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Scoping and Problem Formulation for the Toxicological Review of Polychlorinated Biphenyls (PCBs): Effects Other Than Cancer

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PREFACE

EPA's mission is to protect human health and the environment. EPA's IRIS program contributes to this mission by developing information on how chemicals in the environment can affect human health. Scientific input and peer review of IRIS assessments ensure that national efforts to reduce human health risks can be based on the best available scientific information. The IRIS program engages the public in this work so that all parts of society – individuals, communities, businesses, the scientific community, and government agencies – have access to authoritative scientific information and can effectively participate in discussions involving risks to human health.

In this document the IRIS program is releasing information on the scope of its upcoming assessment of polychlorinated biphenyls and is inviting the public to participate in the problem formulation by identifying the key issues and scientific information available for the assessment. The National Research Council's *Review of EPA's IRIS Process* (NRC, 2014) discussed scoping and problem formulation as these activities apply specifically to IRIS assessments. IRIS assessments critically review the scientific literature to identify potential human health hazards of chemicals in the environment and to characterize exposure-response relationships. Accordingly, the NRC discussed scoping and problem formulation for IRIS assessments as covering the scientific questions that pertain only to hazard identification and dose-response assessment. Exposure assessment and risk characterization (the other components of a risk assessment) are outside the scope of IRIS assessments, as are the legal, political, social, economic, and technical aspects of risk management.

During scoping, the IRIS program seeks input from EPA's program and regional offices to identify the information and level of detail needed to inform their decisions. This includes the exposure pathways and exposed groups that the assessment will consider. The NRC's *Review of EPA's IRIS Process* characterized this practice as consistent with its risk-assessment guidance in *Science and Decisions* (NRC, 2009).

During problem formulation, the IRIS program seeks input from the scientific community and the general public as it frames the scientific questions that will be the focus of systematic reviews in the upcoming assessment. The NRC's *Review of EPA's IRIS Process* identified the major challenge of problem formulation as determining which adverse outcomes are of concern. The NRC suggested a three-step process for conducting problem formulation for IRIS assessments: (1) a literature survey to identify the possible health outcomes associated with the chemical, (2) construction of a table to guide the formulation of questions that will be the subject of systematic reviews, and (3) examination of this table to determine which health outcomes warrant a systematic review. In addition to identifying health outcomes for systematic review, the problem formulation section discusses key issues that the assessment will address.

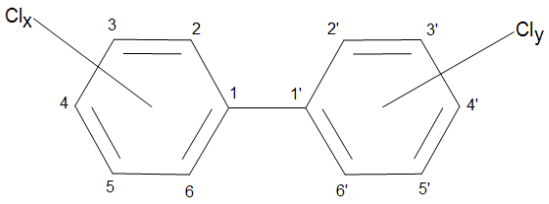
This document begins with brief background information on PCBs, continues with the scope of the upcoming assessment and the three problem-formulation steps that the NRC suggested, and concludes with a preliminary discussion of key issues. Portions of this document were adapted from the *Toxicological Profile for Polychlorinated Biphenyls* (PCBs) (ATSDR, 2011, 2000) under a Memorandum of Understanding with the Agency for Toxic Substances and Disease Registry (ATSDR) entered into as part of a collaborative effort in the development of human health toxicological assessments for the purposes of making more efficient use of available resources and to share scientific information.

Early public involvement should increase the scientific quality and transparency of IRIS assessments. Accordingly, the IRIS program is releasing this document in anticipation of a public science meeting focused on identifying the key issues and scientific information available for this upcoming assessment. The IRIS program encourages the scientific community and the general public to contribute to this problem formulation.

BACKGROUND

1.1. Production and Use

Polychlorinated biphenyls (PCBs) are a class of synthetic compounds characterized by a biphenyl structure with chlorine substitutions at up to ten positions, as shown in Figure 1-1. There are a total of 209 possible PCB congeners, based on the various combinations of the numbers and positions of the chlorine substitutions on the biphenyl molecule. PCBs were manufactured and marketed in the United States between about 1930 and 1977 under the trade name Aroclor (e.g., Aroclors 1016, 1242, 1248, 1254, 1260). It has been estimated that more than 600 million kg of PCBs were commercially produced in the United States, and that worldwide production of PCBs was approximately twice that quantity (HSDB, 2011). PCBs were used in many industrial applications because of their electrical insulating properties, chemical stability, and relative inflammability. They were widely used in capacitors, transformers, and other electrical equipment, and as coolants and lubricants. Other applications included use in plasticizers, surface coatings, inks, adhesives, flame retardants, pesticide extenders, paints, carbonless duplicating paper, and sealants and caulking compounds (ATSDR, 2000). EPA issued final regulations banning the manufacture of PCBs and phasing out most PCB uses in 1979 under the Toxic Substances Control Act (TSCA) (40 CFR 761) due to evidence that they persist and accumulate in the environment, and can cause toxic effects (http://www2.epa.gov/aboutepa/epa-bans-pcb-manufacture-phases-out-uses). Despite the ban on manufacturing, PCBs continue to be present in environmental media (e.g., air, soil, sediment, food) and are redistributed from one environmental compartment to another (ATSDR, 2000). They can also be released through the continued use and disposal of PCB-containing products. PCB-containing building materials such as window glazes, fluorescent light ballasts, ceiling tile coatings, caulk, paints and floor finishes are potential sources of PCBs in the indoor environment (Lehmann et al., 2015).



X = 1 to 5, Y = 1 to 5

Figure 1. Chemical structure of PCBs (ATSDR, 2000)

1.2. Environmental Fate

PCBs are persistent and bioaccumulative. They adsorb readily to organic materials such as sediments and soils, with adsorption increasing with the chlorine content of the mixture and the organic content of the environmental media (ATSDR, 2000). PCBs have low to no mobility in soil and are

relatively insoluble in water. They are highly soluble in biological lipids, accumulate in aquatic and terrestrial animals and humans, and biomagnify in the food chain. Bioconcentration factors (BCFs) in aquatic species range from 5×10^2 to 3×10^5, depending on the PCB congener and aquatic species (ATSDR, 2000). Volatilization from moist soil and water surfaces is expected, but may be attenuated by adsorption to solids (HSDB, 2011). In air, PCBs exist in both the vapor and particulate phases, and atmospheric transport mechanisms have dispersed PCBs globally (ATSDR, 2000; Wania and MacKay, 1996). Vapor-phase PCBs are photolytically degraded with half-lives ranging from 3-490 days (HSDB, 2011). Particulate-phase PCBs are removed from the atmosphere by wet or dry deposition. In general, biodegradation of PCBs is slow with the higher chlorinated congeners being the most resistant to environmental biodegradation (HSDB, 2011). As a result, PCBs have been detected in a wide variety of environmental media that may be sources of human exposure.

1.3. Human Exposure Pathways and Body Burdens

Occupational exposure to PCBs may occur through inhalation and dermal contact at workplaces where PCBs are still present (e.g., handling PCB containing electrical equipment, spills or waste-site materials) (HSDB, 2011). The general population is exposed to PCBs primarily via dietary intake of contaminated food and inhalation of PCB-contaminated air (Lehmann et al., 2015; ATSDR, 2000). The major contributors to dietary exposure to PCBs include fatty foods such as fish, meat, and dairy products. Based on the U.S. Food and Drug Administration's (FDA's) analysis of data from the 2003 Total Diet Study (TDS), the average dietary exposure among the U.S. population is about 2 ng of PCB per kg of body weight per day (ng/kg-day) (FDA, 2014). This represents a decline from FDA TDS estimates from earlier time periods (ATSDR, 2000).

Inhalation has also been shown to be a contributor to total PCB exposure, especially in indoor settings where PCB sources exist (Lehmann et al., 2015; Harrad et al., 2009). For example, elevated indoor air PCB concentrations have been observed in some public school buildings. Since September, 2009, EPA has released a number of reports[1] for school administrators and building managers with important information about managing airborne PCBs, and tools to help minimize possible exposure. General population exposure may also occur via dermal contact with PCBs in soil or other media, or incidental ingestion of PCB-contaminated soil or dust (ATSDR, 2000). The presence of PCBs in blood, adipose tissue, and breast milk of non-occupationally exposed members of the general population of the United States provides evidence of widespread exposure (ATSDR, 2000).

[1] Polychlorinated Biphenyls (PCBs) in School Buildings: Sources, Environmental Levels, and Exposures, EPA-600-R-12-051 (http://www.epa.gov/pcbsincaulk/pdf/pcb_EPA600R12051_final.pdf)
Fact Sheet for Schools: Caulk Containing PCBs May Be Present in Older Schools and Buildings, EPA-747-F-09-003 (http://www.epa.gov/pcbsincaulk/pdf/caulkschools1.pdf; http://www.epa.gov/pcbsincaulk/pdf/caulkschools2.pdf)
Proper Maintenance, Removal, and Disposal of PCB-Containing Fluorescent Light Ballasts (FLBs) in School Buildings: A Guide for School Administrators and Maintenance Personnel (http://www.epa.gov/epawaste/hazard/tsd/pcbs/pubs/ballasts.htm)
How to Test for PCBs and Characterize Suspect Material (http://www.epa.gov/pcbsincaulk/guide/guide-sect3.htm)

In most epidemiological studies, PCB exposure is characterized using current measures of body burden. Body burden measurements are often based on concentrations of PCBs in blood serum, breast milk or adipose tissue. These may be expressed on a whole-tissue basis (e.g., ng of PCB/g of serum) or may be lipid-adjusted (i.e., ng of PCB/g of lipid). Most studies of PCB body burden rely on a limited number of measured congeners. There is general agreement that PCBs 138, 153, and 180 are the most commonly detected congeners in human tissues, and quantitatively they are the dominant congeners in human adipose tissue and breast milk, with congeners 28, 118, and 170 also making large contributions (Thomsen et al., 2010; Hansen, 1998). Concentrations of these congeners are highly correlated with total tissue PCBs, and they serve as a useful index of cumulative exposure to the more persistent PCB congeners. However, it is important to note that exposure data consisting of only a few congeners may not accurately reflect exposures to many other PCBs, which may also be biologically active.

PCB levels observed in human tissues tend to increase with age, but temporal trend studies have indicated that the overall levels in human milk and blood serum have declined over time since the 1970s (ATSDR, 2000). In a U.S. representative National Health and Nutrition Examination Survey (NHANES) subsample of serum from 1999-2000, PCBs 138, 153, and 180 explained 65% of total PCBs, as represented by the sum of 22 congeners (Needham et al., 2005). However, as per the protocol with NHANES reporting, percentiles only were presented, and PCBs 138 and 153 were non-detect as high as the 75% percentile. At the 90^{th} percentile, the lipid-based (ng/g lipid) and serum-based (ng/g serum) concentrations were 54.7 and 0.36 for PCB 138, 83.3 and 0.56 for PCB 153, and 65.5 and 0.44 for PCB 180. At the 90^{th} and 95^{th} percentiles, the total PCB concentrations (sum of the 22 congeners) were 2.18 and 3.04 ng/g serum, respectively (Needham et al., 2005). Later NHANES surveys obtained better detection limits, and median concentrations of the three congeners were presented. For NHANES 2003/4, the following are median lipid-based/serum-based concentrations (ng/g) of the three congeners for ages >20: 138 (presented as the sum of PCBs 138 and co-eluting 158) – 17.6/0.114; 153 – 24.2/0.156; and 180 – 21.5/0.138 (CDC, 2015).

1.4. Populations and Life Stages with Potentially Greater Exposures

Populations with potentially greater than average exposures include recreational fishers and their families, and Native American or subsistence fishers who ingest PCB-contaminated fish at higher rates than that of the general population (ATSDR, 2000). Several researchers have observed direct relationships between the quantity of fish consumed and PCB levels in blood (ATSDR, 2000). For example, Hanrahan et al. (1999) reported on total PCB concentrations in the blood of sport fishers and a referent population. The referent population was composed of “infrequent” consumers of Great Lakes fish and was broken into groups by male and female. Total PCB concentrations were based on the sum of 89 congeners and were reported on a whole-serum basis. The geometric mean concentration of PCBs in blood of males who frequently consumed Great Lakes sports fish (n=252) was 4.8 ng/mL compared to 1.5 ng/mL for the referent population (n=57). For females, the geometric mean PCB blood concentration was 2.1 ng/mL for frequent consumers (n=187), compared to 0.9 ng/mL for the referent population (n=42). Elevations in PCB body burdens reported by NHANES among non-white populations, including non-

Hispanic blacks, Asians, and Native Americans have been hypothesized to be due to higher consumption of fish compared to white populations (Xue et al., 2014; Weintraub and Birnbaum, 2008). Likewise, populations that consume large amounts of contaminated wild game, or eat a higher proportion of food grown in PCB-contaminated areas will likely have higher exposures and body burdens than the general population (ATSDR, 2000). Because PCBs tend to accumulate in body lipids and can be transferred to infants via breast milk, nursing infants are another potentially highly exposed population. Studies have shown that infants who are breastfed for 6 months may receive up to 12% of their lifetime PCB body burden from human milk (ATSDR, 2000). Occupational groups who may come into contact with PCB-contaminated media may also have exposures higher than the general population (i.e., inhalation, dermal contact, or incidental ingestion of PCB residues from contact with contaminated materials in the workplace, during repair and maintenance of electrical equipment containing PCBs, or from accidents or fires involving PCBs) (ATSDR, 2000).

