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The neurotoxicity of polychlorinated biphenyls (PCBs)

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Abstract

Polychlorinated biphenyls (PCBs) are pervasive environmental pollutants. Despite having been banned from production in 1979 by the USA and most parts of the world since the early 2000s, PCBs continue to pose a significant risk to human health. Humans are exposed via diet and inhalation to not only legacy PCBs from commercial mixtures synthesized prior to the ban on PCB production, but also PCBs created as inadvertent byproducts of contemporary manufacturing processes. A major target of concern for PCBs is the developing brain; however, adverse effects on the adult and aging brain have also been reported. In this chapter, we summarize epidemiological and experimental animal studies of early-life and mid-life exposures to PCBs, focusing on outcomes across domains related to cognition (e.g., IQ, language, memory, learning), attention, behavioral regulation and executive function, and social behavior,

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as well as traits related to attention deficit hyperactivity disorder (ADHD), autism spectrum disorders (ASD), affective disorders, and neurodegenerative diseases.

1. Introduction

Epidemiologic (Berghuis et al., 2015; Boucher et al., 2009; Pessah et al., 2019; Schantz et al., 2003) and experimental animal (Klocke and Lein, 2020; Sable and Schantz, 2006; Ulbrich and Stahlmann, 2004) studies have identified the brain as a vulnerable target of polychlorinated biphenyls (PCBs). Much of the scientific literature on PCB neurotoxicity describes the developmental neurotoxicity of PCBs (Fig. 1), which are among the most extensively studied developmental neurotoxicants of the nonmetallic persistent organic pollutants (POPs). Both human and experimental animal studies of early-life exposures to PCBs have documented adverse neurodevelopmental outcomes across domains related to cognition (e.g., IQ, language, memory, learning), attention, behavioral regulation and executive function, and social behavior, including traits related to attention deficit hyperactivity disorder (ADHD) and autism spectrum disorders (ASD) (Carlson et al., 2023). While our knowledge of

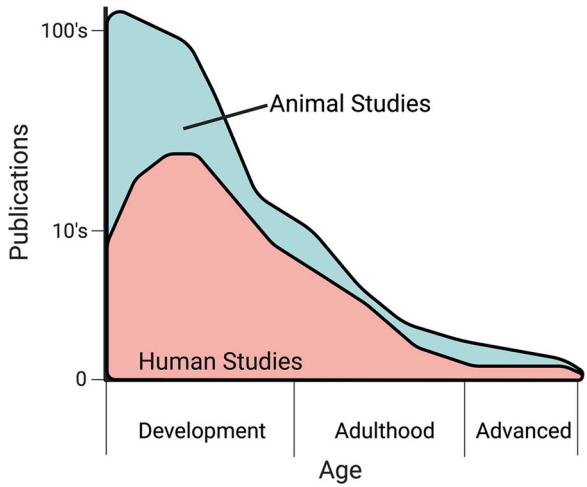

Fig. 1 Distribution of literature assessing neurotoxic effects of PCB exposures in humans and animal studies. The graph is organized by the magnitude of order of number of publications as a function of the age of exposure. The majority of literature is focused on PCB effects on the developing brain, with the number of publications decreasing as the age at which neurotoxic outcomes are assessed.

how early or mid-life exposures to PCBs influence the adult brain is not as comprehensive, there is evidence linking PCBs to increased risk of affective disorders and neurodegenerative outcomes, and this literature is also addressed in this chapter.

PCBs are a class of synthetic halogenated organic compounds (HOCs) that were originally manufactured and marketed in the United States (U.S.) from the late 1920s through the late 1970s under the product name "Aroclor" and in Europe until the early 2000s under the trade name "Clophen". Because of their incredibly stable chemical properties and ability to dissipate heat, PCBs were used as plasticizers, lubricants, and coolants in many different products and applications, including electrical equipment, hydraulic fluids, printing inks and dyes, building materials like caulking compounds and paints, and fluorescent light ballasts. Unfortunately, the chemical stability that made PCBs so useful also rendered them resistant to environmental and metabolic degradation. These properties underlie the ubiquitous environmental distribution and bioaccumulation of PCBs, which have raised global concerns about adverse health consequences of widespread human exposures (Domingo and Bocio, 2007; Faroon and Ruiz, 2016; Stahl et al., 2009). These concerns led to restrictions on the production of PCBs imposed by many governments through the Stockholm Convention on POPs signed in 2001 and appended in 2008 and 2014 to include the goal of eliminating the use of existing PCB-containing equipment by 2025 (Guida et al., 2020). While environmental levels of "legacy" PCBs have declined following these regulatory efforts, legacy PCBs are still routinely detected in the environment and in human tissue (see Chapter 1 for additional details). In addition, humans are exposed to PCBs that were not manufactured as Aroclors, but rather are inadvertent byproducts of contemporary pigment production processes (Hornbuckle, 2022).

PCBs are a complex mixture of congeners that differ in the number and position of chlorine substituents on the biphenyl backbone (Fig. 2). PCB congeners are categorically divided into either lower-chlorinated PCBs (LC-PCBs) that have ≤4 chlorine substituents or higher-chlorinated PCBs (HC-PCBs) that contain > 4 chlorine substituents. LC-PCBs, which are the predominant congener type produced inadvertently during pigment production, are less stable, more volatile and more quickly metabolized than HC-PCBs (Li et al., 2022). The structure of PCBs influences their biological activity. PCBs with zero chlorines in the *ortho* position assume a coplanar biphenyl orientation in solution, while PCBs with one to

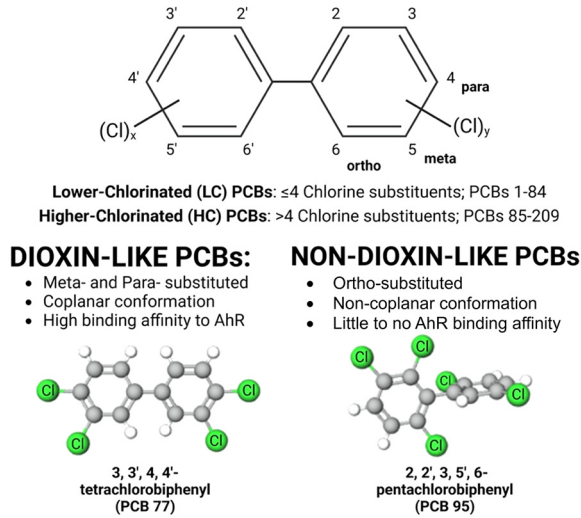

Fig. 2 General chemical structure, classifications, and examples of PCB congeners. PCBs are a structurally related group of chemicals comprised of a biphenyl structure with varying numbers of chlorine substitutions. There are 209 possible congeners that can be categorized as either lower chlorinated (LC) or higher chlorinated (HC) PCBs depending on the number of chlorine substituents. PCBs are also classified as dioxin-like (DL) or non-dioxin-like (NDL) PCBs. DL PCBs, exemplified by PCB 77, assume a coplanar conformation similar to dioxin and bind with relatively high affinity to the aryl hydrocarbon receptor (AhR). In contrast, NDL PCBs, such as PCB 95, which typically have > 1 ortho-substituted chlorine, have a non-coplanar structure and low to negligible AhR binding.

four chlorines in the *ortho* position assume increasing degrees of noncoplanar ring orientation (Fig. 1). Coplanar congeners can bind to and activate the aryl hydrocarbon receptor (AhR) to cause toxic effects similar to those observed for dioxins; hence, coplanar congeners are known as "dioxin-like" PCB congeners. Of the 209 possible PCB congeners, only 12 are classified as dioxin-like. While low-level exposures to dioxin-like PCBs are associated with a number of adverse outcomes in several organ systems, especially liver, skin, and immune function (Bock, 2016; Mellor et al., 2016; Wheeler et al., 2017), and are probable carcinogens (Lauby-Secretan et al., 2013), there is less evidence from epidemiologic and experimental animal studies that they are associated with neurotoxic outcomes (Pessah et al., 2019).

In contrast, non-coplanar PCBs have little to no AhR activity and are thus "non-dioxin-like". Historically, non-dioxin-like PCBs were considered to be biologically inert. However, pioneering research by Richard Seegal of

the New York State Department of Health (Seegal et al., 1990; Shain et al., 1991) and Prasada Kodavanti and Hugh Tilson from the U.S. Environmental Protection Agency (Kodavanti et al., 1993; Kodavanti et al., 1996a; Kodavanti et al., 1996b; Kodavanti and Tilson, 2000) revealed that non-dioxin-like PCBs have considerable biological activity independent of the AhR (Panesar et al., 2022). Non-dioxin-like congeners make up most contemporary human PCB exposures, and there is extensive scientific evidence implicating these congeners as predominantly responsible for the developmental neurotoxicity associated with PCB exposures (Klocke and Lein, 2020; Montano et al., 2022). Additional details about the effects of non-coplanar PCBs on neurotransmitters and calcium signaling can be found in Chapters 4 and 7 of this book series.

Humans are exposed to PCBs via consumption of contaminated foods and inhalation of contaminated air (Fig. 3), although exposure via dermal absorption is also possible, particularly in occupational settings. While the consumption of high-fat foods, predominantly meat, fish and dairy products, has long been considered the main route of human exposure to PCBs, there is increasing appreciation of the importance of inhalation (Grimm et al., 2015). Volatilization of PCBs from building materials such as caulking, paints, and varnishes, as well as leaking of fluids from PCB-containing fluorescent light ballasts, can result in significant indoor air levels of PCBs (Hornbuckle, 2022). Air sampling from schools built or remodeled prior to the PCB production ban has detected PCB levels far exceeding those measured near some of the largest PCB-contaminated Superfund sites in the U.S. (Hornbuckle, 2022). The recent AESOP (Airborne Exposure to Semivolatile Organic Pollutants) study found that indoor air PCB concentrations were the main factor affecting human blood levels of PCBs, and modeling of dietary intake and inhalation exposures relative to serum PCB levels revealed that for some children, inhalation exposures were greater than their dietary exposure (Ampleman et al., 2015). While dietary ingestion is thought to be the primary route of exposure to HC-PCBs and inhalation the primary route of exposure to the more volatile LC-PCB (Ampleman et al., 2015; Grimm et al., 2015), recent data suggest this may be an oversimplification. The LC-PCB, PCB 11, was detected in commercial milk products in northern California, and PCB 95, a HC-PCB, was the second most abundantly detected PCB congener in school air samples within the U.S. (reviewed in Klocke and Lein, 2020). Collectively, these observations suggest that human exposure to HC- and LC-PCBs occurs through both diet and inhalation.

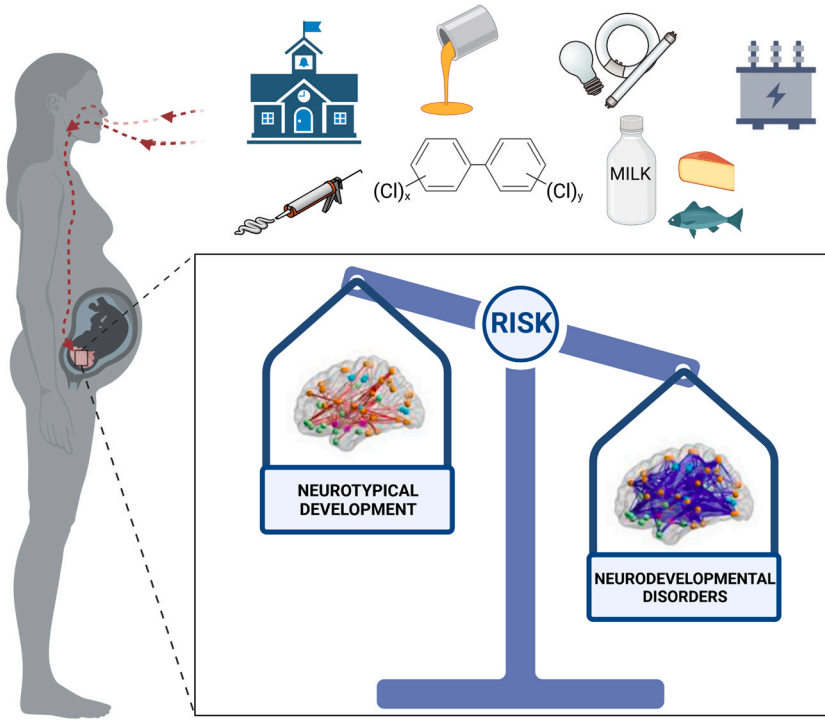

Fig. 3 Developmental PCB neurotoxicity. There is documented widespread exposure of pregnant and lactating women to PCBs via ingestion of contaminated foods and inhalation of contaminated air. Sources of PCBs include indoor air, especially in municipal buildings constructed prior to the ban on PCB production, such as public schools, paints and caulking, fluorescent light ballasts, electrical transformers, and fatty foods, particularly dairy products and fatty fish. Epidemiological and experimental data suggest that exposure to PCBs during critical neurodevelopmental windows may increase risk of neurodevelopmental disorders.

PCBs are lipophilic and thus are readily transferred from mother to fetus prenatally via the placenta (Fig. 3) and postnatally through breast milk. According to the National Health and Nutrition Examination Survey (NHANES), there is widespread exposure to HC- and LC-PCBs, with U.S. women of child-bearing age having average total PCB blood levels in the 30–200 ng/g range (Panesar et al., 2020). Similar levels are reported in other countries. A recent study investigating the age-, sex-, and brain region-specific distribution of all 209 PCBs using gas chromatography-tandem mass spectrometry (GC-MS/MS) in neonatal ($N = 7$) and adult ($N = 7$) postmortem brain samples found that HC-PCBs were observed at higher levels in samples from adult vs young donors, while LC-PCBs

predominated in samples from young vs adult donors (Li et al., 2022). Interestingly, this same study also detected hydroxylated PCB metabolites in human brain samples. The AESOP study had previously detected 58 OH-PCB congeners in serum samples collected between 2010 and 2011 from adolescents and mothers and found that HC-OH-PCBs predominated while LC-OH-PCB congeners were rarely detected in the serum samples (Marek et al., 2014). PCBs are hydroxylated by cytochrome P450 monooxygenases. While some OH-PCBs are readily eliminated, most undergo phase 2 metabolism (Grimm et al., 2015). Levels of hydroxylated and sulfated PCBs found in human blood and tissues, like placenta, can be quite high, and data from both human and experimental models have implicated these metabolites in PCB neurotoxicity (Panesar et al., 2022).

