1. Introduction

The primary purpose of this Interaction Profile for chlorinated dibenzo-*p*-dioxins (CDDs), polybrominated diphenyl ethers (PBDEs), and phthalates 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 (i.e., endocrine disruption, neurobehavioral effects, and developmental toxicity), adequacy of the data as the basis for a mixture minimal risk level (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 the Agency for Toxic Substances and Disease Registry (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 Division of Toxicology and Human Health Sciences (DTHHS) 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.

Interactions between CDDs, PBDEs, and phthalates are of interest to ATSDR because these chemicals are ubiquitous in the environment, are detected in human biological samples from the general population, and cause similar types of certain adverse health effects in humans or animals. The national data suggest that PBDE and phthalate exposures continue to increase while dioxin toxic equivalents (TEQ) exposures have decreased. Nevertheless, there are site-specific opportunities for high dioxin TEQ exposures. These elevated exposure cases now occur while the nationwide baseline exposures to PBDE and phthalates are higher than in the past. Such situations underscore the need to consider the interaction of these chemicals. This profile focuses on neurobehavioral effects, developmental toxicity, and endocrine disruption, as these are important toxic effects observed in common among these chemical classes.

CDDs are widely present in air, water, and soil primarily due to combustion processes, especially waste incineration (ATSDR 1998). PBDEs previously had widespread use as flame retardants (ATSDR 2017).

Phthalates are most commonly used to make plastics flexible, and as such, are present in food storage containers, automobiles, household goods, and medical tubing (ATSDR 1995, 1997, 2001, 2002). Although all of these chemicals have been detected in air samples, the main source of human exposure to these chemicals is likely to be dietary. CDDs and PBDEs (especially the lower brominated diphenyl ethers [BDEs]) are persistent in fatty animal tissues. Phthalate esters are rapidly metabolized and eliminated, but due to their ubiquitous presence in the environment, they are continuously present in body fluids and tissues.

CDDs, PBDEs, and phthalates are lipophilic and have been detected in human biological samples. ATSDR (1998, 2012) reported that the average concentration of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) in the adipose tissue of the U.S. population is 5.8 pg/g lipid (Orban et al. 1994). For all CDD congeners, excluding dioxin-like polychlorinated biphenyls (PCBs), the national average was approximately 28 pg TEQ/g lipid (see Section 2.2.1.1 for a brief discussion of TEQ). A background exposure level of approximately 0.7 pg 2,3,7,8-TCDD/kg/day (assuming a 70-kg reference body weight) has been estimated for the general population in the United States (Travis and Hattemer-Frey 1987 as cited in ATSDR 1998). If other CDD and chlorinated dibenzofuran (CDF) congeners are included, the background exposure level increases to approximately 18–192.3 pg TEQ/day (0.26–2.75 pg/kg/day using a 70-kg reference body weight) (Schecter et al. 1994b as cited in ATSDR 1998). Schecter et al. (2005) reported that CDD levels in blood serum have decreased since 1973. The concentration of CDD reported for a pooled blood serum sample drawn from U.S. citizens in 2003 was 449 ppt lipid (pg TEQ/g). This value is lower than previously detected in the pooled serum sample from 1973 (3,979 ppt lipid). A large number of studies in the general population in the United States, Canada, Germany, and France during 1972–1999 show a trend of substantial (almost 10-fold) decreases in human TCDD-only body burden over that time period (Aylward and Hays 2002). Considering the long half-life of TCDD, a one-compartment pharmacokinetic model estimated that the decrease in intake must have been more than 95%.

Schecter et al. (2005) reported that PBDE levels in blood samples taken from U.S. citizens have risen significantly since 1973, when they were essentially non-detectable (detection limits=0.03–1 ppb lipid), to a level in 2003 that was the highest detected anywhere in the world (61.84 ppb lipid or ng/g, total PBDE in pooled whole blood sample). Schecter et al. (2005) reported the highest concentrations in pooled whole-blood samples for BDE-47 (44.2 ng/g lipid), BDE-99 (12.8 ng/g lipid), and BDE-153 (11.2 ng/g lipid); other BDE congeners detected in humans include BDE-209, BDE-183, BDE-154, BDE-138, BDE-100, BDE-85, BDE-77, BDE-28, and BDE-17. BDE-209 is decaBDE, and is the predominant

congener in formerly manufactured and used commercial decaBDE mixtures of flame retardants. Lipid-adjusted serum levels collected in NHANES 2003–2004 also reported the highest geometric means for BDE-47 (20.5 ng/g lipid), with a second highest geometric mean for BDE-153 (5.7 ng/g lipid); BDE-28, BDE-99, BDE-47, BDE-100, and BDE-153 were in ≥60% of participants (Sjödin 2008). PBDEs are also detected in human milk samples at similarly high concentrations, with reported concentrations for total PBDEs ranging from 19.948 to 67.8 ng/g lipid in U.S. and Canadian samples collected between 2002 and 2012 (Guo et al. 2015; Ryan and Rawn 2014; Schecter et al. 2005). In earlier studies, the tetra- and pentabrominated PBDEs have been the predominant congeners detected in breast milk samples, but more recent studies that assayed for a wider range of PBDE congeners found evidence for distribution of hepta, octa, or decaBDEs into cord serum and breast milk (ATSDR 2017). As reported by ATSDR (2017), the composition of BDE detected in human biological samples is determined by environmental and metabolic factors, and does not reflect the composition of any commercial PBDE-containing flame retardant mixture.