SCOPE OF THIS ASSESSMENT

At present, the IRIS database contains separate quantitative oral reference doses (RfDs) for Aroclor 1016 (http://www.epa.gov/iris/subst/0462.htm) and Aroclor 1254 (http://www.epa.gov/iris/subst/0389.htm), a qualitative discussion regarding non-cancer effects of oral exposure to Aroclor 1248 (http://www.epa.gov/iris/subst/0649.htm), and cancer slope factors for environmental PCB mixtures via oral and inhalation routes (http://www.epa.gov/iris/subst/0294.htm). The non-cancer assessment for Aroclor 1016 was completed in 1993; assessments for Aroclors 1248 and 1254 were completed in 1994. The cancer assessment for environmental PCB mixtures was completed in 1996. There is no IRIS RfD for complex PCB mixtures in general. Nor is there an IRIS inhalation reference concentration (RfC) for PCBs. Since 1994, a number of studies on the non-cancer health effects of exposure to environmentally-relevant PCB mixtures (e.g., similar to those found in contaminated fish or human milk) have been conducted, and new data are available.

Since the U.S. ban on commercial manufacture of PCBs in 1979, their use, manufacture, cleanup and disposal have been regulated under TSCA (40 CFR 761). However, as discussed above, because of their past widespread use and persistence in the environment, humans continue to be exposed to PCBs by inhalation of volatilized PCBs, inhalation of contaminated dust, contact with contaminated dust, contact with primary or secondary sources of PCBs, and ingestion of foods contaminated with PCBs, including breast milk. In addition to regulation under TSCA, PCBs are regulated under the Clean Water Act, the Safe Drinking Water Act, and the Resource Conservation and Recovery Act. Accordingly, PCBs are of interest to several EPA program offices as well as regional offices due to widespread human exposure to PCBs from many sources and through multiple environmental media.

A new IRIS assessment will evaluate non-cancer human health hazards associated with PCB exposure through oral, inhalation and dermal routes, provided adequate data are available. Dose-response information for identified hazards will also be included when feasible because this information can be useful for both characterizing risks at varying exposure levels and analyzing benefits associated with reducing exposures. A dose-response assessment for the dermal route of exposure is not planned at this point because oral and inhalation exposure are generally considered the major exposure routes. However, toxicokinetic data relevant to dermal exposure will be included to support the evaluation of potential risks from dermal exposures. Furthermore, no new assessment for PCB cancer risk is planned because the carcinogenicity of environmentally-relevant PCB mixtures is addressed in the 1996 assessment and an update of the evaluation of cancer risk from PCB exposure has not been identified as a priority need.

PROBLEM FORMULATION

3.1. Preliminary Literature Survey

A preliminary literature survey was performed to identify non-cancer health outcomes whose possible association with PCBs has been investigated. This survey consisted of a search for health assessment information produced by other federal, state, and international health agencies, and an additional broad search of PubMed to locate more recent studies. The review of health assessment information results was used to narrow the list of health effect categories for consideration in the IRIS assessment and was supplemented by the PubMed search covering dates after the health assessments' publication. In addition, the preliminary literature survey was used to identify key scientific issues, including potential mode of action hypotheses that warrant evaluation in the assessment.

The following health assessments, in addition to EPA's IRIS assessments for Aroclor 1016 (http://www.epa.gov/iris/subst/0462.htm), Aroclor 1248 (http://www.epa.gov/iris/subst/0649.htm), and Aroclor 1254 (http://www.epa.gov/iris/subst/0389.htm), are available from several federal, state, and international health agencies (in reverse chronological order):

1. Agency for Toxic Substances and Disease Registry. ATSDR (2011). Addendum to the toxicological profile for polychlorinated biphenyls. http://www.atsdr.cdc.gov/ToxProfiles/pcbs_addendum.pdf
2. National Institute for Occupational Safety and Health. (NIOSH) (2010). NIOSH pocket guide to chemical hazards. RTECS. Chlorodiphenyl (54% chlorine). http://www.cdc.gov/niosh/npg/npgd0126.html
3. National Institute for Occupational Safety and Health. (NIOSH) (2010). NIOSH pocket guide to chemical hazards. RTECS. Chlorodiphenyl (42% chlorine). http://www.cdc.gov/niosh/npg/npgd0125.html
4. Occupational Safety and Health Administration. OSHA (2007). Chemical Sampling Information, Chlorodiphenyl (54% Cl). https://www.osha.gov/dts/chemicalsampling/data/CH_227500.html
5. World Health Organization. WHO (2003). Concise International Chemical Assessment Document 55. Polychlorinated Biphenyls: Human Health Aspects. http://www.who.int/ipcs/publications/cicad/en/cicad55.pdf
6. Agency for Toxic Substances and Disease Registry. ATSDR (2000). Toxicological profile for polychlorinated biphenyls (PCBs). http://www.atsdr.cdc.gov/ToxProfiles/tp17.pdf

Overall, the *Toxicological Profile for Polychlorinated Biphenyls* (PCBs) (ATSDR, 2011, 2000) was found to be the most comprehensive and current resource, including detailed information on the widest array of health effects and synthesizing evidence from the largest number of primary research articles. Information from other assessments listed above was included in the preliminary literature survey to the extent that it added to the information already presented in (ATSDR, 2011, 2000).

The additional PubMed search was limited to publication dates between January, 2009 and January, 2015 in order to identify studies more recent than those included in ATSDR's *Addendum to the Toxicological Profile for Polychlorinated Biphenyls* (ATSDR, 2011). The PubMed search was not intended to be a comprehensive search of the available literature, but was intended to identify PCB non-cancer health outcomes that had not been previously evaluated (i.e., they were not a part of previous study designs) or were not observed in previous studies evaluated in prior health assessments. Search terms focused on each of the health outcomes shown in Table 1 and included a range of related terms. For instance, renal effects search terms included polychlorinated biphenyls in conjunction with kidney and nephrotoxicity. All results of the PubMed search were screened by title and abstract to identify those appropriate for health assessment.

3.2. Health Outcomes Identified by the Preliminary Literature Survey

The preliminary literature survey identified human, animal, and in vitro studies related to multiple non-cancer health outcomes, mechanisms of action, mode of action hypotheses, pharmacokinetics, and susceptible lifestages or subpopulations. Each row in Table 1 summarizes whether data are available on a particular broad health effect category or other toxicologically-relevant information. While the checkmarks in Table 1 indicate the existence of studies that investigated certain health effect categories in the context of PCB exposure, they do not indicate whether or not the data from those studies support associations between PCB exposure and health effects in those categories. Each column in Table 1 indicates the types of studies that are available with respect to test system (i.e., human, animal, or in vitro) and exposure route (i.e., oral or inhalation) for animal studies or exposure setting (i.e., occupational, high fish and/or seafood consumption[2], or general population) for human studies. As discussed in Section 1.3, humans may be exposed to PCBs by more than one exposure route in a single exposure setting. For example, the bulk of an occupational exposure may have occurred through the inhalation and dermal routes while the general population may be exposed through the diet (i.e., oral exposure), through inhalation of contaminated indoor air, and through dermal contact with contaminated dust or soil. In addition, the table indicates whether animal studies of subchronic, chronic, or developmental design[3] are available.

[2] Studies of populations with "high fish and/or seafood consumption" were those in which the study authors identified fish and/or seafood consumption as the PCB exposure source presumed to be dominant in the study population.

[3] In developmental studies, animals are exposed to a chemical during a critical window of development (i.e., the developmental period of vulnerability during which adverse effects may be triggered by exposures to environmental agents or other stressors). The critical windows of development for most biological systems occur during the prenatal and early postnatal periods, but certain systems (e.g., nervous and reproductive systems) do continue to develop throughout early life and adolescence. Studies conducted outside of a critical window of development may be characterized by exposure duration: acute (< 24 hours), short-term (>24 hours up to 30 days), subchronic (>30 days up to 10% of lifetime), and chronic (up to a lifetime).

Table 1. Database of PCB studies by test system, route of exposure, and health effect category[1]

	Human Studies			Animal Studies		In Vitro Studies
	Occupational	High Fish and/or Seafood Consumption[2]	General Population	Oral	Inhalation	
Health Effect Categories						
Cardiovascular	✓	✓	✓	✓ (Subchronic, Chronic)		✓
Dermal and Ocular	✓			✓ (Subchronic, Chronic, Developmental)		
Effects on growth and maturation	✓	✓	✓	✓ (Subchronic, Chronic, Developmental)	✓ (Subchronic)	✓
Endocrine	✓	✓	✓	✓ (Subchronic, Developmental)	✓ (Subchronic)	✓
Gastrointestinal	✓		✓	✓ (Subchronic, Chronic)		
Hematological	✓			✓ (Subchronic, Chronic)	✓ (Subchronic)	
Hepatic	✓	✓	✓	✓ (Subchronic, Chronic, Developmental)	✓ (Subchronic)	✓
Immunological	✓	✓	✓	✓ (Subchronic, Chronic, Developmental)	✓ (Subchronic)	✓
Metabolic disease	✓	✓	✓	✓ (Subchronic, Chronic)		✓
Musculoskeletal	✓	✓		✓ (Subchronic, Chronic)		
Neurological and Sensory	✓	✓	✓	✓ (Subchronic, Developmental)	✓ (Subchronic)	✓
Renal	✓		✓	✓ (Subchronic, Chronic)	✓ (Subchronic)	✓

Reproductive	✓	✓	✓	✓ (Subchronic, Chronic, Developmental)		✓
Respiratory	✓		✓	✓ (Subchronic, Chronic)	✓ (Subchronic)	
Other Data and Analyses						
ADME[3]	✓	✓	✓	✓	✓	✓
Toxicokinetic models[4]	✓	✓	✓	✓		✓
Mode of action hypotheses		✓	✓	✓ (Subchronic, Chronic, Developmental)		✓
Susceptibility data[5]	✓	✓	✓	✓ (Developmental)		
Genotoxicity[6]	✓		✓	✓ (Subchronic)		✓
	[1] Checkmarks indicate that studies have been identified, but do not indicate the results of those studies; the absence of a checkmark indicates that no studies were identified for a given health effect category and study design. [2] Studies of populations with "high fish and/or seafood consumption" were those in which the study authors identified fish and/or seafood consumption as the PCB exposure source presumed to be dominant in the study population. [3] Studies conducted in humans and animals demonstrate rapid absorption of PCBs by inhalation, oral, and dermal routes of exposure. [4] Earliest PBPK models for PCBs were based on i.v. exposure. Models also exist for dermal exposure. [5] Individuals who may be more susceptible to toxic effects include young children, especially those who are breastfed. [6] Includes studies investigating potential epigenetic impacts of PCB exposure					

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3.3. Health Outcomes That May Be Considered for Systematic Review

The literature noted and screened in Section 3.2 was used to identify broad categories of potential health effects considered to be most relevant for assessment. The following is a list of broad health effect categories in which effects were observed and for which there may be enough data to further evaluate specific health endpoints: cardiovascular, dermal and ocular, developmental effects on growth and maturation, endocrine, gastrointestinal, hematological, hepatic, immunological, metabolic, neurological, and reproductive effects. A large number of specific health endpoints could be affected within each of these categories. A review of the literature associated with the broad health effect categories for which effects were noted is proposed to determine if a systematic review should be undertaken related to one or more specific health endpoints within the categories. The systematic reviews to evaluate if an association exists between exposure to PCBs and specific health endpoints would include analyses of available human, experimental animal, and in vitro studies.