2. Human studies

2.1 Developmental neurotoxicity

The relationship between PCBs and neurodevelopment has been studied extensively in many different populations around the world, including Europe, Asia, and the U.S. (Table 1). Two accidental mass poisonings that involved PCB-contaminated cooking oil, the first in Japan in 1968 and the second in Yu-Cheng, Taiwan in 1979, provided the first human evidence of PCB neurotoxicity (Masuda et al., 1985). In Japan, more than 1000 people became ill after ingesting rice oil contaminated with PCBs during the manufacturing process. In Yu-Cheng, more than 2000 people became ill from consuming PCB-contaminated rice oil. Children born to women exposed through ingestion of PCB contaminated rice oil while pregnant had an increased incidence and severity of cognitive and psychomotor deficits (Rogan, 1982).

While the Yusho and Yu-Cheng incidents involved extremely high PCB exposures, subsequent epidemiological studies have identified neuropsychological deficits in populations exposed to much lower levels of PCBs. These latter studies have mostly identified negative associations between prenatal PCB exposure and measures of cognitive function, learning, memory, and IQ (Berghuis et al., 2015; Boucher et al., 2009; Pessah et al., 2019; Schantz et al., 2003). Deficits in these behavioral domains are commonly observed in many neurodevelopmental disorders (NDD), including autism spectrum disorder (ASD) and attention-deficit

Table 1 Epidemiological studies of PCB effects on the developing brain.

Cohort/ Study	Sample Size	Exposure Measure	Median Concentration	Cognitive Tests	Age at Testing	Significant Cognitive Results	Reference (s)
Michigan Cohort	226	Cord serum	0.4 ng/mL	MCSA, Sternberg, Kagan's; WISC- R	4 years; 11 years	↑ Short-term memory task errors ↓ Visual discrimination; ↓ Full-scale IQ	Jacobsen et al. (1992)
Michigan Cohort	212	Cord serum	3 ng/mL	WISC-R WRAT-R WRMT- R	11 years	↓ Full Scale IQ ↓ Verbal IQ ↓ Reading comprehension	Jacobson and Jacobson (1996)
The Dutch Cohorts	~400	Maternal blood, cord serum, and breast milk	2.21 ng/g, 0.45 ng/g, 428.5 ng/g	Prechtl; BSID psychomotor development; K-ABC	10 and 21 days; 18 and 42 months	↓ PDI at 7 months; ↓ Neurological optimality at 18 months; ↓ K-ABC cognition and language at 42 months	Koopman-Esseboom et al. (1996); Reviewed in Schantz et al. (2003) and Pessah Et al. (2019)
Oswego Cohort	309 mom–child pairs	Cord blood, breast milk, and placenta	0.52 ng/g, 153 ng/g, 1.5 ng/g	MSCA; WISC-IIIa	3–4 years; 9 years	↓ MCSA ↓ Full scale IQ ↓ Verbal IQ	Stewart et al. (2003); Stewart et al. (2008); Reviewed in Pessah et al. (2019)

The German Cohort Faroe Islands Cohorts	171 mom–child pairs	Cord blood and breast milk	0.55 ng/mL, 426.5 ng/g	BSID-II menta (MDI) l and psychomotor development index; FTII	7 months	↓ BSID-II MDI; ↓ BNT	Winneke et al. (1998); Reviewed in Schantz et al. (2003); Grandjean et al. (1997), Grandjean et al. (2001), Steuerwald et al. (2000); Reviewed in Schantz et al. (2003) and Pessah et al. (2019)
	435		1.88 μg/L	NES-2 Finger Tapping, Hand-Eye Coordinatio-n; BVMG; WISC-R; CVLT; BNT	7 years		
New Bedford Cohort	393	Cord serum	0.38 ng/g	WRAML	8 years	No significance	Orenstein et al. (2014); Reviewed in Schantz et al. (2003) and Pessah et al. (2019)
Flemish Cohort	206 mom–child pairs	Cord blood; PCBs 138, 153, 180, 118, 170	Total PCBs (183 + 153 + 180) 87.9 ng/g; PCB 118 14.9 ng/g, PCB 170 8.9 ng/g	RTOS, SON, BSID, NES, IBQ	3 years	↓ Activity, delayed first steps, ↓ Language development, ↓ Non-verbal IQ scores in boys, ↓ Gender-specific play	Vermeir et al. (2021)

(*continued*)

Table 1 Epidemiological studies of PCB effects on the developing brain. (*cont'd*)

Cohort/ Study	Sample Size	Exposure Measure	Median Concentration	Cognitive Tests	Age at Testing	Significant Cognitive Results	Reference (s)
Greece Cohort	689	Maternal serum; PCBs 118, 153, 138, 156, 180, 170	20.3, 149.7, 80.0, 8.2, 85.6, 42.3 pg/mL, respectively	MSCA	4 years	↓ Working memory	Kyriklaki et al. (2016)
Norwegian Cohort	1024 children	Dietary exposure; PCB 153	0.81 ng/kg bw/day	D-B Grammar Scale; ASQ	3 years	↑ Instance of incomplete grammar; ↓ Language delay; ↓ Communication score	Casperson et al. (2016)
Collaborative Perinatal Project	894	Maternal serum; Total PCB (PCBs 28, 52, 74, 105, 118, 138, 153, 170,180, 194, 203)	2.85 ug/L	WISC; WRAT-R	7 years	No significance	Gray et al. (2005); Reviewed in Pessah et al. (2019)

ASQ: Ages and Stages Questionnaire; BNT: Boston Naming Test; BSID: Bayley Scales of Infant Development; CVLT: California Verbal Learning Test; D-B Grammar: Dale and Bishop Grammar Scales; IBQ: Infant Behavior Questionnaire; FTII: Fagan Test of Infant Intelligence; MSCA: McCarthy Scales of Children's Abilities; MDI, Major Depression Inventory; NES: Neurobehavioral Evaluation System; PDI, Psychomotor Developmental Index; RTOS: Reynell Taal Ontwikkelings Schalen (language development); SON: Snijders-Oomen Niet (Non-verbal intelligence); WISC: Weschler Intelligence Scale for Children; WRAML: Wide Range Assessment of Memory and Learning; WRAT: Wide Rage Achievement Test.

hyperactivity disorder (ADHD), and emerging evidence implicates PCBs as environmental risk factors for NDDs (Eubig et al., 2010; Keil-Stietz and Lein, 2023; Klocke and Lein, 2020).

Below we briefly summarize selected human studies on PCB developmental neurotoxicity published after 1990 that were chosen based on their historical significance and/or rigorous study design with respect to cohort size, PCB measures in relevant biological samples (maternal blood collected during gestation, umbilical cord blood and/or placenta) and assessment of neuropsychological function.

2.1.1 Yu-Cheng studies

Longitudinal studies of children aged 2–12 years old from the Taiwan cohort employed the Bayley Scales of Infant Development-II (BSID-II) to assess the level of cognition, language, and social development, as well as both fine and gross motor function (Nellis and Gridley, 1994). The Chinese version of the Stanford-Binet IQ Test, Raven's Colored Progressive Matrices and Raven's Standardized Progressive Matrices were also utilized to assess cognitive development. Children of mothers with PCB exposure had reduced scores on these scales compared to control children (Lai et al., 2001), indicating developmental delay. The same participants were followed up when they were aged 26–32 using the Wechsler Adult Intelligence Scale [WAIS-III]. The WAIS-III consists of 13 subtests, four index scores, three IQ assessments and two additional measures of incidental memory (Ryan and Lopez, 2001). Some additional testing was done in conjunction with a functional MRI (fMRI), including the n-back test and picture rotation test (Chu et al., 2019). No differences in cognitive and behavioral testing were found between PCB exposed participants and the control group at this more advanced age, but the PCB exposed group had areas of increased cortical thickness and showed altered task deactivation and activation signals in the fMRI. These results suggest that the cognitive effects of developmental PCB exposures may not persist later in life, and that brain plasticity may be altered at later ages.

2.1.2 Michigan cohorts

The relationship between low-level maternal PCB exposure via dietary intake of Lake Michigan fish and developmental outcomes in children (Jacobson et al., 1984; Jacobson and Jacobson, 1997) was investigated in two separate cohorts using a longitudinal study design. More than 8000

women who delivered babies in western Michigan hospitals during 1980–1981 were interviewed on the day after delivery, and those who had consumed 26 or more pounds of Lake Michigan fish during the preceding 6 years were asked to participate. Women who did not eat Lake Michigan fish were randomly selected and invited to serve as controls. The PCB burden in two birth cohorts was assessed from cord serum and from serum collected from the children at 5 and 7 months and 4 and 11 years of age. Both PCB-exposed cohorts had significant cognitive and psychological deficits relative to control subjects.

2.1.3 Dutch cohort

After the World Health Organization (WHO) announced that levels of PCBs and dioxins found in breastmilk were higher in Europe than in other parts of the world, the Dutch government responded by forming its own longitudinal study to study adverse effects of PCB and dioxin exposure during development (Vreugdenhil et al., 2002). This was the first neurodevelopmental study to use congener-specific analysis to assess PCB exposure. The study included approximately 400 healthy pregnant women, half of whom breast-fed, while the other half formula-fed. The cohort was also separated by geographic location, with half living in Rotterdam, a heavily industrialized area, and the other half in Groningen, a rural area in northern Netherlands. PCB exposure was measured in maternal blood during the last month of pregnancy, in umbilical cord serum, and in breast milk. Four non-dioxin-like PCB congeners, PCBs 118, 138, 153, and 180, were quantified in both maternal and cord serum. The PCB levels in maternal serum were about 4–5 times higher than those in cord serum. However, lipid composition differs greatly between maternal and cord serum, and when expressed on a lipid basis, the PCB levels were similar. ΣPCB levels were 2.21 ng/g, 0.45 ng/g, and 428.5 ng/g in maternal plasma, cord blood, and breast milk, respectively. Neurodevelopment was assessed at 3, 7, 18, 42, and 84 months of age. Many important developmental outcomes were found to be negatively associated with pre- and postnatal exposure to PCBs, but because so many different outcomes were assessed, the results were complex and inconsistent across age. The European Union (EU) funded an opportunity to expand the Dutch cohort study into a transnational, multicenter study that included a German cohort in Dusseldorf and another in the Faroe Islands, which are described below.

2.1.4 German studies

In 1993, 171 German mother–infant pairs were recruited to study PCB exposure. PCBs 138, 153, and 180 were measured in cord serum and breast milk, and neurodevelopment was assessed at 7, 18, 30 and 42 months of age. Similar to findings from the Michigan and Dutch cohorts, a negative association was found between prenatal PCB exposure and measures of cognitive development. The German cohort study found significantly increased omission errors in the computer-based test battery of attention performance (KITAP) in 8.5-year-old boys and girls with high levels of PCBs found in prenatal maternal blood (Neugebauer et al., 2015). However, this study also found a negative association between PCB exposures and ADHD-related behaviors (−10%; 95%-CI: 0.82–0.99). Unlike similar studies (e.g., Michigan, Dutch), the German study identified a relationship between postnatal PCB exposure via breast-feeding and adverse neurodevelopmental outcomes.

2.1.5 Faroe Islands cohort

PCB exposure was assessed in two cohorts from the Faroe Islands, a territory between Norway and Iceland, that originally were studied to evaluate the effects of methylmercury exposure on neurodevelopment. Whale meat and blubber were a primary dietary source of methylmercury and PCBs in both cohorts. The first cohort of 1022 singleton births was recruited in 1986–1987. PCBs were measured in samples of umbilical cord from a subset of 443 children. The sum of three major congeners, PCB 138, 153, and 180, was used to estimate total PCB burden. Twelve adolescent boys from this cohort underwent fMRI, and those with high levels of PCB exposure had more activation across brain regions during both visual and motor tasks than those with lower-level exposures. A second cohort of 182 singleton infants born at term at the National Hospital in Torshavn, Faroe Islands was recruited in 1994–1995 as part of the EU multicenter study. PCB levels were measured in maternal serum, maternal hair, breast milk, and cord blood. PCB levels within this cohort were ~3-fold higher than those in the Dutch cohort, yet PCB exposure had no effect on neurological outcome measures. Interestingly, observations from a rat model of developmental PCB exposure demonstrated a non-monotonic dose–response relationship with deficits in spatial learning and memory observed in weanling rats exposed to Aroclor 1254 in the maternal diet at 1, but not 6, mg/kg/day (Yang et al., 2009).

2.1.6 Oswego, New York cohort

The Owego Newborn and Infant Development Project was a longitudinal study that took place in 1991 and initially started with 309 mom–child pairs. This was a follow up study to the Michigan cohort studies. Behavioral assessments were done at birth, 6, 12, 36, and 54 months of age, then again when subjects were 8 and 9.5 years old. The primary measure of exposure was PCB levels in umbilical cord plasma at birth. The placenta was also collected, and a small subset of women provided breast milk. The NES3 Extended Continuous Performance Tests (E-CPT) revealed that at 9.5 years old, the children had increased impulsivity due to impaired inhibition (executive functioning), but not impaired sustained attention, and these impairments correlated with increased PCB levels (Stewart et al., 2005).

