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NON-DIOXIN-LIKE PCBs: EFFECTS AND CONSIDERATION IN ECOLOGICAL RISK ASSESSMENT

by

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1. Introduction

1.1 Issue

An estimated one million metric tons of commercial mixtures of polychlorinated biphenyls (PCBs), such as Aroclors (USA), Kanechlors (Japan) and Clophens (Germany), were manufactured (WHO, 1993) and used worldwide as dielectric fluids in capacitors and transformers, heat transfer fluids, hydraulic fluids, lubricating oils, and as additives in pesticides, paints, copy paper, adhesives and plastics during the 1930s through the mid-1970s. PCBs have entered the environment during both use and disposal and have been shown to be ubiquitous contaminants, occurring in most environmental media as well as biota.

Historically, analyses of environmental media and associated risk assessments have been conducted using approaches that consider the PCB mixtures as a whole, i.e., "Total PCBs" or Aroclors. Subsequently, it has been shown that the fate of various congeners in the environment varies, such that the PCB congener profiles in environmental media may change significantly from the original commercial mixtures. Likewise, individual PCB congeners have been found to vary significantly in their uptake, distribution, metabolism, and elimination within biological systems such that the congener profile in biological tissues can be quite different from both the original commercial PCB mixture and environmental media. Toxicological effects and dose-response relationships within biological systems can also vary among the different PCB congeners.

As a result, the consensus within the scientific community is that "Total PCB"- and/or Aroclor-based risk analyses may not adequately characterize risks posed by PCB mixtures (WHO, 2001). Those PCB congeners that elicit dioxin-like toxicity have been defined and a toxicity equivalence approach for use in both human health and ecological risk assessment has been developed (U.S. EPA, 2000, 2001, 2003). However, the dioxin-like PCB congeners represent only 12 of the 209 possible congeners. To assess risks posed by the remaining 197 congeners, information on the fate and effects of the non-dioxin-like congeners is required.

1.2 Purpose of this Report

- To provide ecological risk assessors with a concise summary of the state-of-the-science regarding the biological effects of non-dioxin-like PCBs.
- To provide ecological risk assessors with a compilation of references describing the biological effects of non-dioxin-like PCBs. The list of references is comprised primarily of books, reports, and review articles to provide risk assessors with sources from which they may acquire a thorough overview of the topics at hand. These materials should be used as a source for primary literature references.

1.3 ERASC Request & Response

The issues addressed in this report are those specifically requested in the Ecological Risk Assessment Support Center Request Form (Appendix 2). These issues are listed below along with the section(s) of the report where the information addressing each issue can be located.

- Describe the mode of action of non-dioxin-like compounds and types of effects in receptors (i.e., those congeners that "travel" with the listed dioxins, furans, and PCBs but just don't act via the Ah receptor)
  Addressed in Section 4.
- Discuss n-d-l toxicity relative to congener characteristics (something like a QSAR discussion of planes and rings and big chlorines)
  Addressed in Sections 2 & 4.
- Discuss which congeners are of greatest concern (potency) for n-d-l toxicity (dose/response type information in the narcotic range of effects)
  Addressed in Sections 3 & 4.
- Recommend how this scientific info on action, effects, and toxicity should be used in eco risk assessment where PCBs are present (preferred use of the data, considerations for site-specific application, etc.)
  Addressed in Section 5.
- Discuss whether a general narcosis model can or should be used to evaluate n-d-l effects (as a function of range of contaminant concentration typically seen at low, medium, and highly contaminated sites)
  Addressed in Sections 4 & 5.
- Provide an interactive video-conference on this topic and the one related to congener analytical methodology
  This portion of the request requires another process.

2. Chemical Characterization

A brief overview of PCB nomenclature and chemical properties is provided in this section. Several detailed compilations of PCB chemistry and nomenclature have been compiled previously for all PCBs (Erickson, 1997, 2001; ATSDR, 2000) and for non-dioxin-like PCBs (Hansen, 1999).

2.1 Chemical Structure

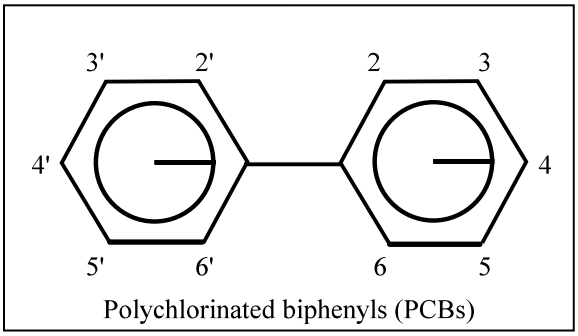

Figure 1. Structure PCBs.

2.2 Nomenclature

Polychlorinated biphenyls (PCBs) are a class of chemicals characterized by a common biphenyl molecular framework to which 2 to 10 chlorine atoms may be attached (Figure 1). Although technically not *poly*chlorinated, mono-chlorinated biphenyls are generally included when referring to PCBs collectively.

Congener **-** one of 209 possible PCB structures having the formula, $C_{12}H_{10-n}Cl_n$, where n = 1-10. Each of the 209 PCB congeners can be specifically defined by standard chemical nomenclature rules in which the number and position of chlorines on the biphenyl ring(s) are designated. Each PCB congener has also been assigned a number, between 1 and 209, by the International Union of Pure and Applied Chemists (IUPAC). The IUPAC numbers provide a convenient shorthand system, but do not provide information as to the specific chemical identity of the congener. A list of all 209 PCB congeners, including IUPAC name, IUPAC # and CAS # are provided in Appendix 1.

Homolog **-** a subset of PCB congeners defined by the degree of chlorination, i.e., monochlorobiphenyls through decachlorobiphenyls (Table 1). PCBs within a homolog group have the same molecular weight and number of chlorines attached to the biphenyl ring, but the pattern of chlorination varies among the individual **isomers** within the homolog group. A list of all PCB homolog groups, including IUPAC name and CAS # are provided in Appendix 1.

Table 1. Chemical Groupings of Polychlorinated Biphenyls

Number of Chlorines	Homolog Group	Molecular Formula	Molecular Weight	Number of Isomers
0	biphenyl	$C_{12}H_{10}$	154.1	1
1	mono-CB	$C_{12}H_9Cl$	188.0	3
2	di-CB	$C_{12}H_8Cl_2$	222.0	12
3	tri-CB	$C_{12}H_7Cl_3$	256.0	24
4	tetra-CB	$C_{12}H_6Cl_4$	289.9	42
5	penta-CB	$C_{12}H_5Cl_5$	323.9	46
6	hexa-CB	$C_{12}H_4Cl_6$	357.8	42
7	hepta-CB	$C_{12}H_3Cl_7$	391.8	24
8	octa-CB	$C_{12}H_2Cl_8$	425.8	12
9	nona-CB	$C_{12}HCl_9$	459.7	3
10	deca-CB	$C_{12}Cl_{10}$	493.7	1

Isomer **-** biphenyls within the same homolog group (i.e., same molecular weight and molecular formula) with different substitution patterns. Specific isomers are defined by the position(s) of the chlorine atoms on the biphenyl rings (e.g., 3,3',4,4',5-pentachlorobiphenyl).

2.3 Physical-Chemical Characteristics

Most pure PCB congeners are colorless, odorless crystals under ambient conditions (Erickson, 2001). Commercial PCB mixtures (e.g. Aroclors) are clear, viscous liquids, with viscosity increasing with degree of chlorination. Generally, PCBs have high boiling points (>200°C), low vapor pressures, low water solubilities (ppm to ppt), moderate to high log K_{ow}s (~4 to 8), high bioconcentration factors (BCFs) and do not degrade readily, which all contribute to their persistence in the environment. These physical-chemical properties may vary widely between the individual congeners. A summary of these properties, presented as averages for homolog group (Erickson, 2001) and for individual congeners (Hansen, 1999), have been compiled. High quality Log K_{ow} values for all 209 PCB congeners, as determined by Hawker and Connell (1988), are provided in Appendix 1 for reference. Primary sources of information on specific congener properties are referenced within these summaries.

2.4 Dioxin-Like PCB Congeners

The 12 PCBs listed in Table 2 act through the aryl hydrocarbon receptor (AHR) to cause the full range of toxic responses elicited by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin. Hence, these PCB congeners are referred to as the dioxin-like PCBs. The structure-activity relationships underlying the distinction of dioxin-like PCBs from the other PCBs have been characterized. The dioxin-like PCBs have chlorines in a minimum of four of the lateral positions (i.e., 3, 3', 4, 4', 5, 5') and none (non-) or only one (mono-) of the *ortho* positions (i.e., 2, 2', 6, or 6') of the biphenyl. The PCBs without *ortho* substituted chlorines are often referred to as *co-planar* PCBs, but this terminology is not technically appropriate since these PCBs do not easily assume a planar conformation similar to that of the dioxins and furans (WHO, 2001). The *non-ortho* dioxin-like PCBs (i.e., PCBs 77, 81, 126 & 169) bind the AHR and cause dioxin-like toxicity in fish, birds and mammals. The mono-ortho chlorinated dioxin-like PCBs are also able to bind the AHR and cause dioxin-like toxicity in birds and mammals, but generally do not cause dioxin-like responses in fish. The toxicological effects which may occur, as a result of exposure to dioxin-like PCBs in fish, birds and mammals, have been well characterized relative to the other PCBs. Dioxin-like toxicity in ecological receptors has been summarized in the scientific literature and in numerous EPA reports (Peterson et al., 1993; Walker and Peterson, 1994; Niimi, 1996; Hoffman et al., 1996; Rice et al., 2002; ATSDR, 2000; U.S. EPA, 1993, 1995a,b, 2001) and will not be discussed in detail further in this report.

Table 2. Dioxin-Like PCBs

IUPAC #	Homolog Group	Substitution Group	IUPAC Name
non-*ortho* substituted PCBs			
77	tetra-CB	non-ortho	3,3',4,4'-tetra-CB
81	tetra-CB	non-ortho	3,4,4',5-tetra-CB
126	penta-CB	non-ortho	3,3',4,4',5-penta-CB
169	hexa-CB	non-ortho	3,3',4,4',5,5'-hexa-CB
mono-*ortho* substituted PCBs			
105	penta-CB	mono-ortho	2,3,3',4,4'-penta-CB
114	penta-CB	mono-ortho	2,3,4,4',5-penta-CB
118	penta-CB	mono-ortho	2,3',4,4',5-penta-CB
123	penta-CB	mono-ortho	2,3',4,4',5-penta-CB
156	hexa-CB	mono-ortho	2,3,3',4,4',5-hexa-CB
157	hexa-CB	mono-ortho	2,3,3',4,4',5'-hexa-CB
167	hexa-CB	mono-ortho	2,3',4,4',5,5'-hexa-CB
189	hepta-CB	mono-ortho	2,3,3',4,4',5,5'-hepta-

In ecological risk assessments, the dioxin-like PCBs should be included in a cumulative assessment with all other chemicals that act via the same mechanism of action (i.e., AHR agonists such as polychlorinated dibenzo dioxins (PCDDs) and furans (PCDFs)). Presently, the most credible approach for assessing mixtures of dioxin-like chemicals is to apply a toxicity equivalence approach in which the concentrations of the individual dioxin-like congeners are converted to TCDD toxicity equivalence concentrations (TEC) using a toxicity equivalence factor (TEF) or a relative potency factor (RPF). Guidance for applying the toxicity equivalence approach in ecological risk assessment is currently being prepared by EPA's Risk Assessment Forum (U.S. EPA, 2003). For complementary information on applying the toxicity equivalence approach for assessment of PCDDs, PCDFs and dioxin-like PCBs, see van den Berg et al. (1998) and U.S. EPA (2000, 2001).

Certain dioxin-like PCBs may act via multiple toxicity pathways. Hence, while the 12 dioxin-like PCBs are known to cause dioxin-like toxicity via the AHR, the 8 mono-ortho dioxin-like congeners may also act via non-AHR mechanisms to cause additional effects. As other toxic pathways for PCBs are elucidated, it is possible that dioxin-like PCBs may be found to cause adverse effects on additional ecologically-relevant endpoints. At this time, information about the mechanisms of action and dose-response relationships in ecological receptors is insufficient to allow assessment of dioxin-like PCBs on the basis of non-AHR mediated pathways. However, a number of studies of effects of PCB mixtures in wildlife species (including both laboratory and field exposure scenarios) have shown that most, if not all, toxicity caused by the mixtures (e.g. Aroclors) can be attributed to the TCDD equivalence concentration (TEC) of the mixture (Walker et al., 1996; Tillitt et al., 1996; Tillitt and Wright, 1997; Giesy and Kannan, 1998).