A brief summary of other agencies' conclusions for each broad health effect category is provided below.

Cardiovascular Effects

ATSDR (2000) identified occupational exposure studies investigating the possible relationship between PCB exposure and increased risk of cardiovascular disease or altered blood pressure. According to ATSDR (2000), conclusions could not be drawn from these studies because of the inconsistency of the results. The inconsistent results could be due to differences in exposure levels, durations, and latencies, as well as types of PCB mixtures and cohort sizes.

Some studies of human populations exposed outside the workplace have identified associations between PCB exposure and hypertension (Goncharov et al., 2011; Kreiss et al., 1981) or cardiovascular disease, defined by the study authors as a physician's diagnosis of any of the following: 1) coronary heart disease; 2) angina/angina pectoris; 3) heart attack/myocardial infarction; or 4) stroke (Ha et al., 2007). However, the results of some of these studies may be confounded by associations between serum PCB levels and (1) age, (2) serum cholesterol and triglyceride levels, and (3) serum levels of other persistent organic pollutants (e.g., dichlorodiphenyltrichloroethane (DDT)).

Data on the cardiovascular toxicity of PCBs in animals are limited to several oral exposure studies conducting histological examinations of the heart and blood vessels (ATSDR, 2000). Pericardial edema occurred in monkeys subchronically exposed to a high PCB dose (i.e., 12 mg/kg-day) in the diet (Allen et al., 1973). However, no effects on cardiac tissue were observed in monkeys exposed to PCBs at much lower doses for a longer duration (Arnold et al., 1997) or in rats exposed at dose levels up to 11.2 mg/kg-day for 24 months (Mayes et al., 1998).

A further review of information related to PCB exposure and cardiovascular effects will be used to determine what questions, if any, on specific endpoints should be addressed using a systematic review approach.

Dermal and Ocular Effects

Dermal alterations (e.g., chloracne) and ocular effects (e.g., hypersecretion of the tarsal glands and abnormal pigmentation of the conjunctiva) are commonly-observed markers of exposure to PCBs and other dioxin-like compounds (e.g., polychlorinated dibenzodioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs)) (ATSDR, 2000). These effects have been observed in individuals occupationally exposed to PCBs. Although dermal and ocular alterations have appeared in these highly-exposed populations, no adverse dermal or ocular effects have been reported in subjects with high consumption of Great Lakes fish contaminated with PCBs and other environmentally persistent chemicals or in other cohorts from the general population although it is unknown if this outcome was systematically studied in these cohorts. PCB-related dermal and ocular effects are well-characterized in monkeys after oral exposure to commercial PCB mixtures and are generally similar to those observed in humans exposed to high concentrations of PCBs (Arnold et al., 1997; Arnold et al., 1995; Arnold et al., 1993b; Arnold et al., 1993a; Schantz et al., 1991; Arnold et al., 1990; Schantz et al., 1989; Levin et al., 1988; Tryphonas et al., 1986b; Tryphonas et al., 1986a; Barsotti and van Miller, 1984; Allen et al., 1980; Becker et al., 1979; Thomas and Hinsdill, 1978; Allen and Barsotti, 1976; Allen and Norback, 1976; Barsotti et al., 1976; Allen et al., 1974).

A further review of information related to PCB exposure and dermal and ocular effects will be used to determine what questions, if any, on specific endpoints should be addressed using a systematic review approach.

Developmental Effects on Growth and Maturation

A number of epidemiology studies have evaluated developmental effects on anthropometric parameters in children following maternal PCB exposure (ATSDR, 2000). The effects observed in these studies varied. Some studies found no association between PCB exposure and anthropometric effects (Konishi et al., 2009; Givens et al., 2007; Longnecker et al., 2005; Vartiainen et al., 1998; Lonky et al., 1996; Rogan et al., 1986) while others observed significant associations with effects including birth weight, gestational age, infant head circumference, and body weight later in life. Of the significant associations reported, some were positive (Verhulst et al., 2009; Dar et al., 1992), and others were negative (Tan et al., 2009; Halldorsson et al., 2008; Hertz-Picciotto et al., 2005; Tajimi et al., 2005; Blanck et al., 2002; Patandin et al., 1998; Rylander et al., 1998; Rylander et al., 1995; Fein et al., 1984b). The wide range of results from these studies may reflect variations in study design and study populations: different degrees of control for confounders; different techniques for PCB analysis; measurement of PCBs in different sample types; different levels of exposure; assessment of exposure at different times; inclusion of different sets of PCB congeners in the analysis; and the presence of a variety of co-contaminants.

In addition to anthropometric effects, prenatal PCB exposure has been reported to affect offspring gender and development, including a reduction in male births (Hertz-Picciotto et al., 2008), undescended testes (Brucker-Davis et al., 2008), and decreased sex hormone levels in males (Cao et al., 2008).

Although studies have reported no effect of prenatal PCB exposure on puberty onset for most male or female endpoints (Leijs et al., 2008; Vasiliu et al., 2004; Gladen et al., 2000), studies of childhood PCB exposure have reported effects on anthropometric measures (Burns et al., 2011) and timing of pubertal development in boys (Den Hond et al., 2011) and girls (Den Hond et al., 2011; Denham et al., 2005).

Developmental effects of perinatal exposure to PCB mixtures have also been reported in animals at doses as low as 0.028 mg/kg-day (reduced birth weight in the offspring of rhesus monkeys exposed to Aroclor 1016 in the diet prior to mating and throughout gestation (Schantz et al., 1991; Schantz et al., 1989; Levin et al., 1988; Barsotti and van Miller, 1984; Allen et al., 1980; Allen and Barsotti, 1976)). Data in rats exposed to PCB mixtures, including a mixture of congeners developed to mimic the congener profile found in human milk, confirm an effect on birth weight and/or postnatal growth in the absence of overt signs of maternal toxicity (Bowers et al., 2004; Kaya et al., 2002; Zahalka et al., 2001; Lilienthal et al., 2000; Hany et al., 1999; Goldey et al., 1995; Overmann et al., 1987; Spencer, 1982; Collins and Capen, 1980).

Fetal mortality following gestational PCB exposure has been observed in monkeys, mink, rats, rabbits and chickens (Brunström et al., 2001; Bäcklin et al., 1998a; Bäcklin et al., 1998b; Bäcklin et al., 1997; Gould et al., 1997; Arnold et al., 1995; Bäcklin and Bergman, 1995; Sager and Girard, 1994; Kihlstrom et al., 1992; Arnold et al., 1990; Wren et al., 1987; Brezner et al., 1984; Spencer, 1982; Allen et al., 1980; Aulerich and Ringer, 1977; Barsotti et al., 1976; Allen et al., 1974; Lillie et al., 1974; Villeneuve et al., 1971). Postnatal death has been observed with perinatal PCB exposure in monkeys, mink, mice and rats (Bowers et al., 2004; Bushnell et al., 2002; Brunström et al., 2001; Huang et al., 1998a; Goldey et al., 1995; Schantz et al., 1991; Schantz et al., 1989; Levin et al., 1988; Wren et al., 1987; Brezner et al., 1984; Allen et al., 1980; Allen and Barsotti, 1976; Linder et al., 1974).

A further review of information related to PCB exposure and developmental effects on growth and maturation will be used to determine what questions, if any, on specific endpoints should be addressed using a systematic review approach.

Endocrine Effects

Studies examining relationships between PCB exposure and thyroid hormone status in children or adults have reported a variety of different results, with findings of both negative and positive significant correlations between PCB exposure and circulating levels of TSH, T_4 or T_3 (Han et al., 2011; Darnerud et al., 2010; Alvarez-Pedrerol et al., 2009; Dallaire et al., 2009a; Dallaire et al., 2009b; Abdelouahab et al., 2008; Alvarez-Pedrerol et al., 2008; Chevrier et al., 2008; Herbstman et al., 2008; Schell et al., 2008; Chevrier et al., 2007; Maervoet et al., 2007; Meeker et al., 2007; Turyk et al., 2007; Takser et al., 2005; Wang et al., 2005; Schell et al., 2004; Persky et al., 2001; Sala et al., 2001; Osius et al., 1999; Gerhard et al., 1998; Winneke et al., 1998a; Koopman-Esseboom et al., 1994). The apparent inconsistency among studies may stem from factors such as the use of different types of PCB analyses (e.g., Aroclor analyses, measures of total PCBs, and congener or isomer analyses), varying ages of cohorts, varying exposure settings (which may differ in both congener profile and route(s) of exposure), and differences in statistical methods employed. The most common findings are negative associations between PCBs and measures of

T_3 and/or T_4 and positive associations with TSH, especially in studies of the effects of post-lactational PCB exposure (Han et al., 2011; Alvarez-Pedrerol et al., 2009; Dallaire et al., 2009a; Abdelouahab et al., 2008; Schell et al., 2008; Meeker et al., 2007; Turyk et al., 2007; Schell et al., 2004; Sala et al., 2001; Osius et al., 1999). Studies focused on developmental exposure often find decreased T_4 with increased PCBs, but no change in TSH, which may suggest that these types of exposures are associated with decreased fT_4 feedback to the hypothalamus (Herbstman et al., 2008; Maervoet et al., 2007; Wang et al., 2005). Chronic, developmental, and subchronic duration animal studies also provide evidence for an effect of PCB exposure on thyroid hormone homeostasis (ATSDR, 2000). Furthermore, effects on the adrenal glands and serum adrenal steroid levels have also been observed in experimental animals exposed orally to PCBs (Rao and Banerji, 1993; Byrne et al., 1988; Rao and Banerji, 1988).

A further review of information related to PCB exposure and endocrine effects will be used to determine what questions, if any, on specific endpoints should be addressed using a systematic review approach.

Gastrointestinal Effects

Gastrointestinal effects, including loss of appetite (Smith et al., 1982), postprandial epigastric distress, epigastric pain with or without a burning sensation, postprandial headache, and intolerance to fatty foods (Maroni et al., 1981), have been observed in occupationally-exposed human populations. However, the study by Maroni et al. (1981) did not include a control group, so the significance of that study's findings are unclear. Baker et al. (1980) reported no signs of gastrointestinal effects in community members exposed to PCB-contaminated sludge or in PCB-exposed workers. Animal studies provide evidence of PCB-induced gastrointestinal effects in monkeys (Tryphonas et al., 1986b; Tryphonas et al., 1986a; Tryphonas et al., 1984; Becker et al., 1979; Allen and Norback, 1976; Allen, 1975; Allen et al., 1974; Allen et al., 1973; Allen and Norback, 1973), mink (Hornshaw et al., 1986; Bleavins et al., 1980), and pigs (Hansen et al., 1976), but not rats (Mayes et al., 1998).

A further review of information related to PCB exposure and gastrointestinal effects will be used to determine what questions, if any, on specific endpoints should be addressed using a systematic review approach.

Hematological Effects

In general, hematological effects have not been observed in humans occupationally exposed to PCBs (ATSDR, 2000). However, anemia has been observed in monkeys exposed to PCBs in studies of subchronic (Allen and Norback, 1976; Allen et al., 1974; Allen et al., 1973; Allen and Norback, 1973) and chronic duration (Arnold et al., 1990; Tryphonas et al., 1986b; Tryphonas et al., 1986a; Tryphonas et al., 1984). A decrease in mean platelet volume was also observed in monkeys exposed to 0.02 mg/kg-day Aroclor 1254 for 37 months (Arnold et al., 1993a). However, monkeys receiving daily doses of 0.08 mg/kg-day Aroclor 1254 for 72 months showed no effect on hematological parameters (Arnold et al., 1997).

No consistent hematologic effects were observed in rats, guinea pigs, rabbits, or mink exposed to PCB mixtures for subchronic durations (Aulerich and Ringer, 1977; Street and Sharma, 1975; Bruckner et al., 1974; Allen and Abrahamson, 1973; Vos and de Roij, 1972; Treon et al., 1956). Exposure to 2.7 mg/kg-day Aroclor 1016 or 1.4 mg/kg-day Aroclor 1260 for 24 months resulted in reduced red blood cell count and hemoglobin concentration in female rats (Mayes et al., 1998); however, in the same study, there were no hematologic effects observed in female rats exposed to Aroclor 1242 or 1254, or in male rats exposed to Aroclor 1016, 1242, 1254, or 1260.

A further review of information related to PCB exposure and hematological effects will be used to determine what questions, if any, on specific endpoints should be addressed using a systematic review approach.

