TOXICOLOGICAL PROFILE FOR GUTHION

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 Guthion, Draft for Public Comment was released in September 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.

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: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY) ***Fax:*** (770) 488-4178
E-mail: cdcinfo@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, 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):

Nickolette Roney, M.P.H.
Selene Chou, Ph.D.
Yee-Wan Stevens, M.S.
ATSDR, Division of Toxicology and Environmental Medicine, Atlanta, GA

Antonio Quinones-Rivera, Ph.D.
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 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 guthion. The panel consisted of the following members:

Draft for Public Comment:

1. Dr. Allan Flesot, Professor and Extention Specialist, Entomology and Environmental Toxicology, Food and Environmental Quality Lab, Washington State University-TriCities, Richland, Washington;

2. Dr. Maryce Jacobs, President, Health Science Institute, Inc., Las Cruces, New Mexico; and

3. Dr. Craig Wheelock, Junior Faculty, Microbiology and Tumorbiology Center, Karolinska Institute, Stockholm, Sweden.

These experts collectively have knowledge of guthion'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 GUTHION? 1
1.2 WHAT HAPPENS TO GUTHION WHEN IT ENTERS THE ENVIRONMENT? 2
1.3 HOW MIGHT I BE EXPOSED TO GUTHION? 3
1.4 HOW CAN GUTHION ENTER AND LEAVE MY BODY? 3
1.5 HOW CAN GUTHION AFFECT MY HEALTH? 4
1.6 HOW CAN GUTHION AFFECT CHILDREN? 4
1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO GUTHION? 5
1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO GUTHION? 5
1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH? 5
1.10 WHERE CAN I GET MORE INFORMATION? 6

2. RELEVANCE TO PUBLIC HEALTH 9
2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO GUTHION IN THE UNITED STATES 9
2.2 SUMMARY OF HEALTH EFFECTS 10
2.3 MINIMAL RISK LEVELS (MRLs) 13

3. HEALTH EFFECTS 25
3.1 INTRODUCTION 25
3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE 25
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 27
3.2.1.4 Neurological Effects 32
3.2.1.5 Reproductive Effects 32
3.2.1.6 Developmental Effects 33
3.2.1.7 Cancer 33
3.2.2 Oral Exposure 33
3.2.2.1 Death 33
3.2.2.2 Systemic Effects 34
3.2.2.3 Immunological and Lymphoreticular Effects 53
3.2.2.4 Neurological Effects 54
3.2.2.5 Reproductive Effects 55
3.2.2.6 Developmental Effects 56
3.2.2.7 Cancer 57

3.2.3 Dermal Exposure 58
3.2.3.1 Death 58
3.2.3.2 Systemic Effects 61
3.2.3.3 Immunological and Lymphoreticular Effects 61
3.2.3.4 Neurological Effects 61
3.2.3.5 Reproductive Effects 63
3.2.3.6 Developmental Effects 63
3.2.3.7 Cancer 64
3.3 GENOTOXICITY 64
3.4 TOXICOKINETICS 64
3.4.1 Absorption 64
3.4.1.1 Inhalation Exposure 64
3.4.1.2 Oral Exposure 68
3.4.1.3 Dermal Exposure 68
3.4.2 Distribution 68
3.4.2.1 Inhalation Exposure 68
3.4.2.2 Oral Exposure 69
3.4.2.3 Dermal Exposure 69
3.4.3 Metabolism 69
3.4.4 Elimination and Excretion 72
3.4.4.1 Inhalation Exposure 72
3.4.4.2 Oral Exposure 73
3.4.4.3 Dermal Exposure 73
3.4.4.4 Other Routes of Exposure 74
3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models 74
3.5 MECHANISMS OF ACTION 77
3.5.1 Pharmacokinetic Mechanisms 77
3.5.2 Mechanisms of Toxicity 77
3.5.3 Animal-to-Human Extrapolations 79
3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS 79
3.7 CHILDREN'S SUSCEPTIBILITY 80
3.8 BIOMARKERS OF EXPOSURE AND EFFECT 82
3.8.1 Biomarkers Used to Identify or Quantify Exposure to Guthion 83
3.8.2 Biomarkers Used to Characterize Effects Caused by Guthion 84
3.9 INTERACTIONS WITH OTHER CHEMICALS 85
3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE 86
3.11 METHODS FOR REDUCING TOXIC EFFECTS 87
3.11.1 Reducing Peak Absorption Following Exposure 87
3.11.2 Reducing Body Burden 88
3.11.3 Interfering with the Mechanism of Action for Toxic Effects 88
3.12 ADEQUACY OF THE DATABASE 89
3.12.1 Existing Information on Health Effects of Guthion 89
3.12.2 Identification of Data Needs 91
3.12.3 Ongoing Studies 99

