Environ Sci Pollut Res (2014) 21:6334–6345
DOI 10.1007/s11356-013-1742-6

PCB MIXTURES IN A COMPLEX WORLD

Hydroxylated polychlorinated biphenyls in the environment: sources, fate, and toxicities

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Received: 20 January 2013 / Accepted: 15 April 2013 / Published online: 2 May 2013

Abstract Hydroxylated polychlorinated biphenyls (OH-PCBs) are produced in the environment by the oxidation of PCBs through a variety of mechanisms, including metabolic transformation in living organisms and abiotic reactions with hydroxyl radicals. As a consequence, OH-PCBs have been detected in a wide range of environmental samples, including animal tissues, water, and sediments. OH-PCBs have recently raised serious environmental concerns because they exert a variety of toxic effects at lower doses than the parent PCBs and they are disruptors of the endocrine system. Although evidence about the widespread dispersion of OH-PCBs in various compartments of the ecosystem has accumulated, little is currently known about their biodegradation and behavior in the environment. OH-PCBs are, today, increasingly considered as a new class of environmental contaminants that possess specific chemical, physical, and biological properties not shared with the parent PCBs. This article reviews recent findings regarding the sources, fate, and toxicities of OH-PCBs in the environment.

Keywords Hydroxylated polychlorinated biphenyls · Persistent organic pollutants · Environmental fate · Toxicity · Biodegradation · PCB metabolites · Abiotic degradation

Responsible editor: Hongwen Sun

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Introduction

Polychlorinated biphenyls (PCBs) are toxic and persistent pollutants that have been widely dispersed in the environment before they were banned by most countries in the 1970s. PCBs exert various detrimental effects on wildlife and humans, including immunotoxicity, neurotoxicity, developmental toxicity, and reproductive toxicity, and they are classified by several agencies as suspected carcinogens (Field and Sierra-Alvarez 2008; Takeuchi et al. 2011).

PCBs may undergo hydroxylation through both natural and anthropogenic mechanisms, including metabolism by living organisms, reaction with atmospheric reactive oxygen species, and transformation in wastewater treatment plants (Totten et al. 2002; Ueno et al. 2007). The first step of the PCB metabolism by higher organisms frequently involves oxidation by the cytochrome P-450 system, resulting in the formation of hydroxylated derivatives (OH-PCBs) (Safe et al. 1975; Kaminski et al. 1981; Letcher et al. 2000; Rezek et al. 2007). Although transformation of PCBs by aerobic bacteria is also well documented, it results primarily in the formation of unstable dihydroxylated metabolites, which may not constitute a significant source of OH-PCBs in the environment (Borja et al. 2005; Furukawa and Fujihara 2008; Pieper and Seeger 2008). On the other hand, increasing evidence has been provided that PCBs in the gas phase react with hydroxyl radicals, which strongly suggests the formation of OH-PCBs in the atmosphere (Totten et al. 2002; Mandalakis et al. 2003). Although they are intermediates of a detoxification sequence potentially leading to their conjugation and excretion, OH-PCBs exert a range of toxic effects at concentrations lower that

the parent PCBs, including inhibition of mitochondrial respiration, generation of reactive oxygen species, oxidative damage to DNA, and endocrine-disrupting effects (Narasimhan et al. 1991; Schultz et al. 1998; Purkey et al. 2004; Kitamura et al. 2005; Takeuchi et al. 2011). PCBs are ubiquitous contaminants of the environment and their OH derivatives have been detected in most compartments of the ecosystem (Jansson et al. 1975; Flanagan and May 1993; Ueno et al. 2007).

Although environmental concerns associated with PCBs have been the topic of an abundant literature, the formation of OH-PCBs and their detection in the environment have received comparatively little attention. Very few review articles focusing specifically on OH-PCBs have been published several years ago (Letcher et al. 2000; Kawano et al. 2005). Since then, additional research has been conducted in response to emerging environmental issues raised by OH-PCBs. OH-PCBs have been detected in more environmental samples, including animal tissues, water, snow, and sediments (Sakiyama et al. 2007; Ueno et al. 2007). In addition, new evidence has been provided suggesting that OH-PCBs are produced in significant amounts by abiotic processes (Persoon et al. 2010; Samuel et al. 2012). Following the observation that PCBs were taken up by plants and metabolized in plant tissues into OH derivatives, several studies have investigated the biodegradation of OH-PCBs by bacteria (Sondossi et al. 2004; Francova et al. 2004; Tehrani et al. 2012). Because of their high toxicity and widespread detection in the environment, OH-PCBs are, today, increasingly considered as a new class of environmental contaminants (Schultz et al. 1998; Cámara et al. 2004; Purkey et al. 2004; Kawano et al. 2005; Kitamura et al. 2005). The objective of the present review is to provide updated information focusing on the sources, environmental fate, and toxicity of OH-PCBs.

PCBs as ubiquitous environmental contaminants

Sources of PCBs

Polychlorinated biphenyls (PCBs) are toxic pollutants that are exclusively generated from human sources. They consist of a suite of 209 congeners made of a biphenyl core to which one to ten chlorine atoms are attached. PCBs are extremely stable and recalcitrant to biodegradation and they are, therefore, classified as persistent organic pollutants (POPs). The high chemical and physical stability and high dielectric constant of PCBs make them useful for a range of industrial applications, including lubricants, dielectric fluids, and plasticizers. Most PCBs were produced as mixtures commercialized under various brand names, such as Aroclor (USA), Kaneclor (Japan), Pyralene (France), or Clophen (Germany). Commercial production of PCBs started in 1929 until the recognition of their toxicity and persistence in the environment led to their interdiction in most countries in the late 1970s (Stockholm Convention) (Kawano et al. 2005). In the meanwhile, an estimated 1.5 mt of PCBs was produced worldwide, of which a significant fraction has been released into the environment. As a consequence, PCBs are, today, detected in every compartment of the ecosystem, including air, water, soil, sediments, and living organisms. Although the production of PCBs has been generally banned in most countries, small amounts of non-Aroclor PCBs are still found in a series of products currently manufactured, including pigments, paints, and resins. For instance, 3,3′-dichlorobiphenyl (DCB) or PCB11, which is only present as traces in Aroclor mixtures, has been recently detected in environmental samples, including Chicago air (IL, USA), and water of Delaware River (NJ, USA) and Hudson River (NY, USA) (Hu et al. 2009; Rodenburg et al. 2010b). Further analysis of the PCB profiles in the Delaware River and Hudson River provided evidence that 3,3′-DCB was not produced by anaerobic dechlorination of Aroclor PCBs (Rodenburg et al. 2010a).

