

**TOXICOLOGICAL PROFILE FOR
SULFUR MUSTARD
(UPDATE)**

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 Sulfur Mustard (previously Mustard Gas), 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, GA 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.

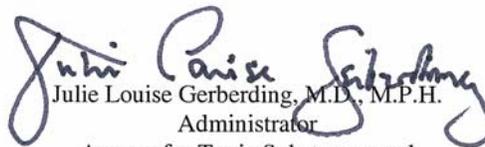
The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels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

Zemoria A. Rosemond, B.A.
ATSDR, Division of Toxicology, Atlanta, GA

Dolores A. Beblo, Ph.D.
Syracuse Research Corporation, North Syracuse, NY

Richard Amata, 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 sulfur mustard. The panel consisted of the following members:

1. Dr. Vincent Garry, M.D. D.A.B.T., Director, Laboratory of Environmental Medicine and Pathology, University of Minnesota Medical School, Minneapolis, Minnesota;
2. Dr. Shane Que Hee, Ph.D., Professor, Center for Occupational and Environmental Health, UCLA School of Public Health, Los Angeles, California; and
3. Dr. James Withey, Ph.D., Retired Senior Research Scientist, Environmental Health Science Center, Ontario, Canada, Ottawa, Ontario.

These experts collectively have knowledge of sulfur mustard'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

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 SULFUR MUSTARD?	1
1.2 WHAT HAPPENS TO SULFUR MUSTARD WHEN IT ENTERS THE ENVIRONMENT?	2
1.3 HOW MIGHT I BE EXPOSED TO SULFUR MUSTARD?	3
1.4 HOW CAN SULFUR MUSTARD ENTER AND LEAVE MY BODY?	3
1.5 HOW CAN SULFUR MUSTARD AFFECT MY HEALTH?	4
1.6 HOW CAN SULFUR MUSTARD AFFECT CHILDREN?.....	5
1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO SULFUR MUSTARD?.....	5
1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO SULFUR MUSTARD?	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 SULFUR MUSTARD IN THE UNITED STATES.....	9
2.2 SUMMARY OF HEALTH EFFECTS	11
2.3 MINIMAL RISK LEVELS	15
3. HEALTH EFFECTS	21
3.1 INTRODUCTION.....	21
3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE	22
3.2.1 Inhalation Exposure	24
3.2.1.1 Death	24
3.2.1.2 Systemic Effects	26
3.2.1.3 Immunological and Lymphoreticular Effects.....	41
3.2.1.4 Neurological Effects	41
3.2.1.5 Reproductive Effects	42
3.2.1.6 Developmental Effects	43
3.2.1.7 Cancer.....	43
3.2.2 Oral Exposure.....	47
3.2.2.1 Death	47
3.2.2.2 Systemic Effects	48
3.2.2.3 Immunological and Lymphoreticular Effects.....	57

3.2.2.3	Neurological Effects	57
3.2.2.4	Reproductive Effects	58
3.2.2.5	Developmental Effects	59
3.2.2.7	Cancer	60
3.2.3	Dermal Exposure	60
3.2.3.1	Death	60
3.2.3.2	Systemic Effects	60
3.2.3.3	Immunological and Lymphoreticular Effects	64
3.2.3.4	Neurological Effects	65
3.2.3.5	Reproductive Effects	65
3.2.3.6	Developmental Effects	65
3.2.3.7	Cancer	65
3.2.4	Other Routes of Exposure	66
3.3	GENOTOXICITY	67
3.4	TOXICOKINETICS	70
3.4.1	Absorption	70
3.4.1.1	Inhalation Exposure	70
3.4.1.2	Oral Exposure	71
3.4.1.3	Dermal Exposure	71
3.4.2	Distribution	72
3.4.2.1	Inhalation Exposure	72
3.4.2.2	Oral Exposure	72
3.4.2.3	Dermal Exposure	72
3.4.2.4	Other Routes of Exposure	73
3.4.3	Metabolism	74
3.4.3.1	Inhalation Exposure	75
3.4.3.2	Oral Exposure	75
3.4.3.3	Dermal Exposure	75
3.4.3.4	Other Routes of Exposure	76
3.4.4	Elimination and Excretion	77
3.4.4.1	Inhalation Exposure	77
3.4.4.2	Oral Exposure	77
3.4.4.3	Dermal Exposure	78
3.4.4.4	Other Routes of Exposure	78
3.4.5	Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models	79
3.5	MECHANISMS OF ACTION	82
3.5.1	Pharmacokinetic Mechanisms	82
3.5.2	Mechanisms of Toxicity	82
3.5.3	Animal-to-Human Extrapolations	89
3.6	TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS	91
3.7	CHILDREN'S SUSCEPTIBILITY	94
3.8	BIOMARKERS OF EXPOSURE AND EFFECT	96
3.8.1	Biomarkers Used to Identify or Quantify Exposure to Sulfur mustard	97
3.8.2	Biomarkers Used to Characterize Effects Caused by Sulfur mustard	99
3.9	INTERACTIONS WITH OTHER CHEMICALS	100
3.10	POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE	100
3.11	METHODS FOR REDUCING TOXIC EFFECTS	100
3.11.1	Reducing Peak Absorption Following Exposure	101
3.11.2	Reducing Body Burden	102
3.11.3	Interfering with the Mechanism of Action for Toxic Effects	105
3.12	ADEQUACY OF THE DATABASE	107

