



Toxicological Profile for Glyphosate

August 2020



U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

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 and EPA.

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, intermediate, 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 the levels of exposure that present a significant risk to human health due to acute, intermediate, and chronic duration exposures; 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
Director, National Center for Environmental Health and
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

Date	Description
August 2020	Final toxicological profile released
April 2019	Draft for public comment toxicological profile released

CONTRIBUTORS & REVIEWERS

Hana R. Pohl, M.D., Ph.D. (Lead)

Melanie Buser, M.P.H.

Breanna Alman, M.P.H.

Selene Chou, Ph.D.

Mike Fay, Ph.D.

Carolyn Harper, Ph.D.

Susan Zells Ingber, A.B., M.S.P.P.

Jennifer Przybyla, Ph.D.

Jane Li, Ph.D.

Angela Ragin-Wilson, Ph.D.

Henry Abadin, M.S.P.H.

ATSDR, Division of Toxicology and Human Health
Sciences, Atlanta, GA

David W. Wohlers, Ph.D.

Mario Citra, Ph.D.

Christina Coley, B.S.

Lisa Ingerman, Ph.D., D.A.B.T.

SRC, Inc., North Syracuse, NY

Kaley Beins, M.P.H.

Lauren Brown, M.S., D.A.B.T.

Paulina Do, M.P.H.

Adriana Antezana, M.P.H.

Hannah Derrick, B.S.

Kerry Diskin, Ph.D.

Andrea Chiger, M.P.H.

Abt Associates, Rockville, MD

Chimeddulam Dalajamts, PhD

Texas A&M University (under
subcontract to Abt Associates)

REVIEWERS

Interagency Minimal Risk Level Workgroup:

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

Additional reviews for science and/or policy:

ATSDR, Division of Community Health Investigations; ATSDR, Office of Science; NCEH, Division of Laboratory Science; NCEH, Division of Environmental Health Science and Practice. EPA.

PEER REVIEWERS

1. Annaclaire De Roos Ph.D., M.P.H., Associate Professor, Environmental and Occupational Health, Dornsife School of Public Health, Drexel University, Philadelphia, Pennsylvania
2. David A. Eastmond, Ph.D., Professor and Toxicologist, Department of Molecular Cell and Systems Biology, University of California, Riverside, Riverside, California
3. Renata Marino Romano, Ph.D., Professora Adjunta, Departamento de Farmácia, Universidade Estadual do Centro-Oeste – UNICENTRO, Guarapuava, Brazil

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.

Peer reviewers for subsequent revision to Section 2.19 (Cancer) and Appendix A (MRL Worksheets) in the Toxicological Profile for Glyphosate were:

1. James V. Bruckner, Ph.D., Professor of Pharmacology & Toxicology, Department of Pharmaceutical & Biomedical Sciences, College of Pharmacy, University of Georgia
2. David A. Eastmond, Ph.D., Professor and Toxicologist, Department of Molecular Cell and Systems Biology, University of California, Riverside, Riverside, California
3. Paul J. Mills, Ph.D., Professor of Family Medicine and Public Health, University of California, San Diego
4. Renata Marino Romano, Ph.D., Professora Adjunta, Departamento de Farmácia, Universidade Estadual do Centro-Oeste – UNICENTRO, Guarapuava, Brazil