Environmental fate of PCBs

PCBs enter the environment through normal manufacture, usage, and disposal operations. Because of their high stability and relative volatility, PCBs are subject to environmental cycling, which typically involves volatilization from contaminated sites, atmospheric transport, and deposition in different areas. Although they are notoriously persistent in the environment, PCBs are metabolized by most living organisms, including mammals, plants, fungi, and bacteria. The formation of highly toxic PCB metabolites (including OH-PCBs) is suspected to play an important role in the PCB recalcitrance to biodegradation (Flanagan and May 1993; Cámara et al. 2004). Recent studies have also suggested that atmospheric reactions could constitute a significant sink for environmental PCBs (see "Oxidation of PCBs in the atmosphere").

Toxicity and environmental concerns of PCBs

Although the occupational toxicity of PCBs has been known since the 1930s, their environmental impact was not reported until 1964, when the Swedish researcher, Soren Jensen, detected them in human blood. PCBs exhibit low to moderate toxicity, with chronic lethal dose 50 % (LD_{50}) in test animals ranging from 0.5 to 11.3 g kg^{-1} of body weight (Borja et al. 2005). PCBs enter the body through ingestion, inhalation, and dermal contact, and because of their hydrophobicity, they tend to accumulate in the liver and fatty tissues. In humans, PCBs are commonly detected in breast milk and blood, with concentrations increasing with age. Reported effects on humans include fatigue, chloracne, liver damage, weight loss, and various effects on the

immune, reproductive, and nervous systems (ATSDR 2000). Studies conducted on workers exposed to PCBs showed an increase in liver cancers and malignant melanomas. PCBs are classified as *suspected human carcinogens* by the US Environmental Protection Agency (EPA) and International Agency for Research on Cancer (IARC). PCBs are also suspected to be mild endocrine disruptors that can be responsible for the decreased fertility observed in aquatic species. PCBs have been shown to negatively impact phytoplankton populations, with potential long-term effects on the oceanic food chain, oxygen production, and carbon dioxide mitigation (Borja et al. 2005). PCBs are included in the US EPA List of Priority Pollutants (http://oaspub.epa.gov/), the 2007 Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) Priority List of Hazardous Substances (http://www.atsdr.cdc.gov/), and the Stockholm Convention on Persistent Organic Pollutants (http://chm.pops.int/default.aspx).

Sources of OH-PCBs in the environment

In essence, OH-PCBs are secondary contaminants that are produced by oxidative transformation of PCBs through both biological and abiotic processes. OH-PCBs formed by metabolic activity in living tissues can be released into the environment and enter the food chain by excretion, predation, and natural vegetation cycling.

Metabolism of PCBs in mammals

The metabolism of PCBs in mammals follows a three-phase sequence that applies to the transformation of most xenobiotic contaminants (reviewed in Letcher et al. 2000). This sequence involves initial activation (phase I), conjugation with an endogenous molecule (phase II), and excretion from the body or sequestration in tissues (phase III). Phase I of the mammalian metabolism of PCBs typically occurs in the liver and involves hydroxylation mediated by a cytochrome P-450-dependent monooxygenase (CYP). Initial hydroxylation of PCBs proceeds either by direct insertion of a hydroxyl group (−OH) or by formation of an arene oxide intermediate that spontaneously rearranges into an OH product (Fig. 1) (Connor et al. 1997; Letcher et al. 2000). Although the resulting OH-PCBs may undergo further reactions (phases II and III), some congeners seem to accumulate preferentially in the blood prior to their excretion from the body. Further metabolism of OH-PCBs includes glucuronidation and sulfonation reactions (phase II), producing conjugates that are more soluble than the parent PCBs and susceptible to fast excretion from the body (phase III) (Letcher et al. 2000). Phase I of the metabolism of PCBs in mammals may, therefore, constitute a significant source of OH-PCBs in the environment.

Metabolism of PCBs in plants

The metabolism of PCBs in plants has been abundantly documented (reviewed in Van Aken et al. 2010). Plants transform PCBs following a sequence of reactions that shares similarities with the PCB mammalian metabolism and is referred to as the *green liver model* (Sanderman 1994). As in other eukaryotic cells, the initial biotransformation of PCBs in plants is catalyzed the cytochrome P-450 system or other oxidative enzymes, such as peroxidases (phase I), resulting in the generation of a variety of mono- and dihydroxylated metabolites (Chroma et al. 2003; Harms et al. 2003). These hydroxylated compounds may undergo transferase-mediated conjugation with sulfonic acid, glucuronic acid, or glutathione (phase II), which is followed by sequestration in the cell vacuole or incorporation into plant structures (phase III) (Sanderman 1994). Several publications have reported the formation of OH derivatives from mono- to tetrachlorinated congeners by different plant species, including *Atropa belladonna*, *Lactuca sativa*, *Populus nigra*×*deltoides*, *Solanum nigrum*, and *Rosa* sp. (Lee and Fletcher 1992; Wilken et al. 1995; Mackova et al. 1997; Rezek et al. 2007; Harms et al. 2003; Zhai et al. 2010). Hydroxylation of PCBs in plants occurs preferentially with lesser chlorinated congeners and seems to be limited to compounds with less than five chlorine atoms. In the absence of further reactions, OH-PCBs formed in plant tissues are likely to be released into the environment through natural vegetation turnover.

