

**INTERACTION PROFILE FOR:  
PERSISTENT CHEMICALS FOUND IN FISH  
(CHLORINATED DIBENZO-*p*-DIOXINS,  
HEXACHLOROBENZENE, *p,p'*-DDE, METHYLMERCURY, and  
POLYCHLORINATED BIPHENYLS)**

**U.S. Department of Health and Human Services  
Public Health Service  
Agency for Toxic Substances and Disease Registry**

May 2004



## **ACKNOWLEDGMENT**

The Agency for Toxic Substances and Disease Registry (ATSDR) wishes to thank the U.S. Environmental Protection Agency (EPA) for its support in the production of this Interaction Profile.



## PREFACE

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) mandates that the Agency for Toxic Substances and Disease Registry (ATSDR) shall assess whether adequate information on health effects is available for the priority hazardous substances. Where such information is not available or under development, ATSDR shall, in cooperation with the National Toxicology Program, initiate a program of research to determine these health effects. The Act further directs that where feasible, ATSDR shall develop methods to determine the health effects of substances in combination with other substances with which they are commonly found.

To carry out the legislative mandate, ATSDR's Division of Toxicology (DT) has developed and coordinated a mixtures program that includes trend analysis to identify the mixtures most often found in environmental media, *in vivo* and *in vitro* toxicological testing of mixtures, quantitative modeling of joint action, and methodological development for assessment of joint toxicity. These efforts are interrelated. For example, the trend analysis suggests mixtures of concern for which assessments need to be conducted. If data are not available, further research is recommended. The data thus generated often contribute to the design, calibration or validation of the methodology. This pragmatic approach allows identification of pertinent issues and their resolution as well as enhancement of our understanding of the mechanisms of joint toxic action. All the information obtained is thus used to enhance existing or developing methods to assess the joint toxic action of environmental chemicals. Over a number of years, ATSDR scientists in collaboration with mixtures risk assessors and laboratory scientists have developed approaches for the assessment of the joint toxic action of chemical mixtures. As part of the mixtures program a series of documents, Interaction Profiles, are being developed for certain priority mixtures that are of special concern to ATSDR.

The purpose of an Interaction Profile is to evaluate data on the toxicology of the "whole" priority mixture (if available) and on the joint toxic action of the chemicals in the mixture in order to recommend approaches for the exposure-based assessment of the potential hazard to public health. Joint toxic action includes additivity and interactions. A weight-of-evidence approach is commonly used in these documents to evaluate the influence of interactions in the overall toxicity of the mixture. The weight-of-evidence evaluations are qualitative in nature, although ATSDR recognizes that observations of toxicological interactions depend greatly on exposure doses and that some interactions appear to have thresholds. Thus, the interactions are evaluated in a qualitative manner to provide a sense of what

influence the interactions may have when they do occur.

The assessments in the document are not intended to trigger a regulatory action, but rather to serve as screening tools to assess the potential for joint toxic action of chemicals in the mixture of concern.

Literature searches for this Interaction Profile were conducted in 1999–2000, with limited updating in 2001. This final version of the document, released in 2004, includes changes made in response to public comments. However, no new literature searches were done.

## CONTRIBUTORS

### CHEMICAL MANAGER(S)/AUTHORS:

Hana Pohl, M.D., Ph.D.  
ATSDR, Division of Toxicology, Atlanta, GA

Peter McClure, Ph.D., DABT  
Syracuse Research Corporation, Syracuse, NY

Marc Odin, M.S., DABT  
Syracuse Research Corporation, Syracuse, NY

Joan Colman, Ph.D.  
Syracuse Research Corporation, Syracuse, NY





## PEER REVIEW

The following expert panel was assembled to review this document on May 30–31, 2000.

**Vladimir Bencko, M.D., Ph.D.**

Institute of Hygiene and Epidemiology  
Charles University of Prague  
Studnickova 7  
CZ 128 00 Prague 2  
Czech Republic

**Ingvar Eide, Ph.D.**

Statoil Research Centre  
N-7005 Trondheim, Norway

**Henry Gardner, Ph.D.**

3407 Rolling Green Drive  
Ft. Collins, CO 80525

**Peter Grevatt, Ph.D.**

U.S. Environmental Protection Agency  
Office of Solid Waste & Emergency Response  
Washington, DC

**John Groten, Ph.D.**

Department of Explanatory Toxicology  
TNO Nutrition and Food Research Institute  
Zeist, Netherlands

