DRAFT
TOXICOLOGICAL PROFILE FOR
TOLUENE DIISOCYANATE AND METHYLENEDIPHENYL DIISOCYANATE

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

September 2015
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.

This information is distributed solely for the purpose of pre dissemination public comment under applicable information quality guidelines. It has not been formally disseminated by the Agency for Toxic Substances and Disease Registry. It does not represent and should not be construed to represent any agency determination or policy.
UPDATE STATEMENT

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 Human Health Sciences
Environmental Toxicology Branch
1600 Clifton Road NE
Mailstop F-57
Atlanta, Georgia 30329-4027
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 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 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 toxic 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. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov. Follow the on-line instructions for submitting comments.

Written comments may also be sent to:
Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
Environmental Toxicology Branch

Regular Mailing Address:
1600 Clifton Road, N.E.
Mail Stop F-57
Atlanta, Georgia 30329-4027

Physical Mailing Address:
4770 Buford Highway
Building 106, 3rd floor, MS F-57
Chamblee, Georgia 30341

***DRAFT FOR PUBLIC COMMENT***
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 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 National Priorities List, 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.

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 is being 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

***DRAFT FOR PUBLIC COMMENT***
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:

Chapter 1 How Can (Chemical X) Affect Children?
Chapter 1 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)
Internet: http://www.atsdr.cdc.gov

The following additional material is available online at www.atsdr.cdc.gov:

Case Studies in Environmental Medicine—Case Studies are self-instructional publications designed to increase primary care provider’s knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients.
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, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: (202) 245-0625 or 1-800-CDC-INFO (800-232-4636).

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.

Clinical Resources

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):

Malcolm Williams, DVM, Ph.D.
G. Daniel Todd, Ph.D.
Hana R. Pohl, M.D., Ph.D.
Jessilynn Taylor, M.S., CDR USPHS
ATSDR, Division of Toxicology and Human Health Sciences, Atlanta, GA

Lisa Ingerman, Ph.D., DABT
Heather Carlson-Lynch, M.S.
Courtney Hard, B.A.
Mario Citra, Ph.D.
SRC, Inc., 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 Environmental Toxicology Branch reviews data needs sections to
   assure consistency across profiles and adherence to instructions in the Guidance.

This page is intentionally blank.
PEER REVIEW

A peer review panel was assembled for toluene diisocyanate and methylenediphenyl diisocyanate. The panel consisted of the following members:

1. Dr. Mark Pemberton; Systox, Ltd.; Wilmslow, Cheshire, United Kingdom;
2. Robyn Prueitt, Ph.D., DABT; Gradient Corporation; Cambridge, Massachusetts; and

These experts collectively have knowledge of toluene diisocyanate and methylenediphenyl diisocyanate 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.
## CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>DISCLAIMER</td>
<td>ii</td>
</tr>
<tr>
<td>UPDATE STATEMENT</td>
<td>iii</td>
</tr>
<tr>
<td>FOREWORD</td>
<td>v</td>
</tr>
<tr>
<td>QUICK REFERENCE FOR HEALTH CARE PROVIDERS</td>
<td>vii</td>
</tr>
<tr>
<td>CONTRIBUTORS</td>
<td>ix</td>
</tr>
<tr>
<td>PEER REVIEW</td>
<td>xi</td>
</tr>
<tr>
<td>CONTENTS</td>
<td>xiii</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>xvii</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>xix</td>
</tr>
<tr>
<td>1. PUBLIC HEALTH STATEMENT</td>
<td>1</td>
</tr>
<tr>
<td>2. RELEVANCE TO PUBLIC HEALTH</td>
<td>7</td>
</tr>
<tr>
<td>2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO TOLUENE DICOSYANATE AND METHYLENEDIIPHENYL DICOSYANATE IN THE UNITED STATES</td>
<td>7</td>
</tr>
<tr>
<td>2.2 SUMMARY OF HEALTH EFFECTS</td>
<td>8</td>
</tr>
<tr>
<td>2.3 MINIMAL RISK LEVELS (MRLs)</td>
<td>12</td>
</tr>
<tr>
<td>3. HEALTH EFFECTS</td>
<td>19</td>
</tr>
<tr>
<td>3.1 INTRODUCTION</td>
<td>19</td>
</tr>
<tr>
<td>3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE</td>
<td>19</td>
</tr>
<tr>
<td>3.2.1 Inhalation Exposure</td>
<td>20</td>
</tr>
<tr>
<td>3.2.1.1 Death</td>
<td>20</td>
</tr>
<tr>
<td>3.2.1.2 Systemic Effects</td>
<td>37</td>
</tr>
<tr>
<td>3.2.1.3 Immunological and Lymphoreticular Effects</td>
<td>52</td>
</tr>
<tr>
<td>3.2.1.4 Neurological Effects</td>
<td>52</td>
</tr>
<tr>
<td>3.2.1.5 Reproductive Effects</td>
<td>54</td>
</tr>
<tr>
<td>3.2.1.6 Developmental Effects</td>
<td>54</td>
</tr>
<tr>
<td>3.2.1.7 Cancer</td>
<td>55</td>
</tr>
<tr>
<td>3.2.2 Oral Exposure</td>
<td>58</td>
</tr>
<tr>
<td>3.2.2.1 Death</td>
<td>58</td>
</tr>
<tr>
<td>3.2.2.2 Systemic Effects</td>
<td>66</td>
</tr>
<tr>
<td>3.2.2.3 Immunological and Lymphoreticular Effects</td>
<td>67</td>
</tr>
<tr>
<td>3.2.2.4 Neurological Effects</td>
<td>67</td>
</tr>
<tr>
<td>3.2.2.5 Reproductive Effects</td>
<td>67</td>
</tr>
<tr>
<td>3.2.2.6 Developmental Effects</td>
<td>68</td>
</tr>
<tr>
<td>3.2.2.7 Cancer</td>
<td>68</td>
</tr>
<tr>
<td>3.2.3 Dermal Exposure</td>
<td>70</td>
</tr>
<tr>
<td>3.2.3.1 Death</td>
<td>70</td>
</tr>
<tr>
<td>3.2.3.2 Systemic Effects</td>
<td>70</td>
</tr>
<tr>
<td>3.2.3.3 Immunological and Lymphoreticular Effects</td>
<td>70</td>
</tr>
<tr>
<td>3.2.3.4 Neurological Effects</td>
<td>71</td>
</tr>
<tr>
<td>3.2.3.5 Reproductive Effects</td>
<td>71</td>
</tr>
<tr>
<td>3.2.3.6 Developmental Effects</td>
<td>71</td>
</tr>
<tr>
<td>3.2.3.7 Cancer</td>
<td>71</td>
</tr>
<tr>
<td>3.3 GENOTOXICITY</td>
<td>71</td>
</tr>
<tr>
<td>3.4 TOXICOKINETICS</td>
<td>80</td>
</tr>
</tbody>
</table>