Metabolism of PCBs in bacteria, fungi, and yeast

Microbial degradation of PCBs is well documented (reviewed by Borja et al. 2005; Furukawa and Fujihara 2008, and Pieper and Seeger 2008). Higher chlorinated congeners (with four or more chlorine atoms) are susceptible to reductive dechlorination mediated by anaerobic bacteria (Bedard et al. 2005), while lesser chlorinated congeners (with three or less chlorine atoms) undergo preferentially aerobic oxidative degradation mediated by *Pseudomonas*, *Burkholderia*, *Comamonas*, *Rhodococcus*, and *Bacillus* species (Pieper and Seeger 2008). Aerobic oxidation of PCBs is catalyzed by dioxygenases and results primarily in the formation of catechol-like dihydroxylated metabolites, which typically undergo breakdown of the biphenyl core by opening one of the aromatic rings (Furukawa and Fujihara 2008). For this reason, the bacterial metabolism of PCBs may not constitute a significant source of OH-PCBs in the environment. Although the metabolism of PCBs by fungi has received little attention, a yeast (*Trichosporon mucoides*) and a filamentous fungus (*Paecilomyces lilacinus*) have been shown to oxidize 4-chlorobiphenyl (4-CB) into hydroxylated congeners (phase I), which led to the formation of muconic acid and lactone conjugates (phase II), suggesting that these organisms

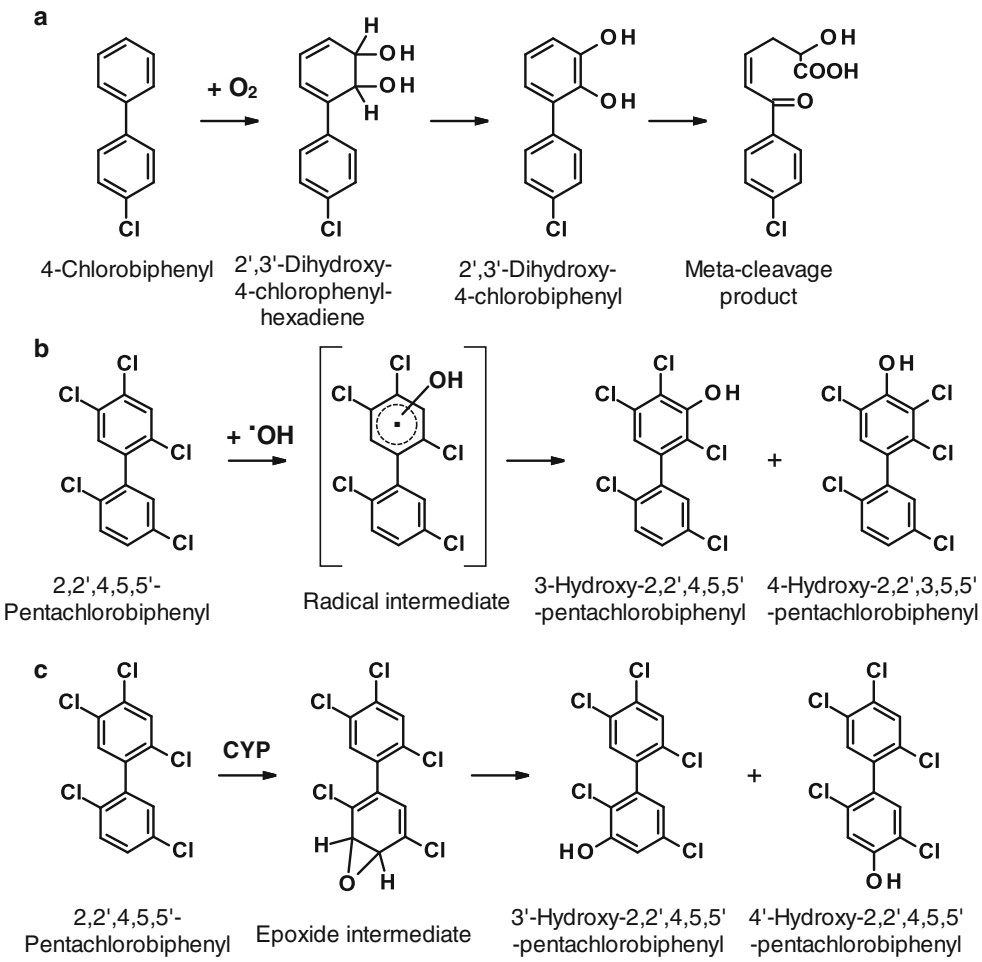

Fig. 1 Potential mechanisms of formation of hydroxylated polychlorinated biphenyls (OH-PCBs). Pathway **a** aerobic bacterial transformation of 4-chlorobiphenyl (CB) through the upper biphenyl pathway; pathway **b** oxidation of 2,2′,4,5,5′-pentachlorobiphenyl (PeCB) by reaction with hydroxyl radicals; pathway **c** cytochrome P-450-mediated oxidation of 2,2′,4,5,5′-PeCB through the formation of an arene oxide. The *structure under brackets* shown in pathway **b** represents the resonance forms of a hypothetical radical intermediate. (**a** Adapted from Furukawa and Fujihara (2008); **b** adapted from Letcher et al. (2000); **c** adapted from Letcher et al. (2000))

are also capable of metabolizing PCBs through a three-step sequence (Sietmann et al. 2006).

Oxidation of PCBs in the atmosphere

Several studies have demonstrated that PCBs in gas phase react with atmospheric hydroxyl radials (•OH), which may contribute to the formation of large amounts of OH-PCBs (Fig. 1). PCBs are semivolatile compounds that are present in significant concentration in the atmosphere, which may have profound implications on their environmental cycling and reactivity (Anderson and Hites 1996; Persoon et al. 2010). Based on measured concentrations of PCBs in air and water, Hornbuckle and Eisenreicht (1996) calculated seasonal PCB fluxes in Lake Superior and established that PCB volatilization and deposition were primarily governed by the ambient temperature and gas-phase PCB concentration. On the other hand, Totten et al. (2002) reported the depletion of tropospheric gas-phase PCBs during daytime in Chicago (IL, USA), Baltimore (MD, USA), and Jersey City (NJ, USA). Based on the observation that depletion rates followed diurnal variations, the authors concluded that PCB removal occurred through reaction with sunlight-generated hydroxyl radicals. This conclusion was supported further by the observation that PCB reduction decreased with the degree of chlorination, which determines the reactivity of PCBs with hydroxyl radicals (i.e., 10–20 % less reactivity for each additional chlorine substituent). Similarly, Mandalakis et al. (2003) provided direct evidence of the reaction of gas-phase PCBs with atmospheric hydroxyl radicals in subtropical regions (Crete and Greece). As it was previously reported, the authors observed diurnal variations of PCB depletion that correlated the level of atmospheric hydroxyl radicals. The reactivity of PCBs with hydroxyl radicals was also shown to be higher for lesser chlorinated congeners. The observed diurnal variations of PCBs could not be explained by temperature-controlled volatilization, which would result in higher PCB levels during the day, as it was described by Hornbuckle and Eisenreicht (1996). It has also been suggested that the reduction of PCBs during daytime could be related to the extension of the boundary layer of the troposphere, leading to larger dilution of PCBs. However, this explanation does not account for the higher reduction rates observed with lesser chlorinated congeners (Mandalakis et al. 2003). Based on the measured reaction constants, the authors calculated half-lives of approximately 10 days for 2,4′-dichlorobiphenyl (DCB) and 20 days for

