

TOXICOLOGICAL PROFILE FOR PHENOL

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

September 2008

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 Phenol, Draft for Public Comment was released in October 2006. 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.

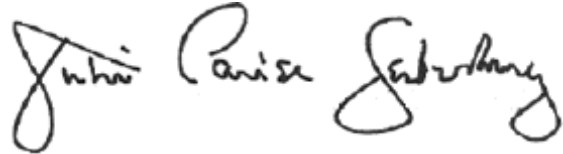
The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

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.



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

*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 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.

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):

Jewel Crawford, M.D.

Obaid Faroon, DVM, Ph.D.

Jewell Wilson, Ph.D.

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

Fernando T. Lladós, Ph.D.

Kristina Garber, M.S.

Sari J. Paikoff, Ph.D.

Michael H. Lumpkin, Ph.D.

Syracuse Research Corporation, North Syracuse, NY

Syracuse Research Corporation, Arlington, VA

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.

This page is intentionally blank.

PEER REVIEW

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

1. Marliisa Campbell, Ph.D., Private Consultant, Pacifica, California;
2. F. Peter Guengerich, Ph.D., Director, Center in Molecular Toxicology, Professor of Biochemistry, Vanderbilt University, School of Medicine, Nashville, Tennessee; and
3. Thomas Zoeller, Ph.D., Professor, Department of Biology, University of Massachusetts at Amherst, Amherst, Massachusetts;

These experts collectively have knowledge of phenol'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.

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 IS PHENOL?	1
1.2 WHAT HAPPENS TO PHENOL WHEN IT ENTERS THE ENVIRONMENT?.....	2
1.3 HOW MIGHT I BE EXPOSED TO PHENOL?	2
1.4 HOW CAN PHENOL ENTER AND LEAVE MY BODY?	3
1.5 HOW CAN PHENOL AFFECT MY HEALTH?	4
1.6 HOW CAN PHENOL AFFECT CHILDREN?.....	5
1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO PHENOL?	5
1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO PHENOL?.....	6
1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?	6
1.10 WHERE CAN I GET MORE INFORMATION?.....	7
2. RELEVANCE TO PUBLIC HEALTH	9
2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO PHENOL IN THE UNITED STATES	9
2.2 SUMMARY OF HEALTH EFFECTS.....	10
2.3 MINIMAL RISK LEVELS (MRLs)	14
3. HEALTH EFFECTS	21
3.1 INTRODUCTION.....	21
3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE	21
3.2.1 Inhalation Exposure	22
3.2.1.1 Death.....	22
3.2.1.2 Systemic Effects.....	23
3.2.1.3 Immunological and Lymphoreticular Effects	40
3.2.1.4 Neurological Effects	41
3.2.1.5 Reproductive Effects.....	43
3.2.1.6 Developmental Effects.....	43
3.2.1.7 Cancer	44
3.2.2 Oral Exposure.....	44
3.2.2.1 Death.....	44
3.2.2.2 Systemic Effects.....	61
3.2.2.3 Immunological and Lymphoreticular Effects	69
3.2.2.4 Neurological Effects	70
3.2.2.5 Reproductive Effects.....	71
3.2.2.6 Developmental Effects.....	72
3.2.2.7 Cancer	75