Hepatic Effects

Hepatic effects have been investigated in a number of epidemiology studies and clinical surveys of PCB-exposed workers (ATSDR, 2000). Increased serum levels of liver-related enzymes, particularly gamma-glutamyl transpeptidase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), and/or lactate dehydrogenase (LDH), were reported in many of these studies (Stehr-Green et al., 1986b; Stehr-Green et al., 1986a; Steinberg et al., 1986; Emmett, 1985; Lawton et al., 1985; Chase et al., 1982; Kreiss et al., 1981; Maroni et al., 1981; Fischbein et al., 1979). Additionally, increases in levels of these serum enzymes have been correlated with serum PCB levels (Cave et al., 2010; Stehr-Green et al., 1986b; Stehr-Green et al., 1986a; Steinberg et al., 1986; Emmett, 1985; Lawton et al., 1985; Chase et al., 1982; Smith et al., 1982; Kreiss et al., 1981; Fischbein et al., 1979).

The hepatotoxicity of PCBs has been investigated in numerous chronic, developmental, and subchronic duration studies in animals, particularly in rats and monkeys, which are the most extensively tested species. Liver effects are similar in nature among species, appear to be reversible when mild, and characteristically include the following:

- hepatic microsomal enzyme induction (e.g., rats exposed to 0.3 mg/kg-day Aroclor 1242 for 2 months (Bruckner et al., 1974));
- increased serum levels of liver-related enzymes indicative of possible hepatocellular damage (e.g., rhesus monkeys exposed to 0.02 mg/kg-day Aroclor 1254 for 6.5 years (Arnold et al., 1997));
- liver enlargement (e.g., rabbits exposed to 0.18 mg/kg-day Aroclor 1254 for 8 weeks (Street and Sharma, 1975); monkeys exposed to 0.2 mg/kg-day Aroclor 1254 for 12-13 months (Tryphonas et al., 1986b); offspring of rats exposed to 0.27 mg/kg-day Aroclor 1254 from mating until weaning on postnatal day (PND) 21 (Overmann et al., 1987); offspring of rats exposed from 50 days prior to mating and throughout gestation to $\geq$ 0.5 mg/kg-day of a mixture of PCB congeners developed to mimic the congener profile found in human milk (Kaya et al., 2002; Hany et al., 1999));

- fat deposition (e.g., rats exposed to 2.4 mg/kg-day Aroclor 1254 for 140 days (Bruckner et al., 1977));
- fibrosis (e.g., rats exposed to 1.4 mg/kg-day Aroclor 1260 for 8 months (Kimbrough et al., 1972));
- necrosis (e.g., rhesus monkeys exposed to 0.2 mg/kg-day Aroclor 1254 for 28 months (Tryphonas et al., 1986a)); and
- hepatic porphyria (e.g., rats exposed to 0.3 mg/kg-day Aroclor 1242 for 2 months (Bruckner et al., 1974)).

The references listed above represent only a subset of an extensive database of animal studies observing hepatic effects from oral exposures; these were selected for the purposes of this document to highlight studies reporting effects at relatively low PCB doses and/or administering environmentally-relevant PCB mixtures, and where possible, to illustrate potential species differences in sensitivity. This list is not intended to reflect either the full list of studies of hepatic effects to be included in the assessment or the criteria by which those studies will be selected. A further review of information related to PCB exposure and hepatic effects will be used to determine what questions, if any, on specific endpoints should be addressed using a systematic review approach.

Immunological Effects

Immunologic changes have been observed in human populations exposed to PCB mixtures (ATSDR, 2000). Findings include alterations in thymic volume (Park et al., 2008), serum antibody levels (Gerhard et al., 1998), white blood cell counts (Svensson et al., 1994; Lawton et al., 1985), and lymphocyte profiles (Glynn et al., 2008; Nagayama et al., 2007; Belles-Isles et al., 2002). Several epidemiological studies have also investigated a possible association between immune effects and early-life PCB exposure (i.e., in utero and/or by breastfeeding). The number of childhood infectious illnesses (i.e., lower respiratory tract, gastrointestinal tract and middle-ear infections) during the first 5 years of life was positively correlated with prenatal PCB exposure in a study of Inuit women who consumed contaminated marine foods (Dallaire et al., 2006; Dallaire et al., 2004) although other immunological endpoints and possible associations with other chemicals in the foods were not investigated. Similarly, decreased antibody response to diphtheria and tetanus was observed in children from a Faroe Island population (Heilmann et al., 2010; Heilmann et al., 2006). The Dutch environmental exposure study (Weisglas-Kuperus et al., 2004; Weisglas-Kuperus et al., 2000) also revealed significant correlations between pre- and postnatal exposure to PCBs and both the incidence of infection (i.e., ear infection and chicken pox) and antibody levels to common childhood vaccines (i.e., mumps and measles) at 42 months of age. These effects were not observed in the same population at 18 months of age (Weisglas-Kuperus et al., 1995), suggesting that developmental effects of PCBs on immune function may not be detectable in very young children. This may help to explain conflicting results in a number of studies of PCB-exposed human infants (Jusko et al., 2010; Glynn et al., 2008). Conflicting results may also occur because the human populations that have been studied differ greatly with respect to sources of PCB exposure. In

addition, these populations are likely to vary with respect to exposure to both non-PCB contaminants and certain nutrients that may affect susceptibility to infections.

The immunotoxicity of PCBs has also been evaluated in various species of animals (ATSDR, 2000). Studies in rats, mice, guinea pigs, rabbits, and monkeys have shown that oral exposure to PCB mixtures can induce morphological alterations in the immune system:

- decreased thymus weight (e.g., rats exposed to 10 mg/kg-day Aroclor 1254 for 15 weeks (Smialowicz et al., 1989); offspring of rats exposed to 0.27 mg/kg-day Aroclor 1254 from mating until weaning on PND 21 (Overmann et al., 1987); offspring of mink exposed to 0.3 mg/kg-day Clophen A50 for 18 months (including 2 breeding seasons) (Brunström et al., 2001);
- decreased spleen weight (e.g., offspring of mice exposed to ~42 mg/kg-day Aroclor 1254 throughout gestation and lactation (Talcott and Koller, 1983));
- thymic atrophy and/or other thymic lesions (e.g., rats exposed to 0.033 mg/kg-day Aroclor 1242 for 30 days (Casey et al., 1999); offspring of mice exposed to 4.3 mg/kg-day of a 2:1 mixture of Aroclors 1242 and 1254 throughout gestation and lactation (Segre et al., 2002); rabbits exposed to 0.18 mg/kg-day Aroclor 1254 for 8 weeks (Street and Sharma, 1975); cynomolgus monkeys exposed to 2 mg/kg-day Aroclor 1248 or 5 mg/kg-day Aroclor 1254 for up to 164 days (Tryphonas et al., 1984); offspring of rhesus monkeys exposed to 0.01 mg/kg-day Aroclor 1248 from 12 months prior to breeding until offspring weaning at 4 months of age (Schantz et al., 1991; Schantz et al., 1989; Levin et al., 1988));
- histopathological changes in the spleen (e.g., rabbits exposed to 2.1 mg/kg-day Aroclor 1254 for 8 weeks (Street and Sharma, 1975); offspring of rhesus monkeys exposed to 0.1 mg/kg-day Aroclor 1248 from 7 months prior to breeding and throughout gestation and lactation (Allen and Barsotti, 1976); rhesus monkeys exposed to 0.2 mg/kg-day Aroclor 1254 for 28 months (Tryphonas et al., 1986a);
- histopathological changes in the lymph nodes (e.g., rabbits exposed to 0.92 mg/kg-day Aroclor 1254 for 8 weeks (Street and Sharma, 1975); rhesus monkeys exposed to 0.2 mg/kg-day Aroclor 1254 for 28 months (Tryphonas et al., 1986a)); and
- histopathological changes in the bone marrow (e.g., offspring of rhesus monkeys exposed to 0.1 mg/kg-day Aroclor 1248 from 7 months prior to breeding and throughout gestation and lactation (Allen and Barsotti, 1976); cynomolgus monkeys exposed to 0.2 mg/kg-day Aroclor 1254 for 12-13 months (Tryphonas et al., 1986b)).

Oral PCB exposure also revealed effects on immune function as indicated by altered responses in humoral and cell-mediated immunity assays and host resistance tests:

- reduced antibody response to tetanus toxoid (e.g., guinea pigs exposed to 0.77 mg/kg-day Aroclor 1260 for 8 weeks (Vos and de Roij, 1972));
- reduced antibody response to keyhole limpet hemocyanin (e.g., rats exposed to 4.3 mg/kg-day Aroclor 1254 for 10 weeks (Exon et al., 1985));
- reduced antibody response to sheep red blood cells (SRBCs) (e.g., mice exposed to 22 mg/kg-day Aroclor 1242 for 6 weeks (Loose et al., 1977); rhesus monkeys exposed to 0.005 mg/kg-day

Aroclor 1254 for 23 months (Tryphonas et al., 1989), offspring of rhesus monkeys exposed to 0.005 mg/kg-day Aroclor 1254 from 37 months before mating and throughout gestation and lactation (Arnold et al., 1995));

- increased susceptibility to infection by S. typhimurium (e.g., mice exposed to 195 mg/kg-day Aroclor 1248 for 5 weeks (Thomas and Hinsdill, 1978));
- increased herpes simplex virus- and ectromelia virus-induced mortality (e.g., mice exposed to 33 mg/kg-day Kanechlor 500 for 31 days (Imanishi et al., 1980)); and
- increased sensitivity to S. typhosa endotoxin, and increased parasitemia and mortality in malaria-inoculated animals (e.g., mice exposed to 22 mg/kg-day Aroclor 1242 for 6 weeks (Loose et al., 1978b)).

Skin reactivity to tuberculin was reduced in guinea pigs exposed to 3.9 mg/kg-day Clophen A60 for 6 weeks (Vos and van Driel-Grootenhuis, 1972), but not in rabbits exposed to 6.5 mg/kg-day Aroclor 1254 for 8 weeks (Street and Sharma, 1975), and there was no effect on delayed-type hypersensitivity to the skin sensitizer oxazolone in the offspring of mice exposed throughout gestation and lactation to ~42 mg/kg-day Aroclor 1254 (Talcott and Koller, 1983). Natural killer cell activity was reduced in rats following subchronic oral exposure to doses ≥ 4.3 mg/kg-day Aroclor 1254 (Smialowicz et al., 1989; Talcott et al., 1985).

The references discussed above represent only a subset of an extensive database of animal studies observing immunological effects associated with oral exposure to PCB mixtures; these were selected for the purposes of this document to highlight effects of PCBs at relatively low doses, and where possible, to illustrate potential species differences in sensitivity. These references are not intended to reflect either the full list of studies of immunological effects to be included in the assessment or the criteria by which those studies will be selected. A further review of information related to PCB exposure and immunological effects will be used to determine what questions, if any, on specific endpoints should be addressed using a systematic review approach.

Metabolic Disease

Epidemiological studies have identified associations between specific components of the metabolic syndrome (i.e., central obesity, high serum triglycerides, low serum HDL-cholesterol, hyperglycemia, hypertension and insulin resistance) and PCB exposure (Dirinck et al., 2011; Goncharov et al., 2011; Lee et al., 2011; Uemura et al., 2009; Langer et al., 2007; Lee et al., 2007a; Emmett et al., 1988a; Stehr-Green et al., 1986b; Stehr-Green et al., 1986a; Steinberg et al., 1986; Emmett, 1985; Lawton et al., 1985; Chase et al., 1982; Smith et al., 1982; Kreiss et al., 1981; Baker et al., 1980). Furthermore, both metabolic syndrome and PCB exposure have been associated with increased risk of developing type 2 diabetes mellitus (Grandjean et al., 2011; Turyk et al., 2009a; Turyk et al., 2009b; Uemura et al., 2008; Wang et al., 2008; Codru, 2007; Everett et al., 2007; Lee et al., 2007b; Rignell-Hydbom et al., 2007; Lee et al., 2006; Vasiliu et al., 2006; Rylander et al., 2005; Fierens et al., 2003) and cardiovascular diseases, including coronary artery disease and stroke (Ha et al., 2007). In a diabetes-prone strain of mice,

subchronic PCB exposure was found to exacerbate whole-body insulin resistance in diet-induced obese animals and to produce hyperinsulinemia in both lean and obese animals (Gray et al., 2013).

