1. Introduction

The primary purpose of this Interaction Profile for chlorinated dibenzo-*p*-dioxins (CDDs), hexachlorobenzene, *p,p'*-DDE, methylmercury, and polychlorinated biphenyls (PCBs) is to evaluate data on the toxicology of the "whole" mixture and the joint toxic action of the chemicals in the mixture in order to recommend approaches for assessing the potential hazard of this mixture to public health. To this end, the profile evaluates the whole mixture data (if available), focusing on the identification of health effects of concern, adequacy of the data as the basis for a mixture MRL, and adequacy and relevance of physiologically-based pharmacokinetic/pharmacodynamic models for the mixture. The profile also evaluates the evidence for joint toxic action—additivity and interactions—among the mixture components. A weight-of-evidence approach is commonly used in these profiles 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 profile provides environmental health scientists with ATSDR DT's recommended approaches for the incorporation of the whole mixture data or the concerns for additivity and interactions into an assessment of the potential hazard of this mixture to public health. These approaches can then be used with specific exposure data from hazardous waste sites or other exposure scenarios.

The Great Lakes basin comprises one-fifth of the total fresh water on the earth's surface; it is a valuable national resource for both the United States and Canada. For over 200 years, the Great Lakes basin has been used as a resource for industry, agriculture, shipping, and recreation. Researchers have identified almost 400 contaminants in the water, sediment, and biota in quantifiable amounts. Based on criteria such as persistence in the environment, bioconcentration, bioaccumulation, and toxicity, the International Joint Commission Water Quality Board identified 11of these substances as critical Great Lakes pollutants. They are polychlorinated biphenyls (PCBs), mirex, hexachlorobenzene, dieldrin, 1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane (*p,p'*-DDT) and its metabolite 1,1-dichloro-2,2-bis (*p*-chlorophenyl)ethylene (*p,p'*-DDE), 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD), 2,3,7,8-tetrachlorodibenzofuran (2,3,7,8-TCDF), benzo[a]pyrene, alkylated lead, toxaphene, and mercury (GLWQB 1985).

In 1990, Congress amended the Federal Water Pollution Control Act and mandated the Environmental Protection Agency (EPA), in consultation with the Agency for Toxic Substances and Disease Registry (ATSDR) and the Great Lakes states, to submit a research report on the adverse human health effects related to water pollutants in the Great Lakes. Since then, ATSDR awarded several research grants and established cooperative agreements to coordinate basin-wide human health effects research. The primary interests of ATSDR's Great Lakes Research Program are to document and characterize the exposure, identify populations at higher risk, identify association between the consumption of contaminated Great Lakes fish and short and long-term harmful health effects, identify the most sensitive endpoints, establish registries and surveillance cohorts, and identify ways to prevent or mitigate exposure and resulting health effects.

This Interaction Profile for CDDs, hexachlorobenzene, *p,p'*-DDE, methylmercury, and PCBs serves as a support document for the ATSDR's Great Lakes Research Program and represents a first step in evaluating possible joint toxic actions of the International Joint Commission Water Quality Board's 11 critical Great Lakes pollutants. These five chemicals were selected because (1) each occurs with high frequency in Great Lakes water, sediment, and biota; (2) each has been associated with a wide array of overlapping toxic effects leading to concerns that they may jointly act on several similar targets of toxicity (see Table 1); (3) neurological development (associated with pre- or post-natal oral exposure) is a critical toxicity target for each (Table 1); and (4) two prospective studies (Jacobson and Jacobson 1996; Stewart et al. 2000b) reported that deficits in neurological development of children were associated with frequent maternal consumption of contaminated Great Lakes fish and increasing levels of PCBs in maternal body fluids (see Section 2.1).

The profile begins with a review of studies of possible health effects associated with the consumption of fish from the North American Great Lakes or fish from the Baltic Sea (Section 2.1). The results of the fish consumption studies are reviewed to evaluate their utility in identifying health problems in human populations that may be associated with exposure to fish likely to have been contaminated with CDDs, hexachlorobenzene, *p,p'*DDE, methylmercury, PCBs, and other chemicals. A companion Interaction Profile on Persistent Chemicals Found in Breast Milk (ATSDR 2001b) similarly reviews studies on whether or not health problems may be associated with exposure to mixtures of persistent chemicals in human breast milk.

Table 1. Health Effects Observed in Humans or Animals after Oral Exposure to Chemicals of Concern. See Appendices A, B, C, D, and E for More Details

Effects	Chemicals of concern[a]				
	2,3,7,8-TCDD	Hexachloro-benzene	*p,p'*-DDE	Methyl-mercury	PCBs
Wasting syndrome	x	x			x
Kidney damage				x	
Liver damage	**X**	**X**[b]	x[b]		x
Immunosuppression	x[b]	x	x	x	x[b]
Thyroid hormone disruption	**X**	**X**			x
Female reproductive organ disruption	x	**X**[b]		x	x
Male reproductive organ disruption	**X**		x	x	x
Neurological impairment	**X**	**X**	**X**	**X**	x
Altered neurological development (pre- and/or post-natal)	x[b]	**X**[b]	x[c]	**X**[b]	**X**[b]
Altered female reproductive organ development	x				x
Altered male reproductive organ development	x		x[b]		x
Other developmental effects (malformations or fetotoxicity)	x	**X**	x	x	x
Cancer[d]	x	x	x	x	x

[a]Upper case and bolded **X** indicates that effects have been observed in humans. Lower case and non-bolded x indicates that effects have been observed only in animals.
[b]Indicates that these are the most sensitive noncancer health effects from oral exposure (i.e., they occur at lower dose levels than other noncancer effects).
[c]No data are available for *p,p'*-DDE effects on this endpoint, but altered neurobehavior was observed in adult rats following exposure to single oral doses of 0.5 mg *p,p'*-DDT/kg on postnatal day 10 (Eriksson et al. 1990, 1992).
[d]Carcinogenic responses have been demonstrated in animals exposed to each of the chemicals. EPA has derived oral slope factors for humans exposed to 2,3,7,8-TCDD, hexachlorobenzene, *p,p'*-DDE, and PCBs based on tumor responses in animals (see Appendices A, B, C, and E). EPA did not derive a slope factor for humans exposed to methylmercury based on evidence that effects on the nervous system and its development would occur at exposure levels much lower than those necessary to produce cancer (see Appendix D).