3.12.1	Existing Information on Health Effects of Sulfur Mustard	109
3.12.2	Identification of Data Needs	109
3.12.3	Ongoing Studies	116
4.	CHEMICAL AND PHYSICAL INFORMATION	119
4.1	CHEMICAL IDENTITY	119
4.2	PHYSICAL AND CHEMICAL PROPERTIES	119
5.	PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL	125
5.1	PRODUCTION	125
5.2	IMPORT/EXPORT	127
5.3	USE	127
5.4	DISPOSAL	127
6.	POTENTIAL FOR HUMAN EXPOSURE	131
6.1	OVERVIEW	131
6.2	RELEASES TO THE ENVIRONMENT	131
6.2.1	Air	133
6.2.2	Water	133
6.2.3	Soil	134
6.3	ENVIRONMENTAL FATE	134
6.3.1	Transport and Partitioning	134
6.3.2	Transformation and Degradation	137
6.3.2.1	Air	137
6.3.2.2	Water	137
6.3.2.3	Sediment and Soil	139
6.3.2.4	Other Media	140
6.4	LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT	140
6.4.1	Air	140
6.4.2	Water	141
6.4.3	Sediment and Soil	141
6.4.4	Other Environmental Media	141
6.5	GENERAL POPULATION AND OCCUPATIONAL EXPOSURE	142
6.6	EXPOSURES OF CHILDREN	142
6.7	POPULATIONS WITH POTENTIALLY HIGH EXPOSURES	143
6.8	ADEQUACY OF THE DATABASE	143
6.8.1	Identification of Data Needs	144
6.8.2	Ongoing Studies	146
7.	ANALYTICAL METHODS	149
7.1	BIOLOGICAL MATERIALS	149
7.2	ENVIRONMENTAL SAMPLES	152
7.3	ADEQUACY OF THE DATABASE	156
7.3.1	Identification of Data Needs	157
7.3.2	Ongoing Studies	158
8.	REGULATIONS AND ADVISORIES	159
9.	REFERENCES	167
10.	GLOSSARY	211

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS.....A-1

APPENDIX B. USER'S GUIDE.....B-1

APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLSC-1

APPENDIX D. ACUTE EXPOSURE GUIDELINE LEVELS (AEGLS) FOR
SULFUR MUSTARD.....D-1

LIST OF FIGURES

3-1.	Levels of Significant Exposure to Sulfur Mustard -Inhalation	29
3-2.	Levels of Significant Exposure to Sulfur Mustard -Oral	53
3-3.	Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance	81
3-4.	Existing Information on Health Effects of Sulfur Mustard.....	110
5-1.	Locations of Sulfur Mustard Stockpile and Non-stockpile Sites in the United States.....	126
6-1.	Frequency of NPL Sites with Sulfur Mustard Contamination	132
6-2.	Primary Hydrolysis Pathways of Sulfur Mustard in the Environment	138

LIST OF TABLES

3-1.	Levels of Significant Exposure to Sulfur Mustard-Inhalation	27
3-2.	Levels of Significant Exposure to Sulfur Mustard-Oral	49
3-3.	Genotoxicity of Sulfur Mustard <i>In Vitro</i>	69
3-4.	Ongoing Studies on Health Effects of Sulfur Mustard	117
4-1.	Chemical Identity of Sulfur Mustard	120
4-2.	Typical Composition of Sulfur Mustard (H) from an Old Chemical Munition	121
4-3.	Typical Composition of Sulfur Mustard (HD) in 1-Ton Storage Containers (Aberdeen, Maryland).....	122
4-4.	Physical and Chemical Properties of Sulfur Mustard	123
5-1.	Original Stockpile Quantities of Sulfur Mustard as Munitions and Bulk Agent	128
6-1.	Location of Historical Dumping Areas for Sulfur Mustard (H) in Coastal Waters of the United States	135
6-2.	Ongoing Studies on the Environmental Fate of Sulfur Mustard.....	147
7-1.	Analytical Methods for Determining Sulfur Mustard in Biological Samples.....	150
7-2.	Analytical Methods for Determining Sulfur Mustard in Environmental Samples.....	153
8-1.	Regulations and Guidelines Applicable to Sulfur Mustard.....	160
8-2.	Acute Exposure Guideline Level (AEGL) Values for Sulfur Mustard (ppm [mg/m ³]).....	164
8-3.	U.S. Army Toxicity Values for Sulfur Mustard.....	165