A further review of information related to PCB exposure and metabolic disease will be used to determine what questions, if any, on specific endpoints should be addressed using a systematic review approach.

Musculoskeletal Effects

One study on the musculoskeletal toxicity of PCBs in humans was identified by ATSDR (2000). In this study, joint and muscle pain were reported by workers exposed to various Aroclors at mean area concentrations of 0.007–11 mg/m3 (Fischbein et al., 1979). Information on the severity or constancy of the joint and muscle pain was not reported, physiological testing was not performed, and there was failure to distinguish between past and present symptoms. More recent studies of populations exposed to PCBs via consumption of contaminated seafood provide preliminary evidence that long-term PCB exposure may be associated with developmental defects of tooth enamel (Jan and Reinert, 2008; Jan and Vrbic, 2000). Studies on the musculoskeletal effects of PCBs in animals include a subchronic oral exposure study in growing rats, which reported weaker bones in PCB-exposed animals (Andrews, 1989) and a chronic oral exposure study in rats, which reported no histopathologic changes in skeletal muscle with PCB exposure up to 11.2 mg/kg-day (Mayes et al., 1998). Since there is very little evidence linking PCB exposure to musculoskeletal effects, a systematic review is not planned to evaluate these effects in response to PCB exposure.

Neurological Effects

Neurological effects resulting from PCB exposure in adulthood: Neurological effects of PCB exposure in adults have been reported following occupational exposure (Prince et al., 2006; Ruder et al., 2006; Steenland et al., 2006; Peper et al., 2005; Sinks et al., 1992; Emmett et al., 1988b; Smith et al., 1982; Fischbein et al., 1979), consumption of contaminated fish and other marine foods (Haase et al., 2009; Petersen et al., 2008; Koldkjaer et al., 2004; Schantz et al., 2001; Schantz et al., 1999; Schantz et al., 1996), or other environmental exposure (Fitzgerald et al., 2008; Corrigan et al., 2000; Corrigan et al., 1998). Of these exposure routes, the neurological effects of PCB exposure from consumption of contaminated fish or marine life are the best-characterized. These dietary exposure studies can be organized into two groups: studies that compared results of neuropsychological tests among groups with varying levels of PCB exposure (Haase et al., 2009; Schantz et al., 2001; Schantz et al., 1999; Schantz et al., 1996); and studies that compared results of neurobehavioral tests and Parkinson's Disease (PD) mortality to healthy controls (Petersen et al., 2008; Koldkjaer et al., 2004).

Animal studies have reported neurobehavioral effects following subchronic PCB exposure. These effects include decreased motor activity, hyperactivity and impulsivity in rats (Berger et al., 2001; Casey et al., 1999; Nishida et al., 1997) as well as altered neurotransmitter levels in monkeys (Seegal et al., 1994, 1992, 1991).

Neurological effects in children resulting from prenatal and/or early postnatal PCB exposure: There is an extensive database of epidemiological studies evaluating the association between PCB exposure during development and neurobehavioral parameters in infants and children. These studies include examinations of children following maternal consumption of PCB-contaminated fish and marine life (Boucher et al., 2012; Boucher et al., 2010; Plusquellec et al., 2010; Verner et al., 2010; Newman et al., 2009; Stewart et al., 2008; Newman et al., 2006; Saint-Amour et al., 2006; Stewart et al., 2006; Despres et al., 2005; Stewart et al., 2005; Jacobson and Jacobson, 2003; Stewart et al., 2003b; Stewart et al., 2003a; Grandjean et al., 2001; Darvill et al., 2000; Steuerwald et al., 2000; Stewart et al., 2000; Jacobson and Jacobson, 1997, 1996; Lonky et al., 1996; Jacobson et al., 1992; Jacobson et al., 1990a, b; Jacobson et al., 1985; Fein et al., 1984a; Fein et al., 1984b; Jacobson et al., 1984) as well as studies of children following maternal PCB exposure from the general environment (Sagiv et al., 2012; Park et al., 2010; Sagiv et al., 2010; Pan et al., 2009; Park et al., 2009; Roze et al., 2009; Sagiv et al., 2008; Trnovec et al., 2008; Wilhelm et al., 2008b; Wilhelm et al., 2008a; Nakajima et al., 2006; Gray et al., 2005; Winneke et al., 2005; Longnecker et al., 2004; Riva et al., 2004; Vreugdenhil et al., 2004; Daniels et al., 2003; Vreugdenhil et al., 2002b; Vreugdenhil et al., 2002a; Walkowiak et al., 2001; Boersma and Lanting, 2000; Patandin et al., 1999; Lanting et al., 1998b; Winneke et al., 1998b; Koopman-Esseboom et al., 1996; Huisman et al., 1995b; Huisman et al., 1995a; Gladen and Rogan, 1991; Rogan and Gladen, 1991; Gladen et al., 1988; Rogan et al., 1986).

Possible associations between early-life PCB exposure and decrements in neurodevelopment have been investigated at different stages of childhood:

<u>Neonates</u>

- Neonatal Behavioral Assessment Scale (NBAS) (Sagiv et al., 2008; Stewart et al., 2000; Lonky et al., 1996; Rogan et al., 1986; Fein et al., 1984a; Jacobson et al., 1984)
- Neurological Optimality Score (NOS) (Wilhelm et al., 2008b; Steuerwald et al., 2000; Lanting et al., 1998b; Huisman et al., 1995b; Huisman et al., 1995a; Fein et al., 1984a; Fein et al., 1984b)

<u>Infants and toddlers</u>

- Fagan Test for Infant Intelligence (Darvill et al., 2000; Winneke et al., 1998b; Jacobson et al., 1985)
- Bayley Scales of Infant Development (BSID) (Park et al., 2010; Wilhelm et al., 2008b; Wilhelm et al., 2008a; Nakajima et al., 2006; Daniels et al., 2003; Walkowiak et al., 2001; Boersma and Lanting, 2000; Winneke et al., 1998b; Koopman-Esseboom et al., 1996; Lai et al., 1994; Rogan and Gladen, 1991; Gladen et al., 1988)

<u>Preschoolers and elementary school children</u>

- McCarthy Scales of Children's Abilities (Stewart et al., 2003b; Jacobson and Jacobson, 2002; Vreugdenhil et al., 2002a; Gladen and Rogan, 1991)
- Kaufman Assessment Battery for Children (KABC) (Winneke et al., 2005; Walkowiak et al., 2001; Patandin et al., 1999)

- Wechsler Intelligence Scales for Children (WISC) (Roze et al., 2009; Stewart et al., 2008; Gray et al., 2005; Jacobson and Jacobson, 2003, 2002; Grandjean et al., 2001; Lai et al., 1994; Chen et al., 1992)
- Wide Range Achievement tests (WRAT) (Jacobson and Jacobson, 2002)
- Woodcock Reading Mastery tests (Newman et al., 2009; Jacobson and Jacobson, 2002)
- Raven's Progressive Matrices (Newman et al., 2009; Guo et al., 1995)

Children of elementary school age who were exposed to PCBs prenatally and/or during infancy have also been assessed for impairments of executive function (i.e., response inhibition, working memory, attentional control, cognitive flexibility, planning, and error monitoring) (Boucher et al., 2012; Sagiv et al., 2012; Boucher et al., 2010; Eubig et al., 2010; Verner et al., 2010; Roze et al., 2009; Stewart et al., 2008; Stewart et al., 2006; Stewart et al., 2005; Vreugdenhil et al., 2004; Jacobson and Jacobson, 2003; Stewart et al., 2003a; Vreugdenhil et al., 2002a; Jacobson and Jacobson, 1996; Jacobson et al., 1992; Jacobson et al., 1990b).

Potential effects of PCB exposure on memory and learning functions and auditory processing have been evaluated in teenagers (i.e., 13-18 years old) following consumption of contaminated fish (Newman et al., 2009; Newman et al., 2006). In this case, the exposure assessment was based on a child's current body burden rather than on prenatal and/or early postnatal exposure metrics. However, for neurological endpoints, exposure during adolescence is considered to be a form of developmental exposure because human neurodevelopment continues into early adulthood (Adams et al., 2000).

A number of studies in non-human primates have examined the behavioral effects of prenatal and/or postnatal exposure to PCBs (Rice and Hayward, 1999; Rice, 1998, 1997; Rice and Hayward, 1997; Schantz et al., 1991; Schantz et al., 1989; Levin et al., 1988; Bowman and Heironimus, 1981; Bowman et al., 1981; Bowman et al., 1978). In one series of studies, rhesus monkeys born to dams fed Aroclor 1248 in their diet were hyperactive at 6 and 12 months of age, even in offspring cohorts conceived after cessation of maternal PCB exposure (Bowman et al., 1981; Bowman et al., 1978). When the perinatally-exposed rhesus monkeys were observed at later time points, the authors reported that the monkeys remained hyperactive as juveniles, but were hypoactive as adolescents (Bowman and Heironimus, 1981).

Another series of reports evaluated long-term neurobehavioral effects in rhesus monkeys following perinatal exposure to Aroclor 1016 or Aroclor 1248 (Schantz et al., 1991; Schantz et al., 1989; Levin et al., 1988). The Aroclor mixtures were fed to the dams prior to conception, with exposure continuing through gestation in one offspring cohort and ending at least 1 year prior to conception in two other cohorts (Schantz et al., 1991; Schantz et al., 1989). The offspring were subjected to behavioral tests at 14 months and 4-6 years of age, and these tests indicated impaired spatial position discrimination, facilitated learning ability for shape discrimination, and significantly impaired spatial alternation performance (Schantz et al., 1991; Schantz et al., 1989; Levin et al., 1988).

A longitudinal series of primate studies on postnatal PCB exposure following a single cohort of monkeys over several years was presented by Rice (1998, 1997) and Rice and Hayward (1999, 1997). Briefly, male cynomolgus monkeys were dosed from birth to 20 weeks of age with a PCB mixture developed to mimic the congener profile found in human milk (Rice and Hayward, 1999; Rice, 1998,

1997; Rice and Hayward, 1997). The monkeys were tested for impairment in a variety of neurobehavioral tests between 3 and 5 years of age; the results revealed learning deficits, perseverative behavior, and an inability to inhibit inappropriate responding (Rice, 1999a).

Impairments in inhibitory control, similar to those observed in monkeys, have also been observed in rats following prenatal and postnatal exposure to a mixture of PCB congeners developed to mimic a human PCB exposure from fish (Sable et al., 2009; Sable et al., 2006). Rodent studies have also reported other types of neurodevelopmental effects in offspring following prenatal, postnatal, or perinatal PCB exposure, including increased brain weight (Roegge et al., 2004; Kaya et al., 2002), ototoxicity (Powers et al., 2009; Powers et al., 2006; Crofton et al., 2000a; Crofton et al., 2000b; Goldey and Crofton, 1998; Herr et al., 1996; Goldey et al., 1995), memory errors (Yang et al., 2009; Roegge et al., 2000), and behavioral alterations (Elnar et al., 2012; Meerts et al., 2004; Widholm et al., 2004; Widholm et al., 2001; Lilienthal and Winneke, 1991; Lilienthal et al., 1990; Storm et al., 1981). Furthermore, changes in the neurochemistry and electrophysiology of various brain regions have been observed in both monkeys and rats exposed to PCB mixtures during development (Meerts et al., 2004; Gilbert et al., 2000; Provost et al., 1999).

A further review of information related to PCB exposure and neurological effects will be used to determine what questions, if any, on specific endpoints should be addressed using a systematic review approach.

Renal Effects

In general, renal effects have not been observed in humans occupationally exposed to PCBs (ATSDR, 2000). Most information on the renal toxicity of PCBs comes from studies in animals. Studies in rats exposed to PCBs for a subchronic duration have reported renal tubular degeneration, increased kidney weight, biochemical alterations suggestive of functional renal damage, and cortical tubular protein cast formation (Gray et al., 1993; Andrews, 1989; Treon et al., 1956). Other studies have reported no renal effects in rats, rabbits, guinea pigs or monkeys following subchronic PCB exposure (Street and Sharma, 1975; Allen et al., 1974; Bruckner et al., 1974; Vos and de Roij, 1972), or in rats or monkeys exposed for a chronic duration (Mayes et al., 1998; Arnold et al., 1997). Since there is very little evidence linking PCB exposure to renal effects, a systematic review is not planned to evaluate these effects in response to PCB exposure.

