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
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Agency for Toxic Substances and Disease Registry

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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.

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PEER REVIEW

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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 minium 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, methyl-mercury, 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

LIST OF TABLES

LIST OF ACRONYMS, ABBREVIATIONS, AND SYMBOLS

Ah	arylhydrocarbon
AHH	arylhydrocarbon hydroxylase
ATSDR	Agency for Toxic Substances and Disease Registry
BINWOE	binary weight-of-evidence
BROD	benzoxylresorufin-O-deethylase
CDD	chlorinated dibenzo-*p*-dioxin
CDF	chlorinated dibenzofuran
CI	confidence interval
CYP	cytochrome P450
DNA	deoxyribonucleic acid
DTH	delayed-type hypersensitivity
EGF	epidermal growth factor
EPA	Environmental Protection Agency
EROD	ethoxyresorufin O-deethylase
HCB	hexachlorobenzene
IARC	International Agency Research on Cancer
IRIS	Integrated Risk Information System
kg	kilogram
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
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 pharamacokinetic
PCB	polycholrinated biphenyl
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
RfC	Reference Concentration
RfD	Reference Dose
SD	standard deviation
SRBC	sheep red blood cells
T4	thyroxin
TT3	total triiodothyronine
TT4	total thyroxine and free thyroxine
TAO	triacetyloleandomycin
TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin
TCDF	tetrachlorodibenzofuran
TCHQ	tetrachlorohydroquinone
TEF	Toxic Equivalency Factor
TEQ	toxic equivalents
TGF	transforming growth factor
TSH	thyroid stimulating hormone
TTD	target-organ toxicity dose
UDP	uridine-5'-diphosphate
UF	uncertainty factor
U.S.	United States
WOE	weight-of-evidence
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to