

**TOXICOLOGICAL PROFILE FOR
PYRETHRINS AND PYRETHROIDS**

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

September 2003

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 pyrethrins and pyrethroids, Draft for Public Comment was released in September, 2001. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. 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 E-29
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.

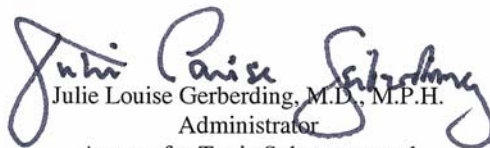
The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels 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 October 25, 2001 (66 FR 54014). 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); and October 21, 1999 (64 FR 56792). 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 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):

G. Daniel Todd, Ph.D.
ATSDR, Division of Toxicology, Atlanta, GA

David Wohlers, Ph.D.
Mario Citra, Ph.D.
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 pyrethrins and pyrethroids. The panel consisted of the following members:

1. Sam Kacew, Ph.D., Professor of Pharmacology, Department of Cellular & Molecular Medicine, University of Ottawa, Ottawa, Ontario, Canada;
2. Harihara Mehendale, Ph.D., DABT, Professor and Kitty DeGree Endowed Chair in Toxicology, School of Pharmacy, The University of Louisiana at Monroe, Monroe, Louisiana; and
3. Stephen B. Tucker, M.D., Clinical Professor of Dermatology, The University of Texas-Houston Medical School, The Woodlands, Texas.

These experts collectively have knowledge of pyrethrins and pyrethroids 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

DISCLAIMER	ii
UPDATE STATEMENT	iii
FOREWORD	v
CONTRIBUTORS	ix
PEER REVIEW	xi
CONTENTS	xiii
LIST OF FIGURES	xvii
LIST OF TABLES	xix
1. PUBLIC HEALTH STATEMENT	1
1.1 WHAT ARE PYRETHRINS AND PYRETHROIDS?	1
1.2 WHAT HAPPENS TO PYRETHRINS AND PYRETHROIDS WHEN THEY ENTER THE ENVIRONMENT?	3
1.3 HOW MIGHT I BE EXPOSED TO PYRETHRINS AND PYRETHROIDS?	4
1.4 HOW CAN PYRETHRINS AND PYRETHROIDS ENTER AND LEAVE MY BODY?	4
1.5 HOW CAN PYRETHRINS AND PYRETHROIDS AFFECT MY HEALTH?	5
1.6 HOW CAN PYRETHRINS AND PYRETHROIDS AFFECT CHILDREN?	6
1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO PYRETHRINS AND PYRETHROIDS?	7
1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO PYRETHRINS AND PYRETHROIDS?	8
1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?	9
1.10 WHERE CAN I GET MORE INFORMATION?	10
2. RELEVANCE TO PUBLIC HEALTH	13
2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO PYRETHRINS AND PYRETHROIDS IN THE UNITED STATES	13
2.2 SUMMARY OF HEALTH EFFECTS	16
2.3 MINIMAL RISK LEVELS (MRLs)	18
3. HEALTH EFFECTS	23
3.1 INTRODUCTION	23
3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE	23
3.2.1 Inhalation Exposure	26
3.2.1.1 Death	26
3.2.1.2 Systemic Effects	27
3.2.1.3 Immunological and Lymphoreticular Effects	29
3.2.1.4 Neurological Effects	29
3.2.1.5 Reproductive Effects	31

3.2.1.6	Developmental Effects	31
3.2.1.7	Cancer	31
3.2.2	Oral Exposure	31
3.2.2.1	Death	31
3.2.2.2	Systemic Effects	35
3.2.2.3	Immunological and Lymphoreticular Effects	57
3.2.2.4	Neurological Effects	58
3.2.2.5	Reproductive Effects	61
3.2.2.6	Developmental Effects	62
3.2.2.7	Cancer	65
3.2.3	Dermal Exposure	66
3.2.3.1	Death	66
3.2.3.2	Systemic Effects	67
3.2.3.3	Immunological and Lymphoreticular Effects	68
3.2.3.4	Neurological Effects	68
3.2.3.5	Reproductive Effects	70
3.2.3.6	Developmental Effects	70
3.2.3.7	Cancer	70
3.3	GENOTOXICITY	71
3.4	TOXICOKINETICS	77
3.4.1	Absorption	84
3.4.1.1	Inhalation Exposure	84
3.4.1.2	Oral Exposure	84
3.4.1.3	Dermal Exposure	86
3.4.2	Distribution	87
3.4.2.1	Inhalation Exposure	87
3.4.2.2	Oral Exposure	88
3.4.2.3	Dermal Exposure	90
3.4.2.4	Other Routes of Exposure	90
3.4.3	Metabolism	91
3.4.3.1	Inhalation Exposure	94
3.4.3.2	Oral Exposure	94
3.4.3.3	Dermal Exposure	95
3.4.4	Elimination and Excretion	95
3.4.4.1	Inhalation Exposure	95
3.4.4.2	Oral Exposure	96
3.4.4.3	Dermal Exposure	98
3.4.4.4	Other Routes of Exposure	99
3.4.5	Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models	99
3.5	MECHANISMS OF ACTION	102
3.5.1	Pharmacokinetic Mechanisms	102
3.5.2	Mechanisms of Toxicity	103
3.5.3	Animal-to-Human Extrapolations	106
3.6	TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS	106
3.7	CHILDREN'S SUSCEPTIBILITY	108
3.8	BIOMARKERS OF EXPOSURE AND EFFECT	112
3.8.1	Biomarkers Used to Identify or Quantify Exposure to Pyrethrins and Pyrethroids	113
3.8.2	Biomarkers Used to Characterize Effects Caused by Pyrethrins and Pyrethroids	113
3.9	INTERACTIONS WITH OTHER CHEMICALS	114
3.10	POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE	115
3.11	METHODS FOR REDUCING TOXIC EFFECTS	116