Reproductive Effects

In humans, PCB exposure has been associated with disrupted reproductive endpoints in both women (e.g., endometriosis, reduced fecundability, and miscarriage) (Cohn et al., 2011; Buck Louis et al., 2009; Porpora et al., 2009; Roya et al., 2009; Tsuchiya et al., 2007; Porpora et al., 2006; Quaranta et al., 2006; Reddy et al., 2006; Heilier et al., 2005; Law et al., 2005; De Felip et al., 2004; Fierens et al., 2003; Sugiura-Ogasawara et al., 2003; Buck et al., 2002; Pauwels et al., 2001; Gerhard et al., 1998; Lebel et al., 1998; Buck et al., 1997) and men (e.g., reduced sperm quality, conception delay, and infertility) (Cok et

al., 2010; Cok et al., 2008; Hauser et al., 2003; Dallinga et al., 2002; Hauser et al., 2002; Buck et al., 2000; Buck et al., 1999; Courval et al., 1999; Pines et al., 1987; Bush et al., 1986).

Studies have also reported reproductive toxicity following exposure to PCBs in adult animals: decreased conception in female monkeys and rodents (Arnold et al., 1995; Schantz et al., 1991; Schantz et al., 1989; Levin et al., 1988; Welsch, 1985; Brezner et al., 1984; Barsotti et al., 1976; Allen et al., 1974); decreased fetal survival in monkeys and mink (Brunström et al., 2001; Bäcklin et al., 1997; Bäcklin and Bergman, 1995; Kihlstrom et al., 1992; Aulerich and Ringer, 1977); prolonged estrus, decreased sexual receptivity, and decreased implantation in female rodents (Welsch, 1985; Brezner et al., 1984); and impaired spermatogenesis and fertility in male rodents (Krishnamoorthy et al., 2007; Faqi et al., 1998; Huang et al., 1998b; Gray et al., 1993; Smits-van Prooije et al., 1993; Sager et al., 1991; Sager et al., 1987; Sager, 1983; Gellert and Wilson, 1979). Hany et al. (1999) and Kaya et al. (2002) exposed female rats to 4 mg/kg-day of a mixture of PCB congeners developed to mimic the congener profile found in human milk. Exposure began 50 days prior to mating and was terminated at the day of birth (PND 0). The offspring continued to be exposed via lactation until PND 21. Adult male offspring of exposed dams had reduced relative testes weights and serum testosterone levels long after termination of exposure (Hany et al., 1999) as well as a significantly higher saccharin consumption than controls, suggesting a behavioral feminization (Kaya et al., 2002; Hany et al., 1999).

A further review of information related to PCB exposure and reproductive effects will be used to determine what questions, if any, on specific endpoints should be addressed using a systematic review approach.

Respiratory Effects

Effects on the respiratory system have been observed in occupationally-exposed populations. Observed effects include upper respiratory tract irritation, cough, tightness of the chest, reduced forced vital capacity, and reduced forced expiratory volume (Lawton et al., 1986; Smith et al., 1982; Warshaw et al., 1979). The significance of these effects is unclear due to study design issues, including lack of a control group (Warshaw et al., 1979), and lack of confirmation by follow-up evaluations (Lawton et al., 1986). The occurrence of self-reported respiratory effects was not elevated among residents who lived within 0.5 mile of three PCB-contaminated waste sites (Stehr-Green et al., 1986b).

One animal study provides evidence of PCB-induced respiratory effects following oral exposure: pulmonary congestion and hemorrhage were reported in pigs exposed to Aroclor 1242 or Aroclor 1254 for 91 days (Hansen et al., 1976). However, there were no histological alterations in the lungs of rats exposed to 50 mg/kg-day PCBs for 3 weeks (Bruckner et al., 1973), to doses up to 11.2 mg/kg-day for 24 months (Mayes et al., 1998), in mice exposed to 22 mg/kg-day for 6 weeks (Loose et al., 1978a; Loose et al., 1978b), or in rhesus monkeys exposed to doses up to 0.080 mg/kg-day for 72 months (Arnold et al., 1997). Hu et al. (2012) observed “minimal cellular infiltrates and mild degenerative changes” in the nasal passages and trachea of female Sprague-Dawley rats exposed via nose-only inhalation to 520 $\mu g/m^3$ of a PCB mixture developed to mimic the congener profile of air in Chicago for an average of 1.6 hours/day, 5 days/week for 4 weeks. There was no change in the numbers of macrophages, neutrophils, and

lymphocytes, total protein, lactate dehydrogenase activity, or cytokine levels in bronchoalveolar lavage fluid, and no significant difference in cytochrome P450 (CYP) enzyme activity, total glutathione (GSH) level, glutathione disulfide (GSSG) level, or GSSG/GSH ratio in the lungs. Other studies of animals exposed to PCBs by inhalation have not provided information on exposure-related respiratory effects (Casey et al., 1999; Treon et al., 1956). Since there is very little evidence linking PCB exposure by any route to respiratory effects, a systematic review is not planned to evaluate these effects in response to PCB exposure.

3.4. Key Issues To Be Addressed in the Assessment

Impact of Congener Profile on the Toxicity of PCB Mixtures

Humans are environmentally exposed to PCBs as complex mixtures of congeners. PCB congeners differ not only structurally but also qualitatively and quantitatively with respect to biological responses. And, there may be important differences between the PCB mixtures administered to laboratory animals in toxicological studies and the mixtures that humans are exposed to in the environment. The Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures (U.S. EPA, 2000) recommends several approaches to quantitative health risk assessment of a chemical mixture, depending upon the type of available data. The preferred approach is to use toxicity data on the mixture of concern. Alternatively, when toxicity data are not available for the mixture of concern, use of toxicity data on a "sufficiently similar" mixture is recommended.

Out of all the possible congener combinations that may exist, a relatively small subset of complex PCB mixtures has been tested in animal studies. Most animal studies have administered commercial PCB mixtures (e.g., "Aroclors", including Aroclors 1016, 1242, 1248, 1260, and two distinct types of Aroclor 1254, one produced prior to 1974, and another produced between 1974 and 1977, which contained a much higher concentration of dioxin-like congeners). One disadvantage of these studies is that the congener profiles of commercial PCB mixtures do not match those that occur in the environment. Prior to human exposure, commercial mixtures in the environment undergo processes such as volatilization and preferential bioaccumulation, which dramatically alter a PCB mixture's congener profile.

Important relationships exist among congener structure, environmental occurrence, and human exposure to PCBs. Oral exposures to PCBs occur primarily via consumption of contaminated foods, particularly fish, meat, and poultry. These foods contain mixtures of persistent PCB congeners that have been biomagnified through the food chain. Biomagnification of PCBs roughly increases with higher congener chlorination; the PCB mixtures most often consumed by humans consist largely of PCBs with 5, 6, or 7 chlorine substitutions (e.g., PCBs 138, 153 and 180). Exposures to PCBs through dermal (and, to some extent, oral) contact with soil may be relatively enriched with the most highly chlorinated congeners (i.e., 8–10 chlorine substitutions) because these tend to bind tightly to soil, sediment, and organic matter. The prominent PCB congeners found in air samples are not determined by biomagnification but rather by volatility and the congener profile of the source material. Volatility is greatest for the lower chlorinated congeners (i.e., 1–4 chlorine substitutions); the proportion of these congeners making up an inhalation exposure to PCBs may be relatively large compared to what might be found for an oral or dermal

exposure. However, inhalation (as well as dermal and oral) exposure to higher chlorinated congeners bound to dust may also occur.

A few studies have utilized mixtures of PCB congeners formulated to mimic an environmental exposure (e.g., formulations representing the congeners found in human milk or in contaminated fish or soil); for a typical oral exposure, these mixtures may best represent the "mixture of concern." Thus, these studies may be preferred for human health risk assessment because they minimize the uncertainty that results from using research on one PCB mixture to assess the risk from exposure to a different mixture. However, despite the fact that their congener profiles do not precisely replicate that of an environmental PCB mixture, studies administering commercial PCB mixtures have generally observed toxicological effects within the same dose range as environmental mixtures. Furthermore, as noted by U.S. EPA (1996), commercial PCB mixtures contain overlapping groups of congeners that, together, span the range of congeners most frequently found in environmental mixtures. Therefore, commercial PCB mixtures may be "sufficiently similar" to environmental mixtures, and animal studies using commercial PCB mixtures may be useful to support human health hazard identification and dose-response assessment for PCBs in the environment.

Based on the available data, some key issues EPA will evaluate regarding the impact of congener profile on toxicity include the following:

- Relative toxic potencies of complex PCB mixtures (e.g., environmental and commercial) for various non-cancer health effects observed in animal studies

- Implications of using toxicological data from a limited set of PCB mixtures for human health risk assessment in a wide variety of exposure contexts (e.g., breastfeeding infant exposure to PCBs in human milk, exposure to PCBs from fish consumption, inhalation exposure to PCBs in contaminated indoor air)

- Considerations when using media-specific data (e.g., soil, groundwater, sediment, fish) collected using various analytical techniques (e.g., Aroclor analyses, measures of total PCBs, and congener or isomer analyses) with toxicity information to be provided in the assessment

Evaluation of Epidemiological Studies for PCB Dose-Response Assessment

Human data are generally preferred over animal data for human health hazard identification and dose-response assessment. However, certain study design and methodologic considerations are important for determining which human studies, if any, are appropriate for use in an assessment: documentation of study design, methods, population characteristics, and results; definition and selection of the study group and comparison group; ascertainment of disease or health effect; duration of exposure and follow-up and adequacy for assessing the occurrence of effects; sample size and statistical power to detect anticipated effects; participation rates and potential for selection bias as a result of the achieved participation rate; potential confounding and other sources of bias addressed in the study design or in the analysis of results; ascertainment of exposure to the chemical or mixture under consideration; and characterization of

exposure during critical periods of development. Of particular concern for epidemiological studies of PCBs is the common practice of characterizing exposure using current measures of body burden, often relying on a limited number of measured congeners. This approach to exposure assessment may be appropriate for some applications, but may be of limited utility for characterizing the extent of human PCB exposure and the relationship between exposure and effect:

(1) Current body burden reflects cumulative exposure to persistent PCB congeners, but only recent exposure to labile congeners. The half-life and elimination characteristics of PCB congeners vary significantly. And, the relative contributions of less-persistent and more-persistent PCB congeners to toxicological outcomes are poorly-defined. In recent years, a better appreciation has been gained for the full scope of human exposure to PCBs in the general environment, including the potential for significant inhalation and dermal exposure to lower-chlorinated, less-persistent congeners. Especially given this new understanding, it seems likely that, except in cases where the response to an exposure is known to occur during a defined period of relatively short duration (e.g., prenatal exposure), cross-sectional estimates of body burden may capture only a portion of past exposure levels which may have precipitated observed health effects.

(2) Most current body burden estimates rely on only a subset of PCB congeners selected because of their relative occurrence in biological samples and/or the ability to detect them using a given analytical method–not because of their biological activity or their potential to induce a particular health effect. Again, use of this approach results in an incomplete exposure assessment that may easily miss important relationships between exposure and effect.

(3) Even for persistent congeners that are routinely measured in epidemiological studies (e.g., PCBs 138, 153 and 180), a current, cross-sectional estimate of body burden may not be useful for assessing exposure during a time period critical for the development of a particular toxicological outcome (e.g., developmental outcomes known to be sensitive to PCB exposure). Depending on the endpoint of concern, the timing of exposure could be just as important as the magnitude. It is generally possible to envision several different exposure scenarios that could lead to the same current PCB body burden. And, for each scenario, although the resulting body burden is the same, the toxicological implications could be very different.

