INTERACTION PROFILE FOR:

CHLORINATED DIBENZO-*p*-DIOXINS, POLYBROMINATED DIPHENYL ETHERS, AND PHTHALATES

U.S. Department of Health and Human Services
Public Health Service
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 these legislative mandates, ATSDR's Division of Toxicology and Human Health Sciences (DTHHS) 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.

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHORS:

Hana Pohl, M.D., Ph.D.
ATSDR, Division of Toxicology and Human Health Sciences (DTHHS), Atlanta, GA

Michele Anatra-Cordone, Ph.D.
Peter McClure, Ph.D., DABT
Fernando Llados, Ph.D.
Lisa Ingerman, Ph.D., DABT
Kimberly Zaccaria, Ph.D., DABT
SRC, Inc., Syracuse, NY

PEER REVIEW

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

- Dale B. Hattis, PhD, Research Professor, George Perkins Marsh Institute, Clark University, Worcester, MA 01610-1477

- Raymond S. H. Yang, Ph.D., Professor Emeritus, Center for Environmental Toxicology and Technology, Colorado State University, Fort Collins, CO 80523-1680

- Harihara M. Mehendale, Ph.D., Professor of Toxicology, Kitty DeGree Endowed Chair, Department of Toxicology, College of Pharmacy, University of Louisiana at Monroe, Monroe, LA 71209-0497

All reviewers were selected in conformity with the conditions for peer review specified in CERCLA Section 104(I)(13).

Scientists from 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 interaction profile. 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

The purpose of this profile is to investigate the possible joint actions of chlorinated dibenzo-*p*-dioxins (CDDs), polybrominated diphenyl ethers (PBDEs), and phthalates (also known as phthalate esters) on endocrine, developmental, and neurobehavioral endpoints in humans. Chemicals from all three of these classes are found in human blood, adipose tissue, and breast milk. In assessing the available information on possible interactions between these chemicals, this profile concludes with recommendations for conducting screening-level assessments of public health concerns from join exposures to mixtures of these chemical classes.

CDDs, PBDEs, and phthalates are ubiquitous in the environment. CDDs originate through incomplete combustion processes such as incineration. PBDEs had previous wide use as flame retardants in plastics and textiles. Phthalates are commonly used to make plastics soft and pliable. Oral exposure through food is believed to be the predominant mode of human exposure to these chemicals. CDDs and PBDEs are bio-persistent by virtue of their slow degradation and elimination from the body. Of the PBDEs, the lower brominated forms (primarily tetra- and pentabrominated diphenyl ethers [BDEs]) are the primary forms found in human tissues and fluids. Deca-brominated BDEs (decaBDE) are not readily absorbed into the body. Phthalates are rapidly metabolized and eliminated from the body, but as exposure to phthalates is considered continuous, phthalates and their metabolites are continuously cycling through the body.

Observations in humans and laboratory animals following exposure to each of these chemicals alone raise concern about the nature and magnitude of possible effects associated with concurrent exposure. Exposure to chemicals in each of these classes alone has been associated with disruption of thyroid function in humans and/or animals, and with adverse effects on fetal development, especially fetal endocrine disruption in animals. Animal studies indicate that 2,3,7,8-tetrachloro dibenzo-*p*-dioxin (TCDD) and lower-brominated PBDEs each disrupt neurobehavioral development, and that 2,3,7,8-TCDD, di-(2-ethylhexyl)phthalate (DEHP), and di-*n*-butyl phthalate (DBP) each disrupt male reproductive structure and function. Animals studies also demonstrate that 2,3,7,8-TCDD and phthalates (DEHP and DBP) disrupt both male and female reproductive development. Both TCDD and lower-brominated PBDEs each disrupt thyroid function in gestationally exposed animals.

Of the CDDs, 2,3,7,8-TCDD is widely believed to be the most toxic, and is considered representative of the class. There is a large body of evidence that supports a pivotal role for the aryl hydrocarbon receptor (AhR) in the mechanism of TCDD-induced toxicity. Due to structural similarities to 2,3,7,8-TCDD, PBDEs have been investigated for dioxin-like activity; however, a group of expert scientists assembled under the aegis of the World Health Organization (WHO) in 2005 concluded that PBDEs do not meet commonly accepted criteria to be considered "dioxin-like" with regard to their toxicity. Recent *in vitro* investigations from a variety of mammalian cell lines have demonstrated that PBDEs have negligible ability to bind to the AhR and are incapable of activating it to induce the cascade of events (*the AhR signal transduction pathway*) leading to induction of enzymes that are the hallmark of dioxin-like activity. However, companion *in vitro* studies designed to investigate the joint action of PBDEs and 2,3,7,8-TCDD on various stages of the AhR signal transduction pathway indicate that the lower PBDE congeners (such as those found in human blood, adipose tissue, and breast milk) antagonize TCDD-induced activation of the AhR signal transduction pathway, but the molecular nature of this antagonism is currently unclear. Given that these observations were made on isolated cells and at concentrations orders of magnitude higher than concentrations of PBDEs found in human body fluids, the environmental relevance of this apparent antagonism is uncertain. There is no evidence to suggest that phthalates interact with the AhR or express dioxin-like toxicity. In fact, the fetal and developmental toxicity of DEHP is likely mediated through the peroxisome proliferator-activated receptor (PPAR).

