Abstract. The developmental origins of health and disease concept illustrates that exposure in early life to various factors may affect the offspring's long-term susceptibility to disease. During development, the nervous system is sensitive and vulnerable to the environmental insults. Polychlorinated biphenyls (PCBs), which are divided into dioxin-like (DL-PCBs) and non-dioxin-like PCBs (NDL-PCBs), are synthetic persistent environmental endocrine-disrupting chemicals. The toxicological mechanisms of DL-PCBs have been associated with the activation of the aryl hydrocarbon receptor and NDL-PCBs have been associated with ryanodine receptor-mediated calcium ion channels, which affect neuronal migration, promote dendritic growth and alter neuronal connectivity. In addition, PCB accumulation in the placenta destroys the fetal placental unit and affects endocrine function, particularly thyroid hormones and the dopaminergic system, leading to neuroendocrine disorders. However, epidemiological investigations have not achieved a consistent result in different study cohorts. The present review summarizes the epidemiological differences and possible mechanisms of the effects of intrauterine PCB exposure on neurological development.

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1. Introduction

Polychlorinated biphenyls (PCBs) are a class of synthetic organic compounds, which contain 209 congeners (1). Based on their three-dimensional structure, PCBs can be divided into two main categories: Dioxin-like PCBs (DL-PCBs) and non-dioxin-like PCBs (NDL-PCBs). Owing to their chemical and thermal stability, PCBs were used widely in various industrial and commercial applications, including lubricating oils, plasticizers, hydraulic fluids, paint and ink (2-4). Commercial production of PCBs began in 1929 in the United States and were sold worldwide as commercial mixtures, such as Aroclor®, Clophen® and Phenclor® in the 20th century before stopping in the late 1970s (1,5,6). PCBs are often used in long-life products, with some reaching >30 years, such as capacitors and sealants (7). For the PCBs used in closed electrical systems, large release of chemicals do not occur as long as the electrical equipment remains intact during use or storage; however, significant release may occur if these systems are not properly managed during the waste and recovery phases (8). Persistent PCB emitters are likely to be released continuously and/or intermittently over the next few decades (9). The non-degradable property of PCBs makes them persistent organic pollutants, which exist in food chains, water, soil and even in air circulation (2,10).

In 1992, Hales and Barker (11) proposed the concept of developmental origins of health and disease, which is a hypothesis describing the fetal basis of adult disease. As of late, it has been widely accepted that early lifetime exposure to environmental endocrine-disrupting chemicals (EDCs) could affect the long-term susceptibility of offspring to disease (12,13). Intrauterine development is a critical period of plasticity for most organs and systems, wherein the fetus changes the structure and function of its organs, which is known as 'programming', to prepare for improved extraterine survival (12). Neurodevelopment, one of the most fragile processes, which occurs from the embryo to adolescence, is sensitive to environmental insults. Delayed neurotoxicity can develop even years after discontinuation of
the adverse exposure (14). Using structural MRI and functional MRI, intrauterine PCB exposure was found to increase cortical thickness over the right inferior parietal lobule in 30-year-old men, suggesting long-term effects on brain plasticity and compensatory neuropsychological performance (15). Prenatal exposure to a variety of environmental EDCs can cause fetal epigenetic disorders and neurodevelopmental defects, which may induce subsequent developmental disorders and diseases (16-18). A growing number of epidemiological studies conducted worldwide demonstrated the association between perinatal PCB exposure and neurobehavioral effects, including cognition (19,20), intelligence (21), hearing (22), behavior (20) and autism (23); however, these epidemiological investigations have not yielded consistent results, and the epidemiological differences and the underlying mechanisms have not been described in detail.

Therefore, the PubMed MEDLINE electronic database (https://www.ncbi.nlm.nih.gov/pubmed) was searched using ‘polychlorinated biphenyl’, ‘neurological’, ‘nervous’, ‘gestational’, ‘prenatal’ and ‘intrauterine’ as key words from the last two decades (2001-2020) and a total of 129 articles were retrieved. After excluding non-English and irrelevant articles, 78 articles were used. The key aim of the present review was to systematically analyze the epidemiological differences and describe the possible mechanisms of intrauterine PCB exposure on the development of the nervous system, which will further the understanding of life-long neurotoxic effects following developmental exposure to PCBs.