2.5 Non-Dioxin-Like Congeners

The 197 PCB congeners which were not discussed in the previous section are currently referred to collectively as "non-dioxin-like" congeners. These congeners are also often referred to as the "non-coplanar" or "*ortho*-substituted" congeners. However, experts attending an international World Health Organization Consultation in 2001 established preference for the biologically-based term "non-dioxin-like" for several reasons, the most compelling being that even the non-ortho substituted PCBs are not strictly planar in configuration and some *ortho*-substituted PCB congeners have both dioxin-like and non-dioxin-like activity (WHO, 2001). As more research is conducted on these congeners it is likely that they will be classified more specifically into additional subsets based on toxicological effects endpoints (e.g., endocrine active PCBs; neurotoxic PCBs, immunotoxic PCBs; etc.) and/or mechanisms of action (estrogen receptor agonists/antagonists; serotonin biosynthesis inhibitors; etc.). Current knowledge of non-AHR-mediated effects of PCBs are the subject of Part 4 of this report.

3. Detection, Transport and Disposition of PCBs in the Environment

3.1 Analytical Methods for Detection of PCBs

The various congener-specific analytical methods have been reviewed in detail elsewhere; several recent reviews are summarized here. The second edition of a book dedicated to this topic, *Analytical Chemistry of PCBs*, was published in 1997 (Erickson, 1997). Analytical methods are reviewed more briefly in a recent compilation of papers presented at a PCB workshop held in 2000 (Robertsen and Hansen, 2001). Frame (2001) presents a concise overview of various analytical methods for quantifying PCBs, dedicating most of the text to "the *ultimate* PCB mixture analytical procedure" he refers to as Comprehensive, Quantitative, Congener-Specific (CQCS) PCB Analysis. EPA's Method 1668A is highlighted and is predicted to become the "gold standard" of CQCS PCB analysis. A more pragmatic presentation of congener-specific methods is provided by Beliveau (2001) of EPA's Region 1. Beliveau also provides an examination of Aroclor and partial congener analyses as well as full references for the various EPA methods for analysis of PCBs in various environmental matrices. Hansen (1999) has compiled important details to consider in interpreting and presenting congener-specific data. U.S. EPA Region 9's Biological Technical Assistance Group has also reviewed various analytical methods for routine congener-specific analysis and report that methods currently available are adequate and cost-effective (Valoppi et al., 1999). This report also presents a phased approach for PCB congener-specific analysis specifically for use within the context of performing site-specific ecological risk assessments.

As European and U.S. regulatory agencies move away from "Total PCB" and Aroclor analyses, it has been recognized that analysis of all possible PCB congeners may not be necessary, possible or practical on a routine basis (WHO, 2001). The analysis of subsets of PCB "indicator-congeners", selected based on abundance, prevalence and distribution in the environment, has been proposed as an approach for hazard identification, estimating exposure, and prioritizing risk assessment activities (WHO, 2001). It should be noted that the WHO expert panel did not support the use of "indicator congeners" for measures of *toxicity* however, due to the limited data available on the effects of non-dioxin-like congeners (WHO, 2001). Hence, while it has been recognized that a full 209 congener-specific analysis may not be necessary for all phases or tiers of risk assessment and efforts are underway to identify subsets of congeners to measure for particular applications (e.g. hazard identification, screening, remedial monitoring, etc.), characterization of the relative contribution of non-dioxin-like PCB congeners to PCB mixture toxicity remains a significant data gap. Several different lists of potential indicator congeners have emerged from various sources (WHO, 2001; Frame, 2001; Valoppi et al., 1999; NOAA, 1993; McFarland and Clarke, 1989). To date, EPA has not established a definitive list of "indicator congeners", standardized an approach for analyzing PCBs nor has any of EPA's programs *promulgated* a congener-specific method (Beliveau, 2001).

3.2 Fate, Transport and Disposition in the Environment

Historically (1930s-1970s), commercial mixtures of PCBs were used worldwide as dielectric fluids in capacitors and transformers, heat transfer fluids, hydraulic fluids, lubricating oils, and additives in pesticides, paints, copy paper, adhesives and plastics (ATSDR, 2000; Hansen, 1999). PCBs have been released into the environment as a consequence of historical use and disposal; releases of newly manufactured PCBs having been stopped within the U.S. since banning of the manufacture and use of PCBs in commerce in the 1970s. Examples of primary sources include landfills, hazardous waste sites, incineration of PCB-containing wastes, leakage from old electrical equipment and improper disposal or spills (ATSDR, 2000).

The fate of individual PCB congeners is determined by both environmental processes and the physical-chemical properties of individual congeners. In general, PCB congeners that are more highly chlorinated and have fewer *ortho* substitutions are less volatile, less water soluble, bind more readily to organic particulate matter and are more amenable to anaerobic dechlorination processes (typically in buried sediments). Thus, these congeners are more prominent in soils and sediments, less prominent in water and in the atmosphere, and have higher bioaccumulation factors (BAFs). Congeners that are less chlorinated and have more ortho substitutions are more volatile, more water soluble and are much more readily metabolized in mammals. Consequently, these congeners are more prominent in the atmosphere, surface waters and in fish from temperate waters (Hansen, 1999). Hydrophobicity is the most important chemical property that controls bioavailability from water, sediment or soils. Hydrophobicity can be estimated by the octanol-water partition coefficient, K_{ow}. Generally, log K_{ow}s for PCBs increase from approximately 3 to 9 as degree of chlorination increases (Hansen, 1999). Hence, lower chlorinated PCBs having lower K_{ow}s are more bioavailable than higher chlorinated congeners having higher K_{ow}s. PCBs that are highly hydrophobic are difficult to measure in water because of the very small concentrations in solution. Conversely, concentrations in surficial sediments or soils are often measurable and can be used effectively to reference each PCB congener's distribution to abiotic and biotic components of the ecosystem. In aquatic ecosystems, concentrations measured in surficial sediments can be used to estimate average concentrations in water.

Specifics regarding non-dioxin-like PCB congener disposition in environmental compartments and transfers among them are detailed by Hansen (1999). A detailed discussion of the dynamics and interplay between these processes is beyond the scope of this document, but have been presented in detail elsewhere for PCBs generally (ATSDR, 2000; Robertson and Hansen, 2001) and for non-dioxin-like congeners specifically (Hansen, 1999).

3.3 Disposition in the Environment: Media

Due to historical releases and redistribution among environmental compartments, PCBs are widely distributed in environmental media and biota. Of the 209 possible congeners,

~113 are found in environmental media and/or biota (McFarland and Clarke, 1989). Reports of PCBs, either measured as total PCBs or Aroclors, in environmental media and biota are abundant in the literature. Fewer congener-specific characterizations are found, especially in the older literature. In the environment, PCBs are always found as mixtures of both dioxin-like and non-dioxin-like PCB congeners. Hansen (1999) provides a more recent summary of the disposition of PCBs in the environment, with special emphasis on the non-dioxin-like congeners. Hansen points out that global disposition may not be relevant to site-specific assessment, but there will always be an atmospherically derived background PCB concentration which will often be regionally similar. While it is possible to generalize about specific congener fate, transport and disposition based on physical-chemical properties of PCBs, ultimately the congener profile of interest for a site-specific ecological risk assessment will be dependent upon the specific congeners present in the source material (e.g., which Aroclors were used/disposed of) and the physical and/or chemical processes relevant for the location. For example, the congener profile present in media and biota at a site where only a single Aroclor mixture was ever used/disposed may be quite different from the profile found at a manufacturing plant which produced the full spectrum of PCB products. The literature is also replete with reports of PCBs in environmental media and organisms from numerous sites around the world. Physical, chemical and ecological similarities (e.g., sources, transport pathways, biological systems – lentic vs. lotic, etc.) between sites may serve as a basis for extrapolating congener profiles.

3.4 Disposition in the Environment: Biota

PCB toxicity cannot be determined simply by examining the environmental concentrations of the congeners. Differential rates of uptake, metabolism and elimination will influence the congener profile to which target tissues are ultimately exposed. Detailed discussions of the disposition of PCBs in various taxa and the role of various toxicokinetic factors that influence the bioaccumulation of PCB congeners is beyond the scope of this report, but have been summarized elsewhere (Hansen, 1999; Robertson and Hansen, 2001; ATSDR, 2000). Some generalizations can be made however. Aquatic invertebrates serve as a major source of PCBs in food chains and seem to retain polar metabolites of metabolizable PCBs, which then biomagnify in the food chain. Uptake of PCBs in fish and invertebrates occurs via contact with media (i.e., respiration of water; contact with sediment), but food chain transfer is a major contributor for predatory organisms. Uptake of PCBs in piscivorous mammals and birds is primarily from ingestion of fish. As a class of compounds, PCBs are relatively resistant to metabolism by animals and the resistence to metabolism increases with degree of chlorination. Most congeners are metabolized to some extent and differential or selective metabolism among species appears to have the greatest influence on net PCB accumulation (Hansen, 1999). PCB congener profiles in mammals are generally similar, but species-specific differences in absorption, disposition and metabolism certainly exist. The PCB congener profiles in fish differ considerably from birds and mammals and consistently include greater proportions of congeners that are more labile in mammals. For example, measurements

of biota-sediment accumulation factors (BSAFs) for fish clearly demonstrate that very few PCB congeners are significantly metabolized, but that PCB 77 is a notable exception (Endicott and Cook, 1994; U.S. EPA, 1995c).

Overviews of dose-, congener-, species- and time-dependent PCB profiles in aquatic and marine food chains is presented by Hansen (1999). McFarland and Clarke (1989) provide a congener-specific summary of the occurrence and abundance of all 209 PCBs found in several classes of animals from various trophic levels collected from several different sites world-wide. Although this paper presents only a "snapshot" of PCB profiles for organisms from specific sites, it provides a template of the sort of data one might desire to collect for an ecological risk assessment. The literature pertaining to bioaccumulation and biotransformation of PCBs in birds has been reviewed by Barron et al. (1995). Bioaccumulation and clearance of 42 individual PCB congeners following exposure of American kestrels to a mixture of Aroclors has been characterized by Drouillard et al. (2001). Congener-specific bioaccumulation of a number of individual PCB congeners in three trophic levels of an aquatic food web has been described and biotransfer factors for four water bird species determined (Zimmermann et al., 1997). Numerous reports document PCB profiles in higher trophic level birds collected from the field (e.g., Custer et al., 2002; Herzke et al., 2002; Elliot et al., 2001; van den Brink and Bosveld, 2001). Information on the PCB profiles present in aquatic and avian species will also serve as a basis for examining exposure of wildlife mammals via ingestion of such species.

4. Biological Effects of Non-Dioxin-Like PCBs

Some non-dioxin-like PCBs have been shown to elicit different types of responses than the dioxin-like PCBs, including neurological, neuroendocrine, endocrine, immunological and carcinogenic effects. These effects occur via multiple toxicity pathways, not involving the AHR. Currently, only a small number of individual non-dioxin-like PCBs have been linked to any one of these effects and it should be realized that a single congener may act through one or more pathways. Likewise, some weak dioxin-like congeners, or their metabolites (i.e., mono-ortho chlorinated congeners), may also initiate toxicity via these pathways, independent of the AHR. However, in order to assess risks posed via these toxicity pathways, the pathways must be demonstrated to be active in a particular organism or class of organisms. Furthermore, dose-response relationships for toxicity elicited via these other pathways must be characterized to determine whether effects of non-dioxin-like PCBs are occurring at concentrations less than those elicited by dioxin-like PCBs that are always found in the environment along with the non-dioxin-like PCBs.

While PCBs have been shown to affect various physiological system(s) in some classes of organisms, this is not necessarily the case for all taxa. Table 3 summarizes the toxicity pathways that have, to date, been shown to be affected by non-dioxin-like PCBs and those organisms in which PCBs have elicited effects attributable to those toxicity pathways.

The following sections summarize what is currently known regarding the toxicity pathways activated by non-dioxin-like PCBs in different biological systems. The congener-specific data provided represents the data that currently exists in the literature (i.e., only a very small number of individual congeners have been examined for activity through the various non-dioxin-like toxicity pathways). Lack of mention of a particular congener in association with a toxicity pathway does **not** imply that the congener does not act through this pathway, rather that the congener has not been tested for activity via the pathway. The data presented here should not be interpreted to be all-inclusive, as characterization of non-AHR-mediated effects of PCBs is an active area of research and new data appear in the literature daily.

