# TOXICOLOGICAL PROFILE FOR CHLORINE

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

November 2010

## **DISCLAIMER**

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

### **UPDATE STATEMENT**

A Toxicological Profile for Chlorine, Draft for Public Comment was released in October 2007. This edition supersedes any previously released draft or final profile.

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

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine/Applied Toxicology Branch
1600 Clifton Road NE
Mailstop F-62
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 these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

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

Each profile includes the following:

- (A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;
- (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and
- (C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

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

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

Thomas R. Frieden, M.D., M.P.H.

Administrator

Agency for Toxic Substances and

Disease Registry

#### \*Legislative Background

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

CHLORINE vii

#### 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:** 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY) **Fax:** (770) 488-4178 **E-mail:** cdcinfo@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.

CHLORINE viii

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, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

CHLORINE is

#### **CONTRIBUTORS**

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

G. Daniel Todd, Ph.D.
Patricia Ruiz, Ph.D.
Larry Cseh, R.S.
Pam Tucker, M.D.
John Doyle, M.P.A.
ATSDR, Division of Toxicology and Environmental Medicine, Atlanta, GA

Fernando T. Llados, Ph.D. Daniel J. Plewak, B.S. Mario Citra, Ph.D. SRC, Inc., North Syracuse, NY

#### THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

- 1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.
- 2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.
- 3. Data Needs Review. The Applied Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.
- 4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

CHLORINE x

CHLORINE x

#### PEER REVIEW

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

- 1. John Balmes, M.D., Professor in Residence, Department of Medicine, University of California, San Francisco, San Francisco, California;
- 2. Meryl Karol, Ph.D., Professor Emeritus, Associate Dean for Academic Affairs and Research, University of Pittsburgh, Pennsylvania; and
- 3. Dennis Shusterman, M.D., MPH, Professor Emeritus, Department of Medicine, University of California, San Francisco, California.

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

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

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

CHLORINE xii

## **CONTENTS**

DISCLAIMER		ii
	FEMENT	
QUICK REFERENCE FOR HEALTH CARE PROVIDERS		
CONTRIBUTORS		
	<i>I</i>	
CONTENTS		xiii
LIST OF FIGURES		xvii
LIST OF TABI	ES	xix
	ALTH STATEMENT	
	Γ IS CHLORINE?	
	THAPPENS TO CHLORINE WHEN IT ENTERS THE ENVIRONMENT?	
1.3 HOW	MIGHT I BE EXPOSED TO CHLORINE?	3
	CAN CHLORINE ENTER AND LEAVE MY BODY?	
1.5 HOW	CAN CHLORINE AFFECT MY HEALTH?	4
	CAN CHLORINE AFFECT CHILDREN?	
1.7 HOW	CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO CHLORINE?	5
1.8 IS TH	ERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSE	D
TO CI	ILORINE?	6
1.9 WHA	FRECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO	
PROT	ECT HUMAN HEALTH?	6
1.10 WHE	RE CAN I GET MORE INFORMATION?	7
2. RELEVANO	CE TO PUBLIC HEALTH	9
	GROUND AND ENVIRONMENTAL EXPOSURES TO CHLORINE IN THE	
	ED STATES	9
	MARY OF HEALTH EFFECTS	
	MAL RISK LEVELS (MRLs)	
3. HEALTH E	FFECTS	25
3.1 INTRO	DDUCTION	25
3.2 DISCU	JSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE	25
3.2.1 In	halation Exposure	26
3.2.1.1		
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	
	ral 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	
3.2.2.6	Developmental Effects	
3.2.2.7	Cancer	
5.4.4.1	CM11001	

3.2.3 Dermal Exposure	
3.2.3.1 Death	
3.2.3.2 Systemic Effects	100
3.2.3.3 Immunological and Lymphoreticular Effects	104
3.2.3.4 Neurological Effects	104
3.2.3.5 Reproductive Effects	104
3.2.3.6 Developmental Effects	104
3.2.3.7 Cancer	104
3.3 GENOTOXICITY	105
3.4 TOXICOKINETICS	107
3.4.1 Absorption	107
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	
3.4.2.3 Dermal Exposure	
3.4.3 Metabolism	
3.4.4 Elimination and Excretion.	
3.4.4.1 Inhalation Exposure	
3.4.4.2 Oral Exposure	
3.4.4.3 Dermal Exposure	
3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Mode	
3.5 MECHANISMS OF ACTION	
3.5.1 Pharmacokinetic Mechanisms	
3.5.2 Mechanisms of Toxicity	
3.5.3 Animal-to-Human Extrapolations	
3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS	115
3.7 CHILDREN'S SUSCEPTIBILITY	
3.8 BIOMARKERS OF EXPOSURE AND EFFECT	120
3.8.1 Biomarkers Used to Identify or Quantify Exposure to Chlorine	
3.8.2 Biomarkers Used to Characterize Effects Caused by Chlorine	
3.9 INTERACTIONS WITH OTHER CHEMICALS	
3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE	
3.11 METHODS FOR REDUCING TOXIC EFFECTS	
3.11.1 Reducing Peak Absorption Following Exposure	
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	
3.12.1 Existing information on Health Effects of Chlorine	
3.12.2 Identification of Data Needs	
5.12.5 Oligonia studies	139
4. CHEMICAL AND PHYSICAL INFORMATION	1/12
4. CHEMICAL AND PHYSICAL INFORMATION	
4.1 CHEMICAL IDENTITY  4.2 PHYSICAL AND CHEMICAL PROPERTIES	
4.2 THI SICAL AND CHEWICAL PROPERTIES	143
5 DRODUCTION IMPORT/EYPORT LISE AND DISDOSAL	151
5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL	
5.2 IMPORT/EXPORT	
J.2 IVII OK1/EAI OK1	,132