2.1.7 The New Bedford, Massachusetts studies

In 1982, the New Bedford harbor in southeastern Massachusetts was designated a Superfund site because of heavy PCB contamination of the sediment. A prospective birth cohort study conducted near this site included 788 mother–infant pairs recruited from 1993 to 1998. Infants born by Cesarean section or whose mothers did not speak English were excluded. Umbilical cord serum and maternal milk were collected and analyzed for PCBs using a congener-specific technique that quantified 51 individual PCB congeners. The concentrations of key indicator congeners, PCBs 118, 138, 153, and 180, were about one-half those reported in the Dutch cohort, but quite similar to those reported in the Oswego, New York cohort. Attention was assessed when the children were 8 years of age using the Continuous Performance test (CPT) and Wechler Intelligence Scale for Children (WISC-III). Boys with higher exposures to PCBs had more errors of omission, or the number of nonresponses, in the CPT and slower processing speed in the WISC-III than the control population, suggesting an attention deficit. Girls had a less errors of omissions in the CPT than the males (Sagiv et al., 2012).

2.1.8 Inuit cohort

The Inuit people depend on sea mammals (seal, beluga whale, and walrus) as the primary source of protein and fat in their diet. As a result, they have unusually high body burdens of PCBs. In the early 1990 s, PCB concentrations in breast milk samples collected from Inuit women were 7 times higher than the PCB concentrations in Caucasian women residing in southern Quebec. Between September 2005 and February 2010, 294 children and their mothers participated in neurocognitive assessments in

the three largest Nunavik villages in Canada. The concentrations of PCB 153 in this cohort were similar to those in the Dutch cohort and about 2-fold higher than those in the New Bedford cohort; however, there was no clear evidence of adverse effects of PCB exposure on neurocognitive measures in the Inuit children.

2.1.9 Flemish environmental health survey

Between 2002 and 2006, 206 mother–child pairs were recruited and levels of PCBs 118 and 170 in addition to levels of "indicator" PCBs (138, 153, and 180) were measured in cord blood. The children were assessed during the first year of life for crawling and age at which they took their first steps, and higher PCB exposure levels were associated with delayed activity. At 1 year of age, the children were assessed using the Infant Behavior Questionnaire (IBQ), and at 36 months of age, they received the Reynell Taal Ontwikkelings Schalen (RTOS) test for language development. Increased PCB exposures were associated with slower development of language, suggesting early-life PCB exposure reduced language capabilities. The Snijders-Oomen non-verbal intelligence (SON) test, also taken at 36 months of age, showed PCB 118 exposure was associated with lower IQ in males only, and that sum PCBs was associated with deficits in non-gender specific play in both males and females. These data suggest lower-level PCB exposures adversely affect the neurobehavioral development of young children, especially boys (Vermeir et al., 2021).

2.1.10 Rhea study, Crete, Greece

This study included 689 mother–child pairs in which the pregnancy occurred within one year of February 2007. PCBs 118, 138, 153, 156, 170, and 180 were measured in maternal serum collected in the first trimester of pregnancy, and neurodevelopment was assessed at 4 years. Concentrations of various PCBs correlated with behavioral scores from the McCarthy Scales of Children's Abilities (MSCA), which is a well validated test for assessing delays in verbal information processing, perceptual information processing, numerical abilities, general cognition, memory, and motor skills. Alternate scales for executive function, working memory, memory span, and cognitive functions were also included based on the underlying construct between brain region and behavior (Julvez et al., 2007). High exposure to PCBs during pregnancy (>90th percentile) was associated with deficits in a working memory task and decreased scores in perceptual performance, general cognitive, and executive function (Kyriklaki et al., 2016).

2.1.11 Norwegian study

This study included 1024 children enrolled in a longitudinal prospective study of ADHD with participants recruited from The Norwegian Mother and Child Cohort Study (MoBa). Boys and girls aged 3.5 years participated in extensive clinical assessments. Levels of dietary PCB 153 were used as a measure of PCB exposure. Clinical assessments included the preschool version of the Behavior Rating Inventory of Executive Function (BRIEF-P), the Preschool Age Psychiatric Assessment interview (PAPA), Stanford-Binet 5th revision (SB-5), Child Development Inventory (CDI), and Behavior Rating Inventory of Executive Function. No associations were found between low-level exposure to PCB 153 and ADHD-symptoms, verbal/non-verbal IQ, or executive functions, including working memory, in preschoolers. However, the findings did show that maternal dietary exposure to PCB 153 during pregnancy was significantly associated with poorer expressive language skills in preschool girls (Caspersen et al., 2016; Skogan et al., 2014). It should be noted that the study population was designed to recruit adolescents with ADHD symptoms, which may have skewed results.

2.1.12 The Collaborative Perinatal Project

The Collaborative Perinatal Project (CPP) was a prospective study designed to identify determining factors of neurodevelopmental deficits (Gray et al., 2005). More than 56,000 pregnant women were recruited from 12 centers across the USA between 1959 and 1966 and followed longitudinally through pregnancy and after birth. Serum was collected during the third trimester and analyzed for 11 specific PCB congeners: PCBs 28, 52, 74, 105, 118, 138, 153, 170, 180, 194, and 203. Cognitive function was assessed when children were 7 years of age using the intelligence quotient (IQ) scores on the Wechsler Intelligence Scale for Children. In this study, *in utero* exposure to PCBs was not associated with lower IQ at age 7 years.

2.2 PCBs as environmental risk factors for neurodevelopmental disorders (NDDs)

Reviews of the human literature on PCB developmental neurotoxicity have consistently concluded that the weight of evidence indicates that PCBs are developmental neurotoxicants (Berghuis et al., 2015; Boucher et al., 2009; Pessah et al., 2019; Schantz et al., 2003), but whether PCBs are associated with an increased risk for specific NDDs is less clear. There has

been significant interest in investigating PCBs as a risk factor for autism in particular (Alampi et al., 2021; Bernardo et al., 2019; Lyall et al., 2017; Mehri et al., 2021). Autism spectrum disorder (ASD) is a complex, multifactorial neurodevelopmental condition that is defined clinically by core deficits in social reciprocity and communication, restrictive interests and repetitive behaviors, although the severity and symptom profile vary considerably between individuals. Research on ASD has focused primarily on genetic factors, identifying a strong hereditary component and hundreds of genes that influence autism risk; however, solely genetic causes account for approximately 10–30% of all autism cases (Ansel et al., 2016; Lai et al., 2014; Masini et al., 2020). It is now thought that gene–environment interactions underlie most cases of ASD (Lein, 2015).

The MARBLES study, a longitudinal study that began in 2006, was designed to identify possible pre- and postnatal biological and environmental risk factors that may contribute to the development of autism. This study recruited pregnant women living in northern California who already had a child with a NDD and, therefore, had an increased risk of having a second child with an NDD (Hertz-Picciotto et al., 2018b). A total of 104 mother–child pairs were included in a study to assess association of PCBs with autism. Maternal serum was collected through gestation and analyzed for PCB composition. Interestingly, of the 12 most abundant PCB congeners detected in these samples, LC-PCBs 11 and 28 constituted 70% of the total PCB burden (Sethi et al., 2019). Multinomial logistic regression was used to assess the relative risk of a clinical outcome classification of ASD and non-typical development (Non-TD) compared to typically developing (TD) in the children at 3 years of age. There were no significant associations between these outcome measures and total PCB levels; however, there were borderline significant associations between DL-PCBs and decreased risk for Non-TD outcome classification [adjusted OR: 0.41 (95% CI 0.15–1.14)] and between ryanodine receptor-activating PCBs and increased risk for ASD outcome classification [adjusted OR: 2.63 (95% CI 0.87–7.97)]. While this study provided modest supporting evidence that PCBs are risk factors for ASD or Non-TD, these analyses suggested the need to investigate associations between neurodevelopmental outcomes and specific PCB congeners based on their biological activities.

A subsequent study of the MARBLES cohort examined the association between maternal PCB levels, placental DNA methylation patterns and child neurodevelopmental outcomes (Mouat et al., 2023). A complete

congener profile (all 209 PCB congeners) was assessed in 104 maternal serum samples collected at delivery, and DNA methylation networks were identified from 147 placenta samples. PCBs 153, 168, 170, 180, 187 and 193 were detected in over 50% of maternal serum samples and were highly correlated with one another. Maternal age was the strongest predictor of serum PCB levels, with PCB levels also influenced by calendar year in which samples were collected (samples collected in earlier years had higher PCB levels), pre-pregnancy BMI and polyunsaturated fatty acid levels. Twenty-seven modules of placental DNA methylation were identified, including five that significantly correlated with one or more PCBs, and four that correlated with child neurodevelopment. Two modules associated with both maternal PCB levels and child neurodevelopment mapped to two genes, *CSMD1* and *AUTS2*, implicated in ASD and identified as differentially methylated regions in mouse brain and placenta following gestational exposure to a "MARBLES" PCB mixture. These findings suggest that at least some PCB congeners may be associated with altered methylation patterns implicated in autism.

In 2019, a review of the literature (Pessah et al., 2019) identified human studies of prenatal exposure to PCBs and neurodevelopmental outcomes across domains related to cognition (e.g., IQ, language, memory, learning), attention, behavioral regulation, executive function, and social behavior, including traits related to ADHD and ASD. The authors were able to identify 29 papers that met their inclusion criteria, which included: (1) a sample size of 100(+) subjects; (2) study design that measured prenatal PCB exposure; (3) quantification of PCBs in relevant biological matrices; and (4) subjects tested at 3 years of age or older. Of these 29 papers, 12 focused on impacts of PCB exposure on cognitive function in children aged 3–11, and most (8/12) found associations of developmental exposure and cognitive deficits. Seventeen studies from 11 different cohorts examined associations of prenatal PCBs with attention, behavioral regulation and social behavior among 3–12-year-old children. The majority (10 of 17) reported PCB-related associations with impulse control, hyperactivity, and attention. Only 2 of the 17 studies examined PCBs in relation to social behavior and autistic traits, with one study reporting that total PCB levels were associated with fewer autistic traits, and the other reporting congener-specific associations with autistic traits.

Overall, the authors (Pessah et al., 2019) concluded that most studies found prenatal PCB exposures were associated with poorer cognitive

function and/or increased risk of behavior problems (Pessah et al., 2019). However, a significant limitation of the available data was that associations with specific PCB congeners or mechanism-based classes of congeners were not evaluated since most epidemiologic studies report total sum PCB levels or levels of indicator PCBs. Moreover, the variety of analytical techniques used to detect PCBs in human tissues and the differing PCB congener profiles analyzed across cohorts made it exceedingly difficult to discern whether adverse neurodevelopmental outcomes were predominantly associated with specific PCB congeners. The significance of this limitation is underscored by a recent study suggesting that NDL PCBs with activity at the ryanodine receptor, but not DL PCBs or total PCBs, are weakly associated with ASD (Granillo et al., 2019). Another complication is that the genetic substrate likely also influences the impact of PCBs on NDD-relevant outcomes (Lein, 2015). This is illustrated by a study not included in the Pessah et al. (2019) review that identified a trend towards a positive association between PCB 153 levels and ASD in individuals with a deletion mutation in the gene encoding glutathione-*S*-transferase (GST) (Bach et al., 2020). A 2017 study not included in the summary because it did not specify the age of the child at the time of ASD diagnosis also found elevated ASD risk associated with specific PCB congeners (Lyall et al., 2017). Specifically, the authors found increased ASD risk for the highest vs. lowest quartile of PCB 138/158 and PCB 153 and for the highest deciles of other congeners examined in secondary analyses. Finally, a 2019 study reported an association between plasma PCB concentrations measured during pregnancy and increased incidence of autistic behaviors in children aged 3–4 years old when the data were analyzed using Bayesian predictive odds ratios (Bernardo et al. 2019). When considering the additional studies that have examined the impact of prenatal PCB on ASD phenotypes together with the two studies included in the focused review, most (5 of 6) found that PCB exposures are associated with increased expression of autistic traits. In line with this simple review of the literature is the conclusion of a meta-analysis of studies published through 2019 that reported odds ratios for PCB exposure and autism from case–control or cross-sectional studies. The authors used random-effects models to examine the association among five different studies representing five independent cohorts from across North America and Finland using pooled odds ratios. A significant association was found between PCB exposure during pregnancy and autism risk (Mehri et al., 2021).

2.3 Data gaps in the human literature on PCB developmental neurotoxicity

While the majority of human studies suggest adverse effects of PCBs on the developing brain, the epidemiological data are variable, with a small number of studies reporting no effects of PCBs on neuropsychological outcomes, and an even smaller number reporting a positive association between PCB exposure and behavioral outcomes (Klocke and Lein, 2020; Pessah et al., 2019). These discrepancies across studies likely reflect differences in study design, including outcome measures and how they were assessed, the age at which the child is tested, and how PCB exposures were determined, as well as differences between cohorts with respect to socioeconomic status or home environment of the child, co-exposures to other neurotoxic compounds (e.g. methylmercury), genetic background and PCB exposures (in terms of both levels and congener profiles). Epidemiological studies of PCB effects on NDD are further complicated by the fact that many NDDs are phenotypically and genetically heterogeneous, thus masking clear associations between diagnosis and exposure (Keil-Stietz and Lein, 2023; Klocke and Lein, 2020; Lein, 2015).

