

**DRAFT
TOXICOLOGICAL PROFILE FOR
CRESOLS**

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

September 2006

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.

This information is distributed solely for the purpose of pre dissemination public comment under applicable information quality guidelines. It has not been formally disseminated by the Agency for Toxic Substances and Disease Registry. It does not represent and should not be construed to represent any agency determination or policy.

UPDATE STATEMENT

A Toxicological Profile for Cresols was released in 1991. 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-32
Atlanta, Georgia 30333

This page is intentionally blank.

FOREWORD

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

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

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

Each profile includes the following:

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

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

Comments should be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road, N.E.
Mail Stop F-32
Atlanta, Georgia 30333

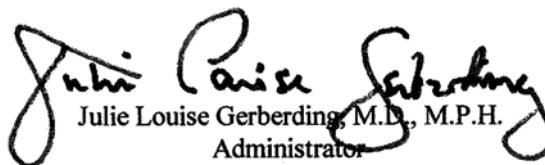
The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare 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 December 7, 2005 (70 FR 72840). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999 (64 FR 56792); October 25, 2001 (66 FR 54014); and November 7, 2003 (68 FR 63098). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

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



Howard Frumkin, M.D., Dr. P.H.
Director

National Center for Environmental Health/
Agency for Toxic Substances and
Disease Registry



Julie Louise Gerberding, M.D., M.P.H.
Administrator

Agency for Toxic Substances and
Disease Registry

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

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

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

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

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

Other Sections of Interest:

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

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636)	Fax: (770) 488-4178
1-888-232-6348 (TTY)	
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.

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.

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHOR(S):

Malcolm Williams, Ph.D.

John Risher, Ph.D.

Mike Fay, Ph.D.

ATSDR, Division of Toxicology and Environmental Medicine, Atlanta, Georgia

Fernando Llados, Ph.D.

Sari Paikoff, Ph.D.

Jennifer Rhoades, B.S.

Syracuse Research Corporation, North Syracuse, New York

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.
4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

This page is intentionally blank.

PEER REVIEW

A peer review panel was assembled for the Toxicological Profile for Cresols. The panel consisted of the following members:

1. David Kalman, Ph.D., Chair and Professor, Department of Environmental and Occupational Health Sciences, University of Washington, Health Sciences Building, F-463, Seattle, Washington,
2. John R. Balmes, M.D., Professor, Pulmonary and Critical Care Division, University of California San Francisco, San Francisco General Hospital, San Francisco, California, and
3. Rolf Hartung, Ph.D., DABT, Consultant in Environmental Toxicology, Professor of Environmental Toxicology (Retired) ,University of Michigan, 3125 Fernwood Avenue, Ann Arbor, Michigan.

These experts collectively have knowledge of cresols' 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.

This page is intentionally blank.

CONTENTS

DISCLAIMER	ii
UPDATE STATEMENT	iii
FOREWORD	v
QUICK REFERENCE FOR HEALTH CARE PROVIDERS.....	vii
CONTRIBUTORS	ix
PEER REVIEW	xi
CONTENTS.....	xiii
LIST OF FIGURES	xvii
LIST OF TABLES	xix
1. PUBLIC HEALTH STATEMENT.....	1
1.1 WHAT ARE CRESOLS?.....	1
1.2 WHAT HAPPENS TO CRESOLS WHEN THEY ENTER THE ENVIRONMENT?	2
1.3 HOW MIGHT I BE EXPOSED TO CRESOLS?.....	3
1.4 HOW CAN CRESOLS ENTER AND LEAVE MY BODY?.....	3
1.5 HOW CAN CRESOLS AFFECT MY HEALTH?.....	4
1.6 HOW CAN CRESOLS AFFECT CHILDREN?.....	5
1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO CRESOLS?.....	6
1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO CRESOLS?	7
1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?.....	7
1.10 WHERE CAN I GET MORE INFORMATION?	8
2. RELEVANCE TO PUBLIC HEALTH	11
2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO CRESOLS IN THE UNITED STATES	11
2.2 SUMMARY OF HEALTH EFFECTS	12
2.3 MINIMAL RISK LEVELS (MRLs)	14
3. HEALTH EFFECTS	23
3.1 INTRODUCTION	23
3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE	23
3.2.1 Inhalation Exposure	24
3.2.1.1 Death	24
3.2.1.2 Systemic Effects	25
3.2.1.3 Immunological and Lymphoreticular Effects.....	26
3.2.1.4 Neurological Effects.....	26
3.2.1.5 Reproductive Effects	27
3.2.1.6 Developmental Effects	27
3.2.1.7 Cancer.....	27
3.2.2 Oral Exposure.....	27
3.2.2.1 Death	27
3.2.2.2 Systemic Effects	72
3.2.2.3 Immunological and Lymphoreticular Effects.....	80
3.2.2.4 Neurological Effects.....	81
3.2.2.5 Reproductive Effects	83

