INTERACTION PROFILE FOR: PERSISTENT CHEMICALS FOUND IN BREAST MILK (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, following peer review. 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

A peer review panel was assembled for this profile. The panel consisted of the following members:

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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

Breast-feeding offers the developing infant the benefits of balanced nutrition and passive immunization, but the detection of persistent, environmental chemicals in human breast milk samples from various regions of the world has led to concerns that these chemicals may have detrimental effects on the health and/or development of children. Chlorinated dibenzo-*p*-dioxins (CDDs), hexachlorobenzene, *p,p'*-DDE, methylmercury, and polychlorinated biphenyls (PCBs) were selected as an important subset of persistent chemicals detected in breast milk for the purposes of reviewing data on their joint toxic actions following oral exposure.

Epidemiological studies in Michigan, North Carolina, New York, the Netherlands, and the Faroe Islands found statistically significant associations between increasing concentrations of particular persistent chemicals found in maternal fluid samples (i.e., PCBs, CDDs, *p,p'*-DDE, or mercury in cord serum or breast milk) and deficits in motor and cognitive functions in children. The Netherlands and Faroe Islands studies also demonstrated beneficial effects of breast feeding on neurological development. A study of formula-fed monkeys exposed to a PCB mixture from birth to 20 weeks found evidence that lactational exposure to persistent chemicals may contribute to neurodevelopmental deficits. These studies identify mild neurodevelopmental deficits as a possible health hazard, but the results are suggestive that observed deficits may have been associated with gestational rather than lactational exposure to persistent chemicals. These studies do not establish causal relationships between exposure to persistent chemicals in breast milk and neurological deficits. Furthermore, they are not useful for assessment of health hazards specific to a community or scenarios involving exposures to mixtures of CDDs, hexachlorobenzene, *p,p'*-DDE, methylmercury, and PCBs.

To facilitate exposure-based assessments of possible health effects associated with oral exposures to mixtures of CDDs, hexachlorobenzene, *p,p*'-DDE, methylmercury, and PCBs in environmental media, food, and/or breast milk, available data on the joint toxic action of mixtures of these breast milk contaminants were reviewed, and the weights of evidence were assessed concerning the mode of joint toxic action of pairs of the five chemicals. Only a limited amount of evidence is available on the existence of greater-than-additive or less-than-additive interactions between a few pairs of the chemicals of concern: (1) hexachlorobenzene potentiation of tetrachlorodibenzo-*p*-dioxin (TCDD) reduction of body and thymus weights (a greater-than-additive interaction); (2) PCB antagonism of TCDD immunotoxicity (less-than-additive interaction); (3) PCB antagonism of TCDD developmental toxicity (less-than-additive

interaction); and (4) synergism between PCBs and methylmercury in disrupting regulation of brain levels of dopamine that may influence neurological function and development (greater-than-additive interaction). Weight-of-evidence analyses of these data, however, indicate that scientific evidence for these interactions is limited and is inadequate to characterize the possible modes of joint action on these toxicity targets. For the remaining pairs, additive joint action at shared targets of toxicity is either supported by data (for a few pairs) or is recommended as a public health protective assumption due to lack of interaction data, conflicting interaction data, and/or lack of mechanistic understanding to reliably project potential non-additive interactions. Therefore, it is recommended that additivity be assumed as a public health protective measure in exposure-based assessments of health hazards from exposure to mixtures of these components.

A target-organ toxicity dose (TTD) modification of the hazard index approach is recommended for carrying out exposure-based screening assessments of possible health effects from oral exposure to mixtures of the chemicals. TTDs for the individual chemical components are derived, and application of the approach is described. There are several reasons supporting this recommendation to use a component-based approach. There are no direct data available to characterize health hazards (and dose-response relationships) from mixtures containing all five components. Physiologically-based pharmacokinetic/ pharmacodynamic (PBPK/PD) models have not yet been developed that would predict pertinent target doses of the components under scenarios involving exposure to mixtures of all five components. Finally, available information on toxic actions of the individual components indicates that joint actions of CDDs, hexachlorobenzene, *p,p'*-DDE, methylmercury, and PCBs on several toxicity targets are plausible, including nervous system development, immune functions, reproductive organ development, and cancer. If the screening assessment indicates a potential hazard to public health, 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