

TOXICOLOGICAL PROFILE FOR
***n*-HEXANE**

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

July 1999

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

A draft Toxicological Profile for *n*-Hexane was released in September 1997. This edition supersedes any previously released draft or final profile.

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.



Jeffrey P. Koplan, M.D., M.P.H.
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). This public law directed ATSDR to prepare 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. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on November 17, 1997 (62 FR 61332). For prior versions of the list of substances, see *Federal Register* notices dated April 29, 1996 (61 FR 18744); April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); and February 28, 1994 (59 FR 9486). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

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: Health Effects: Specific health effects of a given hazardous compound are reported by *route of exposure*, by *type of health effect* (death, systemic, immunologic, reproductive), 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:

- Section 1.6** **How Can (Chemical X) Affect Children?**
- Section 1.7** **How Can Families Reduce the Risk of Exposure to (Chemical X)?**
- Section 2.6** **Children's Susceptibility**
- Section 5.6** **Exposures of Children**

Other Sections of Interest:

- Section 2.7** **Biomarkers of Exposure and Effect**
 - Section 2.10** **Methods for Reducing Toxic Effects**
-

ATSDR Information Center

Phone: 1-888-42-ATSDR
or 404-639-6357

E-mail: atsdric@cdc.gov

Fax: 404-639-6359

Internet: <http://www.atsdr.cdc.gov/>

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards*; *Skin Lesions and Environmental Exposures*; *Cholinesterase-Inhibiting Pesticide Toxicity*; and numerous chemical-specific case studies.

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, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

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.

Referrals

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@dgs.dgsys.com • AOEC Clinic Director: <http://occ-env-med.mc.duke.edu/oem/aoec.htm>.

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, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-228-6850 • FAX: 847-228-1856.

CONTRIBUTORS

CHEMICAL MANAGER/AUTHOR:

M. Olivia Harris, M.A.
ATSDR, Division of Toxicology, Atlanta, GA

James Corcoran, Ph.D.
Research Triangle Institute, Research Triangle Park, NC

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 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 *n*-hexane. The panel consisted of the following members:

1. Dr. Martin Alexander, Professor, Cornell University, 708 Bradfield Hall, Ithaca, NY 14853;
2. Dr. Carson C. Conaway, Research Scientist, American Health Foundation, 1 Dana Road, Valhalla, NY 10595;
3. Dr. Ryan Dupont, Professor, Department of Civil and Environmental Engineering, Utah State University, Logan, UT 84322; and
4. Dr. Robert Feldman, Professor and Chairman, Neurology Department, Boston University Medical School, 80 E. Concord St., Boston, MA 02118.

These experts collectively have knowledge of *n*-hexane'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
QUICK REFERENCE FOR HEALTH CARE PROVIDERS	vii
CONTRIBUTORS	ix
PEER REVIEW	xi
LIST OF FIGURES	xvii
LIST OF TABLES	xix
1. PUBLIC HEALTH STATEMENT	1
1.1 WHAT IS <i>n</i> -HEXANE?	1
1.2 WHAT HAPPENS TO <i>n</i> -HEXANE WHEN IT ENTERS THE ENVIRONMENT?	2
1.3 HOW MIGHT I BE EXPOSED TO <i>n</i> -HEXANE?	3
1.4 HOW CAN <i>n</i> -HEXANE ENTER AND LEAVE MY BODY?	4
1.5 HOW CAN <i>n</i> -HEXANE AFFECT MY HEALTH?	4
1.6 HOW CAN <i>n</i> -HEXANE AFFECT CHILDREN?	6
1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO <i>n</i> -HEXANE?	7
1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO <i>n</i> -HEXANE?	8
1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?	8
1.10 WHERE CAN I GET MORE INFORMATION?	9
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	14
2.2.1.3 Immunological and Lymphoreticular Effects	37
2.2.1.4 Neurological Effects	37
2.2.1.5 Reproductive Effects	52
2.2.1.6 Developmental Effects	54
2.2.1.7 Genotoxic Effects	57
2.2.1.8 Cancer	58
2.2.2 Oral Exposure	58
2.2.2.1 Death	58
2.2.2.2 Systemic Effects	59
2.2.2.3 Immunological and Lymphoreticular Effects	65
2.2.2.4 Neurological Effects	65
2.2.2.5 Reproductive Effects	66
2.2.2.6 Developmental Effects	67