3.2.2.6	Developmental Effects	84
3.2.2.7	Cancer	85
3.2.3	Dermal Exposure	86
3.2.3.1	Death	86
3.2.3.2	Systemic Effects	87
3.2.3.3	Immunological and Lymphoreticular Effects	90
3.2.3.4	Neurological Effects	90
3.2.3.5	Reproductive Effects	90
3.2.3.6	Developmental Effects	90
3.2.3.7	Cancer	90
3.3	GENOTOXICITY	91
3.4	TOXICOKINETICS	94
3.4.1	Absorption	96
3.4.1.1	Inhalation Exposure	96
3.4.1.2	Oral Exposure	96
3.4.1.3	Dermal Exposure	97
3.4.2	Distribution	97
3.4.2.1	Inhalation Exposure	97
3.4.2.2	Oral Exposure	97
3.4.2.3	Dermal Exposure	98
3.4.2.4	Other Routes of Exposure	98
3.4.3	Metabolism	98
3.4.4	Elimination and Excretion	101
3.4.4.1	Inhalation Exposure	101
3.4.4.2	Oral Exposure	101
3.4.4.3	Dermal Exposure	101
3.4.4.4	Other Routes of Exposure	101
3.4.5	Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models	102
3.5	MECHANISMS OF ACTION	103
3.5.1	Pharmacokinetic Mechanisms	103
3.5.2	Mechanisms of Toxicity	105
3.5.3	Animal-to-Human Extrapolations	106
3.6	TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS	107
3.7	CHILDREN'S SUSCEPTIBILITY	109
3.8	BIOMARKERS OF EXPOSURE AND EFFECT	111
3.8.1	Biomarkers Used to Identify or Quantify Exposure to Cresols	112
3.8.2	Biomarkers Used to Characterize Effects Caused by Cresols	113
3.9	INTERACTIONS WITH OTHER CHEMICALS	113
3.10	POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE	113
3.11	METHODS FOR REDUCING TOXIC EFFECTS	114
3.11.1	Reducing Peak Absorption Following Exposure	115
3.11.2	Reducing Body Burden	115
3.11.3	Interfering with the Mechanism of Action for Toxic Effects	115
3.12	ADEQUACY OF THE DATABASE	115
3.12.1	Existing Information on Health Effects of Cresols	116
3.12.2	Identification of Data Needs	118
3.12.3	Ongoing Studies	125
4.	CHEMICAL AND PHYSICAL INFORMATION	127
4.1	CHEMICAL IDENTITY	127
4.2	PHYSICAL AND CHEMICAL PROPERTIES	127

