TOXICOLOGICAL PROFILE FOR
HYDRAZINES

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

September 1997
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.

David Satcher, M.D., Ph.D.
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)/AUTHOR(S):

Gangadhar Choudhary, Ph.D.
ATSDR, Division of Toxicology, Atlanta, GA

Hugh Ilansen, Ph.D.
ATSDR, Division of Toxicology, Atlanta, GA

Steve Donkin, Ph.D.
Sciences International, Inc., Alexandria, VA

Mr. Christopher Kirman
Life Systems, Inc., Cleveland, OH

THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Green Border Review. Green Border review assures the 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.
A peer review panel was assembled for hydrazines. The panel consisted of the following members:

1. Dr. Emerich Fiala, Chief, Division of Biochemical Pharmacology, American Health Foundation, Valhalla, NY

2. Dr. Bela Toth, Professor, University of Nebraska Medical Center, Omaha, NE

3. Dr. Raghunip Sharma, Fred C. Davison Professor, University of Georgia, College of Veterinary Medicine, Athens, GA

These experts collectively have knowledge of hydrazines’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 ARE HYDRAZINES? ......................................... 1
   1.2 WHAT HAPPENS TO HYDRAZINES WHEN THEY ENTER THE
       ENVIRONMENT? .................................................. 3
   1.3 HOW MIGHT I BE EXPOSED TO HYDRAZINES? .................. 4
   1.4 HOW CAN HYDRAZINES ENTER AND LEAVE MY BODY? ........ 5
   1.5 HOW CAN HYDRAZINES AFFECT MY HEALTH? ................... 5
   1.6 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN
       EXPOSED TO HYDRAZINES? .................................... 7
   1.7 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE
       TO PROTECT HUMAN HEALTH? ............................... 8
   1.8 WHERE CAN I GET MORE INFORMATION? ....................... 8

2. HEALTH EFFECTS ..................................................... 11
   2.1 INTRODUCTION ................................................... 11
   2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE .... 11
       2.2.1 Inhalation Exposure ....................................... 13
           2.2.1.1 Death ............................................... 13
           2.2.1.2 Systemic Effects ................................... 15
           2.2.1.3 Immunological and Lymphoreticular Effects ....... 33
           2.2.1.4 Neurological Effects ............................... 33
           2.2.1.5 Reproductive Effects ............................... 34
           2.2.1.6 Developmental Effects ............................. 34
           2.2.1.7 Genotoxic Effects ................................. 34
           2.2.1.8 Cancer ............................................. 35
       2.2.2 Oral Exposure .............................................. 36
           2.2.2.1 Death ............................................... 36
           2.2.2.2 Systemic Effects ................................... 36
           2.2.2.3 Immunological and Lymphoreticular Effects ....... 52
           2.2.2.4 Neurological Effects ............................... 52
           2.2.2.5 Reproductive Effects ............................... 53
           2.2.2.6 Developmental Effects ............................. 53
           2.2.2.7 Genotoxic Effects ................................. 54
           2.2.2.8 Cancer ............................................. 54
       2.2.3 Dermal Exposure ............................................ 56
           2.2.3.1 Death ............................................... 56
2.2.3.2 Systemic Effects ........................................... 56
2.2.3.3 Immunological and Lymphoreticular Effects ............ 60
2.2.3.4 Neurological Effects ...................................... 60
2.2.3.5 Reproductive Effects ...................................... 61
2.2.3.6 Developmental Effects .................................... 61
2.2.3.7 Genotoxic Effects ......................................... 61
2.2.3.8 Cancer ..................................................... 61

2.3 TOXICOKINETICS ................................................. 61
2.3.1 Absorption .................................................. 62
2.3.1.1 Inhalation Exposure ....................................... 62
2.3.1.2 Oral Exposure ............................................. 62
2.3.1.3 Dermal Exposure .......................................... 63
2.3.2 Distribution .................................................. 63
2.3.2.1 Inhalation Exposure ....................................... 63
2.3.2.2 Oral Exposure ............................................. 63
2.3.2.3 Dermal Exposure .......................................... 64
2.3.2.4 Other Routes of Exposure ................................ 64
2.3.3 Metabolism .................................................. 65
2.3.4 Excretion .................................................... 70
2.3.4.1 Inhalation Exposure ....................................... 70
2.3.4.2 Oral Exposure ............................................. 70
2.3.4.3 Dermal Exposure .......................................... 70
2.3.4.4 Other Exposure ........................................... 71

