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.

> 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

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 Exposures—is a guide for health care professionals treating patients exposed to hazardous materials.

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

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

	AIMER	
	TE STATEMENT	
	WORD	
-	K REFERENCE FOR HEALTH CARE PROVIDERS	
	RIBUTORS	
PEER 1	REVIEW	xi
CONT	ENTS	xiii
LIST C	OF FIGURES	vii
LIST C	OF TABLES	xix
	BLIC HEALTH STATEMENT	
1.1	WHAT ARE CHLORINE DIOXIDE AND CHLORITE?	
1.2	WHAT HAPPENS TO CHLORINE DIOXIDE AND CHLORITE WHEN THEY ENTER THE ENVIRONMENT?	
1.3	HOW MIGHT I BE EXPOSED TO CHLORINE DIOXIDE AND CHLORITE?	
1.3	HOW CAN CHLORINE DIOXIDE AND CHLORITE ENTER AND LEAVE MY BODY?	
1.4	HOW CAN CHLORINE DIOXIDE AND CHLORITE ENTER AND LEAVE MT BODT?	
1.6	HOW CAN CHLORINE DIOXIDE AND CHLORITE AFFECT MT HEALTH? HOW CAN CHLORINE DIOXIDE AND CHLORITE AFFECT CHILDREN?	
1.7	HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO CHLORINE DIOXIDE	4
1./	AND CHLORITE	5
1.8	IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED	J
1.8	TO CHLORINE DIOXIDE AND CHLORITE?	5
1.9	WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO	J
1.9	PROTECT HUMAN HEALTH?	5
1 10	WHERE CAN I GET MORE INFORMATION?	
1.10	WHERE CAN I GET WORE INFORMATION?	0
2 REI	LEVANCE TO PUBLIC HEALTH	9
2.1	BACKGROUND AND ENVIRONMENTAL EXPOSURES TO CHLORINE DIOXIDE	>
2.1	AND CHLORITE IN THE UNITED STATES	9
2.2	SUMMARY OF HEALTH EFFECTS	
2.3	MINIMAL RISK LEVELS	
2.5		
3. HE	ALTH EFFECTS	. 15
	INTRODUCTION	
	DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE.	
	2.1 Inhalation Exposure	
	3.2.1.1 Death	
	3.2.1.2 Systemic Effects	
	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	2.2 Oral Exposure	
	3.2.2.1 Death	
	3.2.2.2 Systemic Effects	
	3.2.2.3 Immunological and Lymphoreticular Effects	
	3.2.2.4 Neurological Effects	

3.2.2.5 Reproductive Effects	38
3.2.2.6 Developmental Effects	
3.2.2.7 Cancer	
3.2.3 Dermal Exposure	
3.2.3.1 Death	
3.2.3.2 Systemic Effects	
3.2.3.3 Immunological and Lymphoreticular Effects	
3.2.3.4 Neurological Effects	48
3.2.3.5 Reproductive Effects	
3.2.3.6 Developmental Effects	
3.2.3.7 Cancer	48
3.3 GENOTOXICITY	49
3.4 TOXICOKINETICS	50
3.4.1 Absorption	50
3.4.1.1 Inhalation Exposure	
3.4.1.2 Oral Exposure	
3.4.1.3 Dermal Exposure	
3.4.2 Distribution	
3.4.2.1 Inhalation Exposure	
3.4.2.2 Oral Exposure	51
3.4.2.3 Dermal Exposure	52
3.4.3 Metabolism	
3.4.3.1 Inhalation Exposure	52
3.4.3.2 Oral Exposure	
3.4.3.3 Dermal Exposure	
3.4.4 Elimination and Excretion.	
3.4.4.1 Inhalation Exposure	
3.4.4.2 Oral Exposure	
3.4.4.3 Dermal Exposure	53
3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models	
3.5 MECHANISMS OF ACTION	
3.5.1 Pharmacokinetic Mechanisms	55
3.5.2 Mechanisms of Toxicity	57
3.5.3 Animal-to-Human Extrapolations	58
3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS	
3.7 CHILDREN'S SUSCEPTIBILITY	59
3.8 BIOMARKERS OF EXPOSURE AND EFFECT	61
3.8.1 Biomarkers Used to Identify or Quantify Exposure to Chlorine Dioxide and Chlorite	62
3.8.2 Biomarkers Used to Characterize Effects Caused by Chlorine Dioxide and Chlorite	
3.9 INTERACTIONS WITH OTHER CHEMICALS	
3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE	63
3.11 METHODS FOR REDUCING TOXIC EFFECTS	64
3.11.1 Reducing Peak Absorption Following Exposure	64
3.11.2 Reducing Body Burden	
3.11.3 Interfering with the Mechanism of Action for Toxic Effects	
3.12 ADEQUACY OF THE DATABASE	
3.12.1 Existing Information on Health Effects of Chlorine Dioxide and Chlorite	65
3.12.2 Identification of Data Needs	
3.12.3 Ongoing Studies	
4. CHEMICAL AND PHYSICAL INFORMATION	73