***DRAFT FOR PUBLIC COMMENT***
This page is intentionally blank.
LIST OF FIGURES

3-1. Levels of Significant Exposure to Toluene Diisocyanate - Inhalation ............................................... 28
3-2. Levels of Significant Exposure to Methylene diphenyl Diisocyanate - Inhalation ............................. 34
3-3. Levels of Significant Exposure to Toluene Diisocyanate - Oral ........................................................ 62
3-4. Proposed Metabolic Scheme for 2,4-Toluene Diisocyanate in the Rat .............................................. 89
3-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance ..................................................................................................... 97
3-6. Existing Information on Health Effects of Toluene Diisocyanate ....................................................... 112
3-7. Existing Information on Health Effects of Methylene diphenyl Diisocyanate ................................. 113
6-1. Frequency of NPL Sites with 1,3-Toluene Diisocyanate Contamination ............................................... 136

***DRAFT FOR PUBLIC COMMENT***
LIST OF TABLES

3-1. Levels of Significant Exposure to Toluene Diisocyanate - Inhalation ................................................. 21
3-2. Levels of Significant Exposure to Methylenediphenyl Diisocyanate - Inhalation ................................. 31
3-3. Summary of Occupational Exposure Studies Examining the Effects of Toluene Diisocyanate on Lung Function ............................................................................................................................... 41
3-4. Results of Cohort Studies of Diisocyanate Exposure and Mortality from Specific Cancers ............. 56
3-5. Levels of Significant Exposure to Toluene Diisocyanate - Oral ........................................................ 59
3-6. Tumor Incidences in Rats and Mice Exposed to Commercial-Grade Toluene Diisocyanate for 2 Years by Gavage ............................................................................................................................. 69
3-7. Genotoxicity of Toluene Diisocyanate and Methylenediphenyl Diisocyanate In Vitro .................... 72
3-8. Genotoxicity of Toluene Diisocyanate and Methylenediphenyl Diisocyanate In Vivo .................... 76
3-9. Tissue Distribution of $^{14}$C in Male F344 Rats Exposed to $^{14}$C Ring-Labelled 2,4-Toluene Diisocyanate Via Gavage or Inhalation ........................................................ 85
3-10. Tissue Distribution of $^{14}$C in Male Wistar Rats Exposed to $^{14}$C Ring-Labelled 4,4'-Methylenediphenyl Diisocyanate Aerosol Via Inhalation ......................................................... 86
3-11. Metabolites of Methylenediphenyl Diisocyanate (MDI) in Male F344 Rats Exposed to $^{14}$C Ring-Labelled 4,4'-MDI Monomer Via Inhalation ................................................................. 90
3-12. Kinetics of Urinary Toluene Diamine (TDA) Excretion in Rats Exposed to Toluene Diisocyanate Via Topical Application ................................................................. 94
3-13. Upper Reference Limits for Biomarkers of Exposure to Toluene Diisocyanate and Methylenediphenyl Diisocyanate .............................................................................................. 105
4-1. Chemical Identity of Toluene Diisocyanate and Methylenediphenyl Diisocyanate ......................... 122
4-2. Physical and Chemical Properties of Toluene Diisocyanate and Methylenediphenyl Diisocyanate .......................................................................................................................... 124
5-1. Facilities that Produce, Process, or Use Toluene Diisocyanate (Mixed Isomers) ............................ 128
5-2. Facilities that Produce, Process, or Use 2,4-Toluene Diisocyanate ................................................. 130
5-3. Facilities that Produce, Process, or Use 2,6-Toluene Diisocyanate ................................................. 131
6-1. Releases to the Environment from Facilities that Produce, Process, or Use Toluene Diisocyanate (Mixed Isomers) ........................................................................................................... 138
6-2. Releases to the Environment from Facilities that Produce, Process, or Use 2,4-Toluene Diisocyanate..................................................................................................................................... 140

6-3. Releases to the Environment from Facilities that Produce, Process, or Use 2,6-Toluene Diisocyanate..................................................................................................................................... 142

7-1. Analytical Methods for Determining Toluene Diisocyanate and Methylenediphenyl Diisocyanate in Biological Materials.......................................................................................................................... 160

7-2. Analytical Methods for Determining Toluene Diisocyanate and Methylene Diphenyl Diisocyanate in Environmental Samples ........................................................................................................................................ 162

8-1. Regulations, Advisories, and Guidelines Applicable to Diisocyanate and Methylenediphenyl Diisocyanate.......................................................................................................................... 171