In addition to the general limitation of publication bias (e.g., positive findings are more likely to be reported than negative findings), a significant challenge in human studies of PCB developmental neurotoxicity is that most epidemiological studies still rely on total PCBs or levels of indicator PCBs when assessing exposure. While this approach may provide reasonable estimates of overall PCB exposure, it may obscure associations because the influence of individual congeners or functional classes of PCBs on neurotoxic outcomes cannot be evaluated (Panesar et al., 2022; Schantz et al., 2003). Another factor that complicates interpretation of the human literature is the lack of uniformity in both outcome measures and in the tools used to assess any specific outcome, which makes it difficult to compare epidemiological studies. For example, some studies only tested visual-spatial abilities, which have been shown to not be very sensitive to PCBs, where other studies tested IQ or response inhibition, which appear to be more sensitive to PCBs (Boucher et al., 2009). A review summarizing the neuropsychological tests that have been used in human studies of PCB developmental neurotoxicity provides a detailed discussion of tests that may be the most beneficial to perform and proposes standardization of test protocols across studies with the goal of enabling more rigorous comparisons across studies (Boucher et al., 2009). Populations and communities with lower

socioeconomic status are more likely to be exposed to higher levels of pollution, but less likely to be recruited or participate in studies looking at population-level health outcomes. That this may be problematic in the PCB literature is suggested by the observation that most of the participants in the above-mentioned studies were middle-to-upper class Caucasian women with unremarkable pregnancies and births (Hajat et al., 2021).

While discrepancies between human studies of PCB developmental neurotoxicity with respect to the spectrum and persistence of adverse neurobehavioral outcomes, confounding co-exposures and differences in congener profiles that comprise the exposure have raised questions concerning the causative role of PCBs in human developmental neurotoxicity (Winneke, 2011), extensive experimental findings in non-human primate and rodent models confirm that developmental PCB exposure causes deficits in learning and memory (Klocke and Lein, 2020; Sable and Schantz, 2006; Ulbrich and Stahlmann, 2004). These animal data are discussed below.

2.4 Neurotoxic outcomes in adults

PCB exposure has been associated with cognitive deficits, including those in executive functioning, memory, language, and communication in a variety of adult populations. Mohawk adults on the Akwesasne Reserve in New York were observed for executive function after being exposed to PCBs, along with dichlorodiphenyldichloroethylene (DDE), mirex, and hexachlorobenzene (HCB) via consumption of local fish. Adults aged 17–79 years old were assessed for cognitive function measured with the digit symbol substitution test. LC- and HC-PCB exposure was found to increase cognitive and executive function decline in the adults aged 47–79 years old (Sasaki et al., 2023). The association of deficits with DDE and HCB was much weaker, suggesting that PCBs had the greatest adverse effect on executive function at older stages of life.

A limited number of studies have examined PCB effects on learning and memory in adults. The neuropsychological function of Michigan residents, 49- to 86-years old, who regularly ate fish caught from Lake Michigan (>24 pounds eaten per year) was compared to that of residents who ate less than 6 pounds of fish per year. The heavy fish consumers had lower scores than the low fish consumers on the Wechsler Memory Scale and the California Verbal Learning Test. Consistent with this observation, performance scores were inversely associated with serum PCB levels (Schantz et al., 2001).

Language and communication skills may also be negatively affected by PCB exposure in adulthood. A German health program surveillance was done on transformer and capacitor recycling company workers who had increased PCB burden (Rengelshausen et al., 2023). Workers with a PCB burden in the 95-percentile rank or higher exhibited reduced verbal fluency regarding letter and semantic word generation as well as word production and fine motor function as shown by the Regensburg Word Fluency Test RWT. More specifically, workers with an increased LC-PCB burden showed a significantly longer duration in the word response task than those with a smaller LC-PCB burden (Fimm et al., 2017). However, additional neuropsychological and cognitive analyses done with this group found no PCB effects.

Epidemiological studies of PCB effects on affective disorders in adults are relatively limited but include at least one report of a positive association between PCB exposure and risk for bipolar disorder, as well as several other studies linking adult exposure to higher rates of depression (Table 2). A higher-than-average incidence of dementia as well as a significantly higher rate of bipolar disorder diagnoses were observed in a sample of Yusho poisoning survivors relative to healthy controls (Akahane et al., 2018). A 1989 cohort study reported that firefighters who sustained acute, high-level dermal and inhalation exposure to PCBs during a transformer fire experienced more depressed moods several months after the fire than firefighters not present at the fire (Kilburn et al., 1989). More recent evidence of an association between PCB exposure and increased prevalence of depressive symptoms emerged from a large cohort study that examined neuropsychological endpoints in adults living along a segment of the Hudson River highly contaminated with PCBs (Fitzgerald et al., 2008). These findings are consistent with those of a longitudinal study of the German workers exposed to PCBs involved in recycling of transformers and capacitors (Gaum et al., 2014). Participants underwent a psychological screening questionnaire and had blood drawn at three separate timepoints to determine plasma concentrations of individual PCB congeners. Relative to the general German population, PCB-exposed workers had an increased prevalence and severity of depressive symptoms that persisted over multiple years and corresponded with elevated plasma concentrations of HC-, LC-, and dioxin-like PCBs. A more recent study involving a separate cohort occupationally exposed to PCBs also found a significant positive association between depressive symptoms and plasma concentrations of HC-, LC-, and dioxin-like PCBs (Gaum et al., 2017). This latter study also identified

Table 2 Epidemiological studies of PCB effect on affective disorders in adults.

Reference	Study findings	Cohort Location	Subject age (years)	Median/ mean concentrations	Outcome measure	PCB exposure matrix (congeners)	Sample size	Study limitations
Akahane et al. (2018)	Increased prevalence of bipolar disorder among survivors of PCB poisoning, relative to individuals with no history of PCB poisoning	Japan	30–100	~	~	~	2329	No quantification of PCBs in biospecimens
Fitzgerald et al. (2008)	Increase in depressive symptoms with increasing concentrations of PCBs	United States (New York)	55–74	Mean = 3.1 ng/g (wet weight)	NART-R, TOMM, CVLT, WMS, SCWT, WCST, DSST, BDT, SMST, GPT, FOT, BDI, STAI, SIT	Serum (PCBs 28, 74, 99, 105, 118, 138, 153, 170, 180, 183, 187, 194)	253	

(*continued*)

Table 2 Epidemiological studies of PCB effect on affective disorders in adults. (*cont'd*)

Reference	Study findings	Cohort Location	Subject age (years)	Median/ mean concentrations	Outcome measure	PCB exposure matrix (congeners)	Sample size	Study limitations
Guam et al. (2014)	Association between higher PCB concentrations and increases in prevalence and severity of depressive symptoms	Germany	Mean = 47.2	Mean: LPCBs = 3.18 μg/L; HPCBs = 7.78 μg/L; dlPCBs = 2.62 μg/L	PHQ-D	Plasma (PCBs 28, 52, 101, 138, 153, 180, 105, 114, 118, 123, 156, 157, 167, 189)	136	Small sample size

Guam et al. (2017)	Positive associations between depressive symptoms and concentrations of LPCBs, HPCBs, and dlPCBs; association between increased exposure to LPCBs, HPCBs, and dlPCBs and disrupted dopaminergic signaling; positive association between disrupted dopaminergic signaling and depressive symptoms	Germany	Mean = 46.9	Mean: LPCBs = 353.1 ng/g lipid; HPCBs = 933.05 ng/g lipid; dlPCBs = 329.6 ng/g lipid	BDI	Plasma (PCBs 28, 52, 101, 138, 153, 180, 105, 114, 118, 123, 156, 157, 167, 189)	178	Small sample size

(*continued*)

Table 2 Epidemiological studies of PCB effect on affective disorders in adults. (*cont'd*)

Reference	Study findings	Cohort Location	Subject age (years)	Median/ mean concentra-tions	Outcome measure	PCB exposure matrix (congeners)	Sam-ple size	Study limitations
Kilburn et al. (1989)	More depressed mood in PCB-exposed participants	United States (New York)	Mean = 34.3	Median = 6.0 ppb (serum); 0.7 ppm (body fat)	POMS, CRT, WMS, WAIS	Serum; body fat (Aroclor 1248)	28	Small sample size

dlPCBs: dioxin-like PCBs; LPCBs: lower chlorinated PCBs; HPCBs: higher chlorinated PCBs; ALSFRS-R: ALS Functional Rating Scale Revised; ATC: Anatomical Therapeutic Chemical; BDI: Beck's Depression Inventory; BDT: Block Design subtest; CRT: Choice Reaction Time; CVLT: California Verbal Learning Test; DSST: Digit Symbol Substitution Test; FOT: Finger Oscillation Test; GPT: Grooved Pegboard Test; ICD: International Classification of Diseases; NART-R: New Adult Reading Test-Revised; PHQ-D: Patient Health Questionnaire; POMS: Profile of Mood States; SCWT: Stroop Color-Word Test,; SIT: Smell Identification Test; SMST: Static Motor Steadiness Test; STAI: State-Trait Anxiety Inventory; TOMM: Test of Memory Malingering; WAIS: Wechsler Adult Intelligence Scale; WCST: Wisconsin Card Sorting Test; WMS: Weschler Memory Scale.

associations between PCB exposure and altered dopamine metabolism, as well as between altered dopamine metabolism and depressive symptoms. The authors proposed that PCB-mediated disruption of dopaminergic signaling was the cause of PCB-associated depressive symptoms.

The epidemiological data relating PCB exposure to affective disorders in adults is challenging to interpret because of inconsistent findings, relatively few studies, and the small sample sizes of many of the available studies. Results may also be influenced by reliance on self-reporting and questionnaires, which may be subject to bias. Furthermore, affective disorder presentation can vary widely between individuals, and symptoms are often subjective and difficult to quantify. These characteristics may impose an additional level of uncertainty and further complicate the gathering or interpretation of epidemiological findings.

2.5 PCB effects on neurodegenerative diseases

PCBs have been identified as a potential environmental risk factor for neurodegenerative diseases such as Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Alzheimer's disease (AD), although there is only moderate support from epidemiological studies (Table 3). Interestingly, several studies report sex-specific effects of PCB exposure, with statistically significant findings observed only in females. Two studies, in which brain tissue was used to measure PCB exposure, reported significant associations with PD. In one, subjects diagnosed with PD were found to have higher concentrations of PCB 153 in the anterior caudate nucleus, a region that is commonly implicated in PD pathophysiology (Corrigan et al., 1998). In agreement with this finding, a case–control study reported higher concentrations of PCB congeners 153 and 180 in occipital cortex samples obtained from PD patients (Hatcher-Martin et al., 2012). When stratified by sex, their analysis revealed significant elevations in total PCBs and congeners 138, 153, and 180 in female PD patients only. Hatcher-Martin et al. also examined substantia nigral tissue from a separate cohort of females who had not displayed any observable clinical symptoms of PD. Higher concentrations of total PCBs and of individual congeners 138, 170, and 180 were detected in brains exhibiting greater reductions in neuromelanin pigmentation in nigral neurons, a common neuropathological feature of PD.

Earlier findings of electrical capacitor manufacturing plant workers employed between 1939 and 1977 similarly reported sex-specific effects of PCBs. This study investigated the prevalence of neurodegenerative disease in workers who had sustained varying degrees of occupational exposure to PCBs.

Table 3 Epidemiological studies of PCB effects on neurodegenerative diseases.

Reference	Main findings	Cohort	Subject age (years)	Mean/Median PCB concentration	PCB exposure matrix (congeners)	Sample size	Study limitations
Akahane et al. (2018)	Increased prevalence of dementia among survivors of PCB poisoning, relative to individuals with no history of PCB poisoning	Japan	30–100	~	~	2329	No quantification of PCBs in biospecimens
Corrigan et al. (1998)	Higher concentrations of PCB-153 in the anterior caudate nucleus of PD patients	United Kingdom (Scotland, England)	50–85	Median = 9.70 μg/g lipid (PD); 1.06 μg/g lipid (control)	Brain tissue (PCBs 8, 18, 28, 31, 52, 77, 101, 118, 126, 128, 138, 149, 153, 169, 170, 180)	15	Small sample size

Corrigan et al. (2000)	No significant difference in substantia nigra PCB concentrations in PD patients compared to healthy controls	England	~	Mean = 1.013 μg/g lipid	Brain tissue (Aroclor 1254 PCB congeners)	28	Small sample size
Goutman et al. (2019)	Decreased survival in ALS patients with higher PCB concentrations	United States (Michigan)	Median = 61.6	Mean (ng/L): PCB 110 = 2.4; PCB 118 = 34.5; PCB 138 = 64.3; PCB 151 = 50.5 ng/L; PCB 153 = 238; PCB 174 = 0.9; PCB 175 = 1.5; PCB 180 = 94.9; PCB 202 = 3.0	Plasma (PCBs 110, 118, 138, 151, 153, 174, 175, 180, 202)	167	Small sample size

(*continued*)

Table 3 Epidemiological studies of PCB effects on neurodegenerative diseases. (*cont'd*)

Reference	Main findings	Cohort	Subject age (years)	Mean/Median PCB concentration	PCB exposure matrix (congeners)	Sample size	Study limitations
Hatcher-Martin et al. (2012)	Higher PCB concentrations associated with increased nigral neuron depigmentation; Increased concentrations of PCBs 153 and 180 in occipital cortex of PD patients	United States	Mean = 70.7	Mean = 8.65 ng/g (wet weight)	Brain tissue (PCBs 101, 118, 138, 149, 153, 166, 170, 180)	72	Small sample size
	Elevated concentrations of total PCBs and congeners 138, 153, and 180 in females with PD		Mean = 95	Mean = 2.47 ng/g (wet weight)		40	Small sample size

Koldkjær et al. (2004)	No significant difference in PCB concentrations of PD group compared to control group	Greenland	Mean = 63	~	Plasma	153	Small sample size; sample size much smaller for PD than control group; far more male than female PD cases
Petersen et al. (2008)	Consumption of larger amounts of whale meat and blubber linked to greater risk for PD; Serum concentrations of PCB-101 correlated significantly with PD risk	Faroe Islands (Kingdom of Denmark)	Mean = 74.9	Mean = 4.96 mg/g lipid	Serum (PCBs 101, 105, 118, 138, 153, 156, 180)	233	Lack of data on other toxins typically present at elevated concentrations in whale meat

(*continued*)

Table 3 Epidemiological studies of PCB effects on neurodegenerative diseases. (*cont'd*)