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.....	VI
CONTRIBUTORS & REVIEWERS.....	VII
CONTENTS.....	VIII
LIST OF FIGURES.....	XI
LIST OF TABLES.....	XII
CHAPTER 1. RELEVANCE TO PUBLIC HEALTH.....	1
1.1 OVERVIEW AND U.S. EXPOSURES.....	1
1.2 SUMMARY OF HEALTH EFFECTS.....	3
1.3 MINIMAL RISK LEVELS (MRLs).....	7
CHAPTER 2. HEALTH EFFECTS.....	10
2.1 INTRODUCTION.....	10
2.2 DEATH.....	47
2.3 BODY WEIGHT.....	47
2.4 RESPIRATORY.....	49
2.5 CARDIOVASCULAR.....	61
2.6 GASTROINTESTINAL.....	62
2.7 HEMATOLOGICAL.....	64
2.8 MUSCULOSKELETAL.....	64
2.9 HEPATIC.....	64
2.10 RENAL.....	67
2.11 DERMAL.....	69
2.12 OCULAR.....	69
2.13 ENDOCRINE.....	70
2.14 IMMUNOLOGICAL.....	72
2.15 NEUROLOGICAL.....	72
2.16 REPRODUCTIVE.....	74
2.17 DEVELOPMENTAL.....	77
2.18 OTHER NONCANCER.....	80
2.19 CANCER.....	80
2.20 GENOTOXICITY.....	128
2.21 MECHANISMS OF ACTION.....	139
CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS.....	144
3.1 TOXICOKINETICS.....	144
3.1.1 Absorption.....	144
3.1.1.1 Inhalation Exposure.....	144
3.1.1.2 Oral Exposure.....	144
3.1.1.3 Dermal Exposure.....	145
3.1.2 Distribution.....	146
3.1.2.1 Inhalation Exposure.....	146
3.1.2.2 Oral Exposure.....	146
3.1.2.3 Dermal Exposure.....	147
3.1.2.4 Other Routes of Exposure.....	148
3.1.3 Metabolism.....	148
3.1.4 Excretion.....	150
3.1.4.1 Inhalation Exposure.....	150
3.1.4.2 Oral Exposure.....	150
3.1.4.3 Dermal Exposure.....	151
3.1.4.4 Other Routes of Exposure.....	151
3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models.....	152
3.1.6 Animal-to-Human Extrapolations.....	152

3.2	CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE.....	152
3.3	BIOMARKERS OF EXPOSURE AND EFFECT	153
3.3.1	Biomarkers of Exposure	154
3.3.2	Biomarkers of Effect.....	154
3.4	INTERACTIONS WITH OTHER CHEMICALS	154
CHAPTER 4	CHEMICAL AND PHYSICAL INFORMATION	156
4.1	CHEMICAL IDENTITY	156
4.2	PHYSICAL AND CHEMICAL PROPERTIES	156
CHAPTER 5	POTENTIAL FOR HUMAN EXPOSURE	159
5.1	OVERVIEW	159
5.2	PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL	159
5.2.1	Production.....	159
5.2.2	Import/Export	163
5.2.3	Use	163
5.2.4	Disposal	166
5.3	RELEASES TO THE ENVIRONMENT	167
5.3.1	Air.....	167
5.3.2	Water	168
5.3.3	Soil.....	169
5.4	ENVIRONMENTAL FATE	170
5.4.1	Transport and Partitioning	171
5.4.2	Transformation and Degradation	174
5.5	LEVELS IN THE ENVIRONMENT.....	181
5.5.1	Air.....	183
5.5.2	Water	184
5.5.3	Sediment and Soil.....	184
5.5.4	Other Media	184
5.6	GENERAL POPULATION EXPOSURE	194
5.7	POPULATIONS WITH POTENTIALLY HIGH EXPOSURES	200
CHAPTER 6	ADEQUACY OF THE DATABASE	201
6.1	Information on Health Effects.....	201
6.2	Identification of Data Needs	204
6.3	Ongoing Studies.....	208
CHAPTER 7	REGULATIONS AND GUIDELINES	210
CHAPTER 8	REFERENCES	212