Ambient human exposure to the predominant phthalate ester used in the manufacture of plastics, di-2-(ethylhexyl)-phthalate (DEHP), has been estimated to be on the order of 0.21–21 mg/day (3–30 μg/kg body weight/day for a 70-kg adult) (Appendix C: David 2000; Doull et al. 1999; Huber et al. 1996; Kohn et al. 2000; Tickner et al. 2001). DEHP was present in human adipose tissues sampled from accident victims at a concentration of 0.3–1.0 ppm (Appendix C: Mes et al. 1974) and in 48% of the adipose tissue specimens from cadavers autopsied in 1982 as part of the Human Adipose Tissue Survey from the National Human Monitoring Program (Appendix C: EPA 1989b). A significantly higher intake of DEHP was calculated for children (n=254) than for adults (n=85) in the general population (Koch et al. 2006). Exposures at the 95th percentile (25 and 21 μg/kg/day) exceeded the reference dose (RfD) of 20 μg/kg/day.

CDDs, PBDEs, and phthalates, have been associated with adverse effects on endocrine systems, particularly the thyroid and reproductive organs. There is also evidence that PBDEs and CDDs adversely affect neurobehavioral development. Consequently, this profile focuses specifically on possible joint actions related to endocrine disruption, neurobehavioral effects, and developmental toxicity. With regard to developmental toxicity, there is a degree of overlap between the chemicals of concern and disruption of endocrine systems (thyroid and reproductive) following gestational exposures. Appendices to this profile provide background information on health effects and toxicokinetics of CDDs (Appendix A), PBDEs (Appendix B), and phthalates (Appendix C).

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 aryl hydrocarbon receptor (AhR) and a subsequent AhR signal transduction pathway involving changes in expression of certain genes (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 (Appendix A: 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 (Appendix A: 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 ethoxyresorufin O-deethylase [EROD]) similar to effects produced by the individual CDDs at equipotent dose levels (Appendix A: Viluksela et al. 1998a, 1998b).

PBDEs have 209 different molecular configurations (also known as congeners). Certain PBDEs are considered environmentally relevant due to their use in flame retardant mixtures (since the 1970s) and appearance in environmental media and biological samples. Three commercial PBDE mixtures have been produced: decabromodiphenyl ether (decaBDE), octabromodiphenyl ether (octaBDE), and pentabromodiphenyl ether (pentaBDE). DecaBDE has accounted for more than 80% of PBDE usage. The composition of commercial decaBDE is ≥97% of the pure congener (BDE-209) with the remainder mainly nonaBDE. Commercial octaBDE is a mixture of congeners ranging from nona- to hexaBDE, and mixtures of pentaBDE are comprised of tetra-, penta-, and hexaBDE congeners (ATSDR 2004a). People are environmentally exposed to lower PBDEs (e.g., tetra- and pentabrominated congeners) due to differential partitioning and transformation of the individual congeners in the environment, including transformation in animals that are consumed. PBDEs are likely to be retained in the body for long periods of time (years) because they are lipophilic and some congeners are not readily metabolized. Individual environmentally relevant PBDEs that have been studied include BDE-47, BDE-77, BDE-99, BDE-100, BDE-119, BDE-126, BDE-153, BDE-154, and BDE-183 (see ATSDR 2017 for details). Some studies have focused on commercially available mixtures of PBDEs, including octaBDE, pentaBDE, and decaBDE. The European Union banned use of pentaBDE and octaBDE as of August 2004. PentaBDE and octaBDE mixtures were voluntarily withdrawn from the U.S. marketplace by their manufacturers at the end of 2004 and decaBDE was not to be manufactured or imported into the United States after

December 31, 2013 (EPA 2013). Consistent with ATSDR's toxicological profile for PBDEs, this interaction profile considers the effects associated with exposure to the lower PBDEs (predominantly tetra- and pentaBDEs) separately from effects associated with decaBDE. The distinction between decaBDE and "lower" PBDEs is made for two primary reasons. First, lower PBDEs and decaBDE are handled differently in the body, resulting in lower bioavailability of decaBDE. Lower PBDEs preferentially distribute to body fat, while decaBDE tends to distribute to more highly perfused tissue (and to a lesser extent, body fat). However, both lower PBDEs and decaBDE have been detected in human breast milk samples, and have been shown to transfer from dams to fetuses and neonates in animal studies following exposure during gestational and nursing periods. Second, studies in laboratory animals generally indicate that toxicity associated with decaBDE exposure is less pronounced than for lower PBDEs (see Appendix B for more details).

This profile considers the phthalate esters previously assessed in toxicological profiles published by ATSDR, including DEHP, diethyl phthalate (DEP), di-*n*-butyl phthalate (DBP), and di-*n*-octyl phthalate (DNOP). These phthalates have been considered separately due to some important differences in the types and severity of adverse effects each has been demonstrated to cause in mammalian systems. Of the phthalates considered by ATSDR, DEHP and DBP have been associated with endocrine (thyroid and reproductive), fetotoxic, and developmental endocrine effects (reproductive) in animals or humans, and are thus the most relevant phthalates considered in this interaction profile. DNOP has been associated with thyroid changes, but not with adverse developmental effects. DEP has not been associated with the neurodevelopmental, developmental endocrine, or thyroid effects of concern in this profile and is thus given less weight of consideration.

The above restrictions with regard to the representative chemicals in each class considered for this profile did not apply to the searches for interaction data in the available literature database. The search strategy included all possible chemicals in each of the three classes (CDDs, PBDEs, and phthalates) in order to ensure that the available studies addressing possible interactions between members of each class would be identified. To further enhance the possibility of locating available literature relevant to interactions between the chemical classes of interest, searches were not restricted with regard to toxic endpoint, even though this profile is focused on endocrine disruption, developmental toxicity, and neurobehavioral effects.