TOXICOLOGICAL PROFILE FOR ENDOSULFAN

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

ENDOSULFAN

DISCLAIMER

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

ENDOSULFAN iii

UPDATE STATEMENT

A Toxicological Profile for Endosulfan, Draft for Public Comment was released in May 2013. 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 Human Health Sciences /
Environmental Toxicology Branch
1600 Clifton Road NE
Mailstop F-57
Atlanta, Georgia 30329-4027

ENDOSULFAN iv

ENDOSULFAN

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.

Patrick N. Breysse, Ph.D., CIH

PareleuBnagne

Director, National Center for Environmental Health and Agency for Toxic Substances and Disease Registry Centers for Disease Control and Prevention ENDOSULFAN vi

*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.

ENDOSULFAN 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:

Chapter 1 How Can (Chemical X) Affect Children?

Chapter 1 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)

Internet: http://www.atsdr.cdc.gov

The following additional material is available online at www.atsdr.cdc.gov:

Case Studies in Environmental Medicine—Case Studies are self-instructional publications designed to increase primary care provider's knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients.

ENDOSULFAN 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 ($ToxFAQs^{TM}$) 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, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: (202) 245-0625 or 1-800-CDC-INFO (800-232-4636).

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.

Clinical Resources

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.

ENDOSULFAN is

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHOR(S):

Jessilynn Taylor, M.S., CDR USPHS Hana R. Pohl, M.D., Ph.D. Moiz Mumtaz, Ph.D. Patricia Ruiz, Ph.D. ATSDR, Division of Toxicology and Human Health Sciences, Atlanta, GA

Fernando Llados, Ph.D. Courtney Hard, B.S. Catherine Rudisill, M.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 Environmental 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.

ENDOSULFAN x

ENDOSULFAN xi

PEER REVIEW

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

- 1. Marilyn H. Silva, Ph.D. DABT, Department of Pesticide Regulation, Medical Toxicology Branch, Sacramento, California;
- 2. M. Eddleston MA, Ph.D., FRCP Edin, Scottish Senior Clinical Research Fellow, Clinical Pharmacology Unit, University of Edinburgh, Consultant Clinical Toxicologist and Director, National Poisons Information Service Edinburgh, Royal Infirmary, Visiting Professor, University of Copenhagen, Department of International Health, Immunology and Microbiology, Edinburgh, Scotland;
- 3. Mark Gregory Robson, Ph.D., MPH, DrPH (hc), Dean of Agricultural and Urban Programs, Professor of Entomology, School of Environmental and Biological Sciences, Rutgers University, New Brunswick, New Jersey.

These experts collectively have knowledge of endosulfan'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.

ENDOSULFAN

CONTENTS

DISCLAIMER		ii
UPDATE STAT	ΓΕΜΕΝΤ	iii
QUICK REFER	ENCE FOR HEALTH CARE PROVIDERS	vii
CONTRIBUTO	RS	ix
PEER REVIEW	<i>T</i>	xi
CONTENTS		xiii
	RES	
LIST OF TABL	ES	xix
1. PUBLIC HE	ALTH STATEMENT FOR ENDOSULFAN	1
	NE TO DAIDA AGAIN A TINA	
	CE TO PUBLIC HEALTH	
	GROUND AND ENVIRONMENTAL EXPOSURES TO ENDOSULFA	
	ED STATES	
	MARY OF HEALTH EFFECTS	
2.3 MININ	MAL RISK LEVELS (MRLs)	1/
2 115 A 1 TH 51	FFECTS	21
	DDUCTION	
	JSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE	
	halation Exposurehalation Exposure	
3.2.1.1	Death	
3.2.1.1	Systemic Effects	
3.2.1.2	Immunological and Lymphoreticular Effects	
3.2.1.3	Neurological Effects	
3.2.1.4	Reproductive Effects	
3.2.1.6	Developmental Effects	
3.2.1.7	Cancer	
	cal Exposure	
3.2.2.1	Death	
3.2.2.1	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	
	ermal 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	
3.2.3.5	Reproductive Effects	
3.2.3.6	Developmental Effects	
3.2.3.7	Cancer	
	TOXICITY	
	COKINETICS	
	osorption	
	Inhalation Exposure	