2. Bioaccumulation of PCBs

PCBs can accumulate in biota and biomagnify using food webs (24,25). Due to global fractionation, PCBs migrate in the atmosphere, and accumulate even at high latitudes and remote areas (26). Their toxicity can be amplified through bioaccumulation in grassland food networks. In a study of closed-loop food webs in Inner Mongolia (27), the biological amplification of PCBs in mice to snakes was found to be >1,000 times, suggesting that the relatively low concentrations and low toxic equivalent concentrations at the bottom of the food chain are biomagnified at high trophic levels. Various studies have demonstrated that fish products are the main source of PCBs, and that their PCB content varies with the region and type of fish, while grains and vegetables contain fewer PCBs (28-31). However, fish consumption in the general population is relatively low, suggesting that the health risks associated with exposure to PCBs have a certain tolerable daily intake (30). Maternal socioeconomic indicators may be another possible risk factor for PCB accumulation (32), as low-income households may eat fewer fish and have less access to PCBs from fish.

Maternal PCB accumulation can be transferred to the offspring via the placenta and breast milk (33,34). For the mother, breastfeeding is the main method of excreting PCBs, while for the offspring, it is the main source of PCB accumulation. Takagi et al (33) used (14C)PCBs to investigate the association between maternal and progeny PCBs via intragastric feeding in a rat model. In the fetus, the highest PCB concentration was in the fetal placenta, followed by the liver, heart, skin, muscles, blood, lungs and the brain. In suckling offspring, the highest concentration was found in the adipose tissue, while intermediate concentrations existed in the skin, adrenal gland and the liver. The concentration of PCBs in the fetal blood [0.24 parts-per million (ppm)] was similar to that in the maternal blood (0.26 ppm) and was much lower compared with that in the milk (1.84 ppm). Furthermore, the PCB content in nursing rats was significantly lower compared with that in pregnant and virgin rats. However, exposure to PCBs in multiple pregnancies was not lower compared with that in the first pregnancy. The levels of PCBs in the maternal body and breast milk was associated with age, diet, parity, self-nutrition during pregnancy and smoking habits (35,36). The concentration of PCBs was reduced by previous lactation; however, older parturients could accumulate PCBs for longer periods of time. In contrast, younger mothers exhibited a shorter lifetime exposure to environmental pollutants (37).

3. Exposure to PCBs during pregnancy and progeny nervous system development

Language is considered as an indicator of a child's cognitive development and language retardation may be the earliest sign of one or more neurodevelopmental disorders (38,39). Furthermore, in a cohort study, with a large group of mother-child pairs, high exposure to DL-PCBs during pregnancy increased the risk of language delay at age 3 years according to the parental report and Ages and Stages Questionnaire (40). However, due to the neurotoxicity of methylmercury, the neurotoxic effects of PCB cannot be assessed when individuals are exposed to both methylmercury and PCB (41).

Intrauterine PCB exposure could have a long-term impact on intellectual function. The effects of PCBs on intelligence seem to vary with age. Negative effects could develop or progress over time. A study by Berghuis et al (42) analyzed the association between the blood concentration of PCBs in pregnant women in the second and/or third trimester and intelligence using Touwen examination. They found that higher gestational exposure to several PCBs was positively associated with neurological functioning in 3-month-old babies. In addition, an early study revealed no statistically significant association between perinatal exposure to PCBs and the abilities of the children at 3-5 years, which were examined using the McCarthy Scales (43). However, as children become older, the negative effects of PCB on intelligence are becoming more notable (21,44,45). Lower levels of PCBs might be associated with higher intelligence in infants by stimulating the neuronal and/or hormonal processes, which leads to positive effects, while higher exposure levels might exert negative effects (42), suggesting the effects were dose-dependent. This is consistent with the way PCBs are transferred from the mother to the offspring. Since breastfeeding is the primary source of PCB exposure for newborns, from their mothers, it is possible that breastfeeding children have higher PCB accumulation (33).