2,3,3′,4′,6-pentachlorobiphenyl (PeCB) in tropical and subtropical regions (versus 60 and 120 days in polar regions, respectively) (Mandalakis et al. 2003). Hydroxyl radicals are instable, short-life species that are among the strongest known oxidants, and they are susceptible to react with most organic molecules, including PCBs. Hydroxyl radicals are formed by photochemical reactions and they are present at low concentrations in the atmosphere and surface water. Hydroxyl radicals have been reported to be present in the troposphere at average levels of approximately $6.5 \cdot 10^5$ molecules cm^{-3} (Sinkkonen and Paasivirta 2000). Based on calculated reaction constants, Anderson and Hites (1996) estimated that approximately 8,300 t of PCBs are removed annually from the atmosphere by reaction with hydroxyl radicals (as comparison values, 240 and 2 t of PCBs are estimated to be removed annually by sediment burial in marine and fresh water, respectively). However, although several publications have presented evidence of reaction between PCBs and hydroxyl radicals in the atmosphere, no study has demonstrated the actual formation OH-PCBs through this mechanism. It is noteworthy that reaction between PCBs and hydroxyl radicals in the atmosphere likely results in the formation of a range of oxidation products in addition to OH-PCBs. For instance, studying the gas-phase reaction of PCBs with hydroxyl radicals under laboratory conditions, Brubaker and Hites (1998) reported the detection of several oxidation products, including mainly chlorobenzoic acids and only traces of OH-PCBs. The reaction between hydroxyl radicals and aromatic compounds proceeds through complex, multistep mechanisms resulting in transient loss of aromaticity and generating unstable structures with multiple resonance (mesomeirc) forms. The complex nature of such radical reaction is reflected in Fig. 1 (pathway b) by the structure under brackets representing the resonance forms of a hypothetical radical intermediate.

Oxidation of PCBs in water and sediments

Although hydroxyl radicals have been suggested to be responsible for the formation of OH-PCBs in water and sediments, their concentrations in these matrices are likely to be very low due both to their slow formation rate (low irradiation energy) and their high reactivity with organic matter (Sinkkonen and Paasivirta 2000).

Oxidation of PCBs by advanced oxidation processes

Analyzing OH-PCBs in surface water in several sites in Canada, Ueno et al. (2007) reported relatively higher concentrations of total OH-PCBs in the vicinity of sewage treatment plants in urban areas (130 and 35 pg L^{-1}) than offshore Lake Ontario (1.6 pg L^{-1}), suggesting the formation of these compounds during wastewater treatment processes. As suggested by the authors, OH-PCBs could be formed in sewage treatment plants either through microbial oxidation of PCBs or by reactions with hydroxyl radicals generated by advanced oxidation processes (e.g., ozonation) (Dasary et al. 2010). Indeed, PCBs have been reported to be present in significant amounts in the influents of wastewater treatment plants: by the analysis of large data sets on PCB congener concentrations in the influents and effluents of wastewater treatment plants in the Delaware River Basin (DE, NJ, and PA, USA) and New York City metropolitan area (NY, USA), Rodenburg et al. (2010a, 2012) provided evidence that significant dechlorination occurred in the sewage collection system. The resulting lesser chlorinated congeners would, therefore, be more susceptible to microbial and abiotic oxidation in wastewater treatment facilities. On the other hand, the documented reactivity of PCBs with hydroxyl radicals under laboratory conditions has led to the idea of developing potential in situ remediation strategies that could generate OH-PCBs, including treatment by Fenton reagent and photocatalytic degradation by titanium dioxide (TiO_2) (Huang and Hong 2000; Manzano et al. 2004).

OH-PCBs as a new class of environmental contaminants

The first publication referring to the presence of OH-PCBs in the environment is due to Jansson et al. (1975), who detected a suite of OH-PCBs in the feces of Baltic guillemot (*Uria algae*) and gray seals (*Halichoerus grypus*). Since then, numerous OH-PCB congeners have been found in living tissues, water, and sediments (Letcher et al. 2000; Darling et al. 2004; Sakiyama et al. 2007; Kawano et al. 2005; Ueno et al. 2007).

OH-PCBs in wildlife

OH-PCBs can accumulate in higher trophic organisms by three ways: hydroxylation of ingested PCBs, ingestion of contaminated organisms, and ingestion of OH-PCBs produced by microorganisms in water and sediments (Letcher et al. 2000). Besides humans, animal models, plants, and fungi (see "Sources of OH-PCBs in the environment"), OH-PCBs have been detected in the tissues and blood of a range of animals, including fishes, marine mammals, polar bears, and birds (Letcher et al. 2000; Kawano et al., 2005). Because of their higher polarity and their stereochemistry allowing specific binding to plasma proteins, OH-PCBs were previously believed to partition preferentially in the blood of higher organisms prior to their rapid excretion or transformation into glucuronide and sulfonate conjugates (Bergman et al. 1994; Letcher et al. 2000; Robertson and Hansen 2001). However, recent studies showed that OH-PCBs, even though more water soluble than their corresponding parent PCBs, retain high hydrophobicity leading to their potential accumulation in the liver and adipose tissues or their persistence in blood by association with plasma