3.4.1.2 Oral Exposure	145
3.4.1.3 Dermal Exposure	
3.4.2 Distribution	
3.4.2.1 Inhalation Exposure	147
3.4.2.2 Oral Exposure	
3.4.2.3 Dermal Exposure	
3.4.2.4 Other Routes of 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	
3.4.4.4 Other Routes of Exposure	
3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models	
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	
3.7 CHILDREN'S SUSCEPTIBILITY	
3.8.1 Biomarkers Used to Identify or Quantify Exposure to Endosulfan	
3.8.2 Biomarkers Used to Characterize Effects Caused by Endosulfan	
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	185
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 Endosulfan	
3.12.2 Identification of Data Needs	
3.12.3 Ongoing Studies	202
4. CHEMICAL AND PHYSICAL INFORMATION	203
4.1 CHEMICAL IDENTITY	
4.2 PHYSICAL AND CHEMICAL PROPERTIES	
1.2 THISICILE IN D. CHENTEL I NOT EXTENSION.	203
5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL	213
5.1 PRODUCTION	
5.2 IMPORT/EXPORT	
5.3 USE	
5.4 DISPOSAL	
6. POTENTIAL FOR HUMAN EXPOSURE	
6.1 OVERVIEW	
6.2 RELEASES TO THE ENVIRONMENT	223
6.2.1 Air	223
6.2.2 Water	224
6.2.3 Soil	224
6.3 ENVIRONMENTAL FATE	224

6.3.1 Transport and Partitioning	224
6.3.2 Transformation and Degradation	
6.3.2.1 Air	229
6.3.2.2 Water	229
6.3.2.3 Sediment and Soil	230
6.3.2.4 Other Media	232
6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT	232
6.4.1 Air	232
6.4.2 Water	237
6.4.3 Sediment and Soil	244
6.4.4 Other Environmental Media	
6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE	258
6.6 EXPOSURES OF CHILDREN	262
6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES	266
6.8 ADEQUACY OF THE DATABASE	268
6.8.1 Identification of Data Needs	268
6.8.2 Ongoing Studies	272
7. ANALYTICAL METHODS	
7.1 BIOLOGICAL MATERIALS	273
7.2 ENVIRONMENTAL SAMPLES	274
7.3 ADEQUACY OF THE DATABASE	278
7.3.1 Identification of Data Needs	283
7.3.2 Ongoing Studies	284
8. REGULATIONS, ADVISORIES, AND GUIDELINES	285
9. REFERENCES	291
10. GLOSSARY	325
APPENDICES	
A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS	
B. USER'S GUIDE	
C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS	

ENDOSULFAN xvi

ENDOSULFAN xvii

LIST OF FIGURES

2-1.	Health Effects of Ingesting Endosulfan	16
3-1.	Levels of Significant Exposure to Endosulfan—Inhalation	36
3-2.	Levels of Significant Exposure to Endosulfan—Oral	78
3-3.	Proposed Metabolic Pathway for Endosulfan	153
3-4.	Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance	160
3-5.	Existing Information on Health Effects of Endosulfan	188
5-1.	Endosulfan Use in California	219
5-2.	State Clean Sweep Programs by Category	220
6-1.	Frequency of NPL Sites with Endosulfan Contamination	222
6-2.	Conceptual Model of the Potential Effects of Endosulfan Application on Ecological Receptors	226