2.2.2.7	Genotoxic Effects	68
2.2.2.8	Cancer	68
2.2.3	Dermal Exposure	68
2.2.3.1	Death	68
2.2.3.2	Systemic Effects	68
2.2.3.3	Immunological and Lymphoreticular Effects	70
2.2.3.4	Neurological Effects	70
2.2.3.5	Reproductive Effects	70
2.2.3.6	Developmental Effects	70
2.2.3.7	Genotoxic Effects	70
2.2.3.8	Cancer	71
2.3	TOXICOKINETICS	71
2.3.1	Absorption	71
2.3.1.1	Inhalation Exposure	71
2.3.1.2	Oral Exposure	72
2.3.1.3	Dermal Exposure	73
2.3.2	Distribution	73
2.3.2.1	Inhalation Exposure	74
2.3.2.2	Oral Exposure	75
2.3.2.3	Dermal Exposure	75
2.3.3	Metabolism	75
2.3.4	Elimination and Excretion	82
2.3.4.1	Inhalation Exposure	82
2.3.4.2	Oral Exposure	82
2.3.4.3	Dermal Exposure	82
2.3.5	Physiologically based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models	83
2.3.5.1	Summary of PBPK Models	84
2.3.5.2	<i>n</i> -Hexane PBPK Model Comparison	84
2.3.5.3	Discussion of Models	86
2.4	MECHANISMS OF ACTION	90
2.4.1	Pharmacokinetic Mechanisms	90
2.4.2	Mechanisms of Toxicity	94
2.4.3	Animal-to-Human Extrapolations	98
2.5	RELEVANCE TO PUBLIC HEALTH	98
2.6	CHILDREN'S SUSCEPTIBILITY	120
2.7	BIOMARKERS OF EXPOSURE AND EFFECT	123
2.7.1	Biomarkers Used to Identify or Quantify Exposure to <i>n</i> -Hexane	124
2.7.2	Biomarkers Used to Characterize Effects Caused by <i>n</i> -Hexane	126
2.8	INTERACTIONS WITH OTHER CHEMICALS	127
2.9	POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE	130
2.10	METHODS FOR REDUCING TOXIC EFFECTS	130
2.10.1	Reducing Peak Absorption Following Exposure	131
2.10.2	Reducing Body Burden	131
2.10.3	Interfering with the Mechanism of Action for Toxic Effects	131
2.11	ADEQUACY OF THE DATABASE	132
2.11.1	Existing Information on Health Effects of <i>n</i> -Hexane	132
2.11.2	Identification of Data Needs	132
2.11.4	Ongoing Studies	145

3. CHEMICAL AND PHYSICAL INFORMATION	147
3.1 CHEMICAL IDENTITY	147
3.2 PHYSICAL AND CHEMICAL PROPERTIES	147
4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL	151
4.1 PRODUCTION	151
4.2 IMPORT/EXPORT	153
4.3 USE	153
4.4 DISPOSAL	155
5. POTENTIAL FOR HUMAN EXPOSURE	157
5.1 OVERVIEW	157
5.2 RELEASES TO THE ENVIRONMENT	157
5.2.1 Air	163
5.2.2 Water	164
5.2.3 Soil	164
5.3 ENVIRONMENTAL FATE	165
5.3.1 Transport and Partitioning	165
5.3.2 Transformation and Degradation	166
5.3.2.1 Air	166
5.3.2.2 Water	166
5.3.2.3 Sediment and Soil	168
5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT	168
5.4.1 Air	170
5.4.2 Water	172
5.4.3 Sediment and Soil	172
5.4.4 Other Environmental Media	173
5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE	174
5.6 EXPOSURES OF CHILDREN	175
5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES	176
5.8 ADEQUACY OF THE DATABASE	177
5.8.1 Identification of Data Needs	177
5.8.2 Ongoing Studies	180
6. ANALYTICAL METHODS	181
6.1 BIOLOGICAL SAMPLES	181
6.2 ENVIRONMENTAL SAMPLES	184
6.3 ADEQUACY OF THE DATABASE	189
6.3.1 Identification of Data Needs	189
6.3.2 Ongoing Studies	191
7. REGULATIONS AND ADVISORIES	193
8. REFERENCES	197
9. GLOSSARY	221

APPENDICES

A.	ATSDR MINIMAL RISK LEVELS AND 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 <i>n</i> -Hexane—Inhalation	26
2-2	Levels of Significant Exposure to <i>n</i> -Hexane—Oral	63
2-3	Proposed Scheme for the Metabolism of <i>n</i> -Hexane	76
2-4	Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance	85
2-5	Perbellini PBPK Model	87
2-6	Fisher PBPK Model	90
2-7	Reaction of 2,5-Hexanedione with Protein	97
2-8	Existing Information on Health Effects of <i>n</i> -Hexane	133
5-1	Frequency of NPL Sites with <i>n</i> -Hexane Contamination	158
5-2	Degradation of <i>n</i> -Hexane in Air by Free Radicals	167
5-3	Aerobic Biodegradation of <i>n</i> -Hexane in Sediment and Soil	169

LIST OF TABLES

2-1	Levels of Significant Exposure to <i>n</i> -Hexane—Inhalation	15
2-2	Levels of Significant Exposure to <i>n</i> -Hexane—Oral	60
2-3	Levels of Significant Exposure to <i>n</i> -Hexane—Dermal	69
2-4	Parameters Used in the Perbellini PBPK Model for <i>n</i> -Hexane	88
2-5	Parameters Used in the Fisher PBPK Model for <i>n</i> -Hexane	91
2-6	<i>In Vivo</i> Genotoxicity of <i>n</i> -Hexane	115
2-7	<i>In Vitro</i> Genotoxicity of <i>n</i> -Hexane	116
3-1	Chemical Identity of <i>n</i> -Hexane	148
3-2	Physical and Chemical Properties of <i>n</i> -Hexane	149
4-1	Facilities That Manufacture or Process <i>n</i> -Hexane	152
5-1	Releases to the Environment from Facilities That Manufacture or Process <i>n</i> -Hexane	159
5-2	Demand Patterns for Major Petroleum Products (1992)	162
6-1	Analytical Methods for Determining <i>n</i> -Hexane in Biological Samples	182
6-2	Analytical Methods for Determining Biomarkers of <i>n</i> -Hexane in Biological Samples	185
6-3	Analytical Methods for Determining <i>n</i> -Hexane in Environmental Samples	186
7-1	Regulations and Guidelines Applicable to <i>n</i> -Hexane	196