pups exhibited slight, but statistically significant differences in some hematological parameters, relative to controls. No other effects were seen in pups of this exposure level, and the hematological effects were not considered to be adverse. Mid-dose pups exhibited a significant decrease in maximum response to an auditory startle stimulus on postnatal day 24, but not on postnatal day 60. At this exposure level, F_1 pups also exhibited reduced liver weight. At the high dose, significant effects included reduced absolute and relative liver weight in F_1 males and females, reduced pup survival, reduced body weight at birth and throughout lactation in F_1 and F_2 rats, lowered thymus and spleen weight in both generations, lowered incidence of pups exhibiting normal righting reflex and with eyes open on postnatal day 15, decreased absolute brain weight for F_1 males and F_2 females, delayed sexual development in males (preputial separation) and females (vaginal opening) in F_1 and F_2 rats, and lowered red blood cell parameters in F_1 rats.

Dose and end point used for MRL derivation: 2.9 mg/kg/day

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[X] 10 for interspecies extrapolation
[X] 3 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? The study authors calculated sodium chlorite intakes (in mg/kg/day) from measured water consumption and body weight data. These intakes were multiplied by a factor of 0.75 to adjust for the fraction of chlorite in sodium chlorite, resulting in calculated doses of chlorite in units of mg/kg/day.

Was a conversion used from intermittent to continuous exposure? NA

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

Other additional studies or pertinent information that lend support to this MRL: The principal study is supported by the developmental studies of Orme et al. (1985), Taylor and Pfohl (1985), Mobley et al. (1990), and Toth et al. (1990), in which rats administered chlorite (as sodium salt) or chlorine dioxide at similar dosages in drinking water showed alterations in exploratory and locomotor behavior and reduced brain weights. These studies supported NOAELs and LOAELs of approximately 3 and 14 mg/kg/day, respectively.

Chlorine dioxide in drinking water rapidly degrades to chlorite (Michael et al. 1981). In laboratory animals, orally administered chlorine dioxide is rapidly converted to chlorite and chloride ion (Abdel-Rahman et al. 1980b). Being a strong oxidizer and water soluble, chlorine dioxide is not likely absorbed in the gastrointestinal tract to any great extent. Chlorite is the most likely source of systemic toxicity resulting from oral exposure to either chlorine dioxide or chlorite (soluble salts). Therefore, the intermediate-duration oral MRL derived for chlorite should also be applicable to chlorine dioxide.

Agency Contact (Chemical Manager): Jessilynn B. Taylor, M.S.

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.

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

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology 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 judgment, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgment or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest 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.

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 exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (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 are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 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 regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “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 harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

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

(11) CEL. A 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^3 or ppm and oral exposure is reported in mg/kg/day.

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

(17) CEL. Key number 38r is 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.

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

from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

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

SAMPLE

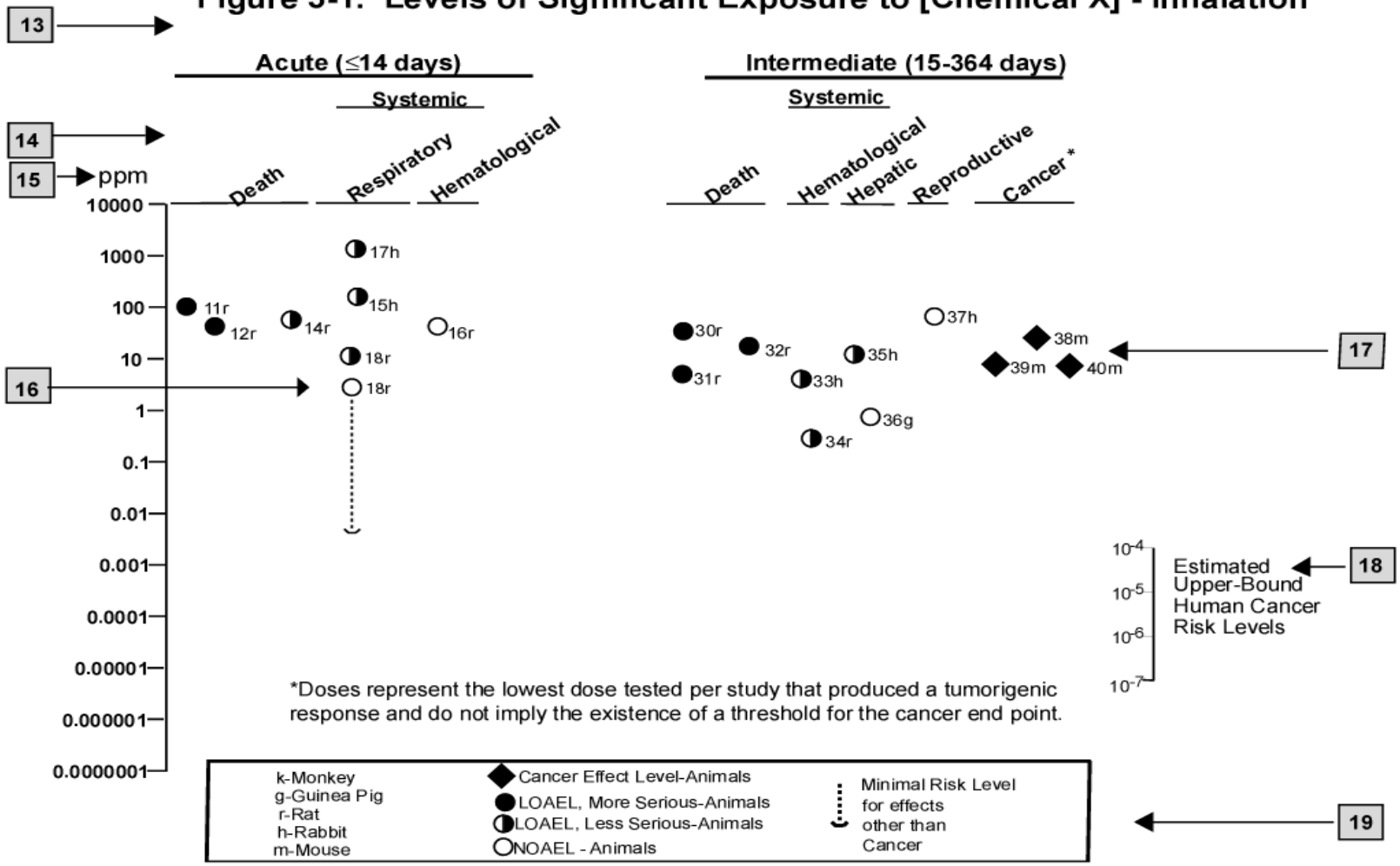
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

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

12 → a The number corresponds to entries in Figure 3-1.
b Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ 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 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	benchmark dose
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
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

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

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
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
OW	Office of Water

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

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

APPENDIX D. INDEX