Table 3. Toxicity Pathways Documented for Non-Dioxin-Like PCBs

	Organism Class			
Toxicity Pathway	Invertebrate	Fish	Birds	Mammals
Narcosis	X	X	X	X
Liver Effects	N/A	?	?	X
Neurochemical / behavioral	?	?	?	X
Endocrine / Neuroendocrine	?	hydroxy PCBs	?	X
Immunological	X	?	?	X

4.1 Toxicity Pathways

Narcosis is a non-specific mechanism of toxicity that may be elicited in any organism by any organic compound, including non-dioxin-like PCBs, at sufficiently high concentrations. Other potential toxicity pathways, such as endocrine/neuroendocrine disruption, neurotoxicity, and immunotoxicity, of non-dioxin-like PCBs are currently being studied in all classes of organisms and as they are elucidated, some toxic effects of non-dioxin-like PCBs observed in any of these classes of organisms may be attributable to them. Non-dioxin-like PCB toxicity occurring via other toxicity pathways has been established for mammals. Although evidence for non-dioxin-like PCB activity via other toxicity pathways in birds, fish and invertebrates is mounting, the majority of information on PCB toxicity has not focused on measures of effects associated with these toxicity pathways. Hence, most PCB toxicity data for birds characterize dioxin-like toxicity and those for fish characterize either narcosis (acute exposures; high concentrations) or dioxin-like toxicity (early life stage toxicity; low concentrations). The bulk of existing data for invertebrates describe their general insensitivity to PCBs, with toxicity observed at high concentrations, consistent with narcosis as the mode of action. It is assumed that non-dioxin-like PCB toxicity that occurs via any of the more specific toxicity pathways will occur at concentrations lower than those which induce narcosis (Carey et al., 1998).

4.1.1 Narcosis

Narcosis, also referred to as "baseline toxicity" or "anesthesia", is elicited by organic chemicals in all organisms given sufficient exposure and assuming a more potent toxicity pathway is not initiated at a lower dose. Narcosis is thought to be initiated through chemical-mediated perturbations of membrane-bound proteins, either through direct interactions or modification of the protein-membrane lipid interface or micro-environment. Narcotic effects are generally considered to be reversible until death occurs. For aquatic organisms, narcosis has been characterized in laboratory toxicity tests, and relationships between octanol/water partition coefficients, lethality and critical body residues are well established. The common toxicity pathway and established concentration-residue-response relationships allow mixtures of chemicals (including PCBs) to be assessed cumulatively using additivity approaches (DiToro and McGrath, 2000; DiToro et al., 2000; Van Leeuwen et al., 1992). Narcotic mode of action and toxicity are summarized concisely by Carey et al. (1998) and presented in detail in numerous reviews (DiToro and McGrath, 2000; DiToro et al., 2000; Bradbury et al., 1989).

Mammals & Birds - Examples of PCB-induced narcosis in laboratory studies for mammals and birds are generally not available because sufficiently high steady-state blood concentrations of PCBs can not be attained through oral exposures. Under chronic exposure scenarios with lower doses, effects of PCBs via AHR-mediated toxicity pathways have been well documented. Likewise, effects that may be found to occur via non-dioxin-like toxicity pathways as described in the following sections would also be expected to occur at concentrations below those which cause toxicity via narcosis (Carey et al., 1998). Therefore, for most ecological risk assessment scenarios, mammalian and avian assessment endpoints should be based on toxicity endpoints other than narcosis.

Fish - Lethality of PCB mixtures (e.g., Aroclors) and individual non-dioxin-like PCBs in fish following acute aqueous exposures are generally attributed to narcosis. For example, there are numerous reports of Aroclor-induced lethality in fish (see ECOTOX/AQUIRE database: www.epa.gov/ECOTOX). The symptomology observed in these tests shows responses characteristic of narcosis and the toxicity can be accurately described using related QSARs (Van Leeuwen et al., 1992; Veith et al., 1983). Other toxic effects of non-dioxin-like PCBs that occur at lower concentrations/doses and through longer exposures, which are elicited through other toxicity pathways (e.g. endocrine disruption), are beginning to be elucidated as described in the following sections. It is anticipated that effects occurring via these more specific toxicity pathways would occur at concentrations below those which cause toxicity via narcosis (Carey et al., 1998).

Invertebrates - Distinction between dioxin-like and non-dioxin-like PCBs in reference to invertebrate toxicity is obviated due to the apparent lack of an AHR-mediated toxicity pathway in this class of organisms. Although AHR homologs have been identified in a variety of invertebrate species (Hahn, 1998) they apparently lack the ability to bind the

prototypical AHR ligands, 2,3,7,8-TCDD and β-naphthoflavone (Butler et al., 2001). Hence, all toxicity elicited by PCB in invertebrates is considered to occur via non-dioxin-like toxicity pathways. Several studies are of particular interest in evaluating the toxicity of individual congeners to invertebrates. These studies include Borgmann et al. (1990; PCB 52 in *Hyalella azteca*), Dillon et al. (1990; PCBs 52, 101, 118, 138, 153, 180 in *Daphnia magna*), Dillon and Burton (1991; PCBs 18, 116, 128, 153, 171, 194 in *Daphnia magna*), Fisher et al. (1999; PCBs 1, 15, 47, 153 in *Lubriculus variegatus*), Smith and Johnston (1992; PCB 15 in shrimp, *Crangon crangon*) and Schweitzer et al. (1997; PCBs 47 and 153 in purple sea urchin, *Stongylocentrotus prupuratus*). The PCB concentrations used in these studies were very high (often exceeding water solubility) and the invertebrates were most often found to be unaffected by the PCBs. A report by Hwang et al. (2001; PCB 153 in *Chironomus riparius*) is a recent addition to the database of effects of PCBs on invertebrate fecundity and development. Comprehensive summaries of toxic effects caused by PCB mixtures and individual PCB congeners in a variety of invertebrates are provided by Niimi (1996) and Jarvinen and Ankley (1999). In those cases where toxicity was observed in these studies, it occurred at relatively high concentrations and was consistent with narcosis (West et al., 1997; Fisher et al., 1999). Many of these studies have been summarized and evaluated by the U.S. EPA for their potential utility for deriving wildlife criteria values (U.S. EPA, 2002).

4.1.2 Liver Effects

Hepatotoxicity of commercial mixtures of PCBs in mammals is well documented and includes a number of endpoints including increased liver weight, biochemical changes (e.g., enzyme induction, porphyrin accumulation), histopathology, and tumors as compiled recently by ATSDR (2000). However, congener-specific effects data, generally, and non-dioxin-like congener effects data, specifically, are quite limited. Furthermore, such endpoints are typically not used as measurement endpoints in ecological risk assessments because it is often difficult to clearly link these effects to adverse outcomes on either individuals or populations of ecological receptors. Although not necessarily useful for ecological risk assessment, a brief summary of reports of liver effects, particularly those that may be useful in distinguishing dioxin-like effects from non-dioxin-like effects, is provided.

A few studies utilizing various mammalian models have examined effects of specific congeners on liver endpoints. The general trend is for the endpoints examined to be responsive to dioxin-like PCBs, but not non-dioxin-like PCBs (reviewed in ATSDR, 2000). Structure-activity relationships for PCB-induced biochemical and histopathological responses are not well established, but have been reviewed previously (Safe, 1994; Marks, 1985). Liver effects in birds and fish have largely been described within the context of dioxin-like effects, or lack thereof. Hence, several non-dioxin-like congeners have been assessed for their ability to cause non-specific liver lesions (e.g., weight changes, protein concentration changes) and/or induce CYP1A, but effects

specific to non-dioxin-like congeners have not been established. These data for mammals, birds and fish are summarized below.

Mammals - Both dioxin-like and non-dioxin-like PCBs are hepatic tumor promoters in rodents. In two-year bioassays of Aroclors 1016, 1242, 1254 and 1260, all of these mixtures were considered carcinogenic, particularly in female rat livers. When the doses of these mixtures were expressed on a TEC basis (i.e., dioxin-like PCBs only), the dose-response relationship for Aroclor-induced tumors in female rat liver is similar to that observed for TCDD, except for the Aroclor 1016 mixture. The Aroclor 1016 mixture contains the lower chlorinated PCBs and has little dioxin-like activity and the carcinogenic effect of this mixture may be attributed to the non-dioxin-like PCBs present. Unlike TCDD, liver tumors were observed in the male rats receiving Aroclor 1260, suggesting that these effects are mediated through pathways other than the Ah receptor.

Other liver effects, including increased liver weight, biochemical changes (e.g., enzyme induction, porphyrin accumulation) were also observed in the aforementioned studies. Similar to the carcinogenic effects, the female rats were more sensitive than the males and Aroclor 1016 was much less potent than the other mixtures. These studies suggest that the hepatic toxicity of mixtures of PCBs are largely due to the dioxin-like congeners in these mixtures (ATSDR, 2000). In mammals, induction of liver enzymes distinct from cytochrome P4501A, namely cytochrome P450s 2A and 3B (CYP2A/3B), have been linked to non-dioxin-like PCBs (reviewed by Bandiera, 2001). Although the molecular mechanism(s) underlying CYP2B/3A induction has not been elucidated, this endpoint, in the absence of CYP1A induction, could be used as a biomarker of non-dioxin-like PCB exposure and/or effects (WHO, 2001; Bandiera, 2001).

Liver porphyrin accumulation in response to PCB exposure, both PCB mixtures and individual PCB congeners, has been studied in several mammalian species (see ATSDR, 2000 for review). Dioxin-like PCB congeners 105, 128 and 126, but not 77, cause porphyrin accumulation in rats (ATSDR, 2000; van Birgelen et al., 1996). In contrast, non-dioxin-like PCB congeners 28, 118, 153 and 156 reportedly are not porphyrinogenic in rats. While a strong association between AHR responsiveness and porphyrinogenic responses indicates that the porphyrinogenic response in mammals is largely AHR-mediated (ATSDR, 2000), non-dioxin-like PCBs have been reported to greatly enhance AHR-mediated porphyrin accumulation. It appears that both dioxin-like and non-dioxin-like PCBs may affect the heme biosynthetic pathway via different molecular mechanisms (van Birgelen et al., 1996; Marks, 1985).

Birds - While induction of cytochrome P450s isozymes other than 1A1 have been associated with exposure to non-dioxin-like PCBs in mammals, this relationship has not been established in birds. Kennedy et al. (1996) have reported induction of EROD activity in chicken embryo hepatocytes treated with the non-dioxin-like congeners #2, 12, 35, 37, 78, 79, 80, 66, 70, 110, 122, 128, 138, 139, 167, 170, 180, and 194. Lorenzen et

al. (1997) report that PCBs 52, 54, 101, 136 and 153 failed to induce EROD activity or CYP1A protein in chicken embryo hepatocytes, but were able to induce porphyrin accumulation at high concentrations. Quail exposed to PCB 153 displayed increased liver weights, but the occurrence of porphyria and CYP1A induction caused the authors to suspect that the PCB was contaminated with dioxin-like congeners, which was confirmed by chemical analysis (Elliot et al., 1997). *In ovo* exposure of chicken eggs to PCB 153 failed to cause liver lesions and other early life stage effects associated with exposure to dioxin-like congeners (Zhao et al., 1997).

Like the CYP1A induction response, the porphyrinogenic response to PCB exposure in birds is not clearly associated with only the dioxin-like PCB congeners. Several studies using chick embryo liver cells show that although dioxin-like PCB congeners are more potent porphyrinogenic agents, certain non-dioxin-like congeners (e.g., 66, 128, 153, 155, (non-dioxin-like) also possess porphyrinogenic activity, albeit much weaker (Goldstein et al., 1976; Kawanishi et al., 1978; Marks, 1985; Sassa et al., 1986). Similarly, Miranda et al. (1987) have reported porphyrinogenic responses in Japanese quail exposed to both PCB 77 (dioxin-like) and 47 (non-dioxin-like). Sassa et al. (1986) have used the chick embryo liver data to demonstrate that porphyrinogenic potency is correlated with chlorine substitution patterns that convey planarity of the PCB molecule. Hence, while the structural determinants for porphyrinogenic potency of dioxin-like PCBs are the same as those which determine AHR responsiveness, it remains to be determined whether non-dioxin-like PCBs may act on the heme biosynthetic pathway via other mechanisms as has been postulated to occur in mammals (van Birgelen et al., 1996).