proteins (Tampal et al. 2002). Moreover, some OH-PCBs seem to exhibit structural resistance to conjugation (e.g., glucuronation) and they have been shown to persist in the body for long periods of time (Tampal et al. 2002). The concentration and congener profiles of OH-PCBs detected in human and animal tissues are highly variable among species, but they involve mostly higher chlorinated congeners (with five or more chlorine atoms) (Letcher et al. 2000; Kawano et al. 2005). Reported ratios total OH-PCBs-to-total PCBs are also species-specific: relatively low ratios were reported in fishes and marine mammals (<0.01 % in Great Lakes fishes), although higher ratios were reported in birds and terrestrial mammals (Kawano et al. 2005). Different ratios total OH-PCBs-to-total PCBs among species may reflect different metabolic capabilities and kinetics. Major congeners frequently detected in animal and human tissues include 4-OH-2,3,3′,4′,5-pentachlorobiphenyl (PeCB) or PCB107, 4′-OH-2,3,3′,4,5′-PeCB or PCB108, 4-OH-2,2′,3,4′,5,5′-hexachlorobiphenyl (HCB) or PCB146, 3-OH-2,2′,4,4′,5,5′-HCB or PCB153, 4′-OH-2,3,3′,4,5,5′-HCB or PCB159, 4-OH-2,2′,3,4′,5,5′,6-heptachlorobiphenyl (HeCB) or PCB187, and 4′-OH-2,2′,3,3′,4,5,5′-HeCB or PCB172, which suspected parent PCBs are constituents of Araclor 1254 and Aroclor 1260 (from 0.82 to 13.59 %) (Letcher et al. 2000; Kawano et al. 2005). Interestingly, these congeners all bear two chlorine atoms adjacent to the hydroxyl group and are mostly dissociated at near neutral pH (pK_a ranging from 5.57 to 4.48), which may explain their recalcitrance to conjugation and persistence in tissues and body fluids (see "Chemical and physical properties of OH-PCBs").

To the best of our knowledge, no study has reported the detection of OH-PCBs in the tissues of natural plants collected from PCB-contaminated sites (Van Aken et al. 2010). However, detectable levels of PCBs have been measured in plant species cultivated in the greenhouse using soil collected from actual Aroclor-contaminated sites (Zeeb et al. 2006; Aslund et al. 2008). Together with the detection of OH-PCBs in plants artificially exposed to PCBs in the greenhouse and the laboratory (see "Metabolism of PCBs in plants"), this observation strongly suggests that natural plants growing on PCB-contaminated environments would contain traces of OH-PCBs. Due to their high hydrophobicity, PCBs are poorly taken up inside plant tissues, which also suggests that OH-PCB concentrations in natural plants would be very low.

OH-PCBs in water and sediments

Increasing concerns regarding the toxicity of OH-PCBs have led to attempts at detecting them in various environmental samples (Table 1). To date, a number of lesser chlorinated OH-PCBs have been identified in water and sediment samples (Darling et al. 2004; Sakiyama et al. 2007; Ueno et al. 2007; Kuch et al. 2010). Darling et al. (2004) measured low concentrations of OH-PCBs in various samples, including snow, surface water, and fish tissues, collected in the Great Lakes region (Canada). Several mono- and dichlorinated OH-PCBs were detected in surface water near wastewater treatment plants, which was attributed to microbial oxidation of lesser chlorinated PCB congeners in the activated sludge and/or hydroxylation of PCBs by advanced oxidation processes. Only a few of the 14 lesser chlorinated OH-PCBs detected in surface water were structurally identified. A wider variety of congeners, ranging from mono- to heptachlorinated (including in majority 2′-OH-2,3′,4,6-TeCB, 3′-OH-2,3,5,6-TeCB, and 2′-OH-2,3,3′,5,6-PeCB), were detected from snow samples, reaching a total concentration of 1 to 7 pg L^{-1} (as compared with 100 to 4,000 pg L^{-1} for the total PCBs). Plasma samples from fish (brown bullhead) contained mainly hexa- to nonachlorinated congeners but no mono- or dichlorinated ones. Based on these results, the authors suggested that OH-PCBs were formed by three major processes: microbial oxidation of PCBs in wastewater treatment plant, metabolic transformation of PCBs in fish tissues, and abiotic oxidation in the atmosphere. The authors also mentioned that mono- and dichlorinated OH-PCBs could exist as impurities in other industrial compounds. Ueno et al. (2007) reported the detection of OH-PCBs, ranging from mono- to nonachlorinated, in rain, snow, and surface water samples from different sites in Ontario (Canada). Total OH-PCB concentrations ranged from 0.87 to 130 pg L^{-1} and 230 to 990 pg g^{-1} in surface water and particulate organic matter, respectively. Total OH-PCB fluxes ranged from <1 to 100 pg m^{-2} and from <1 to 44 pg m^{-2} day^{-1} in snow and rainwater, respectively. Higher OH-PCB fluxes were found near urban areas and the highest concentrations in surface water were detected in vicinity of two sewage treatment plants in eastern Toronto (130 pg m^{-2}) and Hamilton Harbor (35 pg m^{-2}), suggesting higher source of PCBs and OH-PCBs from urban areas. A recent study by Sakiyama et al. (2007) showed the presence of a large number of OH-PCB congeners in sediment samples collected from rivers and estuaries of Osaka Bay (Japan). Total OH-PCBs were detected at the average concentration of 24 ng g^{-1} (0.90 to 150 ng g^{-1}) of sediments (dry weight). The ratio total OH-PCBs-to-total PCBs ranged from 1.4 to 13 %. The ratios OH-PCB-to-PCB decreased significantly with the degree of chlorination: from 3.8 to 82 % for monochlorinated congeners to below 0.2 % for octachlorinated congeners, which may reflect the lower reactivity of higher chlorinated PCBs or the enrichment of sediments by atmospheric deposition of the more volatile lesser chlorinated OH-PCBs (Sakiyama et al. 2007). Investigating estrogenic compounds in groundwater downstream of several abandoned landfills, Kuch et al. (2010) recently reported the detection of OH-PCBs, together with other potential estrogens, such as bisphenol A, phthalic acid esters, and hydroxylated polycyclic aromatic hydrocarbons (OH-PAHs). The estrogenic

activity exceeded the provisional benchmark of 0.5 ng 17β-estradiol (E2)L^{-1} at three out of seven sites tested, which was attributed, in part, to the presence of OH-PCBs.