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL	131
5.1 PRODUCTION	131
5.2 IMPORT/EXPORT	138
5.3 USE.....	138
5.4 DISPOSAL	140
6. POTENTIAL FOR HUMAN EXPOSURE	141
6.1 OVERVIEW.....	141
6.2 RELEASES TO THE ENVIRONMENT	146
6.2.1 Air	146
6.2.2 Water.....	153
6.2.3 Soil	159
6.3 ENVIRONMENTAL FATE.....	160
6.3.1 Transport and Partitioning.....	160
6.3.2 Transformation and Degradation	161
6.3.2.1 Air.....	161
6.3.2.2 Water	162
6.3.2.3 Sediment and Soil.....	165
6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT	166
6.4.1 Air	166
6.4.2 Water.....	167
6.4.3 Sediment and Soil	169
6.4.4 Other Environmental Media.....	170
6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE	171
6.6 EXPOSURES OF CHILDREN	173
6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES	174
6.8 ADEQUACY OF THE DATABASE.....	175
6.8.1 Identification of Data Needs	175
6.8.2 Ongoing Studies	178
7. ANALYTICAL METHODS	180
7.1 BIOLOGICAL MATERIALS	180
7.2 ENVIRONMENTAL SAMPLES.....	182
7.3 ADEQUACY OF THE DATABASE.....	186
7.3.1 Identification of Data Needs	187
7.3.2 Ongoing Studies	188
8. REGULATIONS AND ADVISORIES	190
9. REFERENCES	194
10. GLOSSARY	220

APPENDICES

A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS A-1

B. USER’S GUIDE..... B-1

C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS..... C-1

D. INDEX D-1

LIST OF FIGURES

3-1. Levels of Significant Exposure to Cresols – Oral.....	63
3-2. Bioactivation Pathways of <i>p</i> -Cresol in Human Liver Microsomes	100
3-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance.....	104
3-4. Existing Information on Health Effects of Cresols.....	117
6-1. Frequency of NPL Sites with <i>o</i> -Cresol Contamination	142
6-2. Frequency of NPL Sites with <i>m</i> -Cresol Contamination	143
6-3. Frequency of NPL Sites with <i>p</i> -Cresol Contamination	144
6-4. Frequency of NPL Sites with Cresols (Mixed Isomers) Contamination	145

This page is intentionally blank.

LIST OF TABLES

3-1. Levels of Significant Exposure to Cresols – Oral.....	29
3-2. Levels of Significant Exposure to Cresols – Dermal.....	88
3-3. Genotoxicity of Cresols <i>In Vitro</i>	92
3-4. Genotoxicity of Cresols <i>In Vivo</i>	95
4-1. Chemical Identity of Cresols	128
4-2. Physical and Chemical Properties of Cresols	129
5-1. Facilities that Produce, Process, or Use <i>o</i> -Cresol	132
5-2. Facilities that Produce, Process, or Use <i>m</i> -Cresol	133
5-3. Facilities that Produce, Process, or Use <i>p</i> -Cresol	134
5-4. Facilities that Produce, Process, or Use Cresol (Mixed Isomers).....	135
5-5. Current U.S. Producers of Cresol	137
6-1. Releases to the Environment from Facilities that Produce, Process, or Use <i>o</i> -Cresol.....	147
6-2. Releases to the Environment from Facilities that Produce, Process, or Use <i>m</i> -Cresol.....	148
6-3. Releases to the Environment from Facilities that Produce, Process, or Use <i>p</i> -Cresol.....	149
6-4. Releases to the Environment from Facilities that Produce, Process, or Use Cresol (Mixed Isomers).....	150
6-5. Detection of <i>o</i> -Cresol in the Groundwater of Hazardous Waste Sites and Landfills	154
6-6. Detection of <i>m</i> -Cresol in the Groundwater of Hazardous Waste Sites and Landfills.....	155
6-7. Detection of <i>p</i> -Cresol in the Groundwater of Hazardous Waste Sites and Landfills	156
6-8. Detection of <i>p</i> - and <i>m</i> -Cresol in the Groundwater of Hazardous Waste Sites and Landfills	157
7-1. Analytical Methods for Determining Cresols in Biological Materials	180
7-2. Analytical Methods for Determining Cresols in Environmental Materials	182
8-1. Regulations and Guidelines Applicable to Cresols.....	191