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Polychlorinated biphenyls and its potential role in endometriosis☆

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ABSTRACT

With the progress of global industrialization and environmental deterioration, the relationship between human health and the living environment has become an increasing focus of attention. Polychlorinated biphenyls (PCBs, including dioxin-like polychlorinated biphenyls and non-dioxin-like polychlorinated biphenyls), as part of the organic chlorine contaminants, have been suspected as playing a role in the etiopathogenesis of endometriosis. Several population-based studies have proposed that exposure to PCBs may increase the risk of developing endometriosis, while some epidemiological studies have failed to find any association between PCBs and endometriosis. The purpose of this review is to discuss the potential pathophysiological relationship between endometriosis and PCBs with a focus on both dioxin-like polychlorinated biphenyls and non-dioxin-like polychlorinated biphenyls.

1. Introduction

Endometriosis, characterized by extra-uterine growth of endometrial glands and stroma, is a chronic gynecological disorder affecting 8–10% of women of reproductive age (Martinez-Zamora et al., 2015). It causes internal bleeding, inflammation, scarring, chronic pelvic pain, dyspareunia, and infertility (Heilier et al., 2008). Many hypotheses have been advanced to explain the aetiology for the condition including retrograde menstruation, coelomic metaplasia, blood-lymphatic spreading, Müllerian remnants, etc (Vercellini et al., 2014). Recently, roles for both genetic (Ballester et al., 2012; Roya et al., 2009; Treloar et al., 2005) and environmental factors (Anger and Foster, 2008; Bellelis et al., 1992; Birnbaum and Cummings, 2002; Carmona et al., 2013; Porpora et al., 2013; Rier and Foster, 2003; Soave et al., 2015) have been emphasised. Environmental toxins, including some organochlorines e.g., polychlorinated biphenyls (PCBs) and dioxins, are regularly mentioned in this context. Dioxins are composed of 210 chlorinated compounds divided into 75 polychlorinated-dibenzo-dioxins (PCDDs) and 135 polychlorinated-dibenzo-furans (PCDFs) (Heilier et al., 2005). 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), the most toxic dioxin congener, has been widely studied and found to be associated with endometriosis (Cummings et al., 1996; Foster, 2008; Resuehr et al., 2012; Rier et al., 1993, 2001; Shi et al., 2007; Sofo et al., 2015). PCBs may exhibit similar biological toxicity as TCDD since they are structurally related to TCDD. This review provides a summary and discussion of the potential impact of exposure to PCBs on endometriosis.

2. Exposure to PCBs

PCBs are manufactured on a global scale. Owing to their excellent physicochemical properties of stability, uninflammability, viscosity and electrical insulation, they were usually used in closed applications such as heat transfer in capacitors and transformers (Heilier et al., 2008). However they were banned in the United States in 1979 followed by a world-wide ban a few years later (Bruner-Tran and Osteen, 2010). The structure of PCBs is a biphenyl moiety composed of two benzene rings connected by a carbon-carbon bond at the 1,1' position (Bruner-Tran and Osteen, 2010). The biphenyl contains 10 positions to be attached by chlorine atoms, the formula of PCBs is $C_{12}H_{10-x}Cl_x$ (x = 1, 2, …,10). There are 209 possible congeners in the family of PCBs according to the different number or/and position of each chlorine atom(Ahlborg et al., 1994). PCBs are lipophilic compounds that bio-accumulate within food chains. Furthermore, PCBs are stable and resistant to environmental degradation so that they persist in both the environment and body.

Biological toxicity of each PCB is related to its structure. PCBs

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with more chlorines atoms usually mean greater toxicity. However, non-*ortho* or mono-*ortho* PCBs are more toxic than PCBs with chlorines in the ortho positions of each ring (positions 2, 2′, 6 and 6′) (Bruner-Tran and Osteen, 2010). Non-*ortho* or mono-*ortho* PCBs are also referred to as coplanar PCBs because of the absence of chlorine in positions 2, 2′, 6 and 6' that makes the configuration planar. Twelve coplanar PCBs have a similar structure with TCDD and share with dioxins the capacity of binding the aryl hydrocarbon receptor (AhR) which is a ligand-activated nuclear transcription factor (Fernandez-Salguero et al., 1996; Agency for Toxic Substances and Disease Registry, 2000). Twelve coplanar PCBs are also called 12 dioxin-like PCBs (DL-PCBs), including 4 non-*ortho* PCBs (PCB 77, 81, 126 and 169) and 8 mono-*ortho* PCBs (PCB 105, 114, 118, 123, 156, 157, 167 and 189). These DL-PCBs may produce biological effects like dioxins and the biological toxicity of DL-PCBs can be much greater than non-dioxin-like PCBs (NDL-PCBs). Both toxicity and biodegradability of PCBs are dependent upon the number and position of chlorine atoms, which means PCBs with the greatest toxicity are also the most difficult to be degraded (Bruner-Tran and Osteen, 2010). Therefore, the dangers of PCBs, especially dioxin-like PCBs, have come to the attention of both biomedical scientists and environmental toxicologists.