2.4 MECHANISMS OF ACTION ....................................... 72
2.5 RELEVANCE TO PUBLIC HEALTH ................................. 74
2.6 BIOMARKERS OF EXPOSURE AND EFFECT ....................... 90
2.6.1 Biomarkers Used to Identify or Quantify Exposure to Hydrazines ..................................................... 91
2.6.2 Biomarkers Used to Characterize Effects Caused by Hydrazines ..................................................... 92

2.7 INTERACTIONS WITH OTHER SUBSTANCES ..................... 93
2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE ............ 93
2.9 METHODS FOR REDUCING TOXIC EFFECTS ....................... 94
2.9.1 Reducing Peak Absorption Following Exposure ............. 94
2.9.2 Reducing Body Burden ....................................... 95
2.9.3 Interfering with the Mechanism of Action for Toxic Effects .................................................... 95

2.10 ADEQUACY OF THE DATABASE ................................ 97
2.10.1 Existing Information on Health Effects of Hydrazines .......... 97
2.10.2 Identification of Data Needs ................................ 98
2.10.3 On-going Studies ........................................... 106

3. CHEMICAL AND PHYSICAL INFORMATION .......................... 109
3.1 CHEMICAL IDENTITY ........................................... 109
3.2 PHYSICAL AND CHEMICAL PROPERTIES ......................... 109

4. PRODUCTION, IMPORT, USE, AND DISPOSAL ...................... 113
4.1 PRODUCTION .................................................. 113
4.2 IMPORT/EXPORT ............................................... 114
4.3 USE ......................................................... 114
4.4 DISPOSAL .................................................... 118
LIST OF FIGURES

2-1 Levels of Significant Exposure to Hydrazines - Inhalation .................. 25
2-2 Levels of Significant Exposure to Hydrazines - Oral .......................... 48
2-3 Existing Information on Health Effects of Hydrazines ........................ 99
5-1 Frequency of NPL Sites with Hydrazines Contamination .................... 120
LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-1</td>
<td>Levels of Significant Exposure to Hydrazines - Inhalation</td>
<td>16</td>
</tr>
<tr>
<td>2-2</td>
<td>Levels of Significant Exposure to Hydrazines - Oral</td>
<td>38</td>
</tr>
<tr>
<td>2-3</td>
<td>Levels of Significant Exposure to Hydrazines - Dermal</td>
<td>57</td>
</tr>
<tr>
<td>2-4</td>
<td>Genotoxicity of Hydrazines <em>In Vivo</em></td>
<td>85</td>
</tr>
<tr>
<td>2-5</td>
<td>Genotoxicity of Hydrazines <em>In Vitro</em></td>
<td>87</td>
</tr>
<tr>
<td>2-6</td>
<td>On-going Studies on the Health Effects of Hydrazines</td>
<td>107</td>
</tr>
<tr>
<td>3-1</td>
<td>Chemical Identity of Hydrazines</td>
<td>110</td>
</tr>
<tr>
<td>3-2</td>
<td>Physical and Chemical Properties of Hydrazines</td>
<td>111</td>
</tr>
<tr>
<td>4-1</td>
<td>Facilities That Manufacture or Process Hydrazine</td>
<td>115</td>
</tr>
<tr>
<td>4-2</td>
<td>Facilities That Manufacture or Process 1,1-Dimethylhydrazine</td>
<td>117</td>
</tr>
<tr>
<td>5-1</td>
<td>Releases to the Environment from Facilities That Manufacture or Process Hydrazine</td>
<td>122</td>
</tr>
<tr>
<td>5-2</td>
<td>Releases to the Environment from Facilities That Manufacture or Process</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1,1-Dimethylhydrazine</td>
<td>125</td>
</tr>
<tr>
<td>6-1</td>
<td>Analytical Methods for Determining Hydrazines <em>In Biological Materials</em></td>
<td>139</td>
</tr>
<tr>
<td>6-2</td>
<td>Analytical Methods for Determining Hydrazines <em>In Environmental Samples</em></td>
<td>141</td>
</tr>
<tr>
<td>7-1</td>
<td>Regulations and Guidelines Applicable to Hydrazines</td>
<td>148</td>
</tr>
<tr>
<td>7-2</td>
<td>Regulations and Guidelines Applicable to 1,1-Dimethylhydrazine</td>
<td>151</td>
</tr>
<tr>
<td>7-3</td>
<td>Regulations and Guidelines Applicable to 1,2-Dimethylhydrazine</td>
<td>153</td>
</tr>
</tbody>
</table>