

**TOXICOLOGICAL PROFILE FOR
MALATHION**

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 malathion, 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. 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.

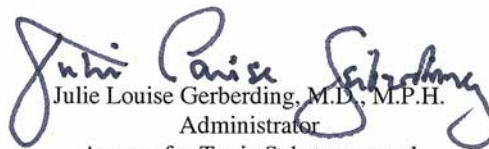
The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels 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):

Jewell D. Wilson, Ph.D.
ATSDR, Division of Toxicology, Atlanta, GA

Fernando T. Lladós, Ph.D.
Syracuse Research Corporation, North Syracuse, NY

Mona Singh, Ph.D.
Syracuse Research Corporation, Arlington, VA

Cheryl A. Sutton, Ph.D.
Syracuse Research Corporation, Arlington, VA

William R. Sutton, Ph.D.
Syracuse Research Corporation, Arlington, VA

Tsutomu Nakatsugawa, Ph.D.
SUNY Environmental Science and Forestry, Syracuse, NY

Amy Benson, M.S.
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 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 malathion. The panel consisted of the following members:

1. Dr. Lucio Costa, Department of Environmental Health, University of Washington, Seattle, Washington 98105-6099.
2. Dr. Loren D. Koller, College of Veterinary Medicine, Oregon State University, Corvallis, Oregon 97331-4801.
3. Dr. Joseph Seifert, Department of Plant and Environmental Protection Sciences, University of Hawaii, Honolulu, Hawaii 96822.

These experts collectively have knowledge of malathion'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. 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

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 MALATHION?.....	1
1.2 WHAT HAPPENS TO MALATHION WHEN IT ENTERS THE ENVIRONMENT?	2
1.3 HOW MIGHT I BE EXPOSED TO MALATHION?.....	3
1.4 HOW CAN MALATHION ENTER AND LEAVE MY BODY?	4
1.5 HOW CAN MALATHION AFFECT MY HEALTH?	4
1.6 HOW CAN MALATHION AFFECT CHILDREN?	6
1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO MALATHION?	7
1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO MALATHION?.....	9
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 MALATHION IN THE UNITED STATES.....	13
2.2 SUMMARY OF HEALTH EFFECTS	15
2.3 MINIMAL RISK LEVELS (MRLs)	19
3. HEALTH EFFECTS	23
3.1 INTRODUCTION.....	23
3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE	23
3.2.1 Inhalation Exposure	25
3.2.1.1 Death	25
3.2.1.2 Systemic Effects	26
3.2.1.3 Immunological and Lymphoreticular Effects.....	32
3.2.1.4 Neurological Effects	33
3.2.1.5 Reproductive Effects	35
3.2.1.6 Developmental Effects	36
3.2.1.7 Cancer.....	37
3.2.2 Oral Exposure	39
3.2.2.1 Death	39
3.2.2.2 Systemic Effects	64
3.2.2.3 Immunological and Lymphoreticular Effects.....	74
3.2.2.4 Neurological Effects	78
3.2.2.5 Reproductive Effects	83
3.2.2.6 Developmental Effects	85
3.2.2.7 Cancer.....	87
3.2.3 Dermal Exposure	89
3.2.3.1 Death	90