Reference	Main findings	Cohort	Subject age (years)	Mean/Median PCB concentration	PCB exposure matrix (congeners)	Sample size	Study limitations
Prince et al. (2006)	Elevated mortality due to diseases of the nervous system and sense organs (including PD and ALS) among women, but not men, who were occupationally exposed to high levels of PCBs; Increased ALS-related deaths among women, but not men, who were occupationally exposed to high levels of PCBs	United States (New York, Massachus-etts)	18.5–102; Mean = 63.6	~	Aroclor 1254, 1242, and 1016	2572	No quantification of PCBs in biospecimens; small cohort size; Low number of deaths; Lack of data on potential confounders

Putschögl et al. (2015)	Reduced levels of the dopamine metabolite HVA detected in urine of individuals exposed to high levels of PCBs	Germany	16–73	Mean (μg/L): LPCBs= 2.5; HPCBs= 7.2; dlPCBs= 2.3	Plasma (PCBs 28, 52, 101, 138, 153, 180, 105, 114, 118,123, 156, 157, 167, 189)	177	Relationship between PCB exposure and HVA not held true for all observed timepoints; Large PCB exposure duration range; Neurotransmitter metabolite concentrations in urine may not accurately reflect neurotransmitter concentrations in CNS

(*continued*)

Table 3 Epidemiological studies of PCB effects on neurodegenerative diseases. (*cont'd*)

Reference	Main findings	Cohort	Subject age (years)	Mean/Median PCB concentration	PCB exposure matrix (congeners)	Sample size	Study limitations
Raffetti et al. (2020)	Higher concentrations of PCBs linked to greater risk for dementia	Italy	Over 50; Mean = 63.2	Mean = 5.88 ng/mL Median = 5.71 ng/mL	Serum (PCBs 28, 31, 52, 77, 81, 101, 105, 114, 118, 123, 126, 128, 138, 153, 156, 157, 167, 169, 170, 180, 189, 194, 206, 209)	699	
Seegal et al. (2010)	Reduced DAT density in caudate, putamen, and combined caudate and putamen (striatum) of women, but not men, who had higher levels of occupational exposure to PCBs	United States (New York)	51–85; Mean=-63.5	Mean = 0.98 ppm	Serum (ΣPCBs)	85	Subjects assessed only at a single timepoint; Small sample size

Steenland et al. (2006)	Increased mortality due to ALS among occupationally exposed women, but not men; Increased numbers of PD- and AD-related deaths among women, but not men, who had the highest levels of occupational PCB exposure	United States (New York, Massachus-etts)	Mean = 64	~	~	16906	No quantification of PCBs in biospecimens

(*continued*)

Table 3 Epidemiological studies of PCB effects on neurodegenerative diseases. (*cont'd*)

Reference	Main findings	Cohort	Subject age (years)	Mean/Median PCB concentration	PCB exposure matrix (congeners)	Sample size	Study limitations
Su et al. (2016)	Plasma concentrations of PCB-151 were elevated and PCB-202 reduced in ALS patients compared to healthy controls	United States (Michigan)	Mean = 60.5	Mean (ng/L): PCB 110 = 2.85, PCB 151 = 11.05, PCB 135/ 144 = 28.55, PCB 118 = 132.63, PCB 132/153 = 390, PCB 138/ 163 = 238.93, PCB 175 = 2.61, PCB 174 = 1.37, PCB 202 = 4.12, PCB 180 = 166.32, PCB 170/ 190 = 12.14, PCB 198 = 1.98	Plasma (PCBs 110, 118, 132, 135, 138, 144, 151, 153, 163, 170, 174, 175, 180, 190, 198, 202)	284	

Weisskopf et al. (2012)	Trend toward decreased risk of PD with increasing serum PCB concentration	Finland	20–79; Mean = 52.1	Mean = 6.74 ng/g serum (PD); 8.02 ng/g serum (control)	Serum (PCBs 6, 8, 16, 18, 25, 26, 28, 31, 33, 37, 41, 44, 47, 49, 52, 60, 66, 70, 74, 84, 87, 95, 97, 99, 101, 105, 110, 118, 128, 135, 136, 138, 141, 146, 149, 151, 153, 156, 157, 167, 170, 171, 174, 177, 201, 180, 183, 187, 189, 194, 195, 196, 199, 203, 206, 209)	450

AD: Alzheimer's disease; ALS: amyotrophic lateral sclerosis; PD: Parkinson's disease; dlPCBs: dioxin-like PCBs; LPCBs: lower chlorinated PCBs; HPCBs: higher chlorinated PCBs; ALSFRS-R: ALS Functional Rating Scale Revised; ATC: Anatomical Therapeutic Chemical; BDI: Beck's Depression Inventory; BDT: Block Design subtest; CRT: Choice Reaction Time; CVLT: California Verbal Learning Test; DSST: Digit Symbol Substitution Test; FOT: Finger Oscillation Test; GPT: Grooved Pegboard Test; ICD: International Classification of Diseases; NART-R: New Adult Reading Test-Revised; PHQ-D: Patient Health Questionnaire; POMS: Profile of Mood States; SCWT: Stroop Color-Word Test; SIT: Smell Identification Test; SMST: Static Motor Steadiness Test; STAI: State-Trait Anxiety Inventory; TOMM: Test of Memory Malingering; WAIS: Wechsler Adult Intelligence Scale; WCST: Wisconsin Card Sorting Test; WMS: Weschler Memory Scale.

Compared to the U.S. general population, female plant workers estimated to have higher levels of PCB exposure also experienced higher rates of PD and AD (Steenland et al., 2006).

In the Faroe Islands, whale meat constitutes a considerable portion of the traditional Faroese diet and poses a relatively higher risk for dietary PCB exposure due to the tendency PCBs to bioaccumulate in marine mammals. Compared to healthy residents, Faroese adults who had been diagnosed with PD reported higher lifetime consumptions of whale meat and blubber (Petersen et al., 2008). In addition, quantification of serum PCB concentrations in these individuals revealed a significant positive association between PCB 101 exposure and PD risk.

There are also epidemiological data suggesting a link between exposure to certain PCBs, especially PCB congener 151, and ALS. A case-control study that screened blood samples for various POPs detected a significant positive correlation between plasma levels of PCB 151 and risk of ALS (Su et al., 2016). Consistent with these findings, a more recent study sampled ALS patients and identified a significant association between elevated plasma concentrations of PCB 151 and increased risk of earlier death after adjusting for patient age at diagnosis (Goutman et al., 2019).

A small number of studies have identified PCB exposure as a possible environmental risk factor for a general clinical diagnosis of dementia. Approximately 40 years after the Yusho mass-poisoning in Japan, various health outcomes were assessed in a sample of poisoning survivors (Akahane et al., 2018). Results of this study indicated significantly higher rates of dementia in Yusho survivors when compared to age-matched controls with no history of Yusho poisoning. Further evidence linking dementia with PCB exposure came from a prospective cohort study that took place in a heavily PCB-contaminated town in Italy. Results indicated that the risk of developing dementia was significantly higher for residents whose blood serum contained higher total concentrations of PCBs at the time of their enrollment in the study (Raffetti et al., 2020).

Despite the epidemiological evidence of PCB exposure as a potential environmental risk factor for neurodegenerative diseases, the limited number of studies and inconsistent findings remain a major shortfall of the literature. Many studies fail to demonstrate an effect. For instance, a 2000 study detected no notable differences in PCB tissue concentrations in brain samples obtained from subjects diagnosed with PD or AD when compared to controls (Corrigan et al., 2000). Inconsistent findings may be due to relatively small sample sizes, differences in study design, including

approaches for assessing PCB exposures. Furthermore, because epidemiological studies of neurodegenerative diseases rely on older populations, it is impossible to rule out survival-imposed selection bias. The higher rate of prescription medication use in older adults presents another complicating factor. The difference in life expectancies for men and women should also be considered, as this may contribute to sex-based differences reported in some studies.

A factor that remains largely unaccounted for in the literature pertains to the question of whether calculated PCB body burden provides an accurate representation of lifetime exposure. The majority of studies incorporate only a single timepoint for biological sample collection and fail to provide estimates of exposure duration or time of occurrence. Furthermore, the effects of LC-PCBs may be under-accounted because they tend to be metabolized faster than HC-PCBs. A small number of longitudinal studies attempt to address this difference but are confounded by few intermittent follow-up assessments and large participant drop-out.

3. Experimental animal studies

A large number of experimental animal studies of PCB neurotoxicity have been published in the peer-reviewed literature (reviewed in Faroon and Ruiz, 2016; Klocke and Lein, 2020; Sable and Schantz, 2006; Ulbrich and Stahlmann, 2004). These studies employed various individual PCB congeners and mixtures, including the commercial legacy Aroclor mixtures, to assess the impacts of PCB exposures, which have been predominantly developmental exposures (Carlson et al., 2023), on behavioral outcomes of translational relevance to humans. The tightly controlled exposures that are feasible in experimental animal studies are critically important for (1) corroborating human epidemiological data; and (2) providing mechanistic insights, such as brain regions likely targeted by PCBs and potential cellular and/or molecular mechanisms. Several reviews of the animal literature on PCB neurotoxicity have previously been published (Faroon and Ruiz, 2016; Klocke and Lein, 2020; Pessah et al., 2019). Here, we highlight selected studies published after 2000 that address PCB-induced behavioral changes using rigorous study designs, validated tests of behaviors relevant to human PCB neurotoxicity and PCB exposures relevant to human exposures in terms of both the congener profile and levels.

3.1 Learning and memory

Learning and memory are complex behaviors that combine situational paradigms with information encoding, storage, and retrieval. Memory is further categorized as working memory, short-term memory, and long-term memory (Crowder, 2019). Not only are learning and memory critical for survival , but they are also important in establishing patterns of neuronal connectivity in the developing brain via effects on dendritic morphogenesis and formation/stabilization of synapses (Ma and Zuo, 2022). Learning and memory are behavioral outcomes with direct translational relevance to behavioral deficits observed in human studies of developmental PCB exposures.

A commonly used test to assess learning and memory in rodent models is the novel object recognition (NOR) task, which engages the hippocampus (CA1 and CA3 regions), insular cortex (IC), perirhinal cortex (PRh), and medial prefrontal cortex (mPFC). Thus, deficits in NOR performance indicate perturbations in one or more of these brain regions (Tanimizu et al., 2018). NOR has been used to assess PCB developmental neurotoxicity in rodent models. For example, the performance of mouse pups in the NOR task was assessed after lactational exposure to 0, 6 or 8 mg/kg/day of Aroclor 1254 (A1254) in the maternal diet from postnatal day (PND) 7–21 and direct oral exposure from PND 22–42. Females, but not males, had significant deficits in this task at PND 35–37, regardless of Aroclor dose (Tian et al., 2011), suggesting that developmental exposure to this PCB mixture causes sex-specific deficits in learning and/or memory in mice. In a similar study, CYP transgenic mouse dams were exposed via oral gavage to the non-dioxin-like PCB congeners 105, 118, 138, 153, and 180 and dioxin-like PCB congeners 77, 126, and 169 at gestational day 10.5 and PND 5. CYP1A2 knockout mice pups were significantly impaired in the NOR task (Curran et al., 2011a).

Deficits in spatial learning and memory have also been measured in rodent models of developmental PCB exposures. Oral gavage of pregnant rats with A1254 at 5, 10, and 20 mg/kg body weight every three days from gestational day 5 to PND 20 caused significant deficits in spatial learning and memory in their pups as determined using the Morris water maze (Liu et al., 2015). Pups exposed to 10 or 20 mg/kg/day in the maternal diet had a significantly worse performance compared to controls (0 mg/kg A1254). Impaired spatial learning was associated with increased intracellular calcium concentrations and ultra-micro structural changes in

the hippocampus (Liu et al., 2015). While the majority of studies have examined learning and memory deficits in animals exposed to PCBs during early life, at least one study examined impacts of PCBs on Morris water maze performance following mid-life exposures. Adult female Sprague-Dawley rats exposed as adults to a PCB mixture simulating the PCB profile found in school air exhibited modest PCB-induced deficits in spatial learning and memory (Wang et al., 2020). The majority of studies have observed PCB-induced learning and memory deficits; however, a limited number of studies have not observed significant memory impairment as a consequence of developmental PCB exposure. For example, following dietary exposure of Sprague-Dawley rat dams to PCB 47 and 77 at 1.25 ppm, 12.5 ppm or 25.0 ppm (w/w) in rat chow provided ad libitum, no effects of PCBs were observed in either short-term or long-term spatial memory as determined using Morris water maze training in PND30 pups (Donahue et al., 2004). The reason for these discrepancies across studies are not clear, but may be due to differences in species, behavioral testing paradigms, or the PCB dosing paradigm with respect to PCB congener profiles or levels.

3.2 Motor function

Motor function is an umbrella term for locomotion, balance, coordination, limb movement, and other aspects of movement. Motor function generally involves the cerebellum and the nigrostriatal pathways of the brain (Salman and Tsai, 2016). Motor function can be readily tested in animal models, and it is an important component of other behavioral tests. For example, changes in motor function can alter performance in cognitive tests that require movement, such as the y-maze and Morris water maze. Thus, many behavioral tests assess motor function as a control (Schönfeld et al., 2017).