**Richard Hertzberg, Ph.D.**

Waste Management Division  
U.S. Environmental Protection Agency  
Atlanta, GA

**Kannan Krishnan, Ph.D.**

Human Toxicology Research Group  
University of Montreal  
Montreal, PQ, Canada

**Scott Masten, Ph.D.**

Environmental Toxicology Program  
National Institute of Environmental  
Health Sciences  
Research Triangle Park, NC

**Mark McClanahan, Ph.D.**

Centers for Disease Control and Prevention  
National Center for Environmental Health  
Health Studies Branch  
Atlanta, GA

**Harihara Mehendale, Ph.D.**

Department of Toxicology  
College of Pharmacy  
University of Louisiana  
Monroe, LA

**Joel Pounds, Ph.D.**

Department of Molecular Biosciences  
Pacific Northwest National Laboratory  
Richland, WA

**Jane Ellen Simmons, Ph.D.**

U.S. Environmental Protection Agency  
Research Triangle Park, NC

**Madhusudan Soni, Ph.D.**

Burdock and Associates, Inc.  
Vero Beach, FL

**Els van Vliet, Ph.D.**

Health Council of the Netherlands  
2500 BB Den Haag  
The Netherlands

**Raymond Yang, Ph.D.**

Center for Environmental Toxicology  
and Technology  
Colorado State University  
Fort Collins, CO

**Technical Reviewer:**

**Patrick Durkin, Ph.D.**

Syracuse Environmental Research Associates  
Fayetteville, NY

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.

## SUMMARY

Chlorinated dibenzo-*p*-dioxins (CDDs), hexachlorobenzene, *p,p'*-DDE (the predominant metabolite of *p,p'*-DDT), methylmercury, and polychlorinated biphenyls (PCBs) occur with high frequency in water, sediment, and fish from the North American Great Lakes and occur, to varying degrees, in other dietary components including fish from other parts of the world (e.g., the Baltic Sea), human milk, dairy products, and meat. The purposes of this profile are (1) to evaluate data (if available) on health hazards, and their dose-response relationships, from oral exposure to this five-component mixture, (2) to evaluate data on the joint toxic actions of components of this mixture, and (3) to make recommendations for exposure-based assessments of the potential impact of joint toxic action of the mixture on public health.

No studies were located that examined health effects in humans or animals exposed to mixtures exclusively containing CDDs, hexachlorobenzene, *p,p'*-DDE, methylmercury, and PCBs, and no physiologically based pharmacokinetic/pharmacodynamic models (PBPK/PD) for this mixture have been developed.

Studies of possible associations between health effects and frequent consumption of Great Lakes and Baltic Sea fish containing the components of this mixture (and other persistent chemicals) were reviewed to determine the degree to which available data may identify pertinent health hazards. Frequent dietary consumption of contaminated Great Lakes fish by child-bearing-aged women has been associated in two prospective epidemiological studies with neurological deficits in their children, but other studies provide no consistent evidence that consumption of Great Lakes fish presents obvious risks for impaired reproduction, impaired immune capabilities, or physical birth defects. Low birth weight was reported in children of mothers who frequently ate Baltic Sea fish, and impaired immunological competence was reported in seals fed Baltic Sea fish, but the data do not clearly demonstrate dose-response relationships.

The weight of evidence for an association between Great Lakes fish consumption and effects on neurological development is greater than that for associations between frequent consumption of contaminated Baltic Sea fish and impaired immune capabilities or low birth weight, but none of the weights are sufficient to establish causal relationships between fish consumption and adverse health effects in humans. PCBs have been proposed as toxicants involved in the possible association between maternal fish consumption and altered childhood neurological development based on statistically significant associations between specific PCB levels in maternal fluids and neurological deficits in

children. Other hypotheses, however, have been proposed, including the possible involvement of other persistent chemicals in contaminated fish or synergistic interactions between PCBs and other neurotoxicants in fish.

The concentrations of persistent chemicals in fish are likely to be highly dependent on species and location, and a minimum risk level (MRL) for fish consumption based on responses in one population may not be applicable to another population. To facilitate exposure-based assessments of possible health effects associated with oral exposures to mixtures of CDDs, hexachlorobenzene, *p,p'*-DDE, methylmercury, and PCBs, available data on the joint toxic action of mixtures of these chemicals were reviewed, and the weights of evidence were assessed concerning the mode of joint toxic action of pairs of the five components. In this analysis, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD) was taken as a representative of CDDs in accordance with the Toxicity Equivalence Factor (TEF) approach to assessing hazards from mixtures of CDDs. PCB mixtures were assessed as an entity in accordance with ATSDR's PCB MRLs which are derived for exposure to complex mixtures of PCBs.