Altogether, these issues may lead to a significant potential for exposure misclassification in epidemiological studies of PCBs that rely entirely on measures of body burden for exposure assessment. Despite this potential limitation, most cohorts studied have revealed adverse health effects associated with PCB exposure, including developmental neurobehavioral outcomes, thyroid hormone disruption, immunological effects, and reduced birth weight. These studies provide important evidence for hazard identification of human health effects. However, to define the quantitative dose-response relationship

between PCBs and associated health effects, EPA will consider certain key issues related to epidemiological studies:

- Importance of specific study design and methodologic aspects for supporting use of epidemiological studies to support PCB hazard identificantion and/or dose-response assessment

- Reliable methods for assessing PCB exposure in humans that provide information sufficient for quantifying potential relationships between exposure to environmental PCB mixtures and health effects

- Implications of using studies with incomplete exposure characterizations for dose-response assessment

- Potential for and limitations of using data from toxicological studies in animals, where the source, level and timing of exposure are known with greater certainty but some uncertainty is introduced by the need for interspecies extrapolation

Potential for Hazard Identification and Dose-Response Assessment for PCB Exposure Via Inhalation

There is evidence to suggest that PCB inhalation may pose a hazard to human health. Hepatotoxic, endocrine, dermal, ocular, immunological, neurological, reproductive and developmental effects have been observed in humans following occupational exposures to PCBs (Langer et al., 1998; Taylor et al., 1989; Emmett et al., 1988a; Bertazzi et al., 1987; Lawton et al., 1985; Taylor et al., 1984; Chase et al., 1982; Fischbein et al., 1982; Smith et al., 1982; Maroni et al., 1981; Fischbein et al., 1979; Meigs et al., 1954). Furthermore, thymic atrophy, urinary bladder epithelial hyperplasia and alterations in open field behavior have been reported in rats exposed at an air PCB concentration relevant to non-occupational human environmental exposure levels (Casey et al., 1999). However, the database of studies investigating health effects resulting from PCB exposure consists primarily of oral exposure studies. It is not clear whether the existing database of inhalation studies will be sufficient to support human health risk assessment for inhalation exposure to PCBs. In cases such as this, data from oral exposure studies may be considered to support the assessment of human health risk from inhalation exposure, using route-to-route extrapolation. This extrapolation is sometimes used for chemicals that are not expected to (1) have different toxicity by the oral and inhalation routes, (2) be impacted significantly by first-pass metabolism, nor (3) cause respiratory (portal of entry) effects. PCBs may generally meet these criteria; however, the congener content of volatilized PCB mixtures is often, but not always, skewed toward lower-chlorinated congeners (i.e., those with ≤ 4 chlorine substitutions) compared with the congener content of a PCB mixture likely to be present in contaminated fish, human milk, or some of the Aroclor mixtures administered in oral exposure studies. It is not clear whether such differences in congener profile translate into meaningful differences in toxicity between the two exposure routes (see *Impact of Congener Profile on the Toxicity of PCB Mixtures*).

Based on the available data, some key issues EPA will evaluate regarding the potential for hazard identification and dose-response assessment in the context of PCB inhalation include the following:

- Availability of information to support hazard identification for PCB inhalation, considering differences in toxicity of congeners that are inhaled versus ingested and differences between the inhalation and oral exposure routes

- Potential options for conducting a dose-response assessment for PCB inhalation exposure, including the use of data from available PCB inhalation studies, the route-to-route extrapolation from oral PCB exposure data, or additional options

- The availability, evaluation, and further development of PBPK models for reliable route-to-route, interspecies, and/or intraspecies extrapolation

Suitability of Available Toxicokinetic Models for Reliable Route-to-Route, Interspecies, and/or Intraspecies Extrapolation

The absorption, distribution, metabolism, and elimination of PCBs have been studied for a variety of individual congeners, a few simple mixtures (e.g., PCB 126+153), and multiple complex PCB mixtures (e.g., Aroclors). Studies conducted in humans and animals demonstrate rapid absorption of PCBs by inhalation, oral, and dermal routes of exposure. Once absorbed, PCBs enter the circulation and may initially accumulate in highly-perfused organs such as the liver, kidney, or spleen although quantitative human data on specific organ distribution are not available. Differential accumulation and retention of PCBs is related to exposure and the rate of congener metabolism, which generally decreases with increasing chlorine substitution (although chlorine position is also important). PCB excretion generally requires biotransformation; therefore, PCB congeners with slow rates of metabolism can retain biological activity long after exposure stops. As mentioned above, inhalation exposure often favors volatile, lower-chlorinated PCB congeners, which tend to be metabolized and eliminated more quickly than higher-chlorinated congeners. On the other hand, oral PCB exposures commonly consist of persistent, higher-chlorinated congeners that have been biomagnified through the food chain. These highly chlorinated congeners tend to have a slow rate of metabolism, and their lipophilicity results in their storage in body lipids where they have long elimination half-lives.

Because this assessment will address non-cancer hazards associated with exposure to complex PCB mixtures, EPA intends to evaluate available toxicokinetic models for their ability to predict the dose metrics of such mixtures. Lipophilicity, binding to liver proteins (e.g., cytochromes, AhR), and rate of elimination (due to metabolism or fecal excretion) are the main determinants of PCB pharmacokinetics. Variation of these pharmacokinetic determinants among individual PCBs limits the application of congener-specific models in the assessment of a complex PCB mixture. A single set of parameters to describe these determinants for the complex mixture may not be justifiable because significant individual pharmacokinetic variation has been observed for different PCB congeners. Additionally, possibilities of

pharmacokinetic interaction, such as competition at binding sites or synergy in the case of induction of enzymes, may exist between PCB congeners in a complex mixture.

Based on the available data, some key issues EPA will evaluate regarding the toxicokinetics of PCBs include the following:

- The availability, evaluation, and further development of PBPK models for reliable route-to-route, interspecies, and/or intraspecies extrapolation
- Available information on toxicokinetic differences among PCB congeners and mixtures
- Available information on inter- and/or intraspecies differences in the toxicokinetics of PCBs, including differences across lifestages

Potential Toxicokinetic Models or Methods to Estimate the Relationship between Continuous Daily Maternal PCB Intake and Milk PCB Concentrations in Humans

PCBs accumulate in body lipids and can be transferred to infants via breast milk, presenting a critically important challenge for human health risk assessment. This lactational exposure occurs at higher levels and over a shorter time period compared to maternal exposure, which occurs over the long-term prior to and during pregnancy and lactation. In addition, because of the relatively small size of a nursing infant, this high exposure may lead to PCB levels in blood and tissues of the infant that far exceed those in the mother. Offspring can also be exposed to PCBs through transplacental transfer; however, lactational transfer of PCBs has been shown to be the major contributor to the body burden of human infants (Lackmann et al., 2004; Ayotte et al., 2003; Patandin et al., 1999; Abraham et al., 1998; Lanting et al., 1998a; Patandin et al., 1997; Yakushiji et al., 1984). Furthermore, developmental effects have been observed in humans and animals exposed to PCBs via lactation (Elnar et al., 2012; Verner et al., 2010; Vreugdenhil et al., 2004; Walkowiak et al., 2001; Jacobson et al., 1990a). Therefore, breastfeeding infants represent a lifestage and population uniquely susceptible to the adverse health effects of PCBs by virtue of both increased exposure and vulnerability to potential disruption of ongoing developmental processes.

Based on the available data, some key issues EPA will evaluate regarding the lactational transfer of PCBs include the following:

- Available information on the lactational transfer of PCBs and the relationship between long-term maternal PCB exposure and consequent exposure in a breastfeeding infant
- The availability, evaluation, and further development of models or methods that could be used to quantitatively predict transfer of PCBs across the placenta or via breast milk

Putative Mechanisms of PCB Toxicity

As mentioned above in the context of PCB mixtures, PCB congeners differ not only structurally but also qualitatively and quantitatively with respect to biological responses. PCB exposure produces an array of toxic effects, likely through multiple and diverse mechanisms. Non-ortho and mono-ortho

substituted PCB congeners are often referred to as "dioxin-like" because they, like other dioxin-like compounds (e.g., PCDDs and PCDFs), can assume a coplanar molecular configuration and bind to and activate the aryl hydrocarbon receptor (AhR) (Hansen, 1998; Connor et al., 1995; Safe, 1994). Thus, one mechanism for coplanar PCB congener toxicity may be AhR-dependent (Safe, 1994; Safe, 1990; Poland and Knutson, 1982). Support for this hypothesis comes from (1) the similarity between PCB effects and effects produced by 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) and related halogenated aromatic hydrocarbons that act through initial AhR mediation, (2) results from in vitro binding studies, and (3) results from congener-specific in vivo studies in rodent strains differing in Ah-responsiveness (Hori et al., 1997; Safe, 1994; Safe, 1990).

Because dioxin-like compounds induce certain human health effects by a shared AhR-dependent mode of action, the component-based TEF approach has been proposed to evaluate human health hazards from complex environmental mixtures containing these toxicants (U.S. EPA, 2010; Van den Berg et al., 2006; Van den Berg et al., 1998; Safe, 1994; Safe, 1990). The TEF approach compares the relative potency of individual congeners, based on in vitro or acute in vivo data, with that of 2,3,7,8-TCDD, the best-studied member of this chemical class, so that the TEF for 2,3,7,8-TCDD is 1. The concentration of each PCB congener is multiplied by that congener's TEF to determine a TEQ; then, the congener TEQs are summed to give the total toxic equivalency of the mixture. The mixture TEQ is compared with reference exposure levels for 2,3,7,8-TCDD to estimate human health hazard. TEFs have been recommended by the World Health Organization for the following PCB congeners: PCB 77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169 and 189 (Van den Berg et al., 2006).

Although the TEF approach can be very useful for quantifying the potential hazards associated with exposure to dioxin-like compounds, its application to the assessment of hazard from complex PCB mixtures is limited for a number of reasons. Evidence suggests that the most potent dioxin-like PCB congeners are minor components in environmental PCB mixtures (Hansen, 1998; Safe, 1998b; Safe, 1998a), and there is evidence that several AhR-independent mechanisms may contribute to PCB toxicity (Kodavanti et al., 2005; Chauhan et al., 2000; Cheek et al., 1999; Mariussen et al., 1999; Fischer et al., 1998; Hansen, 1998; Tilson et al., 1998; Tilson and Kodavanti, 1998; Kodavanti and Tilson, 1997; Tilson and Kodavanti, 1997; Wong and Pessah, 1997; Wong et al., 1997; Seegal, 1996; Wong and Pessah, 1996; Brown and Ganey, 1995; Tithof et al., 1995; Safe, 1994; Ganey et al., 1993; Harper et al., 1993b; Harper et al., 1993a; Shain et al., 1991; Seegal et al., 1990; Seegal et al., 1989). The following discussion describes proposed modes of action, both AhR-dependent and –independent, through which exposure to PCB mixtures may induce various non-cancer health effects.

Hepatic effects

PCBs induce hepatic Phase I (CYP oxygenases) and Phase II (e.g., UDP glucuronyltransferases, epoxide hydrolase, or glutathione transferase) enzyme levels to varying degrees and specificities (Hansen, 1998). According to the results of structure activity studies, CYP1A induction occurs as a result of activation of the aryl hydrocarbon receptor (AhR) by dioxin-like non-ortho PCB congeners while induction of the phenobarbital-type CYPs (i.e., CYP2B1, 2B2, and 3A) is AhR-independent (van der Burght et al., 1999; Hansen, 1998; Schuetz et al., 1998; Connor et al., 1995; Safe, 1994; Schuetz et al.,

1986). Porphyria and porphyria cutanea tardea are additional hepatic effects of PCB exposure that may involve AhR activation (Franklin et al., 1997; Smith et al., 1990a; Smith et al., 1990b) while liver hypertrophy and pathology may involve both AhR-dependent and AhR-independent mechanisms (NTP, 2006a, b; Hori et al., 1997).

Effects on Thyroid Hormone Homeostasis

ATSDR (2000) proposed several modes of action through which PCBs may disrupt the production and disposition of thyroid hormones: (1) disruption of thyroid hormone production, both in the thyroid and in peripheral tissues; (2) interference with thyroid hormone transport to peripheral tissues; and (3) acceleration of the metabolic clearance of thyroid hormones. Studies that have shown depressed levels of adrenal cortical steroids in PCB-exposed animals (Byrne et al., 1988) may also be relevant to PCB-induced hypothyroidism because depressed levels of adrenal steroids have been associated with hypothyroidism in humans (Dluhy, 2000). In hypothyroidism, this effect is thought to result from decreases in both secretion and metabolism of adrenal steroids.

PCB-induced effects on thyroid hormone homeostasis may be the result of a combination of AhR-dependent and AhR-independent mechanisms. Induction of UDP-GT and resulting metabolic elimination of T_4 is an example of an AhR-dependent mechanism of thyroid hormone disruption (McLanahan et al., 2007; Desaulniers et al., 1997; Van Birgelen et al., 1995); however, PCBs can affect serum T_4 levels independent of both AhR activation and UDP-GT induction (Li and Hansen, 1996). Decreased binding of thyroid hormones to transthyretin is an example of an AhR-independent mechanism of thyroid hormone disruption (Chauhan et al., 2000; Cheek et al., 1999; Darnerud et al., 1996). Transthyretin is an important transport protein for both T_4 and T_3. Inhibition of thyroid hormone binding to transthryetin may alter hormone delivery to target tissues and depress levels of serum total T_4 or T_3 (Brouwer et al., 1998).