It remains controversial whether cochlear function is immature in the first few months of human life or whether perinatal PCB exposure affects the auditory function in children. A collaborative perinatal project in the United States (22) suggested no association between PCB levels in serum from pregnant women and sensorineural hearing loss
(based on hearing threshold) in 8-year-old children. Conversely, in fish-eating populations of the Faroe Islands, higher PCB content in the cord tissue was associated with increased hearing thresholds in infants (46). Juskó et al (47) found that PCB-153 concentrations in the maternal and cord serum were not associated with distortion product otoacoustic emissions (DPOAEs) in 45-month-old children, while high levels of PCB-153 in the serum from children at 6, 16 and 45 months were associated with poor DPOAE amplitudes, suggesting that continued PCB exposure was more harmful to auditory function compared with that for a specific period of exposure.

Behavioral problems are also symptoms or signs of neurodevelopmental abnormalities, including externalizing and internalizing behavior problems (48). Internal behavior problems, defined as a lack of control of emotions, seem to be more easily affected by prenatal PCB exposure. Conversely, parental child-rearing attitudes around the birth order may play a more important role in child behavior compared with that in prenatal PCB exposure itself (49). Meanwhile, epidemiological investigations have not revealed a potential association between PCBs and externalizing behavior problems, which include oppositional, hyperactivity and aggressive behaviors according to Behavioral Assessment System for Children-2 at age 8 years (20). Several studies using zebrafish, an ideal model for toxicological research, have confirmed that embryonic exposure to PCBs was associated with anxious behavior and altered reactions to visual threats (50-52).

Autism, also known as autism spectrum disorder (ASD), is a type of neurodevelopmental condition characterized by different degrees of impaired social interaction and communication, repetitive or stereotypic behaviors, narrow interests, and abnormal perceptions (53). The etiology of ASD has not been fully elucidated; however, a previous study has shown that PCB exposure alters the endogenous axis and hormone-dependent neurodevelopment, thereby increasing the risk of ASD (53). However, such associations have not been unanimously supported in all literatures. Granillo et al (23) enrolled high-risk cohort families, with at least one child with ASD and planned to have another baby. They found that there was no significant association between total PCBs and ASD. Furthermore, DL-PCBs decreased the risk of ASD with borderline significance, whereas NDL-PCBs significantly elevated the risk of ASD. In another study, which included 546 mother-infant pairs, in a pregnancy and birth cohort, there was no association between 6 PCB congeners (PCB118, PCB138, PCB158, PCB170, PCB180 and PCB187) in the maternal serum in the first trimester of pregnancy and ASD in their children at 3-4 years of age (54).

4. Analysis of epidemiological differences

The effects of prenatal exposure to PCBs on offspring shows large interindividual variability. This inconsistency in epidemiological investigations may be attributable to a number of reasons, described below.

Genetic susceptibility. Genetic polymorphism refers to the presence of two or more alleles, at a particular locus. Depending on the allele and the gene, these polymorphisms may either protect the individual from pesticides-induced oxidative damage, or conversely, makes its more vulnerable (55,56). For example, two important polymorphisms (Q192R and L55M) in the human paraoxonase 1 (PON1) gene, a hydrolytic enzyme, which protects the toxicity of organophosphates insecticides, have opposing roles. The PON1 Q192R polymorphism enhanced the role of PON1, while PON1 L55M was hypothesized to have the opposite effect (57). Cytochrome P450s (CYPs) plays a key role in detoxification or activation of numerous xenobiotics (55). DL-PCBs bind and activate the aryl hydrocarbon receptor (AhR) to regulate three members of the CYP family: CYP1A1, CYP1A2 and CYP1B1 (58), which play an important role in the detoxification of PCB (59).

Poor-affinity AhRs and high protein levels of CYP1A2 in maternal liver cells provided important protection to the offspring against the sensitivity to gestational PCBs exposure (60-62). Conversely, high-affinity AhRs were found to respond to low levels of DL-PCBs, while the CYP1A2-mediated detoxification pathway could sequester DL-PCBs to prevent transfer to the offspring (60). The affinity of AhR and the expression of CYP1A2 in the liver varies in the population, which indicates that there are large individual differences in the susceptibility to PCBs (63).

