

**TOXICOLOGICAL PROFILE FOR
HEXAMETHYLENE DIISOCYANATE**

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

August 1998

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

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333

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.

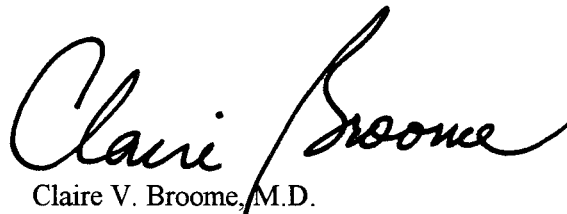
The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels 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.



Claire V. Broome, M.D.
Acting 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). Section 211 of SARA also amended Title 10 of the U. S. Code, creating the Defense Environmental Restoration Program. Section 2704(a) of Title 10 of the U. S. Code directs the Secretary of Defense to notify the Secretary of Health and Human Services of not less than 25 of the most commonly found unregulated hazardous substances at defense facilities. Section 2704(b) of Title 10 of the U. S. Code directs the Administrator of the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare a toxicological profile for each substance on the list provided by the Secretary of Defense under subsection (b).

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHORS(S):

Henry Abadin, MSPH
ATSDR, Division of Toxicology, Atlanta, GA

Wayne Spoo, DVM, DABT, DABVT
Research Triangle Institute, Research Triangle Park, NC

THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures consistency with ATSDR policy.
2. 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.
3. 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.
4. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

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

1. Dr. Herbert Cornish, Private Consultant, Ypsilanti, MI;
2. Dr. Ernest McConnell, Private Consultant, Raleigh, NC; and
3. Mr. Lyman Skory, Private Consultant, Midland, MI.

These experts collectively have knowledge of hexamethylene diisocyanate'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. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

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

FOREWORD v

CONTRIBUTORS vii

PEER REVIEW ix

LIST OF FIGURES xv

LIST OF TABLES xvii

1. PUBLIC HEALTH STATEMENT 1

 1.1 WHAT IS HEXAMETHYLENE DIISOCYANATE? 1

 1.2 WHAT HAPPENS TO HDI WHEN IT ENTERS THE ENVIRONMENT? 2

 1.3 HOW MIGHT I BE EXPOSED TO HDI? 2

 1.4 HOW CAN HDI ENTER AND LEAVE MY BODY? 3

 1.5 HOW CAN HDI AFFECT MY HEALTH? 3

 1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN
 EXPOSED TO HDI? 4

 1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE
 TO PROTECT HUMAN HEALTH? 5