Chemical and physical properties of OH-PCBs

As for PCBs, the environmental behavior of OH-PCBs is largely determined by the degree and pattern of chlorine substitution of the biphenyl core, resulting in important variations in solubility, toxicity, and biodegradation rate (Rayne and Forest 2010). For instance, it has been reported that a higher degree of chlorination results in lower reactivity of PCBs and OH-PCBs by oxidation reactions likely because of the electron-withdrawing effect of chlorine atoms decreasing the electron density of the aromatic rings (Anderson and Hites 1996; Ueno et al. 2007). As a basis for discussing the effects of hydroxylation on the environmental fate and bioavailability of PCBs, relevant physical and chemical constants, including the octanol–water partition coefficient (log K_{ow}), Henry's constant, dissociation constant (pK_a), and water solubility, were estimated using the online SPARC calculator (version 4.6; http://sparc.chem.uga.edu/sparc/) for a suite of PCBs and OH-PCBs (Hilal et al. 2004). PCBs and OH-PCBs were selected based on their relative proportion in Aroclor mixtures and their detection in animal and human tissues (Table 2). Table 2 shows that increasing the degree of chlorination affects OH-PCBs in the same way as PCBs: higher log K_{ow}, lower Henry's constant, and lower water solubility (Anderson and Hites 1996; Tampal et al. 2002; Kawano et al. 2005). On the other hand, hydroxylation of PCBs results in a slightly lower log K_{ow}, which may reduce the adsorption on organic matter and increase the bioavailability of the molecules. Nevertheless, OH-PCBs remain largely hydrophobic (with log K_{ow} ranging from 4.5 to 9.0) because of the presence of one or two chlorinated phenyl rings (Letcher et al. 2000). OH-PCBs also exhibit significantly higher water solubility as compared to the parent PCBs because of both the increase of polarity and the susceptibility to form hydrogen bonds. Hydroxylation then reduces the volatility of PCBs (lower Henry's constant), making them less susceptible to atmospheric transport. Unlike PCBs, OH-PCBs are weak acids because of the presence of the ionizable phenolic group. Table 2 shows that the pK_a of OH-PCBs decreases with the degree of chlorination of the entire molecule and, more significantly, of the phenolic ring. OH-PCBs with two chlorine atoms adjacent to the hydroxyl group are mostly dissociated at neutral pH (pK_a< 7.0) (Letcher et al. 2000; Tampal et al. 2002; Ueno et al. 2007). Ionization of OH-PCBs largely determines their fate and partitioning in the environment by reducing adsorption on organic matter, reducing volatility, and increasing water solubility (Schwarzenbach et al. 2003).

Bacterial degradation of OH-PCBs

Although most living organisms have been shown to be capable of metabolizing PCBs, there is little information about their contribution to the natural attenuation of PCBs in the environment. Unlike higher organisms, which PCB metabolism constitutes a detoxification process, bacteria transform PCBs as a side effect of their energy metabolism. Biodegradation by competent bacteria is, therefore, one of the major sinks of PCBs in the environment. Although bacterial degradation of PCBs is well documented (see "Metabolism of PCBs in bacteria, fungi, and yeast"), little is known about the bacterial metabolism of OH-PCBs. A few publications have shown that lesser chlorinated OH-PCBs were transformed by aerobic PCB-degrading bacteria through the biphenyl pathway: Sondossi et al. (2004) reported the transformation of variety of OH-biphenyls (2-, 3-, and 4-OH-biphenyl) and OH-PCBs (4-OH-2-CB, 4-OH-3-CB, and 4-OH-5-CB) by the bacterium *Comamonas testosteroni* B-356 and by a recombinant *Pseudomonas putida* strain harboring the biphenyl pathway system. Francova et al. (2004) reported the transformation of a series of *ortho*-substituted OH-PCBs (2-OH-3-CB, 2-OH-5-CB, and 2-OH-3,5-DCB) by biphenyl dioxygenases of *Burkholderia xenovorans* LB400 and *C. testosteroni* B-356. Unlike these reports that focused on congeners bearing the hydroxyl and chlorine substituents on the same ring, our group has recently showed that *B. xenovorans* LB400 was capable of transforming 4-CB and three of its derivatives hydroxylated on the nonchlorinated ring (i.e., 2′-OH-, 3′-OH-, and 4′-OH-4-CB) when cultivated under conditions inductive of the biphenyl pathway (Tehrani et al. 2012). Besides oxidative transformation of OH-PCBs, Wiegel et al. (1999) have reported reductive dehalogenation of higher chlorinated OH-PCBs by the anaerobic PCB degrader, *Desulfitobacterium dehalogenans*.

Toxicities and environmental concerns of OH-PCBs

Toxicity toward higher organisms

Increasing evidence suggests that the toxicity of PCBs originates, at least partly, from their OH metabolites. OH-PCBs may be more toxic than their parent compounds and they have been found to exert a range of toxic effects that are not shown by the parent PCBs, including the inhibition of mitochondrial respiration, generation of reactive oxygen species (ROS), damage to DNA, thyroid hormone-disrupting activity, and estrogenic activity.

Several OH-PCBs have been shown to inhibit the mitochondrial respiration in mouse liver (Narasimhan et al. 1991). Different congeners were reported to act through different mechanisms, such as uncoupling oxidative

Table 1 Detection of hydroxylated polychlorinated biphenyls (OH-PCBs) in various environmental samples, excluding living organisms (which were reviewed in Letcher et al. (2000) and Kawano et al. (2005))

Environmental matrix	Collection site	Detected congeners	OH-PCBs	PCBs	Ratio OH-PCBs/PCBs	Reference
River sediments	Upper Hudson River, USA	2-OH-2′-CB, 3-OH-2′-CB, 2,3-diOH-2′-CB	N.D.	N.D.	N.D.	Flanagan and May (1993)
Snow	Great Lakes basin, Canada	2′-OH-2,3′,4,6-TeCB, 4′-OH-2,3′,4,6-TeCB, 3′-OH-2,3,5,6-TeCB, 2-OH-2,3,3′,5,6 PCB	4.0 (1.0–7.0) pg L^{-1}	2.05 (0.1–4.0) ng L^{-1}	N.D.	Darling et al. (2004)
	Southern Ontario, Canada	OH-PeCBs OH-DCBs	43 (0–100) pg m^{-2}	23,000 (10,000–54,000) pg m^{-2}	0.2 %	Ueno et al. (2007)
Surface water	Toronto Harbor, Canada	OH-CBs, OH-DCBs	N.D.	N.D.		Darling et al. (2004)
		OH-DCBs OH-CBs	22 (0.87–130) pg L^{-1}	590 (190–980) pg L^{-1}	2.1 %	Ueno et al. (2007)
Sediments	Osaka Bay, Japan	OH-CB, OH-DCB,	2.4 (0.017–0.71) 1.6 (0.044–6.9)		38 % (3.8–82) 9.9 % (1.1–38)	Sakiyama et al. (2007)
		OH-TCB,	7.2 (0.36–41)		6.2 % (1.8–16)	
		OH-TeCB,	8.1 (0.19–53)		5.3 % (0.66–15)	
		OH-PeCB,	5.2 (0.21–36)		6.5 % (1.3–22)	
		OH-HCB,	1.5 (0.016–14)		3.4 % (0.37–9.6)	
		OH-HeCB,	0.41(0.024–3.5)		2.3 % (0.62–7.0)	
		OH-OCB	0.091 ng g^{-1}		0.19 %	
Rain		OH-DCBs, OH-TCBs, OH-TeCBs	28 (0–44) pg m^{-2} day^{-1}	3,000 (1,500–7,300) pg m^{-2} day^{-1}	1.1 %	Ueno et al. (2007)
Particulate organic matter		OH-TeCBs, OH-TCBs, OH-HCB	610 (230–990) pg g^{-1}	19,000 (9,500–29,000) pg g^{-1}	0.3 %	Ueno et al. (2007)
Groundwater	Unspecified abandoned landfill, USA	4-OH-BP, Unspecified OH-PCBs	N.D.	N.D.	N.D.	Kuch et al. (2010)