Fish - While induction of cytochrome P450s isozymes other than 1A1 have been associated with exposure to non-dioxin-like PCBs in mammals, this relationship has not been established in fish. The ability of a few non-dioxin-like PCB congeners to induce CYP1A protein and/or EROD activity has been assessed. PCBs 128 and 138 were tested in scup (*Stenotomus chrysops*) *in vivo* (Gooch et al., 1989); PCBs 128, 138, 153 and 170 were tested in a zebrafish (*Danio rerio*) liver cell line (Henry et al., 2001) and PCB 153 was tested in a topminnow (*Poeciliopsis lucida*) hepatoma cell line (Bruschweiler et al., 1996). None of the non-dioxin-like congeners tested were effective at inducing fish CYP1A. These data do not provide evidence linking non-dioxin-like PCB exposure in fish tissues to an enzyme induction biomarker as has been established in mammals, but they do reinforce the association of CYP1A induction as an effect that is specific to dioxin-like congeners in fish.

4.1.3 Endocrine / Neuroendocrine Function

A broad range of xenobiotics, including PCBs, may have the potential to alter endocrine function. Endocrine disrupting activity is of concern for ecological risk assessment because most physiological, developmental and reproductive processes in both invertebrates and vertebrates are controlled by one or more endocrine systems. Endocrine disruptors may directly or indirectly mimic or inhibit the production or action of a variety

of steroids including estrogens, progestins, androgens, adrenal steroids and thyroid hormones. Individual PCB congeners may act through one or more endocrine pathways to cause effects and individual congeners in a mixture may have opposing activities (e.g., estrogenic and anti-estrogenic). These actions may occur via a variety of molecular or biochemical events in a number of cells, tissues or organs within a given endocrine system (e.g., hypothalamus, pituitary, gonad, thyroid, adrenal, steroid metabolism, etc.). Characterizing the effects of PCBs on the various endocrine systems is further complicated by the fact that the concentrations, actions and potencies of steroids and other endocrine active compounds can vary considerably during different life stages and reproductive cycles. Thus, the potential for PCBs to disrupt endocrine activity will need to be determined on a congener-specific basis to establish structure-activity relationships for specific endocrine effects and subsequently the means to assess cumulative effects of mixtures of environmental congeners.

It is well established that PCBs, including both dioxin-like and non-dioxin-like congeners and hydroxylated metabolites of some congeners (i.e., hydroxylated PCBs) may affect endocrine systems in vertebrates (Cooke et al., 2001). Issues related to the characterization of endocrine-related effects of PCBs have been reviewed in detail elsewhere (Brouwer et al., 1998; ATSDR, 2000; Cooke et al., 2001). PCB-induced endocrine effects are summarized below for mammals, birds fish and invertebrates. The summaries provided focus on effects that have been attributed specifically to non-dioxin-like PCB congeners, but Aroclor effects data are presented if they are the only data available that demonstrates the *potential* for PCB-induced endocrine effects for a class of organisms.

Mammals - Reports of the effects of PCBs on various endocrine systems in mammals following exposure to Aroclors are abundant and have been reviewed elsewhere (ATSDR, 2000; Brouwer et al., 1998). These reports provided the impetus for further investigating the mechanisms underlying such effects and for determining specific PCB congeners that elicit effects through a common pathway. The Aroclor studies will not be discussed further here. The remainder of this section will focus on describing endocrine/neuroendocrine effects for which causality has been unambiguously linked to non-dioxin-like PCB congeners.

Reproductive - Effects of non-dioxin-like PCBs in a variety of mammalian endocrine systems have been described (Cooke et al., 2001; Fischer et al., 1998). Much of the individual congener data has been collected from *in vitro* model systems in an attempt to elucidate the means by which disruption of endocrine pathways can be initiated. For example, several studies have demonstrated that hydroxylated PCBs bind to the estrogen receptor (Layton et al., 2002; Yoon et al., 2001; Matthews and Zacharewski, 2000; Kuiper et al., 1998). Other studies have demonstrated that hydroxylated PCBs inhibit estrogen sulfation that may result in increases in target tissue concentrations of estradiol (Kester et al., 2000). Congener specific data from *in vivo* studies are limited.

Uterotrophic effects of PCB 153 have been observed in immature female rats (Soontornchat et al., 1994). In addition, developmental exposures to a mixture of PCBs has induced feminization of male behavior in rats (Kaya et al., 2002). However, it is possible that these effects are mediated through the actions of dioxin-like PCBs present in these mixtures. While there are limited *in vivo* studies on individual non-dioxin-like PCBs, it is possible that alterations in the developing reproductive and neurological systems from *in utero* and lactational exposure to PCBs is due, in part, to these effects on estrogen catabolism and receptor interactions.

Initial studies indicated that PCB 138 has an antagonistic effect on androgen receptor activity in transiently co-transfected Chinese Hamster ovary cells (Bonefeld-Jorgensen et al., 2001). Portigal et al. (2002) demonstrated in an *in vitro* system that Aroclors 1260, 1254, 1248, and 1242 antagonize androgen receptor-mediated gene transcription induced by dihydrotestosterone. Three individual congeners lacking dioxin-like activity (congeners 42, 128 and 138) have been tested and were also anti-androgenic in this system (Portigal et al., 2002). A number of studies have demonstrated that either mixtures of PCBs or individual congeners inhibit rat testicular steroid biosynthesis and the authors of the studies suggest this effect is not mediated through the AHR (Kovačević et al., 1995; Andric et al., 2000a,b). However, the importance of these mechanisms in the reproductive and developmental effects of PCBs is uncertain.

Thyroid - A number of studies have demonstrated that both dioxin-like and non-dioxin-like PCBs decrease serum thyroid hormone concentrations. The non-dioxin-like PCBs, while much less potent than the dioxin-like PCBs, produce greater than a 90% decrease in serum thyroxine concentrations. In comparison, the dioxin-like PCBs are much more potent, but only produce a 40-50% decrease in serum thryoxine (Craft et al., 2002). Two different mechanisms have been proposed for the decreases in serum thyroid hormones by PCBs. A number of studies have demonstrated that PCB mixtures or individual congeners increase hepatic thyroxine glucuronidation by inducing UDPGT isoforms (Craft et al., 2002; Hood and Klaassen, 2000). The induction of thryoxine glucuronidation increases the biliary elimination of thyroid hormones (Vansell and Klaassen, 2002a,b). A second mechanism may be the interaction of PCBs with transthyretin (Chauhan et al., 2000). Transthyretin is a serum transport protein for thyroid hormones and certain non-dioxin-like PCBs can displace thyroid hormones from binding to this site and potentially increasing their hepatic uptake and elimination (Chauhan et al., 2000). However, while a number of non-dioxin-like congeners have this activity, so do some dioxin-like congeners (Chauhan et al., 2000). Other potential mechanisms may involve alterations in thyroid hormone sulfation pathways by PCBs (Kester et al., 2000).

Thyroid hormones are critical in the development of the central nervous system. Perinatal exposures to PCBs that result in decreases in thyroid hormones in neonatal rats is associated with decreases in ototoxicity (Goldey et al., 1995). The ototoxicity can be ameliorated by administration of exogenous thyroxine, suggesting the ototoxicity is due

to the hypothyroxinemia (Goldey and Crofton, 1998). In humans, background exposures to PCBs have been associated with decreases in serum thyroid hormones in infants (Koopman-Esseboom et al., 1994). While these changes are also associated with neurological developmental delays (Koopman-Esseboom et al., 1997), it is uncertain whether these associations are causal. Once again, few studies have examined individual non-dioxin-like PCBs for these developmental effects and the role of the dioxin-like chemicals present in these mixtures remains a confounder in ascribing these effects solely to the non-dioxin-like PCBs.

Birds - Effects of PCBs on endocrine endpoints in birds is actively being explored, but currently available studies are largely limited to Aroclor or field exposures. No studies describing endocrine effects attributable specifically by non-dioxin-like PCBs in birds have been reported.

***Reproductive* -** Plasma androgen and estrogen concentrations were unaffected in American kestrels (*Falco sparverius*) exposed to a mixture of Aroclors 1248, 1254 and 1260 although the altered courtship behaviors, reproduction and fertility was attributed to non-persistent, non-dioxin-like congeners, based on bioaccumulation and clearance rates measured for individual PCB congeners (Fisher et al., 2001; Fernie et al., 2001a,b; Drouillard et al., 2001). No correlations were found between steroid hormone concentrations and PCB concentrations in common tern eggs collected from the field (French et al., 2001; Nisbet et al., 1996). However, common tern embryos collected from a site contaminated with an unusual mixture of congeners comprised predominantly of less chlorinated congeners displayed ovarian morphology indicative of feminization. While correlations between feminization and individual PCB congeners measured in the embryos were not statistically significant, the authors noted that the strongest correlation was found between concentrations of PCB 29, which is structurally similar to PCBs 30 and 61. The hydroxylated metabolites of these two congeners are strongly estrogenic (Korach et al., 1988). The authors also report that extracts of these tern eggs were found to be estrogenic in an estrogen receptor binding assay (Hart et al., 1998).

Thyroid - The role of thyroid hormones in normal behavior and development in wildlife and the evidence supporting potential disruption of this pathway by xenobiotics have been reviewed recently (Colborn, 2002; Brucker-Davis, 1998). Abnormal thyroid gland development and aberrant thyroid hormone levels have been widely reported in birds; however, clear association between such endpoints and ecologically relevant adverse effects and specific environmental contaminants are lacking (Colborn, 2002). Association between thyroid effects and PCB exposure is further complicated by the fact that thyroid disruption may be mediated via both AHR- and non-AHR-mechanisms.

In ovo exposure of chicken embryos to Aroclors 1242 and 1254 decrease plasma thyroxine concentrations and reduce activity of hepatic type I monodeiodinase, an enzyme responsible for thyroid hormone homeostasis (Gould et al., 1999; Quinn et al., 2002).

Neither PCB 54 or PCB 80 (non-dioxin-like) caused similar effects; however, the authors propose that the effects are mediated via a non-dioxin-like mechanism because PCB 77 (dioxin-like) also did not produce the effects. Aroclor 1254 has also been reported to decrease plasma thyroid hormone (T3; triiodothyronine) and increase thyroid gland weight in adult mallards (Fowles et al., 1997).

The use of Aroclor mixtures in all the studies described above does not allow a clear causal relationship between exposure to non-dioxin-like PCB congeners and endocrine effects in birds to be established at this time. However, Janz and Bellward (1996a,b) have provided a body of evidence demonstrating that *in ovo* exposure of birds to TCDD had no effect on plasma thyroid hormone concentrations, plasma sex hormone concentrations or hepatic estrogen receptors in several species of birds (chicken, pigeon, great blue heron). Taken together, these data implicate non-dioxin-like congeners in the etiology of endocrine effects observed in birds exposed to Aroclors.

Fish - A variety of xenobiotics cause endocrine disruption in fish, but data regarding endocrine activity of PCBs are generally limited and the majority of existing data are for Aroclors.

Reproductive - In Atlantic salmon the non-dioxin-like PCB congeners 58, 104, 112 and 188 were not estrogenic as measured by induction of the egg yolk protein vitellogenin, a hallmark for estrogenic activity in oviparous animals. However, the authors note that the route of exposure that was used (intraperitoneal) may not have provided an accurate assessment (Norrgren et al., 1999). Hydroxylated metabolites of PCB 9, 15, 18 and 61 have been tested for their ability to bind to Atlantic croaker estrogen receptor, but only hydroxylated PCB 61 displayed affinity (Loomis and Thomas, 1999). Hydroxylated PCB 30 also has affinity for Atlantic croaker progestogen receptor (Thomas et al., 1998). Hydroxylated PCBs, OH-30, OH-50, OH-72 and OH-112 were found to induce vitellogenin in rainbow trout hepatocytes *in vitro* and OH-30 was more active than the other congeners (Andersson, et al., 1999). Hydroxylated metabolites of PCB 30 and PCB 61 were estrogenic *in vivo*, as measured by vitellogenin induction, in rainbow trout (*Oncorhynchus mykiss*) with OH-PCB 30 approximately 100-fold more potent than OH-PCB 61 (Carlson and Williams, 2001).