The weight-of-evidence analysis indicates that only a limited amount of evidence is available to support the possible existence of greater-than-additive or less-than-additive joint actions of a few pairs of the components: (1) hexachlorobenzene potentiation of 2,3,7,8-TCDD reduction of body and thymus weights; (2) PCB antagonism of TCDD immunotoxicity and TCDD developmental toxicity; and (3) synergism between PCBs and methylmercury in disrupting regulation of brain levels of dopamine that may influence neurological function and development. Confidence in these assessments of deviations from additivity was low. For a few of the remaining pairs, additive joint action at shared targets of toxicity is supported by data, and for the rest, data were not available to characterize the modes of joint toxic action.

Component-based approaches that assume additive joint toxic action are recommended for exposure-based screening assessments of possible noncancer or cancer health hazards from oral exposure to mixtures of CDDs, hexachlorobenzene, *p,p'*-DDE, methylmercury, and PCBs, because there are no direct data available to characterize health hazards (and dose-response relationships) from the five-component mixture. The weight-of-evidence analysis indicated that data are inadequate to characterize the modes of joint action of the components, but the additivity assumption appears to be suitable in the interest of protecting public health since the components have several shared toxicity targets.

In making the recommendation, it is acknowledged that results from two epidemiological studies identify

altered neurological development as a possible health hazard from frequent consumption of fish contaminated with biopersistent chemicals. However, the results do not establish a causal relationship and are not directly useful for exposure-based assessments of hazards that are specific to a community or an exposure-scenario. The recommended approaches allow assessment of the possibility of altered neurological development as well as other potential health hazards including cancer.

A target-organ toxicity dose (TTDs) modification of the Hazard Index approach is recommended for conducting exposure-based screening assessments of noncancer health hazards. TTDs for several toxicity targets have been derived for each of the components including TTDs for hepatic, endocrine, immunological, neurological, reproductive, and developmental. For a screening assessment of cancer risks from joint toxic action of the mixture, a similar component-based approach is recommended that involves multiplication of intakes of the components by EPA cancer slope factors and summation of the resultant risk estimates. If the screening assessment indicates a potential hazard, further evaluation is needed, using biomedical judgment and community-specific health outcome data, and taking into account community health concerns.



## CONTENTS

ACKNOWLEDGMENT .....	iii
PREFACE .....	v
CONTRIBUTORS .....	vii
PEER REVIEW .....	ix
SUMMARY .....	xi
CONTENTS .....	xv
LIST OF TABLES .....	xvii
LIST OF ACRONYMS, ABBREVIATIONS, AND SYMBOLS .....	xix
1. Introduction .....	1
2. Joint Toxic Action Data for the Mixture of Concern and Component Mixtures .....	7
2.1 Mixture of Concern .....	7
2.1.1 Studies of Health Effects Associated with Consumption of Great Lakes Fish ...	7
2.1.2 Studies of Health Effects Associated with Consumption of Baltic Sea Fish ...	25
2.2 Component Mixtures .....	30
2.2.1 2,3,7,8-TCDD and Hexachlorobenzene .....	30
2.2.2 2,3,7,8-TCDD and <i>p,p'</i> -DDE .....	35
2.2.3 Hexachlorobenzene and <i>p,p'</i> -DDE .....	39
2.2.4 2,3,7,8-TCDD and Methylmercury .....	40
2.2.5 Hexachlorobenzene and Methylmercury .....	42
2.2.6 <i>p,p'</i> -DDE and Methylmercury .....	46
2.2.7 PCBs and 2,3,7,8-TCDD .....	46
2.2.8 PCBs and Hexachlorobenzene .....	67
2.2.9 PCBs and <i>p,p'</i> -DDE .....	67
2.2.10 PCBs and Methylmercury .....	68
2.3 Relevance of the Joint Toxic Action Data and Approaches to Public Health .....	78
3. Recommendation for Exposure-Based Assessment of Joint Toxic Action of the Mixture .....	113
4. Conclusions .....	119
5. List of References .....	121
Appendix A: Background Information for Chlorinated Dibenzo- <i>p</i> -Dioxins (CDDs) .....	149
A.1 Toxicokinetics .....	149
A.2 Health Effects .....	150
A.3 Mechanisms of Action .....	151
A.4 Health Guidelines .....	153
A.5 Derivation of Target-Organ Toxicity Dose (TTD) Values .....	155