ENDOSULFAN xviii

ENDOSULFAN xix

LIST OF TABLES

2-1.	Incidence of Marked Progressive Glomerulonephrosis in Male Rats Exposed to Endosulfan for 2 Years	25
2-2.	Incidence of Marked Progressive Glomerulonephrosis in Female Rats Exposed to Endosulfan for 2 Years	26
2-3.	Data for the Change in Body Weight Gain in Male Rats Exposed to Endosulfan for 2 Years	27
2-4.	Data for the Change in Body Weight Gain in Female Rats Exposed to Endosulfan for 2 Years	28
3-1.	Levels of Significant Exposure to Endosulfan—Inhalation	34
3-2.	Levels of Significant Exposure to Endosulfan—Oral	47
3-3.	Levels of Significant Exposure to Endosulfan—Dermal	123
3-4.	Genotoxicity of Endosulfan In Vivo	138
3-5.	Genotoxicity of Endosulfan In Vitro	139
4-1.	Chemical Identity of Endosulfan	204
4-2.	Chemical Identity of α-Endosulfan	205
4-3.	Chemical Identity of β-Endosulfan	206
4-4.	Chemical Identity of Endosulfan Sulfate	207
4-5.	Physical and Chemical Properties of Endosulfan	208
4-6.	Physical and Chemical Properties of α-Endosulfan	210
4-7.	Physical and Chemical Properties of β-Endosulfan	211
4-8.	Physical and Chemical Properties of Endosulfan Sulfate	212
5-1.	Endosulfan Crop Uses and Last Use Dates	216
5-2.	2002 Estimated Annual Agricultural Use of Endosulfan	217
6-1.	Average Concentrations of Gas-Phase α - and β -Endosulfan in Air from the Great Lakes Region.	235
6-2.	Average Concentrations of α - and β -Endosulfan Particulates in Air from the Great Lakes Region	236

ENDOSULFAN xx

6-3.	α-Endosulfan and Endosulfan Sulfate Detected in Groundwater Sampled for the USGS National Water Quality Assessment Between 2002 and 2011	. 239
6-4.	α -Endosulfan and Endosulfan Sulfate Detected in Surface Water and Bed Sediment Sampled for the USGS National Water Quality Assessment Between 2006 and 2011	. 240
6-5.	Endosulfan Concentrations (µg/L) in Surface Water Measured from the South Florida Water Management District (SFWMD)	. 242
6-6.	Sediment Concentrations (ng/g Dry) Obtained by the National Oceanic and Atmospheric Administration (NOAA) National Status and Trends (NS&T) Program Between 2005 and 2009.	. 245
6-7.	U.S. Department of Agriculture (USDA) Pesticide Data Program: Distribution of Endosulfan Residues in Fruits and Vegetables (2010)	. 249
6-8.	Endosulfan Levels in Food Products Sampled for the 2003–2005 Market Basket Survey	. 250
6-9.	Concentration of Total Endosulfans (µg/kg Dry Weight) in Bivalves from the National Oceanic and Atmospheric Administration (NOAA) Mussel Watch Database	. 255
6-10	California Department of Pesticide Regulation (CDPR) Acute and Chronic Dietary Exposure (μg/kg/day) to Anticipated Endosulfan Residues on Raw Agriculture Commodities (RACs) and the Resulting Dietary Margins of Exposure (MOE) from 1989 to 1992	. 259
6-11	. U.S. Environmental Protection Agency (EPA) Summary of Acute and Chronic Dietary Exposure (µg/kg/day) for Endosulfan	. 260
6-12	. Endosulfan and Metabolite Concentrations in Adipose Tissue, Placenta, Umbilical Cord Blood, and Breast Milk of Fertile Women and Mothers from Southern Spain	. 264
6-13	. Dermal, Inhalation, and Aggregatea Short-term Exposure Estimates by CDPR and EPA (mg/kg/day)	. 267
7-1.	Analytical Methods for Determining Endosulfan in Biological Samples	. 275
7-2.	Analytical Methods for Determining Endosulfan in Environmental Samples	. 279
8-1.	Regulations, Advisories, and Guidelines Applicable to Endosulfan	. 288