3.2.3.2	Systemic Effects	90
3.2.3.3	Immunological and Lymphoreticular Effects	96
3.2.3.4	Neurological Effects	97
3.2.3.5	Reproductive Effects	98
3.2.3.6	Developmental Effects	99
3.2.3.7	Cancer	99
3.3	GENOTOXICITY	99
3.4	TOXICOKINETICS	104
3.4.1	Absorption	105
3.4.1.1	Inhalation Exposure	106
3.4.1.2	Oral Exposure	106
3.4.1.3	Dermal Exposure	106
3.4.2	Distribution	110
3.4.2.1	Inhalation Exposure	110
3.4.2.2	Oral Exposure	110
3.4.2.3	Dermal Exposure	112
3.4.2.4	Other Routes of Exposure	112
3.4.3	Metabolism	112
3.4.4	Elimination and Excretion	117
3.4.4.1	Inhalation Exposure	118
3.4.4.2	Oral Exposure	118
3.4.4.3	Dermal Exposure	119
3.4.4.4	Other Routes of Exposure	120
3.4.5	Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models	120
3.5	MECHANISMS OF ACTION	125
3.5.1	Pharmacokinetic Mechanisms	126
3.5.2	Mechanisms of Toxicity	128
3.5.3	Animal-to-Human Extrapolations	130
3.6	TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS	131
3.7	CHILDREN'S SUSCEPTIBILITY	134
3.8	BIOMARKERS OF EXPOSURE AND EFFECT	138
3.8.1	Biomarkers Used to Identify or Quantify Exposure to Malathion	139
3.8.2	Biomarkers Used to Characterize Effects Caused by Malathion	140
3.9	INTERACTIONS WITH OTHER CHEMICALS	141
3.10	POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE	145
3.11	METHODS FOR REDUCING TOXIC EFFECTS	146
3.11.1	Reducing Peak Absorption Following Exposure	146
3.11.2	Reducing Body Burden	147
3.11.3	Interfering with the Mechanism of Action for Toxic Effects	147
3.12	ADEQUACY OF THE DATABASE	148
3.12.1	Existing Information on Health Effects of Malathion	148
3.12.2	Identification of Data Needs	150
3.12.3	Ongoing Studies	165
4.	CHEMICAL AND PHYSICAL INFORMATION	167
4.1	CHEMICAL IDENTITY	167
4.2	PHYSICAL AND CHEMICAL PROPERTIES	167
5.	PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL	171
5.1	PRODUCTION	171
5.2	IMPORT/EXPORT	171
5.3	USE	173
5.4	DISPOSAL	174

6.	POTENTIAL FOR HUMAN EXPOSURE	175
6.1	OVERVIEW	175
6.2	RELEASES TO THE ENVIRONMENT	177
6.2.1	Air	177
6.2.2	Water	179
6.2.3	Soil	181
6.3	ENVIRONMENTAL FATE	182
6.3.1	Transport and Partitioning	183
6.3.2	Transformation and Degradation	186
6.3.2.1	Air	187
6.3.2.2	Water	187
6.3.2.3	Sediment and Soil	190
6.3.2.4	Other Media	192
6.4	LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT	192
6.4.1	Air	192
6.4.2	Water	194
6.4.3	Sediment and Soil	195
6.4.4	Other Environmental Media	196
6.5	GENERAL POPULATION AND OCCUPATIONAL EXPOSURE	196
6.6	EXPOSURES OF CHILDREN	202
6.7	POPULATIONS WITH POTENTIALLY HIGH EXPOSURES	206
6.8	ADEQUACY OF THE DATABASE	207
6.8.1	Identification of Data Needs	208
6.8.2	Ongoing Studies	212
7.	ANALYTICAL METHODS	215
7.1	BIOLOGICAL SAMPLES	215
7.2	ENVIRONMENTAL SAMPLES	219
7.3	ADEQUACY OF THE DATABASE	223
7.3.1	Identification of Data Needs	224
7.3.2	Ongoing Studies	224
8.	REGULATIONS AND ADVISORIES	225
9.	REFERENCES	237
10.	GLOSSARY	279

APPENDICES

A.	ATSDR MINIMAL RISK LEVELS AND WORKSHEETS	A-1
B.	USER'S GUIDE	B-1
C.	ACRONYMS, ABBREVIATIONS, AND SYMBOLS	C-1

LIST OF FIGURES

3-1. Levels of Significant Exposure to Malathion – Inhalation	28
3-2. Levels of Significant Exposure to Malathion – Oral	60
3-3. Metabolic Pathways for Malathion.....	113
3-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance	122
3-5. Existing Information on Health Effects of Malathion	149
6-1. Frequency of NPL Sites with Malathion Contamination.....	176

LIST OF TABLES

3-1. Levels of Significant Exposure to Malathion – Inhalation	27
3-2. Levels of Significant Exposure to Malathion – Oral	42
3-3. Levels of Significant Exposure to Malathion – Dermal	91
3-4. Genotoxicity of Malathion <i>In Vivo</i>	101
3-5. Genotoxicity of Malathion <i>In Vitro</i>	103
3-6. Kinetic and Physiological Parameters and Constants Used in PBPK Human Malathion Deposition Model.....	124
4-1. Chemical Identity of Malathion.....	168
4-2. Physical and Chemical Properties of Malathion.....	169
5-1. Facilities that Produce, Process, or Use Malathion	172
6-1. Releases to the Environment from Facilities that Produce, Process, or Use Malathion.....	180
7-1. Analytical Methods for Determining Malathion or Biomarkers of Exposure in Biological Samples.....	217
7-2. Analytical Methods for Determining Malathion in Environmental Samples	220
8-1. Regulations and Guidelines Applicable to Malathion	226