PCBs have been shown to alter motor function in experimental animals in a congener- and sex-specific manner. Sprague-Dawley rats at an age corresponding to human puberty were given a diet augmented with PCB-contaminated fish from the St. Lawrence River or Aroclor 1248 at a concentration approximating that found in the contaminated fish. After being exposed for 30-days, the rats received operant conditioning training to assess activity level, impulsiveness, and visual discrimination. Both PCB-exposed groups had significantly higher lever pressing rates than controls, suggesting PCB induced hyperactivity (Berger et al., 2001). Similar results were reported in Swiss albino mice exposed to 0, 1, 10, or 100 ng/kg of

PCBs 28, 52, 101, 138, 153, and 180 dissolved in rapeseed oil and administered daily by oral gavage from PND 0 until weaning at PND 21. Females exposed to 100 ng/kg exhibited increased latency to turn in the Negative Geotaxis (NG) test at PND 7 and 9 (Elnar et al., 2012). In contrast, other studies have found little to no effect of PCBs on motor behavior. For example, an ad libitum diet-based exposure to PCB 153 during gestation and lactation did not change motor function, including grasping reflexes, righting reflexes, and forelimb in BALB/c mice when tested from PND 5–15 (Haave et al., 2011). However, the amount of PCB that animals received was not controlled in this study, and the dose was lower than in the other two studies described here, suggesting PCB-induced motor deficits exhibit a classic dose-response relationship with deficits increasing as PCB dose increases.

3.3 Attention

Attention can be defined as behaviors related to obtaining and maintaining the alert state, orienting to sensory stimuli, and resolving conflict among competing responses (Petersen and Posner, 2012). Attentional deficits are a primary component of NDDs, particularly ADHD. Attention is mediated by two major networks: (1) the alerting network, which is modulated by the brain's norepinephrine system and involves major nodes in the frontal and parietal cortex; and (2) the executive network, which resolves competing actions during tasks with conflicting demands. This network involves the anterior cingulate cortex, areas of the prefrontal cortex, and the striatum (Soydaner, 2022).

Rodent models can be used to assess attention behavior following PCB exposure. Spontaneously hypertensive rats (SHR/NCrl) were exposed to 1, 3, and 6 mg/kg of PCB 153 at PND 8, 14, and 20 using a gastric tube. Compared to controls, the SHR/NCrl rats demonstrated dose-dependent differences in a lever pressing test of attention. Sustained attention was significantly increased in the 1 mg/kg dose group, but significantly decreased in the 3 and 6 mg/kg dose group. The 6 mg/kg dose group also had increased inter-response times (IRT), suggesting reduced attention in the higher dose groups (Johansen et al., 2014). There is also evidence of altered attention following inhalation exposure. Compared to control animals, rats exposed to air-borne Aroclor 1248 or sediment vapor containing PCBs showed significantly higher rates of bar pressing (indicating hyperactivity and frustration) in a multiple fixed interval extinction operant

behavior paradigm (Lombardo et al., 2015). These results support clinical findings of attentional deficit in PCB-exposed humans.

3.4 Social behavior

Many NDDs are associated with PCB exposures, including ASD (Alampi et al., 2021; Bernardo et al., 2019; Keil-Stietz and Lein, 2023; Lyall et al., 2017; Mehri et al., 2021) and ADHD (Eubig et al., 2010). Impaired social behavior, including poor social cue recognition, reduced social interaction and communication are common to multiple NDDs (Baribeau et al., 2019; Keil-Stietz and Lein, 2023). Behavioral tests, such as ultrasonic vocalizations and the social approach test (Rein et al., 2020), have been used to assess social deficits in rodent models of autism, making them excellent candidates for behavioral tests of PCB exposure.

Multiple studies have examined social behavior following developmental exposure to PCBs (Klocke and Lein, 2020). As an example, one study assessed social behavior in pups born to female mice exposed to 0, 0.1, 1, or 6 mg/kg/day of the MARBLES PCB mix during gestation and lactation. The MARBLES PCB mix simulates the relative proportions of the twelve most abundant PCB congeners found in the serum of pregnant women enrolled in the MARBLES cohort who are at increased risk for having a child with a NDD (Sethi et al., 2019). Ultrasonic vocalizations were measured at PND 7 and social approach was tested at PND 32. Exposure to the MARBLES PCB mix resulted in significantly less ultrasonic vocalizations in male and female pups in all dose groups. In contrast, only the males in the 0.1 mg/kg dose exhibited decreased sociability in the social approach task (Sethi et al., 2021). Similar results were observed in rat pups exposed PCBs 47 and 77 at 12.5 mg/kg/day and 25 mg/kg/day in the maternal diet during gestation and lactation (Jolous-Jamshidi et al., 2010). PCB exposure significantly impaired social recognition in PND 21 males (Jolous-Jamshidi et al., 2010). This same group of investigators assessed adult male rats for social investigation behavior using the social port test following exposure to the same doses of PCBs. The adult rats that were isolation housed had decreased social investigation, which reflected the developmental exposure results (Jolous-Jamshidi et al., 2010).

There are also data showing that PCBs affect sociosexual behavior in a sex- and time-dependent manner. For example, Bell et al. (2016) exposed Sprague-Dawley rats to Aroclor 1221 (A1221) prenatally through the dam, who received i.p. injections of 0 or 1 mg/kg A1221 at embryonic day 16, 18, and 20, and/or via i.p. injections in the pups at PND 24, 26, and 28.

Prenatal exposure resulted in more sociosexual behavioral changes than juvenile exposure. Additionally, whereas female rats had significant deficits in social behavior between PND 30 and 39 (juvenile age) following the dual exposure paradigm and the juvenile only exposure, males showed significant alterations in sociosexual choice assessed between PND 90 and 110 in adulthood following prenatal or juvenile, but not the combined exposures (Bell et al., 2016).

3.5 Insights from behavioral studies of mechanisms of PCB neurotoxicity

Behavioral studies can provide insights regarding mechanisms by which PCBs cause neurotoxicity. One example is a study that investigated PCB neurotoxicity in transgenic mouse lines expressing high levels of hepatic cytochrome P450 (CYP) 1A2 vs. CYP 1A2 knockout, as well as lines with variable levels of AhR affinity. Behavioral responses were assessed in these mice following exposure to a PCB mixture of dioxin-like (PCBs 77, 126 and 169), and non-dioxin-like (PCBs 105, 118, 138, 153, and 180) congeners found in food, human tissue, and breast milk mixture. Mice were exposed at gestational day 10 and PND 5 via oral gavage of the dam (Curran et al., 2011b). The high-affinity AhR CYP1A2 knockout mice had the greatest impairment in the NOR test and Morris water maze for spatial learning (Curran et al., 2011a), suggesting that PCB neurotoxicity is related to AhR affinity and that CYP1A2-mediated metabolism is neuroprotective. The assessment of motor behavior in these same mice by rotarod, gait analysis, sticker removal, pole test, and challenging balance beam, revealed that developmental PCB exposure significantly decreased performance on the rotarod test and that the CYP knockout mice were less impaired than the wildtype mice (Colter et al., 2018). Similar results were seen with the gait analysis. In the challenging balance beam test, the high affinity AhR genotypes exposed to PCBs showed significantly more slips than the PCB-exposed wildtype controls. These findings suggest that CYP metabolism of PCBs negatively affects motor behavior and AhR affinity may influence the magnitude of the PCB effect.

4. Conclusions

There is compelling evidence from human epidemiological and experimental animal studies that PCBs are developmental neurotoxicants

associated with a number of neurological deficits in early life. While there are discrepancies across studies, the majority of human epidemiological studies have found an association between exposure to PCBs and detrimental effects on the developing brain across diverse human populations in multiple geographic locations. The developmental neurotoxicity of PCBs has been largely corroborated in experimental animal models. Although less well studied, the influence of PCB exposure on the risk, onset and severity of affective disorders in adults and late-onset neurodegenerative disorders are suggestive. A significant data gap, however, is the paucity of animal studies to corroborate the human observations of PCB effects on neurological outcomes in mid- and later life.

It is important to note that the diversity of PCB chemistry (degree and position of chlorination, chirality, and diverse metabolites) make the design of animal and epidemiological studies challenging. This complication underlies another key data gap in the field, which is a comprehensive understanding of which of the 209 PCB congeners influence PCB neurotoxicity, and how their metabolism alters neurotoxic outcomes. Addressing this data gap is stymied by a general lack of understanding of the predominant PCB congeners and metabolites present in human tissues, and how this congener profile is impacted by population demographics (age, sex, and socioeconomic status), specific life-stages of exposure and changing environmental PCB profiles.

Experiments designed to assess the consequences of PCB exposures on complex neurological conditions present a unique set of challenges. Gene–environment interactions are implicated in many neurodevelopmental disorders (Hertz-Picciotto et al., 2018a; Keil-Stietz and Lein, 2023; Lein, 2015) and aging-related declines in cognitive capacity, clinical dementia, and the major neurodegenerative disorders such as Parkinson's disease (PD), Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS) have both genetic and environmental components that contribute to temporal onset, progression and severity (Hersi et al., 2017; Martino et al., 2017; Wang et al., 2017). A major challenge in the field is the identification of specific genetic risk factors that influence neurotoxic responses to PCBs, and the elucidation of the mechanisms by which genetic factors interact with PCBs to determine individual risk for adverse neurological outcomes.

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Declaration of competing interests

PJL was hired as an expert witness by lawyers representing a group of plaintiffs alleging, they were harmed by exposure to PCBs in school air. In that capacity, she testified as an expert witness on PCB neurotoxicity. The defendant was Pharmacia, a successor company to Monsanto.

References

Akahane, M., Matsumoto, S., Kanagawa, Y., Mitoma, C., Uchi, H., Yoshimura, T., et al., 2018. Long-term health effects of pcbs and related compounds: a comparative analysis of patients suffering from yusho and the general population. Arch. Environ. Contam. Toxicol. 74, 203–217.

Alampi, J.D., Lanphear, B.P., Braun, J.M., Chen, A.M., Takaro, T.K., Muckle, G., et al., 2021. Association between gestational exposure to toxicants and autistic behaviors using bayesian quantile regression. Am. J. Epidemiol. 190, 1803–1813.

Ampleman, M.D., Martinez, A., Dewall, J., Rawn, D.F., Hornbuckle, K.C., Thorne, P.S., 2015. Inhalation and dietary exposure to pcbs in urban and rural cohorts via congener-specific measurements. Environ. Sci. Technol. 49, 1156–1164.

Ansel, A., Rosenzweig, J.P., Zisman, P.D., Melamed, M., Gesundheit, B., 2016. Variation in gene expression in autism spectrum disorders: an extensive review of transcriptomic studies. Front. Neurosci. 10, 601.

Bach, M.A., Samms-Vaughan, M., Hessabi, M., Bressler, J., Lee, M., Zhang, J., et al., 2020. Association of polychlorinated biphenyls and organochlorine pesticides with autism spectrum disorder in Jamaican children. Res. Autism Spectr. Disord. 76, 101587. https://doi.org/10.1016/j.rasd.2020.101587.

Baribeau, D.A., Dupuis, A., Paton, T.A., Hammill, C., Scherer, S.W., Schachar, R.J., et al., 2019. Structural neuroimaging correlates of social deficits are similar in autism spectrum disorder and attention-deficit/hyperactivity disorder: analysis from the pond network. Transl. Psychiatry 9, 72.

Bell, M.R., Thompson, L.M., Rodriguez, K., Gore, A.C., 2016. Two-hit exposure to polychlorinated biphenyls at gestational and juvenile life stages: 1. Sexually dimorphic effects on social and anxiety-like behaviors. Horm. Behav. 78, 168–177.

Berger, D.F., Lombardo, J.P., Jeffers, P.M., Hunt, A.E., Bush, B., Casey, A., et al., 2001. Hyperactivity and impulsiveness in rats fed diets supplemented with either aroclor 1248 or pcb-contaminated st. Lawrence river fish. Behav. Brain Res. 126, 1–11.

Berghuis, S.A., Bos, A.F., Sauer, P.J., Roze, E., 2015. Developmental neurotoxicity of persistent organic pollutants: an update on childhood outcome. Arch. Toxicol. 89, 687–709.

Bernardo, B.A., Lanphear, B.P., Venners, S.A., Arbuckle, T.E., Braun, J.M., Muckle, G., et al., 2019. Assessing the relation between plasma pcb concentrations and elevated autistic behaviours using bayesian predictive odds ratios. Int. J. Enviorn. Res. Public Health 16, 457.

Bock, K.W., 2016. Toward elucidation of dioxin-mediated chloracne and ah receptor functions. Biochem. Pharmacol. 112, 1–5.

Boucher, O., Muckle, G., Bastien, C.H., 2009. Prenatal exposure to polychlorinated biphenyls: A neuropsychologic analysis. Environ. Health Perspect. 117, 7–16.

Carlson, L.M., Christensen, K., Sagiv, S.K., Rajan, P., Klocke, C.R., Lein, P.J., et al., 2023. A systematic evidence map for the evaluation of noncancer health effects and exposures to polychlorinated biphenyl mixtures. Environ. Res. 220, 115148.

Caspersen, I.H., Aase, H., Biele, G., Brantsaeter, A.L., Haugen, M., Kvalem, H.E., et al., 2016. The influence of maternal dietary exposure to dioxins and pcbs during pregnancy on adhd symptoms and cognitive functions in norwegian preschool children. Environ. Int. 94, 649–660.

Caspersen, I.H., Haugen, M., Schjølberg, S., Vejrup, K., Knutsen, H.K., Brantsæter, A.L., et al., 2016. Maternal dietary exposure to dioxins and polychlorinated biphenyls (PCBs) is associated with language delay in 3year old Norwegian children. Environ Int 91, 180–187.

Chu, C.P., Wu, S.W., Huang, Y.J., Chiang, M.C., Hsieh, S.T., Guo, Y.L., 2019. Neuroimaging signatures of brain plasticity in adults with prenatal exposure to polychlorinated biphenyls: Altered functional connectivity on functional mri. Environ. Pollut. 250, 960–968.

Colter, B.T., Garber, H.F., Fleming, S.M., Fowler, J.P., Harding, G.D., Hooven, M.K., et al., 2018. Ahr and cyp1a2 genotypes both affect susceptibility to motor deficits following gestational and lactational exposure to polychlorinated biphenyls. Neurotoxicology 65, 125–134.