5.3 US	E	152
5.4 DIS	SPOSAL	158
C DOTENIT	IAL FOR HUMAN EXPOSURE	150
	ERVIEW	
	LEASES TO THE ENVIRONMENT	
6.2.1	Air	
6.2.1	Water	
6.2.3	Soil	
	VIRONMENTAL FATE	
6.3.1	Transport and Partitioning.	
6.3.2	Transformation and Degradation	
6.3.2.		
6.3.2.		
6.3.2.		
6.3.2.		
6.4 LE	VELS 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	168
6.5 GE	NERAL POPULATION AND OCCUPATIONAL EXPOSURE	169
6.6 EX	POSURES OF CHILDREN	170
6.7 PO	PULATIONS WITH POTENTIALLY HIGH EXPOSURES	170
6.8 AD	EQUACY OF THE DATABASE	171
6.8.1	Identification of Data Needs	172
6.8.2	Ongoing Studies	174
	EVALVA METEVA DA	1.55
	FICAL METHODS	
	DLOGICAL MATERIALS	
	VIRONMENTAL SAMPLES	
	EQUACY OF THE DATABASE	
7.3.1	Identification of Data Needs	
7.3.2	Ongoing Studies	183
8. REGULA	ATIONS, ADVISORIES, AND GUIDELINES	185
9. REFERE	NCES	191
10 GLOSS	ARY	213
		213
APPENDIC	ES MINIMAL RISK LEVELS AND WORKSHEETS	A 1
	GUIDEYMS, ABBREVIATIONS, AND SYMBOLS	
	YMS, ABBREVIATIONS, AND SYMBOLS	
D. INDEA.		リー1

CHLORINE xvi

CHLORINE xvii

## **LIST OF FIGURES**

3-1.	Levels of Significant Exposure to Chlorine – Inhalation	42
3-2.	Levels of Significant Exposure to Hypochlorite Solution – Oral	88
3-3.	Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance	. 113
3-4.	Existing Information on Health Effects of Chlorine Gas	. 127
3-5.	Existing Information on Health Effects of Hypochlorite Solution	. 128
<b>4-</b> 1.	Speciation of Cl <sub>2</sub> , HOCl, and OCl <sup>-</sup> as a Function of pH	. 148

CHLORINE xviii

CHLORINE xix

## **LIST OF TABLES**

3-1.	Levels of Significant Exposure to Chlorine – Inhalation	30
3-2.	Acute Effects of Chlorine Exposure on the Respiratory Tract of Humans	47
3-3.	Levels of Significant Exposure to Hypochlorite Solution – Oral	77
3-4.	Levels of Significant Exposure to Hypochlorous Acid and/or Sodium Hypochlorite Chlorine - Dermal	101
3-5.	Genotoxicity of Sodium Hypochlorite In Vivo	106
3-6.	Genotoxicity of Sodium Hypochlorite In Vitro	108
<b>4-</b> 1.	Chemical Identity of Chlorine	144
<b>4-</b> 2.	Commonly Used Terms Related to Chlorinated Water	145
4-3.	Physical and Chemical Properties of Chlorine	146
5-1.	Companies that Produce Chlorine in the United States and Annual Capacities for 2006	153
5-2.	Facilities that Produce, Process, or Use Chlorine	155
5-3.	U.S. Chlorine Imports and Exports by Year in Metric Tons	157
6-1.	Releases to the Environment from Facilities that Produce, Process, or Use Chlorine	161
6-2.	Ongoing Studies Regarding the Potential for Human Exposure to Chlorine	175
7-1.	Analytical Methods for Determining Chlorine in Environmental Samples	180
8-1.	Regulations, Advisories, and Guidelines Applicable to Chlorine and Chlorine Compounds	187