Thomas and co-workers have tested several Aroclor mixtures for their ability to bind progesterone, estrogen and androgen receptors from the marine fishes, spotted seatrout (*Cynoscion nebulosus*) and Atlantic croaker (*Micropogonias undulatus*) (Thomas, 2000; Sperry and Thomas, 1999; Loomis and Thomas, 1999; Pinter and Thomas, 1997). Overall, the Aroclors tested (1210 and 1254) either showed no or very low binding affinity toward these fish receptors (Thomas, 2000). Aroclor 1254 bound to a small degree to carp estrogen receptor, but the affinity was so low that incomplete binding curves were not obtainable (Kloas et al., 2000). Thomas and co-workers have also complemented these binding studies with *in vivo* studies that demonstrate that Aroclor

1254 interferes with the neuroendocrine system in fish at the level of the hypothalamus and results in effects throughout the brain-pituitary-gonadal axis of Atlantic croaker (Khan et al., 2001; Khan and Thomas, 2001, 2000, 1996). These studies with Aroclors serve well as screens for potential endocrine activity within the mixture of PCB congeners, but do not allow an assessment of the activity of specific non-dioxin-like congeners.

Thyroid - Abnormal thyroid gland development and aberrant thyroid hormone levels have been widely reported in fish; however, clear association between such endpoints and ecologically relevant adverse effects and specific environmental contaminants are lacking (Colborn, 2002). The role of thyroid hormones in normal behavior and development in wildlife and the evidence supporting potential disruption of this pathway by xenobiotics have been reviewed recently (Colborn, 2002; Brucker-Davis, 1998). While disruption of the thyroid hormone system in fish by PCB mixtures (Besselink et al., 1996) and dioxin-like PCBs (Palace et al., 2001; Adams et al., 2000) has been reported, effects of non-dioxin-like PCBs are essentially unexplored.

With the exception of a few hydroxylated metabolites, virtually all studies of potential effects of PCBs on fish endocrine systems have been conducted using Aroclors. The Aroclor data indicate that PCB mixtures do have endocrine activity in fish, but do not allow assignment of the activity to either dioxin-like or non-dioxin-like congeners, since both types of PCBs may act as endocrine disruptors (Cooke et al., 2001). The lack of congener-specific data on endocrine activity in fish also precludes making informed cross-species comparisons or extrapolations.

Invertebrates - The vertebrate steroid hormones (e.g., estrogens, androgens, etc.) are found in some invertebrate phyla. In echinoderms and deuterostomes they perform essentially the same functions (i.e., sex differentiation and reproduction) as in vertebrates, but their functions in other invertebrate phyla are not clear. In invertebrates, many processes and functions controlled by hormones are unique to this class of organisms. Therefore, any comprehensive assessment of xenobiotics to act as potential endocrine disruptors, must include studies in these systems. Given that invertebrates do not possess an AHR that binds prototypical dioxin-like compounds (Butler et al., 2001), it may be concluded that any endocrine effects observed in invertebrates do not occur via an AHR-mediated pathway.

Endocrine disruption by environmental contaminants in invertebrates has received less attention than for vertebrates, hence very little data are available regarding endocrine disruption in general, and data on the potential endocrine activity of PCBs and/or their metabolites are even more scarce. To date, studies on endocrine disruption in invertebrates have focused on disruption of growth and/or developmental processes (e.g., molting, metamorphosis and regeneration) and reproduction in insects and crustaceans which are known to be controlled by hormones. Aroclor 1242 and the non-dioxin-like

congener, PCB 29, has been reported to increase molting time, a process regulated by ecdysteroid hormones, in *Daphnia magna* (Zou and Fingerman, 1997a,b). The authors hypothesized that this effect occurred as a result of competitively blocking the endogenous ecdysteroids from binding to the ecdysteroid receptor (EcR). Oberdorster et al. (1999) tested the ability of Aroclor 1254 to interact with the *Drosophila* EcR and activate gene transcription *in vitro* and found no effect, neither agonistic nor antagonistic, on the reporter-gene. Aroclors 1242 and 1254 are mixtures of both dioxin-like and non-dioxin-like congeners, with PCB 29 present in 1242 but not in 1254. Hence both studies provide some information regarding what PCB congeners may be potential ecdysone pathway disruptors in invertebrates.

Summary - PCBs have been shown to have the *potential* to disrupt the endocrine systems of fish, birds and mammals. Conclusive evidence for PCB-induced endocrine effects in invertebrates is lacking. For fish and birds, endocrine activity cannot currently be assigned to specific PCB congeners, because virtually all studies of effects on endocrine endpoints have been conducted using Aroclors. However, hydroxylated metabolites of certain PCB congeners appear to be consistently estrogenic across animal classes. In mammals, more data on individual congeners are available and some structure-activity relationships are emerging, but the total number of congeners that have been assessed for effects on the various endocrine systems is quite small relative to the number of congeners present in the environment.

4.1.4 Neurochemical / Neurobehavioral Function

A number of studies have demonstrated associations between PCB exposure and developmental delays in humans. One of the difficulties in interpreting theses studies is the co-exposure to dioxins. In experimental animals, both dioxin and non-dioxin-like PCBs induce developmental neurotoxicity (reviewed in Seegal, 2001; Fischer et al., 1998). The present data, while suggesting that non-dioxin-like PCBs are developmental neurotoxicants, do not allow for a rigorous analysis of the role of the non-dioxin-like vs. dioxin-like PCBs in these effects.

Mammals - Both dioxin-like and non-dioxin-like PCBs have been shown to have biochemical effects on the central nervous system. A number of *in vitro* studies have demonstrated that some of the non-dioxin-like PCBs are neuroactive. Some PCBs decrease catecholamine concentrations, particularly dopamine, in the central nervous system (Seegal et al., 1986; Seegal, 2001; Fischer et al., 1998). Structure-activity relationship studies indicate that the non-dioxin-like PCBs are the more active congeners (Shain et al., 1991). Others have reported alterations in calcium, protein kinase C, and phorbol ester signaling in brain tissues by the non-dioxin-like PCBs (Kodavanti and Tilson, 1997; Fischer et al., 1998). These studies suggest potential mechanisms by which the non-dioxin-like PCBs could be neurotoxic. However, the available data on the developmental neurotoxicity of individual PCBs is limited. While qualitative descriptions of the developmental neurotoxicity of the non-dioxin-like PCBs is possible,

quantitatively describing these effects following exposure to complex mixtures of PCBs is currently not possible.

Birds - Neurotoxic effects of non-dioxin-like PCBs in birds have not been reported in the literature. Aroclor 1254 has been demonstrated to reduce neurotransmitter concentrations in brains of ring doves, and the author of this study suggests that these biochemical affects could result in abnormal behaviors (Heinz et al., 1980). Consistent with this hypothesis, Aroclor exposures have elicited behavioral effects in birds. Male kestrels exposed to a mixture of Aroclors 1248, 1254 and 1260, exhibited more sexual and flight behaviors than control animals (Fisher et al., 2001) and Aroclor 1254 affected courting and nesting behaviors in mourning doves (Tori and Peterle, 1983), but because PCB mixtures were used in these studies, it is impossible to attribute the effects to any specific congener(s).

Fish - As mentioned previously, Thomas and co-workers have demonstrated that Aroclor 1254 affects the neuroendocrine system in Atlantic croaker. Endocrine effects have been linked to specific actions on neural tissues (e.g. hypothalamus) and neurotransmitter synthesis pathways (Khan et al., 2001; Khan and Thomas, 2001, 2000, 1996). These studies demonstrate PCBs can affect neural tissues in fish and provide a mechanistic connection between the neurotoxicity and impaired gonadal growth observed in fish exposed to Aroclor 1254. However, because these studies were conducted with a PCB mixture, the neurological effects cannot be attributed specifically to non-dioxin-like PCB congeners.

Invertebrates - A recent study (Smith et al., 1999) demonstrated that exposure of the embryonic marine invertebrate, *Spisula*, to Aroclor 1254 resulted in decreased growth of serotonergic cells. The effect of Aroclor 1254 was dose-dependent, but it is unknown whether the effect is attributable to dioxin-like PCBs, non-dioxin-like PCBs, or both. However, the absence of a functional AHR in invertebrates (Butler et al., 2001) indicates the effects are likely mediated through non-dioxin-like pathway(s). Regardless of the PCB congener(s) involved, this biochemical effect has not been linked to adverse outcomes on either individuals (e.g. mortality) or populations (e.g. fecundity) of invertebrates, hence the toxicological significance of the effect for this class of organisms remains to be established.

Summary - Neurotoxic effects of PCB mixtures in mammals have provided much of the impetus for exploring effects of non-dioxin-like PCB congeners. Neurochemical effects of several non-dioxin-like congeners have been characterized in a number of mammalian cells/tissues (Fischer et al., 1998; Seegal, 2001). Neurotoxic effects of PCBs, dioxin-like or non-dioxin-like, have not been reported in birds. To date, reports of PCB-induced neurotoxicity in fish and invertebrates are limited to biochemical effects of PCB mixtures on specific neuroendocrine or neurological cells/tissues.

4.1.5 Immune Function

Of environmental contaminants studied thus far, PCBs are among the most potent immunotoxicants (Carey et al., 1998). They have been documented to affect the immune systems of multiple species of mammals, birds and fish (Tryphonas, 1995). These effects may include structural alterations of components (e.g., thymus, lymphocytes) or altered function (e.g., antibody production, hypersensitivity) of the immune system. The mechanism(s) by which PCBs are thought to cause immunotoxicity are described by Tryphonas and Feeley (2001). Effects of various Aroclors on several morphologic and functional endpoints of rodent, guinea pig, rabbit and chicken immune systems are summarized by Tryphonas and Feely (2001) and reviewed in detail elsewhere (Tryphonas, 1994).

Mammals - Immunotoxic effects of PCBs have been well studied in rodents and primates. The mammalian evidence indicates that PCBs may have a number of effects on the immune system and that the immune system is one of the most sensitive targets for PCB-induced toxicity (Tryphonas and Feely, 2001). Immunotoxicity data has been collected from studies with Aroclors as well as from individual congeners. In general, higher chlorinated Aroclors (i.e., 1248, 1254 and 1260) are more immunotoxic than lower chlorinated Aroclors (i.e., 1016, 1232 and 1248) (Carey et al., 1998). Much of the congener specific data focus on dioxin-like PCBs. These data are consistent with the Aroclor data, indicating that the dioxin-like congeners exert their immunotoxic effects via the AHR and are more potent immunotoxicants than the non-dioxin-like congeners.

While the data on the dioxin-like congeners include measures of functional effects on the immune system, the data for non-dioxin-like PCBs focus solely on changes in biochemical parameters of specific immune components and have been observed at high concentrations of PCBs. For example, Ganey and colleagues (Fischer et al., 1998) have demonstrated that PCBs alter neutrophil degranulation through a mechanism independent of the AHR. However, it is uncertain if these changes result in alterations in immune integrity. In addition, some of the non-dioxin-like congeners appear to antagonize the immunotoxic effects of dioxin-like congeners, but do so through non-AHR mediated mechanisms (Tryphonas and Feely, 2001). Smialowicz et al. (1997) demonstrated that PCB 153 can enhance the immune response to sheep red blood cells as determined in a plaque forming cell assay. PCB effects on the mammalian immune system have been reviewed in detail elsewhere (Tryphonas, 1994; Tryphonas and Feely, 2001).

Birds - Effects of PCBs on immunological endpoints in birds is largely unexplored and existing studies are limited to Aroclor or field exposures. No studies of immunological effects caused specifically by non-dioxin-like PCBs in birds have been reported. PCB concentrations in plasma and eggs of field exposed Caspian terns have been correlated with immunotoxicity measured by T lymphocyte function and antibody production; however, the changes in the specific endpoints measured also correlated with DDE concentrations in the terns (Grasman and Fox, 2001). Antibody production was affected

in kestrels exposed either via food or *in ovo*, to a mixture of Aroclors 1248, 1254 and 1260 (Smits and Bortolotti, 2001). In contrast, antibody production was not affected in progeny of chickens fed Aroclors 1232, 1242, 1248 and 1254, although spleen and bursa weights were found to be decreased by these Aroclors (Harris et al., 1976). Subchronic exposure of adult male mallards to Aroclor 1254 resulted in no immunotoxic effects, as measured by a battery of immune endpoints, several of which were the same as those measured in the tern and kestrel studies (Fowles et al., 1997). Hence, no clear causal relationship between PCB exposure and immunotoxicity in birds has so far emerged. Because dioxin and dioxin-like PCB congeners have also been reported to cause immune effects in birds (Powell et al., 1996a,b; Hoffman et al., 1996; Nikolaidis et al., 1988), future studies that aim to assess the potential impacts of PCBs on bird immune function should be designed to discern immunological effects caused by dioxin-like and non-dioxin-like congeners.

Fish - Effects of PCBs on immune function in fish have not been reported in the literature.