3.2.3	Dermal Exposure.....	75
3.2.3.1	Death.....	75
3.2.3.2	Systemic Effects.....	77
3.2.3.3	Immunological and Lymphoreticular Effects	85
3.2.3.4	Neurological Effects	85
3.2.3.5	Reproductive Effects.....	86
3.2.3.6	Developmental Effects.....	86
3.2.3.7	Cancer	86
3.3	GENOTOXICITY	87
3.4	TOXICOKINETICS.....	93
3.4.1	Absorption.....	93
3.4.1.1	Inhalation Exposure	93
3.4.1.2	Oral Exposure	94
3.4.1.3	Dermal Exposure	95
3.4.1.4	Other Routes of Exposure.....	97
3.4.2	Distribution	97
3.4.2.1	Inhalation Exposure	97
3.4.2.2	Oral Exposure	98
3.4.2.3	Dermal Exposure	100
3.4.2.4	Other Routes of Exposure.....	100
3.4.3	Metabolism.....	101
3.4.4	Elimination and Excretion.....	105
3.4.4.1	Inhalation Exposure	105
3.4.4.2	Oral Exposure	106
3.4.4.3	Dermal Exposure	107
3.4.4.4	Other Routes of Exposure.....	108
3.4.5	Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models	108
3.4.5.1	Summary of PBPK Models	109
3.4.5.2	Discussion of Models	111
3.5	MECHANISMS OF ACTION	113
3.5.1	Pharmacokinetic Mechanisms.....	113
3.5.2	Mechanisms of Toxicity.....	114
3.5.3	Animal-to-Human Extrapolations	115
3.6	TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS	115
3.7	CHILDREN’S SUSCEPTIBILITY	117
3.8	BIOMARKERS OF EXPOSURE AND EFFECT	122
3.8.1	Biomarkers Used to Identify or Quantify Exposure to Phenol	123
3.8.2	Biomarkers Used to Characterize Effects Caused by Phenol.....	123
3.9	INTERACTIONS WITH OTHER CHEMICALS	124
3.10	POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE	124
3.11	METHODS FOR REDUCING TOXIC EFFECTS.....	125
3.11.1	Reducing Peak Absorption Following Exposure.....	125
3.11.2	Reducing Body Burden	126
3.11.3	Interfering with the Mechanism of Action for Toxic Effects	126
3.12	ADEQUACY OF THE DATABASE.....	126
3.12.1	Existing Information on Health Effects of Phenol	127
3.12.2	Identification of Data Needs.....	129
3.12.3	Ongoing Studies	138

4. CHEMICAL AND PHYSICAL INFORMATION.....	139
4.1 CHEMICAL IDENTITY.....	139
4.2 PHYSICAL AND CHEMICAL PROPERTIES.....	139
5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL.....	143
5.1 PRODUCTION.....	143
5.2 IMPORT/EXPORT.....	143
5.3 USE.....	143
5.4 DISPOSAL.....	147
6. POTENTIAL FOR HUMAN EXPOSURE.....	149
6.1 OVERVIEW.....	149
6.2 RELEASES TO THE ENVIRONMENT.....	151
6.2.1 Air.....	151
6.2.2 Water.....	154
6.2.3 Soil.....	155
6.3 ENVIRONMENTAL FATE.....	155
6.3.1 Transport and Partitioning.....	155
6.3.2 Transformation and Degradation.....	157
6.3.2.1 Air.....	157
6.3.2.2 Water.....	157
6.3.2.3 Sediment and Soil.....	158
6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT.....	159
6.4.1 Air.....	159
6.4.2 Water.....	160
6.4.3 Sediment and Soil.....	163
6.4.4 Other Environmental Media.....	163
6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE.....	164
6.6 EXPOSURES OF CHILDREN.....	166
6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES.....	167
6.8 ADEQUACY OF THE DATABASE.....	168
6.8.1 Identification of Data Needs.....	168
6.8.2 Ongoing Studies.....	172
7. ANALYTICAL METHODS.....	173
7.1 BIOLOGICAL MATERIALS.....	173
7.2 ENVIRONMENTAL SAMPLES.....	176
7.3 ADEQUACY OF THE DATABASE.....	176
7.3.1 Identification of Data Needs.....	181
7.3.2 Ongoing Studies.....	182
8. REGULATIONS AND ADVISORIES.....	185
9. REFERENCES.....	191
10. GLOSSARY.....	221

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 Phenol – Inhalation	30
3-2. Levels of Significant Exposure to Phenol - Oral	58
3-3. Metabolism of Phenol.....	102
3-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance.....	110
3-5. Existing Information on Health Effects of Phenol.....	128
6-1. Frequency of NPL Sites with Phenol Contamination.....	150

This page is intentionally blank.

LIST OF TABLES

3-1. Levels of Significant Exposure to Phenol - Inhalation	24
3-2. Levels of Significant Exposure to Phenol - Oral	46
3-3. Levels of Significant Exposure to Phenol - Dermal	78
3-4. Genotoxicity of Phenol <i>In Vivo</i>	88
3-5. Genotoxicity of Phenol <i>In Vitro</i>	89
4-1. Chemical Identity of Phenol	140
4-2. Physical and Chemical Properties of Phenol	141
5-1. Facilities that Produce, Process, or Use Phenol.....	144
5-2. Current U.S. Producers of Phenol.....	146
6-1. Releases to the Environment from Facilities that Produce, Process, or Use Phenol	152
6-2. Estimated Exposure To Phenol At Various Industry Sites	169
7-1. Analytical Methods for Determining Phenol in Biological Samples.....	174
7-2. Analytical Methods for Determining Phenol in Environmental Samples	177
8-1. Regulations and Guidelines Applicable to Phenol	186