4.1 CHEMICAL IDENTITY	73
4.2 PHYSICAL AND CHEMICAL PROPERTIES	
5 DRODUCTION IMPORT/EVRORT LISE AND DISPOSAL	77
5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL	
5.1 PRODUCTION	
5.3 USE	
J.4 DISI OSAL	02
6. POTENTIAL FOR HUMAN EXPOSURE	85
6.1 OVERVIEW	
6.2 RELEASES TO THE ENVIRONMENT	85
6.2.1 Air	85
6.2.2 Water	87
6.2.3 Soil	87
6.3 ENVIRONMENTAL FATE	90
6.3.1 Transport and Partitioning	90
6.3.2 Transformation and Degradation	90
6.3.2.1 Air	91
6.3.2.2 Water	91
6.3.2.3 Sediment and Soil	
6.3.2.4 Other Media	
6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT	
6.4.1 Air	
6.4.2 Water	
6.4.3 Sediment and Soil	
6.4.4 Other Environmental Media	
6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE	
6.6 EXPOSURES OF CHILDREN	
6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES	
6.8 ADEQUACY OF THE DATABASE	
6.8.1 Identification of Data Needs	
6.8.2 Ongoing Studies	104
7. ANALYTICAL METHODS	105
7.1 BIOLOGICAL MATERIALS	
7.2 ENVIRONMENTAL SAMPLES	
7.3 ADEQUACY OF THE DATABASE	
7.3.1 Identification of Data Needs	110
7.3.2 Ongoing Studies	
7.5.2 Oligonia Studies	111
8. REGULATIONS AND ADVISORIES	113
9. REFERENCES	117
10. GLOSSARY	137
10. GEODGIN 1	13/

APPENDICES

A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS	A-
B. USER'S GUIDE	B-
C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS	
D. INDEX	D-

LIST OF FIGURES

3-1	Levels of Significant Exposure to Chlorine Dioxide and Chlorite—Inhalation	. 21
3-2	Levels of Significant Exposure to Chlorine Dioxide and Chlorite—Oral	31
3-3	Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance	56
3-4	Existing Information on Health Effects of Chlorine Dioxide and Chlorite	. 66
6-1	Frequency of NPL Sites with Chlorine Dioxide and Chlorite Contamination	86
6-2	Percentage of POTW Facilities Reporting to ICR vs. Level of Chlorite in Distribution System Water	

LIST OF TABLES

3-1	Levels of Significant Exposure to Chlorine Dioxide and Chlorite—Inhalation	19
3-2	Levels of Significant Exposure to Chlorine Dioxide and Chlorite—Oral	27
4-1	Chemical Identity of Chlorine Dioxide and Sodium Chlorite	74
4-2	Physical and Chemical Properties of Chlorine Dioxide and Sodium Chlorite	75
5-1	Facilities that Produce, Process, or Use Chlorine Dioxide	78
5-2	Publicly Owned Treatment Works (POTW) Utilizing Chlorine Dioxide for Water Treatment in 1995	81
6-1	Releases to the Environment from Facilities that Produce, Process, or Use Chlorine Dioxide	88
6-2	Chlorine Speciation in Aqueous Solutions	92
7-1	Analytical Methods for Determining Chlorine Dioxide and Chlorite in Environmental Samples	107
8-1	Regulations and Guidelines Applicable to Chlorine Dioxide and Chlorite	114