BP biphenyl, *CB* chlorobiphenyl, *DCB* dichlorobiphenyls, *TCB* trichlorobiphenyl, *TeCB* tetrachlorobiphenyl, *PeCB* pentachlorobiphenyl, *HCB* hexachlorobiphenyl, *HeCB* heptachlorobiphenyl, *OCB* octachlorobiphenyl, N.D. not determined

phosphorylation or inhibiting ATPase activity. Srinivasan et al. (2001) showed that several dihydroxylated PCBs and PCB quinones produced ROS, including hydroxyl radicals, superoxide ions, and singlet oxygen, in vitro and in HL-60 human leukemia cells. The authors also reported that the dihydroxylated PCBs and PCB quinones tested induced oxidative DNA damage in vitro. van den Hurk et al. (2002) demonstrated the inhibitory effect of OH-PCBs on the conjugating enzymes, sulfotransferase and glucuronosyltransferase, involved in the metabolism of environmental pollutants, such as 3-hydroxybenzo[a]pyrene, by catfish intestinal cells, which may have important implications for the detoxification capability of wildlife exposed to OH-PCBs.

In addition to other kinds of toxicity, OH-PCBs have been recognized endocrine-disrupting compounds. OH-PCBs are potent inhibitors of the iodothyronine sulfotransferase activity toward the hormone triiodothyronine (T3) in in vitro assays (Schuur et al. 1998). T3 is an important hormone regulating somatic and brain development, which may explain the reported developmental neurotoxicity of OH-PCBs. Sinjari and Darnerud (1998) have shown that exposure to some OH-PCBs (including 4-OH-3,5,3′,4′-TeCB, which is a major fetal metabolite of the coplanar congener, 3,4,3′,4′-TeCB) induced a reduction of tetraiodothyronine (T4) levels in maternal and fetal mice. The reduction of T4 was suspected to be caused by the disruption of T4 plasma transport by inhibition

Table 2 Environmentally relevant chemical and physical constants of selected PCBs and OH-PCBs estimated using the SPARC calculator (Hilal et al. 2004)

Compounds[a]	Henry's constant (log)	log K_{ow}	pK_a	Water solubility at 25 °C[b] (mg L^{-1})
2-CB	−1.7	4.65	N/A	1.07–3.27
4-OH-2-CB	−5.43	4.62	8.77	40.87–144.2
4′-OH-2-CB	−5.42	4.54	9.55	43.57–153.6
2,4′-DCB	−2.14	5.11	N/A	0.29–0.91
4-OH-2,4′-DCB	−5.88	5.11	8.73	17.62–62.85
2,4-DCB	−1.94	5.22	N/A	0.25–0.79
4′-OH-2,4-DCB	−5.68	5.13	9.51	10.11–36.67
3,5-DCB	−2.02	5.18	N/A	0.28–0.87
4-OH-3,5-DCB[c]	−3.02	5.00	6.36	0.31–1.02
2,2′,5-TCB	−2.05	5.74	N/A	N.D.–0.25
4-OH-2,2′,5-TCB	−5.43	5.54	7.12	3.69–13.10
4′-OH-2,2′,5-TCB	−5.67	5.75	8.64	5.59–20.12
4-OH-2,3,5-TCB[c]	−3.3	5.65	5.66	N.D.–0.18
2,2′,3,5′-TeCB	−2.43	6.37	N/A	N.D.[d]
4′-OH-2,2′,3,5′-TeCB	−5.81	6.17	7.07	0.67–2.47
4-OH-2,2′,3,5-TeCB[c]	−3.31	6.22	5.58	N.D.[d]
2,2′,3,4′,6-PeCB	−2.41	7.04	N/A	N.D.[d]
4-OH-2,2′,3,4′,6-PeCB	−5.94	6.78	6.27	0.17–0.66
4-OH-2,3,3′,4′,5-PeCB[c]	−4.06	6.75	5.57	N.D.[d]
2,2′,3,4′,5′,6-HCB	−2.83	7.67	N/A	N.D.[d]
4-OH-2,2′,3,4′,5′,6-HCB	−6.30	7.42	6.22	N.D.–0.11
4-OH-2,2′,3,4′,5,5′-HCB[c]	−3.77	7.47	5.49	N.D.[d]
2,2′,3,3′,4,5,6′-HeCB	−2.99	8.39	N/A	N.D.[d]
4′-OH-2,2′,3,3′,4,5,6′-HeCB	−6.42	8.12	6.17	N.D.[d]
4-OH-2,2′,3,4′,5,5′,6-HeCB[c]	−4.07	8.13	4.68	N.D.[d]
2,2′,3,3′,4,5,5′,6′-OCB	−3.02	9.04	N/A	N.D.[d]
4′-OH-2,2′,3,3′,4,5,5′,6′-OCB[c]	−4.18	8.83	4.62	N.D.[d]

CB chlorobiphenyl, *DCB* dichlorobiphenyl, *TCB* trichlorobiphenyl, *TeCB* tetrachlorobiphenyl, *PeCB* pentachlorobiphenyl, *HCB* hexachlorobiphenyl, *HeCB* heptachlorobiphenyl, *N/A* not applicable, *N.D.* not determined

[a]Parent PCBs were selected because of their relative abundance in Aroclor mixtures