PCBs usually co-exist with polychlorinated-dibenzo-dioxins (PCDDs) and polychlorinated-dibenzo-furans (PCDFs) in environmental and biological samples as mixtures of various congeners (Bergman et al., 1982). Because of the different environmental and biological degradation of each congener, these mixtures change temporally and spatially so that they are different from the mixtures originally released from factories. The complex nature of PCDD, PCDF and PCB mixtures makes risk evaluation difficult. The World Health Organization (WHO) and U.S Environmental Protection Agency (EPA) derived consensus toxic equivalency factors (TEFs) for 29 compounds with the ability to bind AhR (7 PCDDs, 10 PCDFs and 12 dioxin-like PCBs) as shown in Table 1 (Van den Berg et al., 1998; Van den Berg et al., 2006). TEF values reflect the potential biological potency of a compound relative to TCDD and can be used to calculate concentrations of these compounds which are expressed as toxic equivalent (TEQ) (Van den Berg et al., 1998). TEQ is the sum of the concentration of each compound multiplied by its TEF as shown in the equation:

$$TEQ = \sum n1[PCDDi \times TEFi] \sum n2[PCDFi \times TEFi] \sum n3[PCBi \times TEFi]$$

(Ahlborg et al., 1994).

Ultimately, concentrations of these mixtures are usually expressed as pg TEQ/g lipids because these compounds, with strong lipophilic properties, are mostly accumulated in fat (Heilier et al., 2008).

NDL-PCBs are much more abundant than DL-PCBs in environmental and biological samples though they are less biologically toxic than DL-PCBs. There are six, common NDL-PCBs referred to as "indicators" (Appel, 2003) including PCB 28, 52, 101, 138, 153 and 180. The six "indicators" plus NDL-PCB 170 and DL-PCB 105, 118, 156 and 167 have been reported to account for 50–80% of total PCB content in human serum (Glynn et al., 2000). Focus on NDL- PCBs has increased recently in the fields of biomedical and environmental toxicology (Al-Anati et al., 2009; Delistraty, 2013; Porpora et al., 2006, 2009; Rignall et al., 2013; Severe et al., 2015; Shen et al., 2016; Stecca et al., 2016; Strathmann et al., 2006; Trabert et al., 2010; van der Plas et al., 2000). Although PCBs have been banned as commercial and industrial products, they are still released from industrial incinerators and landfill sites or leaked from old capacitors and transformers. PCBs can cycle through the environment through the food chain, water, soil and even air. They can also be absorbed through the gastrointestinal tract, lung, and skin of mammals. These organochlorines are widely distributed in the body tissue, particularly in fat and liver. The levels of PCBs increase with age though delivery and breastfeeding can reduce the overall content in the body (Abraham et al., 1998; Uemura et al., 2008b). It has been reported that PCBs are harmful to liver, nervous system, endocrine system, immune system, and reproductive system (Arisawa et al., 2005; DeRosa et al., 1998; Huisman et al., 1995; Koopman-Esseboom et al., 1994; Park et al., 2010). PCBs may also be potent human carcinogens (Cancer, 2012; Onozuka et al., 2009).

Table 1
Toxicity equivalency factors from WHO and US EPA.

