



Toxicological Profile for Methyl *tert*-Butyl Ether (MTBE)

September 2023



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

CS274127-A

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

Date	Description
September 2023	Final toxicological profile released
January 2022	Draft for public comment toxicological profile released
August 1996	Final toxicological profile released

CONTRIBUTORS & REVIEWERS

CHEMICAL MANAGER TEAM

Gaston Casillas, Ph.D. (Lead)
Mike Fay, Ph.D.
Jennifer Przybyla, Ph.D.

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

Kimberly Zaccaria, Ph.D., D.A.B.T.
Mario Citra, Ph.D.
Lisa Ingberman, Ph.D., D.A.B.T.
Sabah Tariq, M.S.
David W. Wohlers, 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

Peer Reviewers for the full profile:

1. Clifford P. Weisel, Ph.D.; Professor; Environmental and Occupational Health Sciences Institute; SPH - Rutgers University; 170 Frelinghuysen Road; Piscataway, New Jersey
2. Deborah A. Cory-Slechta, Ph.D.; Professor of Environmental Medicine, Pediatrics and Public Health Sciences; Department of Environmental Medicine, Box EHSC; University of Rochester Medical Center; Rochester, New York
3. James V. Bruckner, Ph.D.; Emeritus; Interdisciplinary Toxicology Program, Professor Pharmaceutical and Biomedical Sciences, College of Pharmacy; University of Georgia, Athens, Georgia

Peer Reviewers for the intermediate-duration oral MRL:

1. Krassimira Hristova, Ph.D.; Associate Professor; Biological Sciences Department; Marquette University; Milwaukee, Wisconsin
2. James V. Bruckner, Ph.D.; Emeritus; Pharmaceutical & Biomedical Sciences, College of Pharmacy; University of Georgia; Athens, Georgia
3. Clifford P. Weisel, Ph.D.; Environmental and Occupational Health Sciences Institute; SPH - Rutgers University; Piscataway, New Jersey

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.....	viii
LIST OF FIGURES	x
LIST OF TABLES	xi
CHAPTER 1. RELEVANCE TO PUBLIC HEALTH	1
1.1 OVERVIEW AND U.S. EXPOSURES	1
1.2 SUMMARY OF HEALTH EFFECTS.....	2
1.3 MINIMAL RISK LEVELS (MRLs)	8
CHAPTER 2. HEALTH EFFECTS.....	12
2.1 INTRODUCTION.....	12
2.2 DEATH	80
2.3 BODY WEIGHT	81
2.4 RESPIRATORY	84
2.5 CARDIOVASCULAR.....	87
2.6 GASTROINTESTINAL.....	89
2.7 HEMATOLOGICAL	91
2.8 MUSCULOSKELETAL	93
2.9 HEPATIC.....	94
2.10 RENAL	99
2.11 DERMAL.....	103
2.12 OCULAR	104
2.13 ENDOCRINE.....	107
2.14 IMMUNOLOGICAL	110
2.15 NEUROLOGICAL.....	113
2.16 REPRODUCTIVE	119
2.17 DEVELOPMENTAL.....	123
2.18 OTHER NONCANCER.....	126
2.19 CANCER.....	127
2.20 GENOTOXICITY	130
CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS.....	135
3.1 TOXICOKINETICS.....	135
3.1.1 Absorption.....	135
3.1.2 Distribution	137
3.1.3 Metabolism.....	139
3.1.4 Excretion	141
3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models	144
3.1.6 Animal-to-Human Extrapolations	147
3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE.....	147
3.3 BIOMARKERS OF EXPOSURE AND EFFECT	150