Invertebrates - Effects of non-dioxin-like PCB 15 on the immune system of the common shrimp (*Crangon crangon*) has been described (Smith and Johnston, 1992). In the same study, dioxin-like PCB 77 also caused the same effect, but this response was considered equivocal based on the magnitude of the response and dose-response relationship observed.

Summary - PCB mixtures have been demonstrated to cause immunological effects in mammals, but effects attributable specifically to non-dioxin-like congeners have not been clearly delineated. Reports of effects of PCB mixtures on immune endpoints in birds are mixed and no data are available which describe exposure and/or effects specifically for non-dioxin-like congeners. PCB-induced immune effects in fish are unstudied. A single study provides some evidence that non-dioxin-like congeners may have immune effects in invertebrates.

4.2 Relative Toxicity of Non-Dioxin-Like vs. Dioxin-Like PCBs

As evidenced by the data review provided in the previous section, most studies of the toxicity of PCBs have focused on either commercial mixtures, concentrated environmental samples or laboratory defined mixtures. All three of these approaches result in mixtures that contain both dioxin-like and non-dioxin-like PCBs. In these studies, it is often difficult to qualitatively determine the relative contribution of dioxin-like and non-dioxin-like PCBs to the toxic effects observed. Quantitative assessments of the role of these chemicals is simply not possible using these study designs. Although PCBs are frequently characterized as dioxin-like and non-dioxin-like, this characterization is an overly simplified description of a structurally diverse class of chemicals. The toxicity of a number of the dioxin-like PCBs have been fairly well characterized. However, these congeners represent just 12 of the 209 possible PCBs.

The remaining PCBs are structurally diverse and may act via one or more toxicity pathways; hence from a mode of action perspective, characterizing them as a single class is inappropriate. Most of the congener-specific toxicity data for these non-dioxin-like PCBs is focused on less than a dozen congeners. Hence, while a compilation of data comparing dioxin-like and non-dioxin-like effects levels (e.g., NOAELs, LOAELs, EC50s, etc.) would be helpful in assessing the relative toxicity of PCB congeners, the limited amount of congener-specific data currently available severely limits the utility of such an exercise.

Presently, it is unclear how to apply this limited congener-specific toxicity data to the assessment of complex mixtures found in environmental samples. In the following discussion, these limitations are described in greater detail for specific toxicity responses. One approach taken in these analyses is to examine the contribution of the dioxin-like effects to the toxic response and determine if the use of the toxicity equivalence methodology would be protective of wildlife species.

4.2.1 Mammals

Relatively few studies are available that characterize the toxicity of non-dioxin-like PCBs individually. Studies of the commercial mixtures indicate that the more sensitive effects described to date are mediated by the dioxin-like chemicals present in these mixtures. For example two different lots of Aroclor 1254 have been examined in a series of studies (Burgin et al., 2001; Kodavanti et al., 2001). These two lots differ in the concentrations of dioxin-like PCB congeners and PCDF contaminants. The toxicity equivalence methodology adequately predicted some responses that were clearly mediated by the Ah receptor. However, effects on thyroid hormones, oxidative stress, Ca^{2+} buffering and phosphokinase C translocation in brain preparations were not predicted by the toxicity equivalence methodology. It is uncertain whether these effects are due solely to the non-dioxin-like chemicals or due to interactions between dioxin-like and the non-dioxin-like chemicals. The data are presently insufficient to ascribe specific effects solely to the non-dioxin-like PCBs present in these mixtures.

Using the available data on neurotoxicological endpoints characterized in mammals, Giesy and Kannan (1998) performed an analysis of the relative toxicity of dioxin-like and non-dioxin-like PCBs to mink. They concluded that it is unlikely for the neurotoxic effects caused by non-dioxin-like PCBs to be critical based on 1) the high concentrations of di-ortho substituted PCB congeners needed to elicit neurotoxic responses; 2) the propensity for the most neurotoxic congeners to be those that are less chlorinated and therefore more easily metabolized and excreted and less bioaccumulative; and 3) field studies indicating that neuroactive congeners do no accumulate to sufficient levels in feral animals (Giesy and Kannan, 1998).

4.2.2 Birds

An evaluation of the relative importance of non-dioxin-like PCB congener toxicity in birds is hindered by lack of data. Evidence from both laboratory and field studies is sufficient to conclude that PCBs produce a wide spectrum of toxic effects in birds, including effects that have been associated with non-dioxin-like PCBs in mammals (e.g., endocrine disruption, neurotoxicity, immunotoxicity). However, the use of Aroclor or field exposures in virtually all studies of PCB effects in birds precludes characterizing the toxicity(ies) that are attributable specifically to non-dioxin-like congeners. Additional studies are needed to establish that non-dioxin-like congeners are toxic in birds and to characterize the type(s) of effects endpoints that are affected by these congeners. Furthermore, it is necessary to demonstrate that non-dioxin-like effects result in whole organism responses that are ecologically relevant (i.e., adverse effects on survival, growth or reproduction) and to evaluate the potential for significant ecological outcomes (e.g. population effects) due to such effects.

4.2.3 Fish

Very few studies are available that characterize toxicity of non-dioxin-like PCB congeners in a manner sufficient for use in ecological risk assessment. The only individual non-dioxin-like congeners studied *in vivo* in fish are PCBs 4, 52, 128, 138 and 170 (Gooch et al., 1989; Zabel et al., 1995). Each of these studies has been summarized (Jarvinen and Ankley, 1999; U.S. EPA, 2002) and evaluated by the U.S. EPA for their potential utility for deriving wildlife criteria values (U.S. EPA, 2002). It should be noted that endpoints evaluated in these studies were those associated with AHR-mediated (dioxin-like) toxicity (e.g. induction of CYP1A; early life stage edema/mortality syndrome) and typically these endpoints have been unresponsive to the non-dioxin-like congeners. So, while these studies can be used to establish no effects levels for dioxin-like endpoints and in establishing effects endpoints that may be used to distinguish among dioxin-like and non-dioxin-like congeners, they do not provide for characterizing non-dioxin-like effects. Available data indicate that non-dioxin-like PCBs and/or their hydroxylated metabolites have the *potential* to cause toxicity via disruption of neuroendocrine pathways, but further studies are needed to demonstrate that the effects endpoints described to date result in whole organism responses that are ecologically relevant (i.e., adverse effects on survival, growth or reproduction) and to evaluate the potential for significant ecological outcomes (e.g. population effects) due to such effects.

4.2.4 Invertebrates

It has been demonstrated that a wide variety of invertebrates including amphipods, cladocerans, midges, mosquito larvae, sandworms, oligochaete worms, snails, clams and grass shrimp are insensitive to dioxin and PCB-induced toxicity (West et al., 1997; Barber et al., 1998; Fisher et al., 1999; see U.S. EPA, 1993 and 2002 for summaries and references prior to 1998). Reported effects of PCBs in invertebrates include arrested development and decreased growth, depressed reproduction and decreased survival. In those cases where toxicity was observed in these studies, it occurred at high

concentrations and was attributed to narcosis (West et al., 1997; Fisher et al., 1999). Clear evidence that PCBs can cause endocrine disruption, neurotoxicity or immunotoxicity in invertebrates at sub-narcotic concentrations is generally lacking.

Acute effects occur at low mg/kg tissue concentrations and chronic effects generally occur at concentrations about an order of magnitude lower than those that cause acute toxicity (these effects concentrations are also consistent with narcosis as the mode of action) . For aquatic organisms, these tissue-residue concentrations are associated with µg/L water concentrations (Jarvinen and Ankley, 1999). While toxicity has been evaluated for a few individual PCBs congeners (Dillon et al., 1990; Dillon and Burton, 1991; Fisher et al., 1999), the majority of studies have been conducted with PCB mixtures (e.g., Aroclors; see Jarvinen and Ankley, 1999) which does not allow determination of the toxicity contributed by non-dioxin-like congeners.

5. Consideration of Non-Dioxin-Like PCBs in Ecological Risk Assessment

5.1 Non-Dioxin-Like Effects Endpoints

Collectively, data currently available from field studies and PCB mixture exposures provide evidence to indicate that wildlife species are susceptible to effects from non-dioxin-like PCBs. However, the existing data are inadequate for use in quantitative ecological risk assessments for several reasons. First, many of the non-dioxin-like PCB effects so far described are specific to particular cells/tissues and/or species (e.g., biochemical changes; neurotoxic effects) or could also be induced by dioxin-like PCBs (e.g., thyroid effects; immunotoxic effects). Furthermore, lack of well-defined dose-response relationships for most of the non-dioxin-like effects does not allow for assessment of the sensitivity of non-dioxin-like effects relative to dioxin-like effects. Finally, even for endpoints for which there may be well defined dose-response relationships (e.g. certain biochemical, cellular and tissue level effects), clear linkages between such effects and typical assessment endpoints in ecological risk assessments (e.g., growth, survival and reproduction) have not been demonstrated.

5.2 Relative Contribution of Dioxin-Like and Non-Dioxin-Like PCBs

5.2.1. Exposure

Environmental PCB congener profiles: 1) often deviate considerably from original commercial PCB mixtures; 2) always include both non-dioxin-like PCBs and dioxin-like PCBs; 3) are often predominately non-dioxin-like congeners on a mass basis. Acknowledging the fact that commercial PCB mixtures (e.g., Aroclors) do not represent environmental exposures, experts at a recent WHO consultation concluded that additional toxicological studies using such mixtures should not be considered relevant from an environmental risk assessment perspective (WHO, 2001). The consultation recommended that future studies aimed at determining exposure levels at which non-

dioxin-like effects occur be conducted using reconstituted mixtures resembling environmental exposures (WHO, 2001). Any evaluation of exposures to the non-dioxin-like PCBs must also include consideration of factors which may vary among the dioxin-like and non-dioxin-like congeners, such as: 1) appropriate dose metric, e.g. lighter chlorinated, relatively volatile, less persistent congeners may be more appropriately measured in air and water than sediments or soils; 2) temporal relationship between exposure and effects, e.g., exposures to some neurotoxic non-dioxin-like congeners during development appear to cause permanent effects; 3) sensitive organisms and/or life stages, e.g., disruption of thyroid system during developmental stages may affect neurological development. However, the modes of action and dose-response relationships by which non-dioxin-like effects are elicited must be better defined before many of these exposure considerations can be accommodated in risk assessments.

5.2.2. Effects

As documented in Section 4, the available data provide evidence that PCB mixtures are likely active via several potential modes of action in mammalian, avian and piscine wildlife. Due to exposure regimens (e.g. Aroclors) and/or effect endpoints, it is rarely possible, however, to attribute any effects specifically to non-dioxin-like PCB congeners. Several previous analyses have indicated that reproductive and/or developmental effects of Aroclors on fish, birds and mammals can be attributed to the TEC (TCDD equivalence concentration) concentration of the mixture, suggesting that the dioxin-like congeners were primarily responsible for the Aroclor toxicity. However, as documented in Section 4, to date non-dioxin-like effects have rarely been looked for (especially in non-mammalian species) and dose-response relationships that are necessary to evaluate relative thresholds among effects are non-existent. The WHO consultation (2001) acknowledged these data gaps and recommended that studies should be conducted with the goal of determining if adverse effects caused by non-dioxin-like PCBs occur at exposure levels less than those caused by dioxin-like PCBs. In summary, the data currently available are not sufficient to assess the relative contributions of dioxin-like and non-dioxin-like congeners to PCB mixture toxicity with any degree of certainty.

5.2.3. Risk

Although current evidence indicates that the greatest potential for effects on endpoints of most concern for ecological receptors (e.g., growth, survival, reproduction) from exposure to PCB mixtures is from the dioxin-like congeners (Giesy and Kannan, 1998; Rice et al., 2002), risk estimates based solely on the 12 dioxin-like PCBs may underestimate the total PCB risk. Given that non-dioxin-like PCBs always occur as mixtures with dioxin-like PCBs and the dioxin-like effects occur at extremely low concentrations, some have assumed that assessment based on the dioxin-like congeners will be protective against potential effects from the non-dioxin-like congeners (Giesy and Kannan, 1998). Others recommend a dual track assessment of both the dioxin-like PCBs and total PCBs (Rice et al., 2002), because so little is currently known regarding the potential effects of the non-dioxin-like congeners. A dual analysis of risks based on total

PCBs and on toxicity equivalence concentrations for dioxin-like PCBs is an approach that may be taken to assess PCB mixtures (Beltman et al., 1997; Brunstrom and Halldin, 2000; Finley et al., 1997; Giesy and Kannan, 1998; note, however, that these examples do not incorporate the 1998 taxa-specific WHO TEFs). EPA currently recommends this combined approach for assessing PCB cancer risks to humans (U.S. EPA, 1996). As more information becomes available about the toxicity mechanisms and relative potency of specific non-dioxin-like PCB congeners, alternative methods for assessing their risk will likely emerge.