3.11.1	Reducing Peak Absorption Following Exposure	116
3.11.2	Reducing Body Burden.....	117
3.11.3	Interfering with the Mechanism of Action for Toxic Effects	117
3.12	ADEQUACY OF THE DATABASE.....	118
3.12.1	Existing Information on Health Effects of Pyrethrins and Pyrethroids	118
3.12.2	Identification of Data Needs	120
3.12.3	Ongoing Studies.....	129
4.	CHEMICAL AND PHYSICAL INFORMATION.....	131
4.1	CHEMICAL IDENTITY	131
4.2	PHYSICAL AND CHEMICAL PROPERTIES.....	141
5.	PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL	153
5.1	PRODUCTION	153
5.2	IMPORT/EXPORT	159
5.3	USE.....	159
5.4	DISPOSAL	159
6.	POTENTIAL FOR HUMAN EXPOSURE	165
6.1	OVERVIEW	165
6.2	RELEASES TO THE ENVIRONMENT	170
6.2.1	Air.....	170
6.2.2	Water.....	174
6.2.3	Soil.....	174
6.3	ENVIRONMENTAL FATE.....	175
6.3.1	Transport and Partitioning	175
6.3.2	Transformation and Degradation	179
6.3.2.1	Air.....	179
6.3.2.2	Water	181
6.3.2.3	Sediment and Soil.....	183
6.4	LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT	185
6.4.1	Air.....	185
6.4.2	Water.....	186
6.4.3	Sediment and Soil	187
6.4.4	Other Environmental Media	188
6.5	GENERAL POPULATION AND OCCUPATIONAL EXPOSURE	194
6.6	EXPOSURES OF CHILDREN	197
6.7	POPULATIONS WITH POTENTIALLY HIGH EXPOSURES	198
6.8	ADEQUACY OF THE DATABASE.....	199
6.8.1	Identification of Data Needs	200
6.8.2	Ongoing Studies.....	203
7.	ANALYTICAL METHODS	205
7.1	BIOLOGICAL MATERIALS	205
7.2	ENVIRONMENTAL SAMPLES.....	206
7.3	ADEQUACY OF THE DATABASE.....	209
7.3.1	Identification of Data Needs	215
7.3.2	Ongoing Studies.....	216
8.	REGULATIONS AND ADVISORIES	217

9. REFERENCES	227
10. GLOSSARY	281
APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS.....	A-1
APPENDIX B. USER'S GUIDE.....	B-1
APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS	C-1

LIST OF FIGURES

3-1. Levels of Significant Exposure to Pyrethroids - Inhalation.....	33
3-2. Levels of Significant Exposure to Pyrethroids - Oral.....	51
3-3. Metabolic Diagram for Deltamethrin, Permethrin, and Cypermethrin.....	93
3-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance	101
3-5. Existing Information on Health Effects of Pyrethrins and Pyrethroids	119
4-1. Four Possible Isomers of Type I Pyrethroids.....	140
4-2. Illustration of the S Conformer about the Alpha Carbon for the Type II Pyrethroid Cyhalothrin ...	152
6-1. Frequency of NPL Sites with Pyrethrins Contamination.....	166
6-2. Frequency of NPL Sites with Pyrethroid Contamination	167

LIST OF TABLES

2-1. Pyrethrins and Pyrethroids Discussed in the Profile.....	14
3-1. Levels of Significant Exposure to Pyrethrins and Pyrethroids - Inhalation.....	32
3-2. Levels of Significant Exposure to Pyrethrins and Pyrethroids - Oral.....	36
3-3. Genotoxicity of Pyrethrins <i>In Vitro</i>	72
3-4. Genotoxicity of Type I Pyrethroids <i>In Vivo</i>	73
3-5. Genotoxicity of Type II Pyrethroids <i>In Vivo</i>	74
3-6. Genotoxicity of Type I Pyrethroids <i>In Vitro</i>	78
3-7. Genotoxicity of Type II Pyrethroids <i>In Vitro</i>	80
4-1. Chemical Identity of the Pyrethrins	132
4-2. Chemical Identity of Selected Pyrethroids	134
4-3. Stereoisomers of Selected Pyrethroids	142
4-4. Physical and Chemical Properties of Pyrethrins.....	144
4-5. Physical and Chemical Properties of Selected Pyrethroids	146
5-1. U.S. Producers of Pyrethrins and Pyrethroids	154
5-2. Facilities that Produce, Process, or Use Pyrethroids	155
5-3. Acid and Alcohol Feedstocks in the Pyrethroids Synthesis	156
5-4. Uses of Pyrethroids.....	160
6-1. Trends of National Pyrethroid Use	171
6-2. Releases to the Environment from Facilities that Produce, Process, or Use Pyrethroids.....	172
6-3. Levels of Pyrethroids Detected in Foods.....	189
6-4. Average Daily Intake (AVDI, ng/kg/day) of Permethrin in Eight Population Groups.....	195
7-1. Analytical Methods for Determining Pyrethrins and Pyrethroids in Biological Materials.....	207
7-2. Analytical Methods for Determining Pyrethrins and Pyrethroids in Environmental Samples	210

8-1. Regulations and Guidelines Applicable to Pyrethrins and Pyrethroids 218

8-2. Tolerances for Residues Applicable to Pyrethrins and Pyrethroids (ppm)..... 222