The toxicological effect of NDL-PCBs has been associated with the ryanodine receptor (RyR). Compared with that in wild-type mice, double mutant (functional mutation in the RyR1 and a human CGG repeat expansion in the fragile X mental retardation gene 1) mice were more susceptible to PCBs. Perinatal exposure to PCBs in the maternal diet caused dysbiosis of the gut microbiota, resulting in behavioral deficits in the double mutant mice (64), which represents a potential role for protein digestion and microbial putrefaction in the gut-brain axis in patients with ASD (65).

Different PCB congeners have different effects and are dose-dependent. PCBs contain 209 homologous complexes and hydroxylated PCBs (OH-PCBs) (1). Due to the inconsistent homologues of PCB contamination in the environment, there are different epidemiological associations between PCB exposure during pregnancy and the nervous system in the offspring, even in the same study (23). On the other hand, gestational PCB exposure was found to be dose-dependent. The amount of PCB exposure in the environment is variable. As aforementioned, higher cord blood PCB concentrations were associated with a higher hearing threshold, indicating that there may be a threshold for prenatal PCB ototoxicity (22,46,47).

Inconsistent study environment and evaluation endpoints. Prenatal PCB exposure is usually detected in the maternal and umbilical cord blood, which may not be reflected in fetal suffering. In practice, cord blood is normally collected at birth, which does not include the sensitive window in early pregnancy associated with progeny health. Amniotic fluid provides another possible fetal environment, which can be analyzed, and amniocentesis is usually performed in the second trimester, during the prenatal diagnosis of advanced chromosomal abnormalities or fetal deformities (66,67). However, amniocentesis is an invasive procedure and is not used for routine prenatal examinations. Therefore, it is not realistic to use it for prospective studies.
Different evaluation endpoints are another reason for the uncertainty with respect to the different results of epidemiological studies, even within the same cohort. As aforementioned, the negative effects of PCBs exposure during pregnancy on the intelligence of the child became more pronounced with age (21,42,68). Furthermore, the age of the mother, education, race, preconception body mass index, fat mass, birth order, birth weight, number of pregnancies, duration of breastfeeding and diet, confound the effects of PCBs on the health of the offspring (69,70).

5. Mechanism of prenatal exposure to PCBs on offspring nervous system development

The possible mechanisms of PCB on the development of the nervous system are described in Fig. 1. The toxicological mechanism of DL-PCBs has been associated with the activation of AhR (60,71), while NDL-PCBs have been associated with RyR-mediated calcium (Ca²⁺) ion channels (72,73). Both DL- and NDL-PCBs may damage the fetoplacental unit (74,75), alter gene expression (76) and epigenetics (77), and affect neuroendocrine function (78).

DL-PCBs affect the development of the nervous system by activating AhR. AhR is a member of the eukaryotic Per-Ah receptor nuclear translocator (ARNT)-Sim domain protein family, which is located in the cytoplasm and binds to chaperone proteins hsp90, and co-chaperone protein p23 (79). Following ligand activation by DL-PCBs, the AhR separates and is translocated into the nucleus, where it binds to DNA response elements with an ARNT and begins transcription (71). In several animal models of development, AhR has been demonstrated to be widely distributed in the cerebral cortex, cerebellum, hippocampus and olfactory bulb neurons (80,81). Increasing evidence has also indicated that the neurotoxicity of prenatal exposure to DL-PCBs was associated with AhR activation in a dose-dependent manner (58,62,82), suggesting it plays an important role in neural development.