Currently, the lack of data regarding the toxicity endpoints and dose-response relationships for non-dioxin-like PCBs precludes performing quantitative ecological risk assessments for these congeners, either individually or cumulatively. This problem is not unique to ecological risk assessment. A 2001 WHO consultation was convened to evaluate the toxicological properties of non-dioxin-like PCBs in the context of human health risk assessment (WHO, 2001). Experts at this workshop considered and evaluated the available exposure, toxicity and epidemiological data for non-dioxin-like PCBs. It was concluded that an in-depth evaluation of all scientific data on PCBs needs to be conducted before a decision can be made as to the necessity or possibility of conducting separate risk assessments for non-dioxin-like PCBs.

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APPENDIX 1: Nomenclature & Log K_{ow}s

PCB NOMENCLATURE: HOMOLOGS

IUPAC #	IUPAC Name	CASRN	IUPAC #	IUPAC Name	CASRN
	Monochlorobiphenyl	27323-18-8		Hexachlorobiphenyl	26601-64-9
	Dichlorobiphenyl	25512-42-9		Heptachlorobiphenyl	28655-71-2
	Trichlorobiphenyl	25323-68-6		Octachlorobiphenyl	55722-26-4
	Tetrachlorobiphenyl	26914-33-0		Nonachlorobiphenyl	53742-07-7
	Pentachlorobiphenyl	25429-29-2			

PCB NOMENCLATURE: MIXTURES

IUPAC #	IUPAC Name	CASRN	IUPAC #	IUPAC Name	CASRN
	Aroclor 1016	12674-11-2		Aroclor 1248	12672-29-6
	Aroclor 1210	147601-87-4		Aroclor 1250	165245-51-2
	Aroclor 1216	151820-27-8		Aroclor 1252	89577-78-6
	Aroclor 1221	11104-28-2		Aroclor 1254	11097-69-1
	Aroclor 1231	37234-40-5		Aroclor 1260	11096-82-5
	Aroclor 1232	11141-16-5		Aroclor 1262	37324-23-5
	Aroclor 1240	71328-89-7		Aroclor 1268	11100-14-4
	Aroclor 1242	53469-21-9		Aroclor (unspecified)	12767-79-2

PCB NOMENCLATURE: DIOXIN-LIKE PCBs

IUPAC #	IUPAC Name	CASRN	IUPAC #	IUPAC Name	CASRN
77	3,3',4,4'-Tetrachlorobiphenyl	32598-13-3	118	2,3',4,4',5-Pentachlorobiphenyl	31508-00-6
81	3,4,4',5-Tetrachlorobiphenyl	70362-50-4	123	2,3',4,4',5'-Pentachlorobiphenyl	65510-44-3
126	3,3',4,4',5-Pentachlorobiphenyl	57465-28-8	156	2,3,3',4,4',5-Hexachlorobiphenyl	38380-08-4
169	3,3',4,4',5,5'-Hexachlorobiphenyl	32774-16-6	157	2,3,3',4,4',5'-Hexachlorobiphenyl	68782-90-7
105	2,3,3',4,4'-Pentachlorobiphenyl	32598-14-4	167	2,3',4,4',5,5'-Hexachlorobiphenyl	52663-72-6
114	2,3,4,4',5-Pentachlorobiphenyl	74472-37-0	189	2,3,3',4,4',5,5'-Heptachlorobiphenyl	39635-31-9

PCB NOMENCLATURE & log K_{ow}s: CONGENERS

IUPAC #	IUPAC Name	CASRN	log K_{OW}	IUPAC #	IUPAC Name	CASRN	log K_{OW}
Monochlorobiphenyls				35	3,3',4-Trichlorobiphenyl	37680-69-6	5.82
1	2-Chlorobiphenyl	2051-60-7	4.46	36	3,3',5-Trichlorobiphenyl	38444-87-0	5.88
2	3-Chlorobiphenyl	2051-61-8	4.69	37	3,4,4'-Trichlorobiphenyl	38444-90-5	5.83
3	4-Chlorobiphenyl	2051-62-9	4.69	38	3,4,5-Trichlorobiphenyl	53555-66-1	5.76
Dichlorobiphenyls				39	3,4',5-Trichlorobiphenyl	38444-88-1	5.89
4	2,2'-Dichlorobiphenyl	13029-08-8	4.65	**Tetrachlorobiphenyls**			
5	2,3-Dichlorobiphenyl	16605-91-7	4.97	40	2,2',3,3'-Tetrachlorobiphenyl	38444-93-8	5.66
6	2,3'-Dichlorobiphenyl	25569-80-6	5.06	41	2,2',3,4-Tetrachlorobiphenyl	52663-59-9	5.69
7	2,4-Dichlorobiphenyl	33284-50-3	5.07	42	2,2',3,4'-Tetrachlorobiphenyl	36559-22-5	5.76
8	2,4'-Dichlorobiphenyl	34883-43-7	5.07	43	2,2',3,5-Tetrachlorobiphenyl	70362-46-8	5.75
9	2,5-Dichlorobiphenyl	34883-39-1	5.06	44	2,2',3,5'-Tetrachlorobiphenyl	41464-39-5	5.75
10	2,6-Dichlorobiphenyl	33146-45-1	4.84	45	2,2',3,6-Tetrachlorobiphenyl	70362-45-7	5.53
11	3,3'-Dichlorobiphenyl	2050-67-1	5.28	46	2,2',3,6'-Tetrachlorobiphenyl	41464-47-5	5.53
12	3,4-Dichlorobiphenyl	2974-92-7	5.22	47	2,2',4,4'-Tetrachlorobiphenyl	2437-79-8	5.85
13	3,4'-Dichlorobiphenyl	2974-90-5	5.29	48	2,2',4,5-Tetrachlorobiphenyl	70362-47-9	5.78
14	3,5-Dichlorobiphenyl	34883-41-5	5.28	49	2,2',4,5'-Tetrachlorobiphenyl	41464-40-8	5.85
15	4,4'-Dichlorobiphenyl	2050-68-2	5.30	50	2,2',4,6-Tetrachlorobiphenyl	62796-65-0	5.63
Trichlorobiphenyls				51	2,2',4,6'-Tetrachlorobiphenyl	68194-04-7	5.63
16	2,2',3-Trichlorobiphenyl	38444-78-9	5.16	52	2,2',5,5'-Tetrachlorobiphenyl	35693-99-3	5.84
17	2,2',4-Trichlorobiphenyl	37680-66-3	5.25	53	2,2',5,6'-Tetrachlorobiphenyl	41464-41-9	5.62
18	2,2',5-Trichlorobiphenyl	37680-65-2	5.24	54	2,2',6,6'-Tetrachlorobiphenyl	15968-05-5	5.21
19	2,2',6-Trichlorobiphenyl	38444-73-4	5.02	55	2,3,3',4-Tetrachlorobiphenyl	74338-24-2	6.11
20	2,3,3'-Trichlorobiphenyl	38444-84-7	5.57	56	2,3,3',4'-Tetrachlorobiphenyl	41464-43-1	6.11
21	2,3,4-Trichlorobiphenyl	55702-46-0	5.51	57	2,3,3',5-Tetrachlorobiphenyl	70424-67-8	6.17
22	2,3,4'-Trichlorobiphenyl	38444-85-8	5.58	58	2,3,3',5'-Tetrachlorobiphenyl	41464-49-7	6.17
23	2,3,5-Trichlorobiphenyl	55720-44-0	5.57	59	2,3,3',6-Tetrachlorobiphenyl	74472-33-6	5.95
24	2,3,6-Trichlorobiphenyl	55702-45-9	5.35	60	2,3,4,4'-Tetrachlorobiphenyl	33025-41-1	6.11
25	2,3',4-Trichlorobiphenyl	55712-37-3	5.67	61	2,3,4,5-Tetrachlorobiphenyl	33284-53-6	6.04
26	2,3',5-Trichlorobiphenyl	38444-81-4	5.66	62	2,3,4,6-Tetrachlorobiphenyl	54230-22-7	5.89
27	2,3',6-Trichlorobiphenyl	38444-76-7	5.44	63	2,3,4',5-Tetrachlorobiphenyl	74472-34-7	6.17
28	2,4,4'-Trichlorobiphenyl	7012-37-5	5.67	64	2,3,4',6-Tetrachlorobiphenyl	52663-58-8	5.95
29	2,4,5-Trichlorobiphenyl	15862-07-4	5.60	65	2,3,5,6-Tetrachlorobiphenyl	33284-54-7	5.86
30	2,4,6-Trichlorobiphenyl	35693-92-6	5.44	66	2,3',4,4'-Tetrachlorobiphenyl	32598-10-0	6.20
31	2,4',5,-Trichlorobiphenyl	16606-02-3	5.67	67	2,3',4,5-Tetrachlorobiphenyl	73575-53-8	6.20
32	2,4',6-Trichlorobiphenyl	38444-77-8	5.44	68	2,3',4,5'-Tetrachlorobiphenyl	73575-52-7	6.26
33	2,3',4'-Trichlorobiphenyl	38444-86-9	5.60	69	2,3',4,6-Tetrachlorobiphenyl	60233-24-1	6.04
34	2,3',5'-Trichlorobiphenyl	37680-68-5	5.66	70	2,3',4',5-Tetrachlorobiphenyl	32598-11-1	6.20
71	2,3',4',6-Tetrachlorobiphenyl	41464-46-4	5.98	107	2,3,3',4',5-Pentachlorobiphenyl	70424-68-9	6.71
72	2,3',5,5'-Tetrachlorobiphenyl	41464-42-0	6.26	108	2,3,3',4,5'-Pentachlorobiphenyl	70362-41-3	6.71

