TOXICOLOGICAL PROFILE FOR 3,3'-DICHLOROBENZIDINE

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

December 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

A Toxicological Profile for 3,3'-Dichlorobenzidine 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 Koplan Jeffrey P. Koplan, M.D., M.P.H.

Administrator

Agency for Toxic Substances and

Disease Registry

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: 1-800-447-1544 (to be replaced by 1-888-42-ATSDR in 1999)

or 404-639-6357 *Fax: 404-639-6359*

E-mail: atsdric@,cdc.nov *Internet:* http://atsdrl.atsdr.cdc.nov:8080

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-MedicalManagement 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 Centerfor 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 2020 1 • 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, 10 10 Vermont Avenue, NW, #5 13, Washington, DC 20005 1 Phone: 202-347-4976 1 FAX: 202- 347-4950 • e-mail: aoec@,dgs.dnsys.com • AOEC Clinic Director: http://occ-envmed.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(S)/AUTHORS(S):

Lori L. Miller, M.P.H. ATSDR Division of Toxicology, Atlanta, GA

Cassandra Smith-Simon, M.S. ATSDR, Division of Toxicology, Atlanta, GA

Fernando Llados, Ph.D. Research Triangle Institute, Research Triangle Park, NC

Steve Kueberuwa, M.S. 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 3,3'-dichlorobenzidine. The panel consisted of the following members :

- 1. Dr. Herbert Cornish, Private Consultant, 830 W. Clark Rd., Ypsilanti, MI 48 198;
- 2. Dr. Arthur Gregory, Private Consultant, 1 Gregory Lane, Luray, VA 22835;
- 3. Dr. Philip Leber, Private Consultant, 1344 Jefferson Ave., Akron, OH 443 13; and
- 4. Dr. Robert Rubin, Johns Hopkins School of Public Health, Environmental Health Sciences, Baltimore, MD 21205.

These experts collectively have knowledge of 3,3'-dichlorobenzidine'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(1)(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

FOREW	ORD	•••••	v
QUICK F	REFERENCE FOR	HEALTH CARE PROVIDERS	vii
CONTRI	BUTORS		ix
PEER RE	EVIEW		xi
LIST OF	FIGURES		xvii
LIST OF	TABLES		xix
1.1	WHAT IS 3,3'-DIO WHAT HAPPENS	TEMENT CHLOROBENZIDINE? S TO 3,3'-DICHLOROBENZIDINE WHEN IT ENTERS THE ?	1
1.3 1.4	HOW MIGHT I BY HOW CAN 3,3'-D	E EXPOSED TO 3,3'-DICHLOROBENZIDINE?	2
1.5 1.6 1.7	HOW CAN 3,3'-D HOW CAN FAMI	ICHLOROBENZIDINE AFFECT MY HEALTH? ICHLOROBENZIDINE AFFECT CHILDREN? LIES REDUCE THE RISK OF EXPOSURE TO	5
1.8	IS THERE A MED	SENZIDINE? DICAL TEST TO DETERMINE WHETHER I HAVE BEEN DICHLOROBENZIDINE?	
1.9	WHAT RECOMM HUMAN HEALTI	IENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PRO	OTECT 7
		ET MORE INFORMATION?	
2. HEAL 2.1 2.2	INTRODUCTION	HEALTH EFFECTS BY ROUTE OF EXPOSURE	11
		Death Systemic Effects Immunological and Lymphoreticular Effects Neurological Effects Reproductive Effects Developmental Effects Genotoxic Effects	12 13 14 14 14
	2.2.1.8	Cancer Osure Death Systemic Effects Immunological and Lymphoreticular Effects Neurological Effects	15 17 24 25
	2.2.2.5	Reproductive Effects	

3,3'-DICHLOROBENZIDINE xiv

		2.2.2.6	Developmental Effects	26
		2.2.2.7	Genotoxic Effects	
		2.2.2.8	Cancer	27
	2.2.3	Dermal E	xposure	
		2.2.3.1	Death	
		2.2.3.2	Systemic Effects	
		2.2.3.3	Immunological and Lymphoreticular Effects	
		2.2.3.4	Neurological Effects	
		2.2.3.5	Reproductive Effects	
		2.2.3.6	Developmental Effects	32
		2.2.3.7	Genotoxic Effects	32
		2.2.3.8	Cancer	32
2.3	TOXICO	OKINETIC	S	34
	2.3.1		on	
		2.3.1.1	Inhalation Exposure	
		2.3.1.2	Oral Exposure	
		2.3.1.3	Dermal Exposure	
	2.3.2	Distributi	on	
		2,3,2,1	Inhalation Exposure	
		2.3.2.2	Oral Exposure	
		2.3.2.3	Dermal Exposure	
	2.3.3		sm	
	2.3.4		on and Excretion	
	,,	2.3.4.1	Inhalation Exposure	
		2.3.4.2	Oral Exposure	
		2.3.4.3	Dermal Exposure	
	2.3.5		ically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models	
2.4			F ACTION	
	2.4.1		kinetic Mechanisms	
	2.4.2		ms of Toxicity	
	2.4.3		o-Human Extrapolations	
2.5			PUBLIC HEALTH	
2.6			SCEPTIBILITY	
2.7			F EXPOSURE AND EFFECT	
2.,			rs Used to Identify or Quantify Exposure to 3,3'-Dichlorobenzidine	
	2.7.2		rs Used to Characterize Effects Caused by 3,3'-Dichlorobenzidine	
2.8			WITH OTHER CHEMICALS	
2.9			THAT ARE UNUSUALLY SUSCEPTIBLE	
			REDUCING TOXIC EFFECTS	
2.10	2.10.1		Peak Absorption Following Exposure	
	2.10.1	_	Body Burden	
	2.10.2	Interferin	g with the Mechanism of Action for Toxic Effects	60
2 11			THE DATABASE	
2.11	2.11.1		Information on Health Effects of 3,3'-Dichlorobenzidine	
	2.11.1		tion of Data Needs	
	2.11.2	Ongoing :		75
	4.11.3		Studies	/ ۱