There are no studies in the literature that address the possible effects of concurrent whole-body exposure of humans or animals to a mixture of CDDs, PBDEs, and phthalates. The available mechanistic understanding of toxicity caused by each class of chemicals alone is not sufficient to reliably predict the direction or magnitude of any interaction between all three chemicals or between any two pairs of chemicals, except for PBDEs and TCDD. Whereas *in vitro* mechanistic evidence indicates that PBDEs antagonize TCDD activation of the AhR signal transduction pathway, there are no studies that address possible joint action of PBDEs and TCDD on any toxicity endpoint. Furthermore, the mechanistic evidence suggesting possible antagonism is offset by thyroid toxicity data for TCDD alone and PBDEs alone that suggest the possibility of joint additivity on the basis of a common non-AhR-mediated mode of action (i.e., inhibition of thyroxine [T_4] binding by hydroxylated intermediates). There are no physiologically based toxicokinetic (PBTK) models that can be used to predict interactions between any pairs or sets of three chemicals from these three chemical classes.

Given the co-occurrence of CDDs, PBDEs, and phthalates in humans and the commonality of certain classes of effects, ATSDR recommends that the default assumption of joint additivity be employed to assess mixtures of these chemicals using a modified hazard index (HI) approach. To facilitate the use of this approach, target toxicity doses (TTDs) have been derived for thyroid disruption in adults, developmental endocrine disruption (either thyroid or reproductive hormone disruption), and neurodevelopmental toxicity for 2,3,7,8-TCDD, lower-brominated PBDEs, decaBDE, DEHP, di-*n*-octyl phthalate (DNOP), and DBP, where toxicity data were indicative of the effect of concern and were suitable for quantification of effect levels. No TTDs were derived for diethyl phthalate (DEP) or decaBDE due to the lack of effects of concern.

Exposure to CDDs should be determined as the sum of all congeners converted by toxic equivalence to TCDD. Exposure to PBDEs should be evaluated separately for the sum of the lower-brominated congeners and decaBDE mixtures. Exposure to DEHP, DNOP, and DBP should each be determined. The HI for each relevant endpoint (endocrine, neurobehavioral, and developmental) can be derived by summing the ratio of exposure to TTD for each chemical in the mixture that is associated with the effect of concern. HIs in excess of 1 indicate the potential for the mixture to be of greater concern than any individual component, usually resulting in the need for further study or limiting exposure through remedial action or education of the community regarding related issues.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AGD	anogenital distance
Ah	aryl hydrocarbon
AhR	aryl hydrocarbon receptor
ATSDR	Agency for Toxic Substances and Disease Registry
BDE	Brominated diphenyl ether
BINWOE	binary weight-of-evidence
BTEX	benzene, toluene, ethylbenzene, and xylene
CDD	chlorinated dibenzo-*p*-dioxin
CDF	chlorinated dibenzofuran
DBP	di-*n*-butyl phthalate
DEP	Diethyl phthalate
DEHP	di-(2-ethylhexyl) phthalate
DNA	deoxyribonucleic acid
DNOP	Di-*n*-octyl phthalate
DRE	dioxin-responsive element
EGF	epidermal growth factor
EPA	Environmental Protection Agency
EROD	ethoxyresorufin O-deethylase
GD	gestation day
HI	Hazard Index
HQ	Hazard Quotient
IARC	International Agency Research on Cancer
IRIS	Integrated Risk Information System
kg	kilogram
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
MBP	monobutylphthalate
MEHP	monoethylhexylphthalate
mg	milligram
MRL	Minimal Risk Level
mRNA	messenger ribonucleic acid
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
PBDD	polybrominated dibenzo-*p*-dioxin
PBDE	polybrominated diphenyl ether
PBDF	polybrominated dibenzofuran
PBPD	physiologically based pharmacodynamic
PBTK	physiologically based toxicokinetic
PCB	polychlorinated biphenyl
PCDD	polychlorinated dibenzo-*p*-dioxin
PCDF	polychlorinated dibenzofurans
PCR	polymerase chain reaction
PND	postnatal day
POD	point of departure
PPAR	peroxisome proliferator-activated receptor
ppb	parts per billion
ppm	parts per million

ppt	parts per trillion
PVC	polyvinyl chloride
RfC	reference concentration
RfD	reference dose
T_3	triiodothyronine
T_4	thyroxine
TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin
TEF	Toxic Equivalence Factor
TEQ	toxic equivalents
TGF	transforming growth factor
THR	thyroid receptor
TSH	thyroid stimulating hormone
TTD	target-organ toxicity dose
TTR	transthyretin
UDP	uridine-5'-diphosphate
U.S.	United States
WHO	World Health Organization
XRE	xenobiotic-responsive element
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to