Appendix B: Background Information for Hexachlorobenzene .....	161
B.1 Toxicokinetics .....	161
B.2 Health Effects .....	161
B.3 Mechanisms of Action .....	162
B.4 Health Guidelines .....	164
B.5 Derivation of Target-Organ Toxicity Dose (TTD) Values .....	165
Appendix C: Background Information for <i>p,p'</i> -DDE .....	169
C.1 Toxicokinetics .....	169
C.2 Health Effects .....	170
C.3 Mechanisms of Action .....	171
C.4 Health Guidelines .....	172
C.5 Derivation of Target-Organ Toxicity Dose (TTD) Values .....	172
Appendix D: Background Information for Methylmercury .....	177
D.1 Toxicokinetics .....	177
D.2 Health Effects .....	177
D.3 Mechanisms of Action .....	179
D.4 Health Guidelines .....	180
D.5 Derivation of Target-Organ Toxicity Dose (TTD) Values .....	181
Appendix E: Background Information for PCBs .....	185
E.1 Toxicokinetics .....	185
E.2 Health Effects .....	188
E.3 Mechanisms of Action .....	191
E.4 Health Guidelines .....	210
E.5 Derivation of Target-Organ Toxicity Dose (TTD) Values .....	211
Appendix F: Chemical Structures of Mixture Components .....	215



## LIST OF TABLES

Table 1.	Health Effects Observed in Humans or Animals after Oral Exposure to Chemicals of Concern . . . . .	3
Table 2.	Mean and Range of Persistent Chemicals in Blood of Consumers of Great Lakes Fish . . . . .	8
Table 3.	Daily Intake of Major Contaminants in Female F1 Rats Exposed to Diets Containing 0, 5, or 20% (w/w) Lyophilized Lake Ontario Salmon Flesh . . . . .	20
Table 4.	Median Levels of Persistent Chemicals in High Consumers and Nonconsumers of Baltic Sea Fatty Fish (Source: Svensson et al. 1994 . . . . .	26
Table 5.	Summary of Available Data on the Influence of 2,3,7,8-TCDD on Toxicity/Carcinogenicity of Hexachlorobenzene and the Influence of Hexachlorobenzene on Toxicity/Carcinogenicity of 2,3,7,8-TCDD by Sequential Exposure . . . . .	34
Table 6.	Summary of Available Data on the Influence of 2,3,7,8-TCDD on Toxicity/Carcinogenicity of <i>p,p'</i> -DDE and the Influence of <i>p,p'</i> -DDE on Toxicity/Carcinogenicity of 2,3,7,8-TCDD by Simultaneous Exposure . . . . .	38
Table 7.	Summary of Available Data on the Influence of Hexachlorobenzene on Toxicity/Carcinogenicity of Mercuric Chloride and the Influence of Mercuric Chloride on Toxicity/Carcinogenicity of Hexachlorobenzene by Simultaneous Exposure . . . . .	45
Table 8.	Summary of Available Data on the Influence of PCBs on Toxicity/Carcinogenicity of 2,3,7,8-TCDD . . . . .	54
Table 9.	Summary of Available Data on the Influence of 2,3,7,8-TCDD on Toxicity/Carcinogenicity of PCBs . . . . .	62
Table 10.	Summary of Available Data on the Influence of PCBs on Toxicity/Carcinogenicity of Methylmercury . . . . .	75
Table 11.	Summary of Available Data on the Influence of Methylmercury on Toxicity/Carcinogenicity of PCBs . . . . .	76
Table 12.	Health Effects Forming the Basis of ATSDR Oral MRLs for Chemicals of Concern . . . . .	78
Table 13.	Binary Weight-of-Evidence Scheme for the Assessment of Chemical Interactions . . . . .	84
Table 14.	Effect of <b>2,3,7,8-TCDD</b> on <b>Hexachlorobenzene</b> . . . . .	85
Table 15.	Effect of <b>Hexachlorobenzene</b> on <b>2,3,7,8-TCDD</b> . . . . .	86
Table 16.	Effect of <b>2,3,7,8-TCDD</b> on <i>p,p'</i> -DDE . . . . .	88
Table 17.	Effect of <i>p,p'</i> -DDE on <b>2,3,7,8-TCDD</b> . . . . .	89
Table 18.	Effect of <i>p,p'</i> -DDE on <b>Hexachlorobenzene</b> . . . . .	90
Table 19.	Effect of <b>Hexachlorobenzene</b> on <i>p,p'</i> -DDE . . . . .	91
Table 20.	Effect of <b>2,3,7,8-TCDD</b> on <b>Methylmercury</b> . . . . .	92
Table 21.	Effect of <b>Methylmercury</b> on <b>2,3,7,8-TCDD</b> . . . . .	94
Table 22.	Effect of <b>Hexachlorobenzene</b> on <b>Methylmercury</b> . . . . .	95
Table 23.	Effect of <b>Methylmercury</b> on <b>Hexachlorobenzene</b> . . . . .	96
Table 24.	Effect of <i>p,p'</i> -DDE on <b>Methylmercury</b> . . . . .	98
Table 25.	Effect of <b>Methylmercury</b> on <i>p,p'</i> -DDE . . . . .	99
Table 26.	Effect of <b>PCBs</b> on <b>2,3,7,8-TCDD</b> . . . . .	100
Table 27.	Effect of <b>2,3,7,8-TCDD</b> on <b>PCBs</b> . . . . .	102
Table 28.	Effect of <b>PCBs</b> on <b>Hexachlorobenzene</b> . . . . .	104
Table 29.	Effect of <b>Hexachlorobenzene</b> on <b>PCBs</b> . . . . .	105
Table 30.	Effect of <b>PCBs</b> on <i>p,p'</i> -DDE . . . . .	106
Table 31.	Effect of <i>p,p'</i> -DDE on <b>PCBs</b> . . . . .	107
Table 32.	Effect of <b>PCBs</b> on <b>Methylmercury</b> . . . . .	108
Table 33.	Effect of <b>Methylmercury</b> on <b>PCBs</b> . . . . .	110