Corrigan, F.M., Murray, L., Wyatt, C.L., Shore, R.F., 1998. Diorthosubstituted polychlorinated biphenyls in caudate nucleus in parkinson's disease. Exp. Neurol. 150, 339–342.

Corrigan, F.M., Wienburg, C.L., Shore, R.F., Daniel, S.E., Mann, D., 2000. Organochlorine insecticides in substantia nigra in parkinson's disease. J. Toxicol. Environ. Health A 59, 229–234.

Crowder, R.G., 2019. Systems and principles in memory theory: another critique of pure memory. Theories of Memory. Psychology Press.

Curran, C.P., Nebert, D.W., Genter, M.B., Patel, K.V., Schaefer, T.L., Skelton, M.R., et al., 2011a. In utero and lactational exposure to pcbs in mice: adult offspring show altered learning and memory depending on cyp1a2 and ahr genotypes. Environ. health Perspect. 119, 1286–1293.

Curran, C.P., Vorhees, C.V., Williams, M.T., Genter, M.B., Miller, M.L., Nebert, D.W., 2011b. In utero and lactational exposure to a complex mixture of polychlorinated biphenyls: Toxicity in pups dependent on the cyp1a2 and ahr genotypes. Toxicol. Sci. 119, 189–208.

Domingo, J.L., Bocio, A., 2007. Levels of pcdd/pcdfs and pcbs in edible marine species and human intake: a literature review. Environ. Int. 33, 397–405.

Donahue, D.A., Dougherty, E.J., Meserve, L.A., 2004. Influence of a combination of two tetrachlorobiphenyl congeners (pcb 47; pcb 77) on thyroid status, choline acetyltransferase (chat) activity, and short- and long-term memory in 30-day-old sprague-dawley rats. Toxicology 203, 99–107.

Elnar, A.A., Diesel, B., Desor, F., Feidt, C., Bouayed, J., Kiemer, A.K., et al., 2012. Neurodevelopmental and behavioral toxicity via lactational exposure to the sum of six indicator non-dioxin-like-polychlorinated biphenyls (sigma 6 ndl-pcbs) in mice. Toxicology 299, 44–54.

Eubig, P.A., Aguiar, A., Schantz, S.L., 2010. Lead and pcbs as risk factors for attention deficit/hyperactivity disorder. Environ. Health Perspect. 118, 1654–1667.

Faroon, O., Ruiz, P., 2016. Polychlorinated biphenyls: new evidence from the last decade. Toxicol. Ind. Health 32, 1825–1847.

Fimm, B., Sturm, W., Esser, A., Schettgen, T., Willmes, K., Lang, J., et al., 2017. Neuropsychological effects of occupational exposure to polychlorinated biphenyls. Neurotoxicology 63, 106–119.

Fitzgerald, E.F., Belanger, E.E., Gomez, M.I., Cayo, M., Mccaffrey, R.J., Seegal, R.F., et al., 2008. Polychlorinated biphenyl exposure and neuropsychological status among older residents of upper hudson river communities. Environ. Health Perspect. 116, 209–215.

Gaum, P.M., Esser, A., Schettgen, T., Gube, M., Kraus, T., Lang, J., 2014. Prevalence and incidence rates of mental syndromes after occupational exposure to polychlorinated biphenyls. Int. J. Hyg. Environ. Health 217, 765–774.

Gaum, P.M., Gube, M., Schettgen, T., Putschogl, F.M., Kraus, T., Fimm, B., et al., 2017. Polychlorinated biphenyls and depression: cross-sectional and longitudinal investigation of a dopamine-related neurochemical path in the german helpcb surveillance program. Environ. Health 16, 106.

Goutman, S.A., Boss, J., Patterson, A., Mukherjee, B., Batterman, S., Feldman, E.L., 2019. High plasma concentrations of organic pollutants negatively impact survival in amyotrophic lateral sclerosis. J. Neurol. Neurosurg. Psychiatry 90, 907–912.

Grandjean, P., Weihe, P., Burse, V.W., Needham, L.L., Storr-Hansen, E., Heinzow, B., et al., 2001. Neurobehavioral deficits associated with PCB in 7-year-old children prenatally exposed to seafood neurotoxicants. Neurotoxicol Teratol 23 (4), 305–317.

Grandjean, P., Weihe, P., White, R.F., Debes, F., Araki, S., Yokoyama, K., et al., 1997. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. Neurotoxicol Teratol 19 (6), 417–428.

Granillo, L., Sethi, S., Keil, K.P., Lin, Y., Ozonoff, S., Iosif, A.M., et al., 2019. Polychlorinated biphenyls influence on autism spectrum disorder risk in the marbles cohort. Environ. Res. 171, 177–184.

Gray, K.A., Klebanoff, M.A., Brock, J.W., Zhou, H., Darden, R., Needham, L., et al., 2005. In utero exposure to background levels of polychlorinated biphenyls and cognitive functioning among school-age children. Am. J. Epidemiol. 162, 17–26.

Grimm, F.A., Hu, D., Kania-Korwel, I., Lehmler, H.J., Ludewig, G., Hornbuckle, K.C., et al., 2015. Metabolism and metabolites of polychlorinated biphenyls. Crit. Rev. Toxicol. 45, 245–272.

Guida, Y., Capella, R., Weber, R., 2020. Chlorinated paraffins in the technosphere: a review of available information and data gaps demonstrating the need to support the stockholm convention implementation. Emerg. Contam. 6, 143–154.

Haave, M., Bernhard, A., Jellestad, F.K., Heegaard, E., Brattelid, T., Lundebye, A.K., 2011. Long-term effects of environmentally relevant doses of 2,2′,4,4′,5,5′ hexachlorobiphenyl (pcb153) on neurobehavioural development, health and spontaneous behaviour in maternally exposed mice. Behav. Brain Funct. 7, 3.

Hajat, A., Maclehose, R.F., Rosofsky, A., Walker, K.D., Clougherty, J.E., 2021. Confounding by socioeconomic status in epidemiological studies of air pollution and health: challenges and opportunities. Environ. Health Perspect. 129, 65001.

Hatcher-Martin, J.M., Gearing, M., Steenland, K., Levey, A.I., Miller, G.W., Pennell, K.D., 2012. Association between polychlorinated biphenyls and parkinson's disease neuropathology. Neurotoxicology 33, 1298–1304.

Hersi, M., Irvine, B., Gupta, P., Gomes, J., Birkett, N., Krewski, D., 2017. Risk factors associated with the onset and progression of alzheimer's disease: a systematic review of the evidence. Neurotoxicology 61, 143–187.

Hertz-Picciotto, I., Schmidt, R.J., Krakowiak, P., 2018a. Understanding environmental contributions to autism: causal concepts and the state of science. Autism Res. 11, 554–586.

Hertz-Picciotto, I., Schmidt, R.J., Walker, C.K., Bennett, D.H., Oliver, M., Shedd-Wise, K.M., et al., 2018b. A prospective study of environmental exposures and early biomarkers in autism spectrum disorder: design, protocols, and preliminary data from the marbles study. Environ. Health Perspect. 126, 117004.

Hornbuckle, K.C., 2022. Common misconceptions about pcbs obscure the crisis of children's exposure in school. Environ. Sci. Technol. 56, 16544–16545.

Jacobson, J.L., Fein, G.G., Jacobson, S.W., Schwartz, P.M., Dowler, J.K., 1984. The transfer of polychlorinated biphenyls (pcbs) and polybrominated biphenyls (pbbs) across the human placenta and into maternal milk. Am. J. Public Health 74, 378–379.

Jacobson, J.L., Jacobson, S.W., 1996. Dose-response in perinatal exposure to polychlorinated biphenyls (PCBs): the Michigan and North Carolina cohort studies. Toxicol ind Health 12 (3–4), 435–445.

Jacobson, J.L., Jacobson, S.W., 1997. Evidence for pcbs as neurodevelopmental toxicants in humans. Neurotoxicology 18, 415–424.

Jacobson, J.L., Jacobson, S.W., Padgett, R.J., Brumitt, G.A., Billings, R.L., 1992. Effects of prenatal PCB exposure on cognitive processing efficiency and sustained attention. Dev Psychol 28, 297–306.

Johansen, E.B., Fonnum, F., Lausund, P.L., Walaas, S.I., Baerland, N.E., Woien, G., et al., 2014. Behavioral changes following pcb 153 exposure in the spontaneously hypertensive rat - an animal model of attention-deficit/hyperactivity disorder. Behav. Brain Funct. 10, 1.

Jolous-Jamshidi, B., Cromwell, H.C., Mcfarland, A.M., Meserve, L.A., 2010. Perinatal exposure to polychlorinated biphenyls alters social behaviors in rats. Toxicol. Lett. 199, 136–143.

Julvez, J., Ribas-Fito, N., Torrent, M., Forns, M., Garcia-Esteban, R., Sunyer, J., 2007. Maternal smoking habits and cognitive development of children at age 4 years in a population-based birth cohort. Int. J. Epidemiol. 36, 825–832.

Keil-Stietz, K., Lein, P.J., 2023. Genexenvironment interactions in autism spectrum disorders. Curr. Top. Dev. Biol. 152, 221–284.

Kilburn, K.H., Warsaw, R.H., Shields, M.G., 1989. Neurobehavioral dysfunction in firemen exposed to polychlorinated-biphenyls (pcbs) - possible improvement after detoxification. Arch. Environ. Health 44, 345–350.

Klocke, C., Lein, P.J., 2020. Evidence implicating non-dioxin-like congeners as the key mediators of polychlorinated biphenyl (pcb) developmental neurotoxicity. Int. J. Mol. Sci. 21, 1013.

Kodavanti, P.R., Shin, D.S., Tilson, H.A., Harry, G.J., 1993. Comparative effects of two polychlorinated biphenyl congeners on calcium homeostasis in rat cerebellar granule cells. Toxicol. Appl. Pharmacol. 123, 97–106.

Kodavanti, P.R., Ward, T.R., Mckinney, J.D., Tilson, H.A., 1996a. Inhibition of microsomal and mitochondrial ca2+-sequestration in rat cerebellum by polychlorinated biphenyl mixtures and congeners. Structure-activity relationships. Arch. Toxicol. 70, 150–157.

Kodavanti, P.R., Ward, T.R., Mckinney, J.D., Waller, C.L., Tilson, H.A., 1996b. Increased [3h]phorbol ester binding in rat cerebellar granule cells and inhibition of 45ca2+ sequestration in rat cerebellum by polychlorinated diphenyl ether congeners and analogs: structure-activity relationships. Toxicol. Appl. Pharmacol. 138, 251–261.

Kodavanti, P.R., Tilson, H.A., 2000. Neurochemical effects of environmental chemicals: In vitro and in vivo correlations on second messenger pathways. Ann. N. Y. Acad. Sci. 919, 97–105.

Koldkjær, O.G., Wermuth, L., Bjerregaard, P., 2004. Parkinson's disease among Inuit in Greenland: organochlorines as risk factors. Int J Circumpolar Health 63 (Suppl 2), 366–368.

Koopman-Esseboom, C., Weisglas-Kuperus, N., de Ridder, M.A., Van der Paauw, C.G., Tuinstra, L.G., Sauer, P.J., 1996. Effects of polychlorinated biphenyl/dioxin exposure and feeding type on infants' mental and psychomotor development. Pediatrics 97, 700–706.

Kyriklaki, A., Vafeiadi, M., Kampouri, M., Koutra, K., Roumeliotaki, T., Chalkiadaki, G., et al., 2016. Prenatal exposure to persistent organic pollutants in association with offspring neuropsychological development at 4 years of age: the rhea mother-child cohort, crete, greece. Environ. Int. 97, 204–211.

Lai, M.C., Lombardo, M.V., Baron-Cohen, S., 2014. Autism Lancet 383, 896–910.

Lai, T.J., Guo, Y.L., Guo, N.W., Hsu, C.C., 2001. Effect of prenatal exposure to polychlorinated biphenyls on cognitive development in children: A longitudinal study in taiwan. Br. J. Psychiatry Suppl. 40, s49–s52.

Lauby-Secretan, B., Loomis, D., Grosse, Y., El Ghissassi, F., Bouvard, V., Benbrahim-Tallaa, L., et al., 2013. Carcinogenicity of polychlorinated biphenyls and polybrominated biphenyls. Lancet Oncol. 14, 287–288.

Lein, P.J., 2015. Overview of the role of environmental factors in neurodevelopmental disorders. In: Costa, L.G., Aschner, M. (Eds.), Environmental Factors in Neurodevelopmental and Neurodegenerative Disorders. Elsevier, Inc., Oxford, UK.

Li, X.S., Hefti, M.M., Marek, R.F., Hornbuckle, K.C., Wang, K., Lehmler, H.J., 2022. Assessment of polychlorinated biphenyls and their hydroxylated metabolites in postmortem human brain samples: Age and brain region differences. Environ. Sci. Technol. 56, 9515–9526. https://doi.org/10.1021/acs.est.2c00581.

Liu, C., Bai, W., Chen, J., Niu, Q., 2015. Effect of gestational and lactational exposure to the polychlorinated biphenyl mixture aroclor 1254 on learning and memory and hippocampus in rat offspring. Chin. J. Behav. Med. Brain Sci. 105–108.

Lombardo, J.P., Berger, D.F., Hunt, A., Carpenter, D.O., 2015. Inhalation of polychlorinated biphenyls (pcb) produces hyperactivity in rats. J. Toxicol. Environ. Health A 78, 1142–1153.

Lyall, K., Croen, L.A., Sjodin, A., Yoshida, C.K., Zerbo, O., Kharrazi, M., et al., 2017. Polychlorinated biphenyl and organochlorine pesticide concentrations in maternal mid-pregnancy serum samples: association with autism spectrum disorder and intellectual disability. Environ. Health Perspect. 125, 474–480.