Compound	Abbreviation	TEF
Polychlorodibenzodioxin		
2,3,7,8-Tetrachlorodibenzodioxin	TCDD	1
1,2,3,7,8-Pentachlorodibenzodioxin	1,2,3,7,8-PeCDD	1
1,2,3,4,7,8-Hexachlorodibenzodioxin	1,2,3,4,7,8-HxCDD	0.1
1,2,3,6,7,8-Hexachlorodibenzodioxin	1,2,3,6,7,8-HxCDD	0.1
1,2,3,6,7,9-Hexachlorodibenzodioxin	1,2,3,6,7,9-HxCDD	0.1
1,2,3,4,6,7,8-Heptachlorodibenzodioxin	1,2,3,4,6,7,8-HpCDD	0.01
Octachlorodibenzodioxin	OCDD	0.0003
Polychlorodibenzofuran		
2,3,7,8-Tetrachlorodibenzofuran	2,3,7,8-TCDF	0.1
1,2,3,7,8-Pentachlorodibenzofuran	1,2,3,7,8-PeCDF	0.03
2,3,4,7,8-Pentachlorodibenzofuran	2,3,4,7,8-PeCDF	0.3
1,2,3,4,7,8-Hexachlorodibenzofuran	1,2,3,4,7,8-HxCDF	0.1
1,2,3,6,7,8-Hexachlorodibenzofuran	1,2,3,6,7,8-HxCDF	0.1
1,2,3,7,8,9-Hexachlorodibenzofuran	1,2,3,7,8,9-HxCDF	0.1
2,3,4,6,7,8-Hexachlorodibenzofuran	2,3,4,6,7,8-HxCDF	0.1
1,2,3,4,6,7,8-Heptachlorodibenzofuran	1,2,3,4,6,7,8-HpCDF	0.01
1,2,3,4,7,8,9-Heptachlorodibenzofuran	1,2,3,4,7,8,9-HpCDF	0.01
Octochlorodibenzofuran	OCDF	0.0003
Non-orthopolychlorinated Biphenyl		
3,3′4,4′-Tetrachlorobiphenyl (PCB 77)	3,3′4,4′-TCB	0.0001
3,4,4′5- Tetrachlorobiphenyl (PCB 81)	3,4,4′5-TCB	0.0003
3,3′,4,4′,5-Pentachlorobiphenyl(PCB 126)	3,3′,4,4′,5-PeCB	0.1
3,3′4,4′,5,5′-Hexachlorobiphenyl(PCB 169)	3,3′4,4′,5,5′-HxCB	0.03
mono- orthopolychlorinated Biphenyl		
2,3,3′,4,4′-Pentachlorobiphenyl(PCB 105)	2,3,3′,4,4′-PeCB	0.00003
2,3,4,4′,5-Pentachlorobiphenyl(PCB 114)	2,3,4,4′,5- PeCB	0.00003
2,3′,4,4′,5-Pentachlorobiphenyl(PCB 118)	2,3′,4,4′,5- PeCB	0.00003
2,3′,4,4′,5-Pentachlorobiphenyl(PCB 123)	2,3′,4,4′,5- PeCB	0.00003
2,3,3′,4,4′,5-Hexachlorobiphenyl(PCB 156)	2,3,3′,4,4′,5-HxCB	0.00003
2,3,3′,4,4′,5-Hexachlorobiphenyl(PCB 157)	2,3,3′,4,4′,5-HxCB	0.00003
2,3′,4,4′,5,5′-Hexachlorobiphenyl(PCB 167)	2,3′,4,4′,5,5′-HxCB	0.00003
2,3,3′,4,4′,5,5′-Heptachlorobiphenyl(PCB 189)	2,3,3′,4,4′,5,5′-HpCB	0.00003

3. Biotransformation of PCBs

PCB metabolism depends on the number and positions of chlorines in the molecule (Grimm et al., 2015; Kato et al., 1980; Mills et al., 1985). The fewer the number of chlorine atoms on biphenyl, the faster the PCB metabolism. PCB congeners with unsubstituted adjacent *meta* and *para* positions, *ortho* and *meta* positions. Absence of *ortho*-chlorine moieties is susceptible to oxidative metabolism, catalyzed predominantly by cytochrome P-450-dependent monooxygenases (Walker and Livingstone, 2013). The biotransformation of PCBs within the human body depends on their structural properties. Miyawaki et al. analyzed PCBs in the blood of Yusho patients collected from medical check-ups conducted in 2012 and found that the total concentration of 65 PCB congeners was comparable to the concentration in blood samples collected in 2005, indicating that these PCB concentrations in Yusho patients were unchanged from 2005 to 2012. Specific congeners including PCB 153, 138, 180, 156, 157 and 189 were highly accumulated in the blood (Miyawaki et al., 2015) because higher chlorinated PCBs (HC-PCBs) were resistant to biotransformation