 1.8 WHERE CAN I GET MORE INFORMATION? 6

2. HEALTH EFFECTS 7

 2.1 INTRODUCTION 7

 2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE 7

 2.2.1 Inhalation Exposure 9

 2.2.1.1 Death 10

 2.2.1.2 Systemic Effects 12

 2.2.1.3 Immunological and Lymphoreticular Effects 45

 2.2.1.4 Neurological Effects 50

 2.2.1.5 Reproductive Effects 51

 2.2.1.6 Developmental Effects 52

 2.2.1.7 Genotoxic Effects 52

 2.2.1.8 Cancer 52

 2.2.2 Oral Exposure 52

 2.2.2.1 Death 53

 2.2.2.2 Systemic Effects 53

 2.2.2.3 Immunological and Lymphoreticular Effects 58

 2.2.2.4 Neurological Effects 58

 2.2.2.5 Reproductive Effects 58

 2.2.2.6 Developmental Effects 58

 2.2.2.7 Genotoxic Effects 58

 2.2.2.8 Cancer 58

 2.2.3 Dermal Exposure 58

 2.2.3.1 Death 58

 2.2.3.2 Systemic Effects 58

2.2.3.3	Immunological and Lymphoreticular Effects	63
2.2.3.4	Neurological Effects	67
2.2.3.5	Reproductive Effects	67
2.2.3.6	Developmental Effects	67
2.2.3.7	Genotoxic Effects	67
2.2.3.8	Cancer	67
2.3	TOXICOKINETICS	67
2.3.1	Absorption	68
2.3.2	Distribution	68
2.3.3	Metabolism	68
2.3.4	Elimination and Excretion	68
2.3.4.1	Inhalation Exposure	68
2.3.4.2	Oral Exposure	69
2.3.4.3	Dermal Exposure	69
2.3.5	Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models	69
2.4	MECHANISMS OF ACTION	71
2.5	RELEVANCE TO PUBLIC HEALTH	73
2.6	BIOMARKERS OF EXPOSURE AND EFFECT	85
2.6.1	Biomarkers Used to Identify or Quantify Exposure to Hexamethylene Diisocyanate.	86
2.6.2	Biomarkers Used to Characterize Effects Caused by Hexamethylene Diisocyanate.	87
2.7	INTERACTIONS WITH OTHER CHEMICALS	88
2.8	POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE	88
2.9	METHODS FOR REDUCING TOXIC EFFECTS	88
2.9.1	Reducing Peak Absorption Following Exposure	89
2.9.2	Reducing Body Burden	90
2.9.3	Interfering with the Mechanism of Action for Toxic Effects	90
2.10	ADEQUACY OF THE DATABASE	90
2.10.1	Existing Information on Health Effects of Hexamethylene Diisocyanate	90
2.10.2	Identification of Data Needs	92
2.10.3	Ongoing Studies	96
3	CHEMICAL AND PHYSICAL INFORMATION	99
3.1	CHEMICAL IDENTITY	99
3.2	PHYSICAL AND CHEMICAL PROPERTIES	99
4	PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL	103
4.1	PRODUCTION	103
4.2	IMPORT/EXPORT	103
4.3	USE	103
4.4	DISPOSAL	104

5. POTENTIAL FOR HUMAN EXPOSURE	105
5.1 OVERVIEW	105
5.2 RELEASES TO THE ENVIRONMENT	108
5.2.1 Air	108
5.2.2 Water	108
5.2.3 Soil	109
5.3 ENVIRONMENTAL FATE	109
5.3.1 Transport and Partitioning	109
5.3.2 Transformation and Degradation	110
5.3.2.1 Air	110
5.3.2.2 Water	112
5.3.2.3 Sediment and Soil	114
5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT	115
5.4.1 Air	115
5.4.2 Water	115
5.4.3 Sediment and Soil	115
5.4.4 Other Environmental Media	116
5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE	116
5.6 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES	120
5.7 ADEQUACY OF THE DATABASE	121
5.7.1 Identification of Data Needs	121
5.7.2 Ongoing Studies	125
6. ANALYTICAL METHODS	127
6.1 BIOLOGICAL SAMPLES	127
6.2 ENVIRONMENTAL SAMPLES	129
6.3 ADEQUACY OF THE DATABASE	132
6.3.1 Identification of Data Needs	132
6.3.2 Ongoing Studies	133
7. REGULATIONS AND ADVISORIES	135
8. REFERENCES	139
9. GLOSSARY	155
APPENDICES	
A. MINIMAL RISK LEVEL (MRL) WORKSHEETS	A-1
B. USER'S GUIDE	B-1
C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS	C-1

LIST OF FIGURES

2-1	Levels of Significant Exposure to Hexamethylene Diisocyanate—Inhalation	21
2-2	Levels of Significant Exposure to Hexamethylene Diisocyanate—Oral	55
2-3	Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance	72
2-4	Existing Information on Health Effects of Hexamethylene Diisocyanate	91
5-1	Selected Isocyanate Structures	106
5-2	Partial Scheme for Hydrolysis Reactions of Hexamethylene Diisocyanate	113

LIST OF TABLES

2-1	Levels of Significant Exposure to Hexamethylene Diisocyanate—Inhalation	13
2-2	Levels of Significant Exposure to Hexamethylene Diisocyanate—Oral	54
2-3	Levels of Significant Exposure to Hexamethylene Diisocyanate—Dermal	59
2-4	Research in Progress Relevant to Hexamethylene Diisocyanate	97
3-1	Chemical Identity of Hexamethylene Diisocyanate	100
3-2	Chemical Identity of Hexamethylene Diisocyanate Prepolymers	101
3-3	Physical and Chemical Properties of Hexamethylene Diisocyanate	102
6-1	Analytical Methods for Determining Biological Degradation Products of Hexamethylene Diisocyanate	128
6-2	Analytical Methods for Determining Hexamethylene Diisocyanate in Environmental Samples	130
7-1	Regulations and Guidelines Applicable to Hexamethylene Diisocyanate	137