APPENDICES

APPENDIX A	ATSDR MINIMAL RISK LEVELS AND WORKSHEETS.....	A-1
APPENDIX B	LITERATURE SEARCH FRAMEWORK FOR GLYPHOSATE	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. Noncancer Health Effects Found in Animals Following Oral Exposure to Glyphosate Technical.....	4
1-2. Summary of Sensitive Targets of Glyphosate Technical – Oral	8
2-1. Overview of the Number of Animal Studies Examining Glyphosate Technical Health Effects*	16
2-2. Overview of the Number of Studies Examining Glyphosate Formulations Health Effects*	17
2-3. Levels of Significant Exposure to Glyphosate Technical – Oral	29
2-4. Risk of non-Hodgkin’s Lymphoma Relative to Self-Reported Glyphosate Use or Exposure.....	116
2-5. Risk of Multiple Myeloma Relative to Self-Reported Glyphosate Use or Exposure.....	117
3-1. Chemical Structures of Glyphosate and Aminomethylphosphonic Acid (AMPA).....	148
5-1. Agricultural Application Trends of Glyphosate in the United States According to U.S. Geological Survey (USGS) Data	165
5-2. Degradation of Glyphosate Under Aerobic Conditions	174
6-1. Summary of Existing Health Effects Studies of Animals Orally Exposed to Glyphosate Technical (Listed by Endpoint)*	202
6-2. Summary of Existing Health Effects Studies on Glyphosate Formulations (Listed by Endpoint)*	203

LIST OF TABLES

1-1. Minimal Risk Levels (MRLs) for Technical Glyphosate	9
2-1. Description of Selected Glyphosate Formulations	11
2-2. Levels of Significant Exposure to Glyphosate Technical – Oral.....	18
2-3. Levels of Significant Exposure to Glyphosate Formulations – Oral.....	34
2-4. Levels of Significant Exposure to Glyphosate Technical – Dermal.....	46
2-5. Noncancer Outcomes in Humans Exposed to Glyphosate-Containing Products	51
2-6. Summary of Meta-Analyses of Results from Studies Examining Possible Association Between Self-Reported Use of Glyphosate and Lymphohematopoietic Cancers.....	82
2-7. Cancer Outcomes for Solid Tumor-Types in Humans Exposed to Glyphosate-Containing Products	87
2-8. Lymphohematopoietic Cancer Outcomes in Humans Exposed to Glyphosate-Containing Products	101
2-9. Incidences of Selected Tumors in Sprague-Dawley Rats Administered Technical Glyphosate (98.7% purity) in the Diet for up to 26 Months	119
2-10. Incidences of Selected Tumors in Albino Sprague-Dawley Rats Administered Technical Glyphosate (96.5% Purity) in the Diet for 2 Years.....	120
2-11. Incidences of Renal Tubular Cell Tumors in Male CD-1 Mice Administered Technical Glyphosate (99.78% Purity) in the Diet for up to 24 Months.....	123
2-12. Incidences of Tumors in Male and Female CD-1 Mice Administered Glyphosate (\geq 97.5% Purity) in the Diet for up to 104 Weeks	123
2-13. Carcinogenicity Classification.....	126
2-14. Genotoxicity of Glyphosate Technical <i>In Vitro</i>	128
2-15. Genotoxicity of Glyphosate Technical <i>In Vivo</i>	130
2-16. Genotoxicity of Glyphosate Formulations <i>In Vitro</i>	130
2-17. Genotoxicity of Glyphosate Formulations <i>In Vivo</i>	132
4-1. Chemical Identity of Glyphosate and Glyphosate Isopropylamine ^a	157
4-2. Physical and Chemical Properties of Glyphosate and its Isopropylamine Salt ^a	158
5-1. Glyphosate Salts	160
5-2. Companies Manufacturing Products Under Pesticide Code 417300 (Glyphosate).....	161
5-3. Glyphosate AI (Pounds) Usage Trends from 1990 to 2014.....	166
5-4. Lowest Limit of Detection Based on Standards	182
5-5. Summary of Environmental Levels of Glyphosate	182
5-6. Outdoor Air Monitoring Data for Glyphosate	183

5-7. Glyphosate and its Degradation Products in Water Samples in Major U.S. River Basins	184
5-8. Surface Water Monitoring Data for Glyphosate.....	186
5-9. Groundwater Monitoring Data for Glyphosate.....	189
5-10. Sediment and Soil Monitoring Data for Glyphosate	191
5-11. Available Glyphosate Human Monitoring Data	196
6-1. Ongoing Studies on Glyphosate	209
7-1. Regulations and Guidelines Applicable to Glyphosate	210