The following mechanisms may be involved in the effect of the DL-PCBs on the development of the nervous system via AhR: i) AhR might act as a common upstream regulatory molecule, that inhibits acetylcholinesterase (AchE) activity via transcriptional regulation of dioxin-response element sites in human AchE promoters and post-translational regulation of AchE-targeting microRNAs (83). AchE is an enzyme with high catalytic activity in the hydrolysis of acetylcholine, an important neurotransmitter. It not only plays a key role in regulating cholinergic neurotransmission, but is also an important enzyme in neurodevelopment (84); ii) DL-PCBs affect estrogen signaling via AhR, thereby reducing estrogen receptors and estrogen levels to disrupt the neuroprotective effect of estrogen in the cerebral cortex (83,85) and iii) over-activated AhR activity impairs neuronal migration during hippocampal development (86).

NDL-PCBs promote dendritic growth and alter neuronal connectivity via RyR-mediated Ca²⁺ ion channels. RyR is a Ca²⁺-regulated ion channel found in the sarcoplasmic reticulum (SR) in muscle cells and in the endoplasmic reticulum (ER)
in non-muscle cells. Activation of RyR can rapidly release Ca\(^{2+}\) from the ER/SR to assist with neuronal network development and endocrine balance (72,87). A NDL-PCB and a single congener increased RyR activity 2.4-19.2 times (88). NDL-PCBs have been associated with neurogenesis, by enhancing the activity of the RyR (72).

Dendritic structure is a key determinant of neuronal connectivity (89). Synaptic connections shape neural circuitry during development and also underlies associative learning (90). The remodeling of the dynamic structure of dendrites during development is primarily driven by Ca\(^{2+}\)-dependent signal transduction pathways triggered by external signals (91,92). NDL-PCBs promote dendritic growth and alter neuronal connectivity in the hippocampus and cerebellar Purkinje cells (73,93). Loss of neuronal connectivity is a common pathological feature of most neurodevelopmental disorders (94). Another developmental neurotoxicity of PCBs is caspase-dependent cell death in the hippocampal neurons via activation of the RyR and increased reactive oxygen species (95,96). Disturbances in the speed or amplitude of apoptosis in the developing hippocampus will change the number of cells, thereby changing the connectivity of neurons, and even leading to deficits in high-level function.

**DL- and NDL-PCBs alter genetic and epigenetic information.**

Epigenetic markers are dynamic and can be affected by the environment, particularly during critical periods of embryonic development and early life (97). Several studies have highlighted the importance of parental exposure to PCBs, which could affect the epigenome of the offspring and the susceptibility of the offspring to disease (97-99). DNA methylation refers to the addition of a methyl group to DNA using the enzyme, DNA methyltransferase, which can regulate genetic expression without changing the DNA sequence (17). In early life, DNA methylation can be affected by environmental factors and can persist even after removal of these factors (99,100). In primordial germ cells, DNA methylation decreased from 92% in post implantation embryos to 6.0% at week 10 in females and 7.8% at week 11 in males. DNA methylation levels gradually increased after 19 weeks until they reached the level of mature germ cells after birth (101). The placenta provides nutrients and oxygen to the fetus. It also contains an epigenome, which enables heritable and sustained changes to gene expression levels without altering the DNA sequence (17). The importance of parental exposure to PCBs, which could affect the epigenome of the offspring and the susceptibility of the offspring to disease (97-99). DNA methylation refers to the addition of a methyl group to DNA using the enzyme, DNA methyltransferase, which can regulate genetic expression without changing the DNA sequence (17).

**PCBs disrupt neuroendocrine function.**

PCBs easily penetrate the placental and blood-brain barriers, resulting in PCB accumulation in the offspring's brain (107). Early exposure to dioxins and PCBs could alter basic cellular signaling processes and endocrine functions, thereby affecting the synthesis and activity of important neurotransmitters in the central nervous system, as well as the development of brain tissue (108,109).

Thyroid hormones, which regulate the migration and maturation of γ-aminobutyric acidergic interneurons, are crucial during fetal development, particularly in the nervous system (110,111). The disruption of this process causes the formation of abnormal neural circuits, which has been hypothesized to underlie some neurodevelopmental disorders in humans, such as ASD (112). In early pregnancy, the fetal thyroid hormone is completely dependent on transport from the mother prior to fetal self-synthesis (113). An increasing number of epidemiological studies have confirmed that gestational PCB exposure was associated with disturbances in the thyroid function of neonates (114-116). This destruction has long-lasting effects in the offspring, potentially lasting until the child is 8 years old (116). The effects of PCBs and OH-PCBs on thyroid function may involve the following mechanisms: i) PCBs may competitively bind to transthyretin, particularly OH-PCBs, which have stronger binding affinity compared with that in their parent compounds; ii) PCBs may interact with thyroxine receptors or suppress DNA transcription and iii) OH-PCBs inhibit thyroid hormone sulfation, affecting the peripheral metabolism of thyroid hormones (114,117).