3.3.1	Biomarkers of Exposure.....	151
3.3.2	Biomarkers of Effect	152
3.4	INTERACTIONS WITH OTHER CHEMICALS	152
CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION		154
4.1	CHEMICAL IDENTITY	154
4.2	PHYSICAL AND CHEMICAL PROPERTIES	154
CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE.....		156
5.1	OVERVIEW	156
5.2	PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL	158
5.2.1	Production	158
5.2.2	Import/Export.....	160
5.2.3	Use	160
5.2.4	Disposal.....	163
5.3	RELEASES TO THE ENVIRONMENT.....	163
5.3.1	Air	164
5.3.2	Water.....	166
5.3.3	Soil	167
5.4	ENVIRONMENTAL FATE	167
5.4.1	Transport and Partitioning.....	167
5.4.2	Transformation and Degradation	168
5.5	LEVELS IN THE ENVIRONMENT.....	171
5.5.1	Air	172
5.5.2	Water.....	175
5.5.3	Sediment and Soil	177
5.5.4	Other Media	178
5.6	GENERAL POPULATION EXPOSURE.....	178
5.7	POPULATIONS WITH POTENTIALLY HIGH EXPOSURES	183
CHAPTER 6. ADEQUACY OF THE DATABASE		185
6.1	INFORMATION ON HEALTH EFFECTS.....	185
6.2	IDENTIFICATION OF DATA NEEDS.....	187
6.3	ONGOING STUDIES.....	194
CHAPTER 7. REGULATIONS AND GUIDELINES		195
CHAPTER 8. REFERENCES		197
APPENDICES		
APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS		A-1
APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR MTBE		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 Following Inhalation Exposure to Methyl <i>tert</i> -Butyl Ether (MTBE)	3
1-2. Health Effects Found in Animals Following Oral Exposure to Methyl <i>tert</i> -Butyl Ether (MTBE)	4
1-3. Summary of Sensitive Targets of Methyl <i>tert</i> -Butyl Ether (MTBE) – Inhalation.....	9
1-4. Summary of Sensitive Targets of Methyl <i>tert</i> -Butyl Ether (MTBE) – Oral.....	10
2-1. Overview of the Number of Studies Examining Methyl <i>tert</i> -Butyl Ether (MTBE) Health Effects.....	16
2-2. Levels of Significant Exposure to Methyl <i>tert</i> -Butyl Ether (MTBE) – Inhalation.....	47
2-3. Levels of Significant Exposure to Methyl <i>tert</i> -Butyl Ether (MTBE) – Oral	69
3-1. Proposed Metabolic Pathway for Methyl <i>tert</i> -Butyl Ether (MTBE) in Rats	140
5-1. Number of NPL Sites with Methyl <i>tert</i> -Butyl Ether (MTBE) Contamination	156
6-1. Summary of Existing Health Effects Studies on Methyl <i>tert</i> -Butyl Ether (MTBE) by Route and Endpoint.....	186

LIST OF TABLES

1-1. Minimal Risk Levels (MRLs) for Methyl <i>tert</i> -Butyl Ether (MTBE)	11
2-1. Health Effects in Humans Exposed to Methyl <i>tert</i> -Butyl Ether (MTBE)—Epidemiological Studies	17
2-2. Levels of Significant Exposure to Methyl <i>tert</i> -Butyl Ether (MTBE) – Inhalation.....	31
2-3. Levels of Significant Exposure to Methyl <i>tert</i> -Butyl Ether (MTBE) – Oral	53
2-4. Levels of Significant Exposure to Methyl <i>tert</i> -Butyl Ether (MTBE) – Dermal	76
2-5. Genotoxicity of Methyl <i>tert</i> -Butyl Ether (MTBE) <i>In Vitro</i>	131
2-6. Genotoxicity of Methyl <i>tert</i> -Butyl Ether (MTBE) <i>In Vivo</i>	132
4-1. Chemical Identity of Methyl <i>tert</i> -Butyl Ether (MTBE).....	154
4-2. Physical and Chemical Properties of Methyl <i>tert</i> -Butyl Ether (MTBE).....	155
5-1. Facilities that Produce, Process, or Use Methyl <i>tert</i> -Butyl Ether (MTBE)	159
5-2. U.S. Production of Methyl <i>tert</i> -Butyl Ether (MTBE) (Thousands of Barrels)	161
5-3. U.S. Exports of Methyl <i>tert</i> -Butyl Ether (MTBE) (Thousands of Barrels)	162
5-4. Releases to the Environment from Facilities that Produce, Process, or Use Methyl <i>tert</i> -Butyl Ether (MTBE).....	164
5-5. Lowest Limit of Detection Based on Standards	171
5-6. Summary of Environmental Levels of Methyl <i>tert</i> -Butyl Ether (MTBE)	172
5-7. Methyl <i>tert</i> -Butyl Ether (MTBE) Levels in Water, Soil, and Air of National Priorities List (NPL) Sites	172
5-8. Percentile Distribution of Daily Mean Methyl <i>tert</i> -Butyl Ether (MTBE) Concentrations (ppbv) Measured in Ambient Air at Locations Across the United States.....	173
5-9. Geometric Mean and Selected Percentiles of Methyl- <i>tert</i> -Butyl Ether (MTBE) Whole Blood Concentrations (in pg/mL) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) (2001–2008)	179
5-10. Geometric Mean and Selected Percentiles of Methyl- <i>tert</i> -Butyl Ether (MTBE) Whole Blood Concentrations (in pg/mL) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) (2011–2016)	181
7-1. Regulations and Guidelines Applicable to Methyl <i>tert</i> -Butyl Ether (MTBE).....	195