In preparing the profile, no studies were located regarding the toxicology of the whole 5-component mixture, but some studies are available that examined joint toxic actions of binary mixtures of the components (Section 2.2). Following the evaluation of data on the joint toxic actions (e.g., additivity, greater-than-additive interactions, or less-than-additive interactions) of the components, the relevance of the data to public health concerns associated with exposures to the mixture is discussed (in Section 2.3), and recommendations are made for approaches to exposure-based assessments of joint toxic action of the mixture (in Section 3).

Each component of the mixture is a persistent chemical that bioaccumulates in higher food-chain organisms including humans, and has been demonstrated to produce a wide range of health effects in humans and animals (see Appendices A–E and Table 1). The ranges of health effects produced by these chemicals overlap, leading to concern that, following regular consumption of mixtures of the chemicals in food such as contaminated fish, all five may jointly act to produce altered neurological development, suppression of immune competence, or cancer, and three (CDDs, *p,p'*-DDE, and PCBs) may jointly act to alter development of reproductive organs (Table 1). In addition to being found in fish from the Great Lakes, these chemicals are found, 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 (ATSDR, 1996, 1998, 1999a, 2001b). The profile focuses on data relevant to concurrent oral exposure scenarios that are of most interest to public health concerns for these chemicals.

For the purposes of this profile, 2,3,7,8-TCDD, the best studied CDD, is taken to be representative of other CDDs based on assumptions that CDDs display joint additive toxic actions that are mediated by a common initial mechanism involving binding to the arylhydrocarbon (Ah) receptor (Appendix A; ATSDR 1998), and that interactions between 2,3,7,8-TCDD and other non-CDD chemicals are representative of interactions between other CDDs and other non-CDD chemicals. Although no data were located to directly support the second assumption, there are several observations supporting the first assumption, including: (1) acute or subchronic exposure of rats to individual CDDs produce a similar spectrum of toxic effects (Kociba et al. 1978; Viluksela et al. 1998a, 1998b); (2) acute oral exposure of rats to a mixture of four CDDs with chlorination in the 2,3,7,8-positions produced decreased body weight and deaths in rats at dose levels equivalent to dose levels of the individual components producing similar effects (Stahl et al. 1992); and (3) 13-week oral exposure of rats to a mixture of four CDDs produced a spectrum of effects (e.g., decreased body weight, increased mortality, induction of hepatic ethoxy-

resorufin *O*-deethylase [EROD]) similar to effects produced by the individual CDDs at equipotent dose levels (Viluksela et al. 1998a, 1998b).

Like CDDs, oral exposure of animals to PCB mixtures elicits a broad array of effects, including a body weight wasting syndrome involving thymic atrophy, induction of hepatic Phase I (CYP oxygenases) and Phase II (e.g., UDP-glucuronyltransferases) enzymes, liver damage and enlargement, porphyria, kidney damage, immunosuppression, thyroid hormone disruption, disruption of female and male reproductive organs, altered development of female and male reproductive organs, neurological impairment, altered neurological development (associated with pre- or post-natal exposure), and cancer (Appendix E; ATSDR 2000). In contrast to CDDs, Ah-receptor mediation may account for only a subset of the wide array of PCB-induced effects. There is increasing evidence from animal studies that several PCB-induced effects may involve multiple mechanisms (ATSDR 2000; Fischer et al. 1998; Hansen 1998; Li and Hansen 1997; Safe 1994). PCB-induced effects that appear to predominately involve Ah-receptor dependent mechanisms include: induction of hepatic activities of CYP1A1, 1A2, and 1B1 (Connor et al. 1995; Hansen 1998; Safe 1994); body weight wasting and thymic atrophy from acute exposure (Hori et al. 1997; Safe 1994); and porphyria and porphyria cutanea tardea (Smith et al. 1990b). PCB-induced effects involving Ah-receptor independent mechanisms include: induction of hepatic activities of CYP2B1, 2B2, 2A1, and 3A (Connor et al. 1995; Hansen 1998); neurological and neurodevelopmental effects involving changes in brain dopamine levels (Seegal 1996b, 1998) and/or changes in brain cell intracellular calcium homeostasis and related signal transduction processes (Tilson and Kodavanti 1997; Tilson et al. 1998; Wong and Pessah 1996, 1997; Wong et al. 1997); and tissue injury related to activation of neutrophils (Brown and Gamey 1995; Gamey et al. 1993; Tithof et al. 1995).

The profile does not focus on a representative PCB congener (or congeners) or subclasses of PCBs to discuss interactions with the other components of the subject mixture, because it is likely that: (1) multiple mechanisms are involved in PCB-induced health effects; (2) different PCB congeners may produce effects by different and multiple mechanisms, and (3) humans are exposed to complex mixtures of PCB congeners with differing biological activities. PCB mixtures are discussed as the entity of concern in parallel with ATSDR's PCB MRLs, which are derived for exposure to PCB mixtures (see Appendix E).