3,3'-DICHLOROBENZIDINE

3.	CHEN	лісаL а	ND PHYSICAL INFORMATION	. 77
	3.1	CHEMI	CAL IDENTITY	77
	3.2	PHYSIC	CAL AND CHEMICAL PROPERTIES	. 77
4.	PROL	DUCTION	N, IMPORT/EXPORT, USE, AND DISPOSAL	. 81
	4.1		CTION	
	4.2	IMPOR'	T/EXPORT	. 81
	4.3	USE		. 83
	4.4	DISPOS	AL	. 83
_	DOTE	י אורייו בי	COD III DAAN EXPORT DE	0.7
Э.	5.1		FOR HUMAN EXPOSURE	
	5.1		SES TO THE ENVIRONMENT	
	3.2	5.2.1	Air	
		5.2.1		
		5.2.2	Water	
	5.3		Soil	
	3.3	5.3.1		
		5.3.2	Transport and Partitioning	
		3.3.2	5.3.2.1 Air	
			5.3.2.2 Water	
			5.3.2.3 Sediment and Soil	
	5.4	LEVEL	S MONITORED OR ESTIMATED IN THE ENVIRONMENT	
	J. 4	5.4.1	Air	
		5.4.2	Water	
		5.4.3	Sediment and Soil	
		5.4.4	Other Environmental Media	
	5.5		AL POPULATION AND OCCUPATIONAL EXPOSURE	
	5.6		URES OF CHILDREN	
	5.7		ATIONS WITH POTENTIALLY HIGH EXPOSURES	
	5.8		JACY OF THE DATABASE	
	5.0	5.8.1	Identification of Data Needs	
		5.8.2	Ongoing Studies	
		3.0.2	Ongoing bradies	100
6.	ANA	LYTICAI	L METHODS	107
	6.1	BIOLO	GICAL SAMPLES	107
	6.2	ENVIRO	ONMENTAL SAMPLES	110
	6.3		JACY OF THE DATABASE	
		6.3.1	Identification of Data Needs	
		6.3.2	Ongoing Studies	
_	DEC:	TT 4 PT 63	VO AND ADAMAGDIES	
7.	REGU	JLATIO	NS AND ADVISORIES	115
8	REFE	RENCES	5	123
9	GLOS	SSARY		130

3,3'-DICHLOROBENZIDINE xvi

APPENDICES

A.	ATSDR MINIMAL RISK LEVEL 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 3,3'-Dichlorobenzidine—Oral	22
2-2	Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance	42
2-3	Existing Information on Health Effects of 3,3'-Dichlorobenzidine	68
5-1	Frequency of NPL Sites with 3,3'-Dichlorobenzidine Contamination	90

		7	
•			

LIST OF TABLES

2-1	Levels of Significant Exposure to 3,3'-Dichlorobenzidine—Oral	8
2-2	Levels of Significant Exposure to 3,3'-Dichlorobenzidine—Dermal	1
2-3	Genotoxicity of 3,3'-Dichlorobenzidine In Vivo	3
2-4	Genotoxicity of 3,3'-Dichlorobenzidine In Vitro	4
3-1	Chemical Identity of 3,3'-Dichlorobenzidine	8
3-2	Physical and Chemical Properties of 3,3'-Dichlorobenzidine	9
4-1	Facilities That Manufacture or Process 3,3'-Dichlorobenzidine	2
5-1	Releases to the Environment from Facilities That Manufacture or Process 3,3'-Dichlorobenzidine	8
6-1	Analytical Methods for Determining 3,3'-Dichlorobenzidine and Metabolites in Biological Samples	8
6-2	Analytical Methods for Determining 3,3'-Dichlorobenzidine in Environmental Samples	1
7-1	Regulations and Guidelines Applicable to 3,3'-Dichlorobenzidine	8

		 ~	
· ·			
		·	