4. CHEMICAL AND PHYSICAL INFORMATION 101
4.1 CHEMICAL IDENTITY 101
4.2 PHYSICAL AND CHEMICAL PROPERTIES 101

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL 105
5.1 PRODUCTION 105
5.2 IMPORT/EXPORT 105
5.3 USE 107
5.4 DISPOSAL 108

6. POTENTIAL FOR HUMAN EXPOSURE 109
6.1 OVERVIEW 109
6.2 RELEASES TO THE ENVIRONMENT 111
6.2.1 Air 111
6.2.2 Water 112
6.2.3 Soil 113
6.3 ENVIRONMENTAL FATE 113
6.3.1 Transport and Partitioning 113
6.3.2 Transformation and Degradation 117
6.3.2.1 Air 117
6.3.2.2 Water 117
6.3.2.3 Sediment and Soil 120
6.3.2.4 Other Media 121
6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT 123
6.4.1 Air 123
6.4.2 Water 124
6.4.3 Sediment and Soil 126
6.4.4 Other Environmental Media 128
6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE 128
6.6 EXPOSURES OF CHILDREN 131
6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES 138
6.8 ADEQUACY OF THE DATABASE 139
6.8.1 Identification of Data Needs 141
6.8.2 Ongoing Studies 144

7. ANALYTICAL METHODS 145
7.1 BIOLOGICAL MATERIALS 145
7.2 ENVIRONMENTAL SAMPLES 148
7.3 ADEQUACY OF THE DATABASE 149
7.3.1 Identification of Data Needs 149
7.3.2 Ongoing Studies 152

8. REGULATIONS AND ADVISORIES 155

9. REFERENCES 159

10. GLOSSARY 177

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 Guthion – Inhalation 30

3-2. Levels of Significant Exposure to Guthion – Oral 47

3-3. Proposed Metabolism of Guthion 70

3-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance 76

3-5. Existing Information on Health Effects of Guthion 90

6-1. Frequency of NPL Sites with Guthion Contamination 110

This page is intentionally blank.

LIST OF TABLES

3-1. Levels of Significant Exposure to Guthion - Inhalation 28

3-2. Levels of Significant Exposure to Guthion - Oral 35

3-3. Levels of Significant Exposure to Guthion - Dermal 59

3-4. Genotoxicity of Guthion *In Vivo* 65

3-5. Genotoxicity of Guthion *In Vitro* 66

4-1. Chemical Identity of Guthion 102

4-2. Physical and Chemical Properties of Guthion 103

5-1. Manufacturers of Technical-Grade or Formulated Products Containing Guthion 106

6-1. Soil Adsorption Characteristics of Guthion in Five European Soils 115

6-2. Aqueous Degradation Rate of Guthion 119

6-3. Soil Properties and Degradation Rate of Guthion in Four Italian Soils 122

6-4. Guthion Levels in Surface Water from the STORET Database 127

6-5. Guthion Residues in Various Foods from 1994 to 2000 129

6-6. Selected Percentile Urine Concentrations (µg/L) of DMP in the U.S. Population from 1999 to 2002 132

6-7. Geometric Mean and Selected Percentile Urine Concentrations (µg/L) of DMTP in the U.S. Population from 1999 to 2002 133

6-8. Selected Percentile Urine Concentrations (µg/L) of DMDTP in the U.S. Population from 1999 to 2002 134

6-9. Dietary Average Daily Intake of Guthion (µg/kg/day) 135

6-10. Excretion of DMTP Following the Dermal Application of Guthion to Volunteers 140

7-1. Analytical Methods for Determining Guthion and Various Metabolites in Biological Samples 147

7-2. Analytical Methods for Determining Guthion in Environmental Samples 150

8-1. Regulations and Guidelines Applicable to Guthion 157