Immunological effects

Harper et al. (1995) compared the potencies of nine PCB congeners (PCBs 77, 105, 118, 126, 156, 169, 170, 180, 189) with respect to their abilities to reduce splenic PFC and antibody responses to trinitrophenyl-lipopolysaccharide (TNP-LPS) in mice. They also compared the potencies of these congeners with those of TCDD and Aroclors 1260, 1254, 1248, and 1242. The results showed that the non-ortho PCB congeners (PCBs 77, 126, 169) were far more potent immunotoxicants than the mono- or di-ortho congeners. Furthermore, there is evidence that non-dioxin-like PCB congeners antagonize the immunotoxic effects of dioxin-like PCB congeners (Zhao et al., 1997; Harper et al., 1995). Such antagonism may explain the observation by Harper et al. (1995) that a TEF approach based on the relative abilities of individual congeners to inhibit the splenic PFC and antibody response to TNP-LPS overestimated the immunotoxicity of common commercial PCB mixtures, which contain a large proportion of non-dioxin-like congeners.

Despite extensive documentation of AhR-dependent immunosuppression, other mechanisms may also contribute to PCB-induced immunological effects (Stack et al., 1999; Harper et al., 1993b; Harper et al., 1993a). Studies measuring the splenic PFC response to SRBCs have reported higher immunotoxic

potencies in this assay for three nonachlorobiphenyls (PCBs 206, 207 and 208) and decachlorobiphenyl PCB 209 than for three hexachlorobiphenyls (PCBs 153, 154 and 155) (Harper et al., 1993b). All of these congeners contain multiple ortho chlorines, and none are effective AhR agonists. These results are consistent with the hypothesis that some PCBs induce immunotoxicity via AhR-independent mechanisms.

Neurological effects

According to the available evidence, PCB exposure could result in neurological effects through a variety of mechanisms including (1) reduction of dopamine levels, (2) disruption of intracellular calcium homeostasis, and (3) thyroid hormone disruption. In vitro studies have reported decreased cellular levels of dopamine in pheochromocytoma cells cultured with PCBs (Seegal et al., 1989). In this in vitro system, the most active PCB congeners, PCBs 48, 50, and 52, had at least two ortho chlorines; dioxin-like congeners, PCBs 77 and 126, had minimal effects on dopamine levels (Shain et al., 1991). In vivo studies in adult primates have reported decreased dopamine concentrations in four regions of the brain: the caudate, putamen, substantia nigra, and hypothalamus (Seegal et al., 1990). Gas chromatographic analysis of samples from these brain regions identified only three PCB congeners, PCBs 28, 47, and 52, and these congeners are poor AhR agonists. Thus, the observed reduction in dopamine levels occurred in the absence of AhR activation. Reduction in dopamine levels following PCB exposure has been postulated to involve decreased dopamine synthesis via direct or indirect PCB inhibition of tyrosine hydroxylase (Choksi et al., 1997; Seegal, 1996) or L-aromatic amino acid decarboxylase (Angus et al., 1997). Alternatively, dopamine levels may be reduced by PCB inhibition of vesicular uptake of dopamine (Mariussen et al., 1999).

Another proposed mechanism for the neurological effects of PCB exposure involves disrupted signal transduction resulting from altered intracellular calcium homeostasis (Kodavanti et al., 2005; Tilson et al., 1998; 1998; Kodavanti and Tilson, 1997; Tilson and Kodavanti, 1997; Wong and Pessah, 1997; Wong et al., 1997; Wong and Pessah, 1996). Similar to the structure-activity relationships reported for PCB effects on dopamine levels (Shain et al., 1991), non-dioxin-like PCB congeners interfered with calcium homeostasis and second messenger systems to a greater extent than dioxin-like PCB congeners (Kodavanti et al., 2005; Kodavanti et al., 1998; Tilson et al., 1998; Kodavanti and Tilson, 1997; Kodavanti et al., 1996, 1995; Safe, 1994; Kodavanti et al., 1993).

As shown by in vitro studies, PCBs may disrupt intracellular calcium homeostasis by (1) altering Ca^{2+} sequestration by microsomes and mitochondria (Kodavanti et al., 1996), and/or (2) altering the function of ryanodine receptor-mediated Ca^{2+} channels (RyRs) (Schantz et al., 1997; Wong and Pessah, 1997; Wong et al., 1997; Wong and Pessah, 1996). In structure activity studies of ryanodine binding in the presence of selected pentachlorobiphenyls, ortho PCB congeners favored binding, non-ortho congeners did not, and para substitution was found to decrease RyR binding activity regardless of the pattern of ortho substitution (Pessah et al., 2010; Wong and Pessah, 1996). In another study using hippocampal slices of rat brains, perfusion with ortho congener PCB 95 both enhanced ryanodine binding and inhibited electrophysiological responses to electrical pulse stimulations (Wong et al., 1997). Conversely, perfusion with mono-ortho congener PCB 66 neither enhanced ryanodine binding nor inhibited electrophysiological responses to stimulation (Wong et al., 1997). Ryanodine binding to calcium

channels was also altered in the offspring of rats exposed to PCB 95 (8 or 32 mg/kg-day) by gavage on gestation days 10–16. These offspring displayed decreased ryanodine binding to calcium channels in the hippocampus and increased ryanodine binding in the cerebral cortex (Schantz et al., 1997).

Dynamic changes in intracellular Ca^{2+} concentrations, such as those mediated by RyR activity, contribute to critical determinants of neuronal connectivity, including neuronal excitability, dendritic synaptic plasticity, cell proliferation, cell differentiation, cell movement, and apoptosis (Zheng and Poo, 2007; Moody and Bosma, 2005; Spitzer et al., 2004; Cline, 2001; Martin, 2001; Segal, 2001; Barone et al., 2000; Kennedy, 2000; Matus, 2000; Sastry and Rao, 2000; Balschun et al., 1999; Korkotian and Segal, 1999; Berridge, 1998). In vitro studies have shown that PCBs can affect some of these processes through RyR activation. PCB 95, a congener with potent RyR activity, promoted dendritic growth in primary cortical neuron cultures, and this effect was blocked by pharmacological antagonism of RyR activity (Yang et al., 2009). However, dendritic growth was not promoted by PCB 66, a congener with negligible RyR activity, PCBs have also been shown to induce apoptosis in cultured neurons; this proapoptotic activity was inhibited by a selective RyR antagonist (Mack et al., 1992; Chiesi et al., 1988).

A third potential mechanism for the developmental neurological effects of PCB exposure is disruption of thyroid hormone homeostasis. As shown by studies in animals, gestational and/or lactational exposure to PCBs depletes levels of circulating thyroid hormone in the fetus or neonate (Zoeller et al., 2000; Provost et al., 1999; Rice, 1999b; Li et al., 1998; Schuur et al., 1998; Cooke et al., 1996; Corey et al., 1996; Darnerud et al., 1996; Morse et al., 1996; Goldey et al., 1995; Seo and Meserve, 1995; Juarez de Ku et al., 1994; Collins and Capen, 1980). Developmental effects of PCBs on thyroid hormone homeostasis have been mechanistically linked to some neurodevelopmental effects (Gerstenberger and Tripoli, 2001; Goldey and Crofton, 1998). Thyroid hormones regulate essential developmental processes such as cell proliferation, cell migration, and differentiation. During critical developmental periods, proper thyroid balance is essential for normal development of the brain (Porterfield and Hendry, 1998). Therefore, to the extent that PCB-induced thyroid hormone disruption is an AhR-dependent effect, some of the neurodevelopmental outcomes occurring downstream of PCB-induced thyroid hormone disruption could also be AhR-dependent. However, as discussed above, structure-activity studies in rats have shown that the effects of PCBs on thyroid hormone homeostasis may occur via both AhR-dependent and AhR-independent mechanisms.

In summary, structure activity relationships have been elucidated for two of the hypothesized modes of action for the neurological and/or neurodevelopmental effects of PCB exposure: reduced neurotransmitter levels and altered intracellular signaling processes. Non-dioxin-like PCB congeners have been shown to be more effective than dioxin-like congeners at both reducing dopamine levels and disrupting calcium homeostasis (Kodavanti et al., 1996, 1995; Shain et al., 1991). Therefore, AhR-independent mechanisms may play an important role in PCB-induced neurological and neurodevelopmental toxicity.

Reproductive effects

Both human and animal studies have reported reproductive effects following PCB exposure, and PCB reproductive toxicity may be mediated by multiple molecular pathways. The reproductive effects of

PCB exposure may result from altered endocrine function, including possible estrogenic or anti-estrogenic activities and disrupted thyroid hormone homeostasis. Available structure-activity data support both AhR-dependent and AhR-independent pathways for the reproductive effects of PCB exposure. Adding to this mechanistic complexity, there is evidence to suggest that at least some of the reproductive effects of PCB exposure are mediated by hydroxylated PCB metabolites.

The estrogenic and anti-estrogenic activities of some commercial PCB mixtures, individual congeners, and hydroxylated metabolites have been assayed using a variety of test systems, both in vivo and in vitro (Andersson et al., 1999; Arcaro et al., 1999; Hansen, 1998; Connor et al., 1997; Gierthy et al., 1997; Kramer et al., 1997; Li and Hansen, 1997; Moore et al., 1997; Nesaretnam et al., 1996; Battershill, 1994; Krishnan and Safe, 1993; Astroff and Safe, 1990; Korach et al., 1988). These studies have observed a variety of responses across types of PCBs and assays, indicating that the estrogenic or anti-estrogenic activities of PCBs may occur through direct binding to the estrogen receptor or by alternative mechanisms, such as inhibition of hydroxy steroid sulfotransferase, which may result in inhibition of estradiol metabolism and indirect estrogenic activity (Kester et al., 2000). Structure-activity relationships are not well defined for estrogenic or anti-estrogenic activities of PCB congeners or their metabolites (Connor et al., 1997; Moore et al., 1997; Nesaretnam et al., 1996); these effects of PCB exposure may occur through a combination of AhR-dependent and AhR-independent mechanisms.

Another potential mechanism for the reproductive effects of PCB exposure is disruption of thyroid hormone homeostasis. As mentioned above, gestational and/or lactational exposure to PCBs has been shown to deplete levels of circulating thyroid hormone in animal offspring. Developmental effects of PCBs on thyroid hormone homeostasis have been mechanistically linked to downstream developmental effects on reproduction (Baldridge et al., 2003; Cooke et al., 1996). Thyroid hormones regulate essential developmental processes such as cell proliferation, cell migration, and differentiation. During critical developmental periods, proper thyroid balance is essential for normal development of male and female reproductive organs (Dijkstra et al., 1996; Cooke and Meisami, 1991; Cooke et al., 1991). As discussed above, mechanistic studies of PCB-mediated thyroid hormone disruption have provided evidence for both AhR-dependent and AhR-independent mechanisms.

Based on the available data, some key issues EPA will evaluate regarding the modes of action of PCB toxicity include the following:

- The relevance of proposed mechanisms of PCB toxicity observed in vitro to health effects observed with in vivo PCB exposure

- The relative contributions of dioxin-like and non-dioxin-like activities to the toxicity of PCB mixtures for each health effect

- How an understanding of the relative contributions of dioxin-like and non-dioxin-like activities might inform the use of this new PCB assessment in conjunction with U.S. EPA's guidance for human health risk assessments of 2,3,7,8-TCDD and dioxin-like compounds (U.S. EPA, 2012, 2010).

- The availability, evaluation, and further development of relative potency factors that could be used to inform human health risk assessment of PCB-induced neurodevelopmental, reproductive, or other non-cancer effects

Factors Influencing Human Susceptibility

Numerous studies have investigated the effects of exposure to PCBs in newborn and young children. The main focus of these studies has been the evaluation of neurobehavioral effects, but information on other end points is also available, including anthropometric measures at birth, growth rate, immunocompetence, and thyroid hormone status. Vulnerability to developmental effects together with the potential for elevated early life exposure to PCBs from breastfeeding identifies human infants and young children as a population that may be particularly susceptible to PCB-induced health effects. Early life susceptibility has already been discussed above in the context of PCB exposure and toxicokinetics. No other potential susceptibility factors have been identified for the toxic effects of PCBs.

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