[b]Estimation of water solubility requires knowledge of the melting point that is unknown for most OH-PCBs. The values presented were computed using the range of reported PCB melting points (24 to 149 °C)

[c]These OH-PCB congeners were selected based on the presence of two chlorine atoms adjacent to the hydroxyl group, leading to low pK_a. The ones with five or more chlorine atoms were detected at high levels in animal and mammal tissues

[d]These congeners can be considered as insoluble in water

of transthyretin (TTR) binding. Certain OH-PCB congeners bearing an OH group in *para* position with adjacent chlorine atoms resemble structurally the thyroid hormones T3 and T4, and they have been shown to compete for binding TTR, which is a major thyroid hormone transport protein in mammals (Letcher et al. 2000). It has been suggested that some thyroidogenic OH-PCBs might be one of the causes of thyroid dysfunctions (i.e., large goiters and thyroid hyperplasia) that has been reported in salmonids of the Great Lakes for more than 30 years (Ueno et al. 2007).

In addition, OH-PCBs have been shown to exert a range of estrogenic and antiestrogenic activities (Bergeron et al. 1994). Korach et al. (1988) reported the binding activity of a series of OH-PCBs to a soluble uterine estrogen receptor protein, with the highest activity recorded in congeners bearing a *para*-hydroxyl group. Using the yeast estrogen screen (YES) assay, Schultz et al. (1998) demonstrated the estrogenic activity of several OH-PCBs. The authors observed that hydroxylation was necessary to induce the estrogenic response and that the presence of chlorine atoms on the phenolic ring reduced the estrogenicity. OH-PCBs have also been recognized as inhibitors of human estrogen sulfotranferase (hEST) (Kester et al. 2000). hEST is a key enzyme in the metabolism of 17β-estradiol (E2). Disruption of the hEST pathway increases the cellular level of E2, which may be responsible for the estrogenic activity of OH-PCBs. Several other studies based on different bioassays have reported the estrogenic or antiestrogenic activity of OH-PCBs. Structure–activity relationships (STARs) have recently been conducted on large suites of OH-PCBs, allowing the identification of key molecular features contributing to the estrogenic activity, such a *para*-hydroxyl group and *ortho*-chlorine substituents on the nonphenolic ring (Shiraishi et al. 2003; Arulmozhiraja et al. 2005; Takeuchi et al. 2011). It is noteworthy that besides specific toxic mechanisms, hydroxylation is also known to increase the solubility and bioavailability of the molecules, which is susceptible to explain the higher toxicity of some OH congeners (Cámara et al. 2004).

Toxicity toward bacteria

OH-PCBs have been shown to be toxic for bacteria, which may have important implications for the biodegradation of PCBs by these organisms. Sondossi et al. (2004) measured a significant decrease of the oxygen uptake in the PCB degrader, *C. testosteroni* B-356, exposed to OH-PCBs. Similarly, Cámara et al. (2004) reported decreased cell viability in a recombinant *E. coli* strain expressing genes involved in the PCB metabolism (biphenyl pathway) following exposure to PCBs, which was attributed to the high toxicity of dihydroxylated derivatives originating from the oxidation of PCBs. Exposure of the PCB degrader, *B. xenovorans* LB400, to the commercial mixture Aroclor 1242 resulted in induction of several detoxification genes, again suggesting the generation of toxic metabolites (Parnell et al. 2006). Similarly, we have recently showed that exposure to OH metabolites of 4-CB resulted in severe inhibition of *B. xenovorans* LB400 under conditions inductive of the biphenyl pathway (Tehrani et al. 2012). OH-PCBs have been shown or suggested to affect bacterial cells by different mechanisms, including changes in membrane structure, uncoupling protonophoric shuttle mechanism, oxidative damage to DNA, inactivation of cytochrome *c* oxidase, and reduction of cell DNA content (Cámara et al. 2004). The increased toxicity of PCBs following their bacterial transformation resembles the metabolic activation of xenobiotics that is commonly observed in higher organisms.

Conclusions

Although OH-PCBs have raised moderate concerns as environmental contaminants, emerging evidence suggests that they may constitute more dangerous species than the corresponding parent PCBs. Because of their diversity of structures, OH-PCBs can interfere with many biological systems (e.g., endocrine system), exhibiting activities that are not shown by the parent PCBs. Because of their higher solubility and lower volatility, OH-PCBs also exhibit environmental behaviors that are expected to be different than these of the parent PCBs.

As it is the case with many other environmental contaminants, limited information is available regarding the toxicology, metabolism, and environmental fate of PCB metabolites. This lack of environmental and toxicological information regarding OH-PCBs may be explained by the limited availability of synthetic OH congeners; the large variety of structures of OH-PCBs (more than 800 for the monohydroxylated group only), each of them exhibiting different physical and chemical properties and biological activities; and the specificity of analytical methods that are different for OH-PCBs and parent PCBs.

Regulations regarding environmental contaminants are primarily based on the parent molecules and usually disregard their potential metabolites. Recently, the European Medicines Agency has set specific guidelines for risk assessment of pharmaceuticals entering the environment as well as any metabolite formed at a concentration greater than 10 % of the parent compound (Celiz et al. 2009). However, to the best of our knowledge, such regulations do not exist regarding other classes of environmental pollutants. The US Safe Drinking Water and Food Quality Protection Act requires monitoring estrogenic substances in drinking water, but it does not formally list OH-PCBs (Wiegel et al. 1999).

PCBs exemplify a larger group of environmental pollutants that exert estrogenic activity after metabolic activation by the cytochrome P-450 system and referred to as *proestrogens*. Besides PCBs, a variety of xenobiotic pollutants are proestrogens, including *trans*-stilbene, bisphenol A, benzophenone, and methoxychlor. As it is the case with PCBs, proestrogens typically become estrogenic (or more estrogenic) after addition of a hydroxyl group on an aryl core in *para* of a bulky hydrophobic group (Kitamura et al. 2008).

Ironically, many remediation processes potentially or actually used for the treatment of PCB-contaminated soil and water are susceptible to generate OH-PCBs, including bioremediation by bacteria or plants (phytoremediation) and advanced oxidation processes (e.g., Fenton oxidation and ozonation) used for in situ soil remediation or wastewater treatment.

Acknowledgments This work was supported by the National Institute of Health (NIH), Award Number 2P42 ES013661-05.

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