PCB NOMENCLATURE & log K_{ow}s: CONGENERS

IUPAC #	IUPAC Name	CASRN	log K_{OW}	IUPAC #	IUPAC Name	CASRN	log K_{OW}
73	2,3',5',6-Tetrachlorobiphenyl	74338-23-1	6.04	109	2,3,3',4,6-Pentachlorobiphenyl	74472-35-8	6.48
74	2,4,4',5-Tetrachlorobiphenyl	32690-93-0	6.20	110	2,3,3',4',6-Pentachlorobiphenyl	38380-03-9	6.48
75	2,4,4',6-Tetrachlorobiphenyl	32598-12-2	6.05	111	2,3,3',5,5'-Pentachlorobiphenyl	39635-32-0	6.76
76	2,3',4',5'-Tetrachlorobiphenyl	70362-48-0	6.13	112	2,3,3',5,6-Pentachlorobiphenyl	74472-36-9	6.45
77	3,3',4,4'-Tetrachlorobiphenyl	32598-13-3	6.36	113	2,3,3',5',6-Pentachlorobiphenyl	68194-10-5	6.54
78	3,3',4,5-Tetrachlorobiphenyl	70362-49-1	6.35	114	2,3,4,4',5-Pentachlorobiphenyl	74472-37-0	6.65
79	3,3',4,5'-Tetrachlorobiphenyl	41464-48-6	6.42	115	2,3,4,4',6-Pentachlorobiphenyl	74472-38-1	6.49
80	3,3',5,5'-Tetrachlorobiphenyl	33284-52-5	6.48	116	2,3,4,5,6-Pentachlorobiphenyl	18259-05-7	6.33
81	3,4,4',5-Tetrachlorobiphenyl	70362-50-4	6.36	117	2,3,4',5,6-Pentachlorobiphenyl	68194-11-6	6.46
Pentachlorobiphenyls				118	2,3',4,4',5-Pentachlorobiphenyl	31508-00-6	6.74
82	2,2',3,3',4-Pentachlorobiphenyl	52663-62-4	6.20	119	2,3',4,4',6-Pentachlorobiphenyl	56558-17-9	6.58
83	2,2',3,3',5-Pentachlorobiphenyl	60145-20-2	6.26	120	2,3',4,5,5'-Pentachlorobiphenyl	68194-12-7	6.79
84	2,2',3,3',6-Pentachlorobiphenyl	52663-60-2	6.04	121	2,3',4,5',6-Pentachlorobiphenyl	56558-18-0	6.64
85	2,2',3,4,4'-Pentachlorobiphenyl	65510-45-4	6.30	122	2,3,3',4',5'-Pentachlorobiphenyl	76842-07-4	6.64
86	2,2',3,4,5-Pentachlorobiphenyl	55312-69-1	6.23	123	2,3',4,4',5'-Pentachlorobiphenyl	65510-44-3	6.74
87	2,2',3,4,5'-Pentachlorobiphenyl	38380–02-	6.29	124	2,3',4',5,5'-Pentachlorobiphenyl	70424-70-3	6.73
88	2,2',3,4,6-Pentachlorobiphenyl	55215-17-3	6.07	125	2,3',4',5',6-Pentachlorobiphenyl	74472-39-2	6.51
89	2,2',3,4,6'-Pentachlorobiphenyl	73575-57-2	6.07	126	3,3',4,4',5-Pentachlorobiphenyl	57465-28-8	6.89
90	2,2',3,4',5-Pentachlorobiphenyl	68194-07-0	6.36	127	3,3',4,5,5'-Pentachlorobiphenyl	39635-33-1	6.95
91	2,2',3,4',6-Pentachlorobiphenyl	68194-05-8	6.13	**Hexachlorobiphenyls**			
92	2,2',3,5,5'-Pentachlorobiphenyl	52663-61-3	6.35	128	2,2',3,3',4,4'-Hexachlorobiphenyl	38380-07-3	6.74
93	2,2',3,5,6-Pentachlorobiphenyl	73575-56-1	6.04	129	2,2',3,3',4,5-Hexachlorobiphenyl	55215-18-4	6.73
94	2,2',3,5,6'-Pentachlorobiphenyl	73575-55-0	6.13	130	2,2',3,3',4,5'-Hexachlorobiphenyl	52663-66-8	6.80
95	2,2',3,5',6-Pentachlorobiphenyl	38379-99-6	6.13	131	2,2',3,3',4,6-Hexachlorobiphenyl	61798-70-7	6.58
96	2,2',3,6,6'-Pentachlorobiphenyl	73575-54-9	5.71	132	2,2',3,3',4,6'-Hexachlorobiphenyl	38380-05-1	6.58
97	2,2',3,4',5'-Pentachlorobiphenyl	41464-51-1	6.29	133	2,2',3,3',5,5'-Hexachlorobiphenyl	35694-04-3	6.86
98	2,2',3,4',6'-Pentachlorobiphenyl	60233-25-2	6.13	134	2,2',3,3',5,6-Hexachlorobiphenyl	52704-70-8	6.55
99	2,2',4,4',5-Pentachlorobiphenyl	38380-01-7	6.39	135	2,2',3,3',5,6'-Hexachlorobiphenyl	52744-13-5	6.64
100	2,2',4,4',6-Pentachlorobiphenyl	39485-83-1	6.23	136	2,2',3,3',6,6'-Hexachlorobiphenyl	38411-22-2	6.22
101	2,2',4,5,5'-Pentachlorobiphenyl	37680-73-2	6.38	137	2,2',3,4,4',5-Hexachlorobiphenyl	35694-06-5	6.83
102	2,2',4,5,6'-Pentachlorobiphenyl	68194-06-9	6.16	138	2,2',3,4,4',5'-Hexachlorobiphenyl	35065-28-2	6.83
103	2,2',4,5',6-Pentachlorobiphenyl	60145-21-3	6.22	139	2,2',3,4,4',6-Hexachlorobiphenyl	56030-56-9	6.67
104	2,2',4,6,6'-Pentachlorobiphenyl	56558-16-8	5.81	140	2,2',3,4,4',6'-Hexachlorobiphenyl	59291-64-4	6.67
105	2,3,3',4,4'-Pentachlorobiphenyl	32598-14-4	6.65	141	2,2',3,4,5,5'-Hexachlorobiphenyl	52712-04-6	6.82
106	2,3,3',4,5-Pentachlorobiphenyl	70424-69-0	6.64	142	2,2',3,4,5,6-Hexachlorobiphenyl	41411-61-4	6.51
143	2,2',3,4,5,6'-Hexachlorobiphenyl	68194-15-0	6.60	179	2,2',3,3',5,6,6'-Heptachlorobiphenyl	52663-64-6	6.73
144	2,2',3,4,5',6-Hexachlorobiphenyl	68194-14-9	6.67	180	2,2',3,4,4',5,5'-Heptachlorobiphenyl	35065-29-3	7.36
145	2,2',3,4,6,6'-Hexachlorobiphenyl	74472-40-5	6.25	181	2,2',3,4,4',5,6-Heptachlorobiphenyl	74472-47-2	7.11

PCB NOMENCLATURE & log K_{ow}s: CONGENERS

IUPAC #	IUPAC Name	CASRN	log K_{OW}
146	2,2',3,4',5,5'-Hexachlorobiphenyl	51908-16-8	6.89
147	2,2',3,4',5,6-Hexachlorobiphenyl	68194-13-8	6.64
148	2,2',3,4',5,6'-Hexachlorobiphenyl	74472-41-6	6.73
149	2,2',3,4',5',6-Hexachlorobiphenyl	38380-04-0	6.67
150	2,2',3,4',6,6'-Hexachlorobiphenyl	68194-08-1	6.32
151	2,2',3,5,5',6-Hexachlorobiphenyl	52663-63-5	6.64
152	2,2',3,5,6,6'-Hexachlorobiphenyl	68194-09-2	6.22
153	2,2',4,4',5,5'-Hexachlorobiphenyl	35065-27-1	6.92
154	2,2',4,4',5,6'-Hexachlorobiphenyl	60145-22-4	6.76
155	2,2',4,4',6,6'-Hexachlorobiphenyl	33979-03-2	6.41
156	2,3,3',4,4',5-Hexachlorobiphenyl	38380-08-4	7.18
157	2,3,3',4,4',5'-Hexachlorobiphenyl	68782-90-7	7.18
158	2,3,3',4,4',6-Hexachlorobiphenyl	74472-42-7	7.02
159	2,3,3',4,5,5'-Hexachlorobiphenyl	39635-35-3	7.24
160	2,3,3',4,5,6-Hexachlorobiphenyl	41411-62-5	6.93
161	2,3,3',4,5',6-Hexachlorobiphenyl	74472-43-8	7.08
162	2,3,3',4',5,5'-Hexachlorobiphenyl	39635-34-2	7.24
163	2,3,3',4',5,6-Hexachlorobiphenyl	74472-44-9	6.99
164	2,3,3',4',5',6-Hexachlorobiphenyl	74472-45-0	7.02
165	2,3,3',5,5',6-Hexachlorobiphenyl	74472-46-1	7.05
166	2,3,4,4',5,6-Hexachlorobiphenyl	41411-63-6	6.93
167	2,3',4,4',5,5'-Hexachlorobiphenyl	52663-72-6	7.27
168	2,3',4,4',5',6-Hexachlorobiphenyl	59291-65-5	7.11
169	3,3',4,4',5,5'-Hexachlorobiphenyl	32774-16-6	7.42
Heptachlorobiphenyls			
170	2,2',3,3',4,4',5-Heptachlorobiphenyl	35065-30-6	7.27
171	2,2',3,3',4,4',6-Heptachlorobiphenyl	52663-71-5	7.11
172	2,2',3,3',4,5,5'-Heptachlorobiphenyl	52663-74-8	7.33
173	2,2',3,3',4,5,6-Heptachlorobiphenyl	68194-16-1	7.02
174	2,2',3,3',4,5,6'-Heptachlorobiphenyl	38411-25-5	7.11
175	2,2',3,3',4,5',6-Heptachlorobiphenyl	40186-70-7	7.17
176	2,2',3,3',4,6,6'-Heptachlorobiphenyl	52663-65-7	6.76
177	2,2',3,3',4,5',6'-Heptachlorobiphenyl	52663-70-4	7.08
178	2,2',3,3',5,5',6-Heptachlorobiphenyl	52663-67-9	7.14
182	2,2',3,4,4',5,6'-Heptachlorobiphenyl	60145-23-5	7.20
183	2,2',3,4,4',5',6-Heptachlorobiphenyl	52663-69-1	7.20
184	2,2',3,4,4',6,6'-Heptachlorobiphenyl	74472-48-3	6.85
185	2,2',3,4,5,5',6-Heptachlorobiphenyl	52712-05-7	7.11
186	2,2',3,4,5,6,6'-Heptachlorobiphenyl	74472-49-4	6.69
187	2,2',3,4',5,5',6-Heptachlorobiphenyl	52663-68-0	7.17
188	2,2',3,4',5,6,6'-Heptachlorobiphenyl	74487-85-7	6.82
189	2,3,3',4,4',5,5'-Heptachlorobiphenyl	39635-31-9	7.71
190	2,3,3',4,4',5,6-Heptachlorobiphenyl	41411-64-7	7.46
191	2,3,3',4,4',5',6-Heptachlorobiphenyl	74472-50-7	7.55
192	2,3,3',4,5,5',6-Heptachlorobiphenyl	74472-51-8	7.52
193	2,3,3',4',5,5',6-Heptachlorobiphenyl	69782-91-8	7.52
Octachlorobiphenyls			
194	2,2',3,3',4,4',5,5'-Octachlorobiphenyl	35694-08-7	7.80
195	2,2',3,3',4,4',5,6-Octachlorobiphenyl	52663-78-2	7.56
196	2,2',3,3',4,4',5,6'-Octachlorobiphenyl	42740-50-1	7.65
197	2,2',3,3',4,4',6,6'-Octachlorobiphenyl	33091-17-7	7.30
198	2,2',3,3',4,5,5',6-Octachlorobiphenyl	68194-17-2	7.62
199	2,2',3,3',4,5,5',6'-Octachlorobiphenyl	52663-75-9	7.62
200	2,2',3,3',4,5,6,6'-Octachlorobiphenyl	52663-73-7	7.20
201	2,2',3,3',4,5',6,6'-Octachlorobiphenyl	40186-71-8	7.27
202	2,2',3,3',5,5',6,6'-Octachlorobiphenyl	2136-99-4	7.24
203	2,2',3,4,4',5,5',6-Octachlorobiphenyl	52663-76-0	7.65
204	2,2',3,4,4',5,6,6'-Octachlorobiphenyl	74472-52-9	7.30
205	2,3,3',4,4',5,5',6-Octachlorobiphenyl	74472-53-0	8.00
Nonachlorobiphenyls			
206	2,2',3,3',4,4',5,5',6-Nonachlorobiphenyl	40186-72-9	8.09
207	2,2',3,3',4,4',5,6,6'-Nonachlorobiphenyl	52663-79-3	7.74
208	2,2',3,3',4,5,5',6,6'-Nonachlorobiphenyl	52663-77-1	7.71
Decachlorobiphenyls			
209	2,2',3,3',4,4',5,5',6,6'-Decachlorobiphenyl	2051-24-3	8.18

Footnotes:

Dioxin-like congeners are indicated by shading.

log K_{ow} values are from Hawker and Connell, 1988.

APPENDIX 2: ERASC Request

ECOLOGICAL RISK ASSESSMENT SUPPORT CENTER REQUEST FORM

Request #0002: What are the non-dioxin-like effects of PCBs and how can they be evaluated in ecological risk assessments?

Requestor : Bruce Duncan (R10)

Background: EPA is developing a framework (using TEFs) to estimate the dioxin-like effects of PCB congeners. It is unclear whether the n-d-l effects can also be significant at the same time. The n-d-l effects will be from a different suite of congeners and via a different mechanism. The ERAF needs to move from evaluating PCBs as totals or aroclors (or even homologues) to evaluating congeners for the range of effects these congeners elicit.

Expected Outcome:
1. Describe the mode of action of non-dioxin-like compounds and types of effects in receptors (i.e., those congeners that "travel" with the listed dioxins, furans, and PCBs but just don't act via the Ah receptor).
2. Discuss n-d-l toxicity relative to congener characteristics (something like a QSAR discussion).
3. Discuss which congeners are of greatest concern (potency) for n-d-l toxicity (dose/response type information in the narcotic range of effects).
4. Recommend how this scientific information on action, effects, and toxicity should be used in ecological risk assessment where PCBs are present (preferred use of the data, considerations for site-specific application, etc.).
5. Discuss whether a general narcosis model can or should be used to evaluate n-d-l effects (as a function of range of contaminant concentration typically seen at low, medium, and highly contaminated sites) - see below as well.
6. Provide an interactive video-conference on this topic and the one related to congener analytical methodology.

Additional Comments :
Summarize and update from the recent review of n-d-l activity. Find an example or two of sites where TEF and n-d-l approaches were used or recommend how they would be used at an example site (example of application).