Dopaminergic systems are another potential target of PCB exposure during critical periods of neuronal development. For example, DL-PCBs may elevate dopamine (DA) concentrations in the prefrontal cortex via an estrogenic effect and alter behavior (78). A coculture model of developing rat striatum and ventral mesencephalon (VM) revealed that the neural toxicity of PCBs increased neuronal cell death and reduced the number of DA neurons in the VM (118). PCBs disturb DA transport into vesicles in the presynaptic terminal by inhibiting the activity of the DA transporter and vesicular monoamine transporter 2, leading to an accumulation of unsequestered DA, and increased production of the DA metabolites, which results in free-radical formation and caspase-mediated neuronal cell death (118,119).

**PCBs damage the fetal placental unit.**

The fetal placental unit connects maternal and fetal circulation and plays an important role in nutrient metabolism and endocrine systems (120). Lipophilic EDCs can accumulate in the placenta and can damage the fetoplacental unit and affect placental endocrine function (121,122). Angiogenesis, in the fetoplacental unit, is the result of cross-communication between different cells, such as invading trophoblasts, endothelial cells and specialized natural killer cells (119). The binding of δ-like (Dll)-4 to Notch receptors induces the proteolytic release of the Notch intracellular domain and regulates VEGF expression, forming a primary vascular network and secondary angiogenesis at the maternal-fetal interface (123,124). The Dll4-Notch4-VEGFR2 signaling axis
is a potential target for PCBs, particularly when the IL-10 gene is knocked out, which leads to poor spiral artery remodeling and reduced angiogenesis in the placenta (74). Animal studies have shown that gestational PCB126 exposure leads to some histopathological changes in the placental tissue, which manifests as hyperemia, hemorrhage, degeneration, apoptosis in the labyrinth layer and spiral arteries of the placenta, resulting in fetal hypothyroidism and endocrine disruption. The presence of hypothyroidism negatively affected the fetal pituitary thyroid axis, the growth hormone/insulin-like growth factor-I axis and cytokine levels, such as leptin, IL-1β, TGF-β and tumor necrosis factor (TNF)-α (75). This fetoplacental unit disruption, caused by maternal PCB exposure, might reduce normal biological function and the general health of the offspring.

6. Conclusions

PCBs are persistent environmental EDCs, and have environmental impacts, even though they have been banned for decades. There are still limitations with respect to understanding of PCB neurotoxicity. The novelty of the present review firstly systematically analyzed prenatal PCB exposure, particularly that gestational exposure affected the development of the nervous system in the offspring and even had long-term effects on the brain. Due to multiple contradictory factors, such as different types of PCB exposure, different exposure doses, different follow-up ages, and individual genetic susceptibility, there is not a consistent conclusion from epidemiology research. The relevant reasons of epidemiological investigation were analyzed, providing areas of future epidemiological investigations on intrauterine PCB exposure. The underlying mechanism of different PCBs congeners, including the activation of AhR, via RyR-mediated Ca^{2+} ion channels, and the epigenetic changes that can occur have been discussed; however, further investigation is required to fully understand the mechanisms involved. Furthermore, there is still no effective method to intervene or block the neurotoxicity of PCBs; therefore, the establishment of an ideal animal model is important. Despite these limitations and challenges, increasing attention should be made to PCB environmental pollution to avoid the potential adverse effects in the offspring.

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Authors' contributions

YFW wrote the manuscript. CCH investigated the association between gestational PCBs exposure and progeny nervous system development. TF contributed to the mechanisms of PCBs. YJ contributed to analysis of epidemiological differences. RJW supervised and revised the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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