Toxicological Profile for Beryllium

September 2023
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.
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 relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. 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 the 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 due to associated acute, intermediate, and chronic exposures;

(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, intermediate, 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.

Christopher M. Reh, Ph.D.
Associate Director
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention
*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 (NPL) 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 NPL, 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.
# VERSION HISTORY

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>September 2023</td>
<td>Final toxicological profile released</td>
</tr>
<tr>
<td>January 2022</td>
<td>Draft for public comment toxicological profile released</td>
</tr>
<tr>
<td>June 2015</td>
<td>Addendum to the toxicological profile released</td>
</tr>
<tr>
<td>September 2002</td>
<td>Final toxicological profile released</td>
</tr>
<tr>
<td>April 1993</td>
<td>Final toxicological profile released</td>
</tr>
<tr>
<td>December 1988</td>
<td>Final toxicological profile released</td>
</tr>
</tbody>
</table>
CONTRIBUTORS & REVIEWERS

CHEMICAL MANAGER TEAM

Rae T. Benedict, Ph.D. (Lead)  
Franco Scinicariello, M.D., M.P.H.  
Breanna Alman, M.P.H.

ATSDR, Office of Innovation and Analytics,  
Toxicology Section, Atlanta, GA

Meghan Lynch, DSc  
Mary Juergens, M.P.H.  
Hannah Derrick, B.S.  
Kerry Diskin, DSc  
Chimeddulam Dalaijamts, Ph.D.

Abt Associates, Cambridge, MA

Lisa Ingerman, Ph.D., D.A.B.T.  
Savannah Sierco, M.S.  
Mario Citra, Ph.D.

SRC, Inc., North Syracuse, NY

REVIEWERS

Interagency Minimal Risk Level Workgroup:
Includes ATSDR; National Center for Environmental Health (NCEH); National Institute for Occupational Safety and Health (NIOSH); U.S. Environmental Protection Agency (EPA); National Toxicology Program (NTP).

Additional reviews for science and/or policy:
ATSDR, Office of Community Health Hazard Assessment; ATSDR, Office of Capacity Development and Applied Prevention Science; ATSDR, Office of Science; NCEH, Division of Laboratory Sciences; NCEH, Division of Environmental Health Science and Practice; EPA.

PEER REVIEWERS

1. Jamie DeWitt, Ph.D., Brody School of Medicine, East Carolina University

2. Milton D. Rossman, MD, Perelman School of Medicine, Hospital of the University of Pennsylvania

3. David C. Dorman, DVM, PhD, DABVT, DABT, University of Eastern Finland-Kuopio

These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

ATSDR scientists review peer reviewers’ comments and determine whether changes will be made to the profile based on comments. The peer reviewers’ comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.
# CONTENTS

DISCLAIMER............................................................................................................................................... ii
FOREWORD ............................................................................................................................................... iii
VERSION HISTORY ....................................................................................................................................... v
CONTRIBUTORS & REVIEWERS ............................................................................................................. vi
CONTENTS ................................................................................................................................................ vii
LIST OF FIGURES ..................................................................................................................................... ix
LIST OF TABLES ....................................................................................................................................... x

## CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES .......................................................................................... 1
1.2 SUMMARY OF HEALTH EFFECTS ....................................................................................... 2
1.3 MINIMAL RISK LEVELS (MRLs) .......................................................................................... 7

## CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION ....................................................................................................................... 11
2.2 DEATH ..................................................................................................................................... 43
2.3 BODY WEIGHT ....................................................................................................................... 48
2.4 RESPIRATORY ....................................................................................................................... 49
2.5 CARDIOVASCULAR ............................................................................................................... 76
2.6 GASTROINTESTINAL ............................................................................................................. 77
2.7 HEMATOLOGICAL .................................................................................................................. 77
2.8 MUSCULOSKELETAL ............................................................................................................. 80
2.9 HEPATIC ................................................................................................................................... 81
2.10 RENAL ..................................................................................................................................... 83
2.11 DERMAL .................................................................................................................................. 85
2.12 OCULAR .................................................................................................................................. 87
2.13 ENDOCRINE .......................................................................................................................... 87
2.14 IMMUNOLOGICAL .................................................................................................................. 88
2.15 NEUROLOGICAL ................................................................................................................... 96
2.16 REPRODUCTIVE ................................................................................................................... 96
2.17 DEVELOPMENTAL ................................................................................................................ 97
2.18 OTHER NONCANCER .......................................................................................................... 98
2.19 CANCER ............................................................................................................................... 99
2.19.1 Cancer in Humans ........................................................................................................... 99
2.19.2 Cancer in Animals ............................................................................................................ 119
2.20 GENOTOXICITY ................................................................................................................... 120
2.21 MECHANISM OF ACTION .................................................................................................... 125
2.21.1 Mechanisms of Toxicity Associated with Respiratory Effects ........................................ 127

## CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS ................................................................................................................... 138
3.1.1 Absorption ......................................................................................................................... 139
3.1.2 Distribution ......................................................................................................................... 143
3.1.3 Metabolism ......................................................................................................................... 147
3.1.4 Excretion ............................................................................................................................. 147
3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models .......... 151
CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE ....................................................................... 180

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION ........................................................... 175

CHAPTER 6. ADEQUACY OF THE DATABASE ................................................................................ 225

CHAPTER 7. REGULATIONS AND GUIDELINES ............................................................................. 242

CHAPTER 8. REFERENCES .................................................................................................................. 245

APPENDICES
APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS .................................................. A-1
APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR BERYLLIUM ........................................... B-1
APPENDIX C. USER’S GUIDE .............................................................................................................. C-1
APPENDIX D. QUICK REFERENCE FOR HEALTH CARE PROVIDERS ........................................ D-1
APPENDIX E. GLOSSARY .................................................................................................................... E-1
APPENDIX F. ACRONYMS, ABBREVIATIONS, AND SYMBOLS ........................................................ F-1
LIST OF FIGURES

1-1. Health Effects Found in Animals and Humans Following Inhalation Exposure to Beryllium............. 6
1-2. Health Effects Found in Animals Following Oral Exposure to Beryllium........................................ 7
1-3. Summary of Sensitive Targets of Beryllium – Inhalation ............................................................... 8
1-4. Summary of Sensitive Targets of Beryllium – Oral ................................................................. 9
2-1. Overview of the Number of Studies Examining Beryllium Health Effects...................................... 14
2-2. Levels of Significant Exposure to Beryllium–Inhalation .......................................................... 23
2-3. Levels of Significant Exposure to Beryllium–Oral .................................................................... 34
2-4. Hypothesized Pathway for Cellular Processing of Beryllium-Containing Particles from Phagocytosis to Antigen Presentation .......................................................... 129
2-5. Steps and Genetic Variants in the Development of Beryllium Sensitization, CBD, and More Severe Forms of Disease ........................................................................................................ 132
2-6. Pathogenesis of CBD ................................................................................................................ 136
5-1. Number of NPL Sites with Beryllium Contamination ............................................................... 180
6-1. Summary of Existing Health Effects Studies on Beryllium by Route and Endpoint ........... 226
LIST OF TABLES

1-1. Minimal Risk Levels (MRLs) for Beryllium ................................................................. 10

2-1. Levels of Significant Exposure to Beryllium—Inhalation ........................................... 15

2-2. Levels of Significant Exposure to Beryllium—Oral .................................................... 29

2-3. Levels of Significant Exposure to Beryllium—Dermal ................................................ 39

2-4. Summary of Epidemiological Studies Evaluating Mortality ....................................... 44

2-5. Beryllium Sensitization and Chronic Beryllium Disease in Occupationally Exposed Populations ............................................................................................................ 51

2-6. Lung Inflammation Severity Scores in Mice Exposed to Beryllium Metal, Beryllium Oxide, or Beryllium Aluminum ................................................................. 95

2-7. Beryllium Facilities Included in Studies Evaluating Cancer Endpoints ....................... 100

2-8. Summary of Epidemiological Studies Evaluating Cancer Endpoints ......................... 101

2-9. Genotoxicity of Beryllium and Its Compounds In Vitro .............................................. 121

3-1. Percentage of Lung Deposition as a Function of MMAD ........................................... 140

3-2. Clearance Mechanisms for Less Soluble and Insoluble Forms of Beryllium ............... 148

3-3. Histologic Characteristics of Beryllium-induced Disease in Mice and Humans ........... 152

3-4. Risk of Beryllium Sensitization and CBD by HLA-DPB1 Glu69 Genotype in Beryllium Workers ........................................................................................................... 158

3-5. Risk of Beryllium Sensitization and CBD by HLA-DPB1 Glu69 Genotype in Former and Current Beryllium Workers ................................................................. 159

4-1. Chemical Identity of Beryllium and Beryllium Compounds ...................................... 175

4-2. Physical and Chemical Properties of Beryllium and Beryllium Compounds ............. 177

5-1. Facilities that Produce, Process, or Use Beryllium .................................................... 184

5-2. Facilities that Produce, Process, or Use Beryllium Compounds ................................ 185

5-3. Releases to the Environment from Facilities that Produce, Process, or Use Beryllium ................................................................. 189

5-4. Releases to the Environment from Facilities that Produce, Process, or Use Beryllium Compounds ........................................................................................................... 190

5-5. National Emission Inventory (NEI) Total National Emissions for Beryllium Estimated by Sector 2017 ................................................................. 193

5-6. Precipitation of Beryllium Compounds in a Neutral (pH 6.5–9.5) Environment ........ 198