Ma, S., Zuo, Y., 2022. Synaptic modifications in learning and memory–a dendritic spine story. Seminars in Cell & Developmental Biology. Elsevier, pp. 84–90.

Marek, R.F., Thorne, P.S., DeWall, J., Hornbuckle, K.C., 2014. Variability in PCB and OH-PCB serum levels in children and their mothers in urban and rural US communities. Environ. Sci. Technol. 48, 13459–13467. https://doi.org/10.1021/es502490w.

Martino, R., Candundo, H., Lieshout, P.V., Shin, S., Crispo, Ja.G., Barakat-Haddad, C., 2017. Onset and progression factors in parkinson's disease: a systematic review. Neurotoxicology 61, 132–141.

Masini, E., Loi, E., Vega-Benedetti, A.F., Carta, M., Doneddu, G., Fadda, R., et al., 2020. An overview of the main genetic, epigenetic and environmental factors involved in autism spectrum disorder focusing on synaptic activity. Int. J. Mol. Sci. 21, 8290.

Masuda, Y., Kuroki, H., Haraguchi, K., Nagayama, J., 1985. Pcb and pcdf congeners in the blood and tissues of yusho and yu-cheng patients. Environ. Health Perspect. 59, 53–58.

Mehri, F., Bashirian, S., Khazaei, S., Jenabi, E., 2021. Association between pesticide and polychlorinated biphenyl exposure during pregnancy and autism spectrum disorder among children: A meta-analysis. Clin. Exp. Pediatr. 64, 286–292.

Mellor, C.L., Steinmetz, F.P., Cronin, M.T., 2016. The identification of nuclear receptors associated with hepatic steatosis to develop and extend adverse outcome pathways. Crit. Rev. Toxicol. 46, 138–152.

Montano, L., Pironti, C., Pinto, G., Ricciardi, M., Buono, A., Brogna, C., et al., 2022. Polychlorinated biphenyls (pcbs) in the environment: occupational and exposure events, effects on human health and fertility. Toxics 10, 365.

Mouat, J.S., Li, X., Neier, K., Zhu, Y., Mordaunt, C.E., La Merrill, M.A., et al., 2023. Networks of placental DNA methylation correlate with maternal serum pcb concentrations and child neurodevelopment. Environ. Res. 220, 115227.

Nellis, L., Gridley, B.E., 1994. Review of the bayley scales of infant development—second edition. J. Sch. Psychol. 32, 201–209.

Neugebauer, J., Wittsiepe, J., Kasper-Sonnenberg, M., Schoneck, N., Scholmerich, A., Wilhelm, M., 2015. The influence of low level pre- and perinatal exposure to pcdd/fs, pcbs, and lead on attention performance and attention-related behavior among german school-aged children: results from the duisburg birth cohort study. Int. J. Hyg. Environ. Health 218, 153–162.

Orenstein, S.T., Thurston, S.W., Bellinge, D.C., Schwartz, J.D., Amarasiriwardena, C.J., Altshul, L.M., et al., 2014. Prenatal organochlorine and methylmercury exposure and memory and learning in school-age children in communities near the New Bedford Harbor Superfund site, Massachusetts. Environ Health Perspect 122 (11), 1253–1259.

Panesar, H.K., Kennedy, C.L., Keil Stietz, K.P., Lein, P.J., 2020. Polychlorinated biphenyls (pcbs): risk factors for autism spectrum disorder? Toxics 8, 70.

Panesar, H.K., Wilson, R.J., Lein, P.J., 2022. Cellular and molecular mechanisms of pcb developmental neurotoxicity. Handbook of Neurotoxicity. Springer.

Pessah, I.N., Lein, P.J., Seegal, R.F., Sagiv, S.K., 2019. Neurotoxicity of polychlorinated biphenyls and related organohalogens. Acta Neuropathol. 138, 363–387.

Petersen, M.S., Halling, J., Bech, S., Wermuth, L., Weihe, P., Nielsen, F., et al., 2008. Impact of dietary exposure to food contaminants on the risk of parkinson's disease. Neurotoxicology 29, 584–590.

Petersen, S.E., Posner, M.I., 2012. The attention system of the human brain: 20 years after. Annu. Rev. Neurosci. 35, 73–89.

Prince, M.M., Hein, M.J., Ruder, A.M., Waters, M.A., Laber, P.A., Whelan, E.A., 2006. Update: cohort mortality study of workers highly exposed to polychlorinated biphenyls (PCBs) during the manufacture of electrical capacitors, 1940–1998. Environ. Health. 5, 13.

Putschögl, F.M., Gaum, P.M., Schettgen, T., Kraus, T., Gube, M., Lang, J., 2015. Effects of occupational exposure to polychlorinated biphenyls on urinary metabolites of neurotransmitters: A cross-sectional and longitudinal perspective. Int J Hyg Environ Health 218 (5), 452–460.

Raffetti, E., Donato, F., De Palma, G., Leonardi, L., Sileo, C., Magoni, M., 2020. Polychlorinated biphenyls (pcbs) and risk of dementia and parkinson disease: a population-based cohort study in a north italian highly polluted area. Chemosphere 261, 127522.

Rein, B., Ma, K., Yan, Z., 2020. A standardized social preference protocol for measuring social deficits in mouse models of autism. Nat. Protoc. 15, 3464–3477.

Rengelshausen, J., Randerath, I., Schettgen, T., Esser, A., Kaifie, A., Lang, J., et al., 2023. Ten years after: Findings from the medical surveillance program on health effects in high-level exposure to pcb (helpcb). Arch. Toxicol. 97, 2609–2623.

Rogan, W.J., 1982. Pcbs and cola-colored babies: Japan, 1968, and taiwan, 1979. Teratology 26, 259–261.

Ryan, J.J., Lopez, S.J., 2001. Wechsler adult intelligence scale-iii. Underst. Psychol. Assess. 19–42.

Sable, H.J.K., Schantz, S.L., 2006. Executive function following developmental exposure to polychlorinated biphenyls (pcbs): what animal models have told us. In: Levin, E.D., Buccafusco, J.J. (Eds.), Animal Models of Cognitive Impairment. CRC Press/Taylor & Francis, Boca Raton (FL).

Sagiv, S.K., Thurston, S.W., Bellinger, D.C., Altshul, L.M., Korrick, S.A., 2012. Neuropsychological measures of attention and impulse control among 8-year-old children exposed prenatally to organochlorines. Environ. Health Perspect. 120, 904–909.

Salman, M.S., Tsai, P., 2016. The role of the pediatric cerebellum in motor functions, cognition, and behavior: a clinical perspective. Neuroimaging Clin. N. Am. 26, 317–329.

Sasaki, N., Jones, L.E., Morse, G.S., Carpenter, D.O., Environm, A.T.F., 2023. Mixture effects of polychlorinated biphenyls (pcbs) and three organochlorine pesticides on cognitive function in mohawk adults at akwesasne. Int. J. Environ. Res. Public Health 20, 1148.

Schantz, S.L., Gasior, D.M., Polverejan, E., Mccaffrey, R.J., Sweeney, A.M., Humphrey, H.E., et al., 2001. Impairments of memory and learning in older adults exposed to polychlorinated biphenyls via consumption of great lakes fish. Environ. Health Perspect. 109, 605–611.

Schantz, S.L., Widholm, J.J., Rice, D.C., 2003. Effects of pcb exposure on neuropsychological function in children. Environ. Health Perspect. 111, 357–576.

Schönfeld, L.-M., Dooley, D., Jahanshahi, A., Temel, Y., Hendrix, S., 2017. Evaluating rodent motor functions: Which tests to choose? Neurosci. Biobehav. Rev. 83, 298–312.

Seegal, R.F., Bush, B., Shain, W., 1990. Lightly chlorinated ortho-substituted pcb congeners decrease dopamine in nonhuman primate brain and in tissue culture. Toxicol. Appl. Pharmacol. 106, 136–144.

Seegal, R.F., Marek, K.L., Seibyl, J.P., Jennings, D.L., Molho, E.S., Higgins, D.S., et al., 2010. Occupational exposure to PCBs reduces striatal dopamine transporter densities only in women: a beta-CIT imaging study. Neurobiol Dis 38, 219–225.

Sethi, S., Morgan, R.K., Feng, W., Lin, Y., Li, X., Luna, C., et al., 2019. Comparative analyses of the 12 most abundant pcb congeners detected in human maternal serum for activity at the thyroid hormone receptor and ryanodine receptor. Environ. Sci. Technol. 53, 3948–3958.

Sethi, S., Stietz, K.K.P., Valenzuela, A.E., Klocke, C.R., Silverman, J.L., Puschner, B., et al., 2021. Developmental exposure to a human-relevant polychlorinated biphenyl mixture causes behavioral phenotypes that vary by sex and genotype in juvenile mice expressing human mutations that modulate neuronal calcium. Front. Neurosci. 15, 766826.

Shain, W., Bush, B., Seegal, R., 1991. Neurotoxicity of polychlorinated biphenyls: structure-activity relationship of individual congeners. Toxicol. Appl. Pharmacol. 111, 33–42.

Skogan, A.H., Zeiner, P., Egeland, J., Rohrer-Baumgartner, N., Urnes, A.G., Reichborn-Kjennerud, T., et al., 2014. Inhibition and working memory in young preschool children with symptoms of adhd and/or oppositional-defiant disorder. Child. Neuropsychol. 20, 607–624.

Soydaner, D., 2022. Attention mechanism in neural networks: Where it comes and where it goes. Neural Comput. Appl. 34, 13371–13385.

Stahl, L.L., Snyder, B.D., Olsen, A.R., Pitt, J.L., 2009. Contaminants in fish tissue from us lakes and reservoirs: A national probabilistic study. Environ. Monit. Assess. 150, 3–19.

Steenland, K., Hein, M.J., Cassinelli 2nd, R.T., Prince, M.M., Nilsen, N.B., Whelan, E.A., et al., 2006. Polychlorinated biphenyls and neurodegenerative disease mortality in an occupational cohort. Epidemiology 17, 8–13.

Steuerwald, U., Weihe, P., Jørgensen, P.J., Bjerve, K., Brock, J., Heinzow, B., Grandjean, P., 2000. Maternal seafood diet, methylmercury exposure, and neonatal neurologic function. J Pediatr 136 (5), 599–605.

Stewart, P.W., Lonky, E., Reihman, J., Pagano, J., Gump, B.B., Darvill, T., 2008. The relationship between prenatal PCB exposure and intelligence (IQ) in 9-year-old children. Environmental health perspectives 116 (10), 1416–1422.

Stewart, P., Reihman, J., Gump, B., Lonky, E., Darvill, T., Pagano, J., 2005. Response inhibition at 8 and 9 1/2 years of age in children prenatally exposed to pcbs. Neurotoxicol. Teratol. 27, 771–780.

Stewart, P.W., Reihman, J., Lonky, E.I., Darvill, T.J., Pagano, J., 2003. Cognitive development in preschool children prenatally exposed to PCBs and MeHg. Neurotoxicol Teratol 25 (1), 11–22.

Su, F.C., Goutman, S.A., Chernyak, S., Mukherjee, B., Callaghan, B.C., Batterman, S., et al., 2016. Association of environmental toxins with amyotrophic lateral sclerosis. JAMA Neurol. 73, 803–811.

Tanimizu, T., Kono, K., Kida, S., 2018. Brain networks activated to form object recognition memory. Brain Res. Bull. 141, 27–34.

Tian, Y.H., Hwan Kim, S., Lee, S.Y., Jang, C.G., 2011. Lactational and postnatal exposure to polychlorinated biphenyls induces sex-specific anxiolytic behavior and cognitive deficit in mice offspring. Synapse 65, 1032–1041.

Ulbrich, B., Stahlmann, R., 2004. Developmental toxicity of polychlorinated biphenyls (pcbs): a systematic review of experimental data. Arch. Toxicol. 78, 252–268.

Vermeir, G., Covaci, A., Van Larebeke, N., Schoeters, G., Nelen, V., Koppen, G., et al., 2021. Neurobehavioural and cognitive effects of prenatal exposure to organochlorine compounds in three year old children. BMC Pediatr. 21, 99.

Vreugdenhil, H.J.I., Lanting, C.I., Mulder, P.C.H., Boersma, E.R., Weisglas-Kuperus, N., 2002. Effects of prenatal pcb and dioxin background exposure on cognitive and motor abilities in dutch children at school age. J. Pediatr. 140, 48–56.

Wang, H., Adamcakova-Dodd, A., Flor, S., Gosse, L., Klenov, V.E., Stolwijk, J.M., et al., 2020. Comprehensive subchronic inhalation toxicity assessment of an indoor school air mixture of pcbs. Environ. Sci. Technol. 54, 15976–15985.

Wang, M.D., Little, J., Gomes, J., Cashman, N.R., Krewski, D., 2017. Identification of risk factors associated with onset and progression of amyotrophic lateral sclerosis using systematic review and meta-analysis. Neurotoxicology 61, 101–130.

Wheeler, M.A., Rothhammer, V., Quintana, F.J., 2017. Control of immune-mediated pathology via the aryl hydrocarbon receptor. J. Biol. Chem. 292, 12383–12389.

Winneke, G., 2011. Developmental aspects of environmental neurotoxicology: Lessons from lead and polychlorinated biphenyls. J. Neurol. Sci. 308, 9–15.

Winneke, G., Bucholski, A., Heinzow, B., Krämer, U., Schmidt, E., Walkowiak, J., et al., 1998. Developmental neurotoxicity of polychlorinated biphenyls (PCBS): cognitive and psychomotor functions in 7-month old children. Tox Lett 102, 423–428.

Yang, D., Kim, K.H., Phimister, A., Bachstetter, A.D., Ward, T.R., Stackman, R.W., et al., 2009. Developmental exposure to polychlorinated biphenyls interferes with experience-dependent dendritic plasticity and ryanodine receptor expression in weanling rats. Environ. Health Perspect. 117, 426–435.