Table 34. Matrix of BINWOE Determinations for Repeated Simultaneous Oral Exposure to Chemicals of Concern ..... 112

Table 35. MRLs and TTDs for Repeated Oral Exposure to Chemicals of Concern ..... 115

## LIST OF ACRONYMS, ABBREVIATIONS, AND SYMBOLS

Ah	arylhydrocarbon	RfC	Reference Concentration
AHH	arylhydrocarbon hydroxylase	RfD	Reference Dose
ATSDR	Agency for Toxic Substances and Disease Registry	SD	standard deviation
		SRBC	sheep red blood cells
BINWOE	binary weight-of-evidence	T4	thyroxin
BROD	benzoxylresorufin-O-deethylase	TT3	total triiodothyronine
CDD	chlorinated dibenzo- <i>p</i> -dioxin	TT4	total thyroxine and free thyroxine
CDF	chlorinated dibenzofuran	TAO	triacytyleandomycin
CI	confidence interval	TCDD	2,3,7,8-tetrachlorodibenzo- <i>p</i> -dioxin
CYP	cytochrome P450	TCDF	tetrachlorodibenzofuran
		TCHQ	tetrachlorohydroquinone
DNA	deoxyribonucleic acid	TEF	Toxic Equivalency Factor
DTH	delayed-type hypersensitivity	TEQ	toxic equivalents
		TGF	transforming growth factor
EGF	epidermal growth factor	TSH	thyroid stimulating hormone
EPA	Environmental Protection Agency	TTD	target-organ toxicity dose
EROD	ethoxyresorufin O-deethylase		
		UDP	uridine-5'-diphosphate
HCB	hexachlorobenzene	UF	uncertainty factor
		U.S.	United States
IARC	International Agency Research on Cancer	WOE	weight-of-evidence
IRIS	Integrated Risk Information System		
		>	greater than
kg	kilogram	≥	greater than or equal to
		=	equal to
LOAEL	lowest-observed-adverse-effect level	<	less than
LSE	Levels of Significant Exposure	≤	less than or equal to
mg	milligram		
MRL	Minimal Risk Level		
mRNA	messenger ribonucleic acid		
NOAEL	no-observed-adverse-effect level		
OR	odds ratio		
PBB	polybrominated biphenyl		
PBPK	physiologically based pharmacokinetic		
PCB	polychlorinated biphenyl		
ppb	parts per billion		
ppm	parts per million		
ppt	parts per trillion		