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Polychlorinated Biphenyls (PCBs), Organochlorine Pesticides, and Neurodevelopment

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Abstract

Purpose of review—Although environmental levels of polychlorinated biphenyls (PCBs) and certain organochlorine pesticides – hexachlorobenzene (HCB), dichlorodiphenyl trichloroethane (DDT) and its primary metabolite, dichlorodiphenyl dichloroethene (DDE) – are generally on the decline, early-life exposures to these prevalent contaminants continue. This review will describe current understanding of the potential neurodevelopmental consequences of low-level exposures to these contaminants.

Findings—Animal models suggest that early-life exposures to PCBs, DDT/DDE, or HCB are associated with decreased cognitive or behavioral function in later development. However, despite almost 30 years of research, results of human studies are inconsistent regarding the nature of the observed effects and their persistence over time. Overall, epidemiologic studies support modest associations of primarily prenatal PCB exposures with differences in neuromotor development, decrements in cognition, and behavioral deficits, particularly regarding attention and impulse control. There are limited published human data regarding potential neurodevelopmental toxicities of early-life exposures to DDT/DDE and HCB.

Summary—Exposures to PCBs, DDT/DDE and HCB are likely detrimental to neurodevelopment. Effective control of exposure is complicated by variable exposure sources and variable contaminant levels in food, particularly fish, for which it is important to balance the risk of contaminants with nutritional benefits.

Keywords

organochlorines; PCBs; pesticides; neurodevelopment

Introduction

This update will review the major prospective studies assessing the relationship of early-life polychlorinated biphenyl (PCB), dichlorodiphenyl-trichloroethane (DDT), dichlorodiphenyl dichloroethene (DDE), and hexachlorobenzene (HCB) exposures with neurodevelopment in infancy and childhood among general population samples. The relation of these organochlorines with premature birth, fetal growth, neonatal behavior, postnatal growth and maturation, and immune function are reviewed elsewhere [1–5]. Studies with published

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results include birth cohorts in the U.S., Canada, Denmark (the Faroe Islands), Germany, Japan, Mexico, the Netherlands, and Spain.

Background

PCBs are lipophilic chemicals first produced in 1929 and commonly used in electronics manufacture, as vehicles for pesticides, and in building materials. DDE is one of the major degradation products of DDT, a broad-spectrum insecticide widely used in agriculture and residential settings and for mosquito control in malaria-endemic regions. The use of the fungicide HCB was discontinued in the U.S. in 1984, but it continues to be formed during incineration or as a byproduct in the manufacture of chlorinated compounds. Because of toxicity and bioaccumulation, use of PCBs and DDT was banned in the U.S. in the 1970s and in most industrialized countries over the subsequent decade. Exposures to these organochlorines have declined, but due to bioaccumulation, deposition in land fills and waste sites, resistance to degradation, presence of PCBs in buildings and electronics, and continued use of DDT for malaria control, exposures are expected to continue for several decades [6].

Non-occupational exposure to organochlorines occurs primarily via diet (for PCBs, particularly via contaminated fish, meat, and dairy products) [7, 8] but also via inhalation and dermal contact with contaminated soils or sediments [9, 10]. Caulking materials used in buildings (including schools) constructed before 1977 may lead to high dust and indoor air PCB levels [11]. The PCB content of fish depends on location, species, and fat content and may be higher among farmed-raised than wild animals because of aquaculture feeding practices [12].

Recognition of PCBs as human neurodevelopmental toxicants was largely a consequence of two accidental mass poisonings, in Japan in 1968 and Taiwan in 1979. Many of those who consumed PCB-contaminated rice oil and their children became ill [13–17]. Taiwanese children exposed prenatally were at increased risk for a syndrome in infancy of intrauterine growth retardation, liver function and ectodermal abnormalities and, in later childhood, lower weight and height, diminished IQ, and behavioral disorders [13, 17–21]. The contaminated oil contained high levels of polychlorinated dibenzofurans (PCDFs), much more potent toxins than PCBs, obscuring the putative causal agent of these outcomes [22].

PCBs, DDE, HCB and Neurodevelopment: Prospective Studies

Because PCBs and organochlorine pesticides readily cross the placenta and bioconcentrate in breast milk, early-life exposure occurs via maternal-fetal transfer prenatally and via breastfeeding postnatally. Because breast milk organochlorine levels correlate with maternal pregnancy blood levels, studies estimate prenatal exposures by measuring levels in peripartum milk, maternal pregnancy serum, and/or cord serum. Here, organochlorine levels in milk or serum samples will generally be referred to as “prenatal PCB (or pesticide) exposure”.

North Carolina Birth Cohort

880 women and their 931 infants born 1978–1982 were enrolled in this longitudinal study in Raleigh-Durham, North Carolina [23]. Prenatal PCB exposure was associated with neuromotor differences up to age 2 years: neonatal hypotonia and hyporeflexia [24] and lower Psychomotor Developmental Index (PDI) scores on the Bayley Scales of Infant Development (BSID) at 6, 12, and 24 months [25, 26]. No subsequent motor development effects or cognitive effects were indicated by the McCarthy Scales of Children’s Abilities at 3 to 5 years, or school report cards from grades 3–5 (ages 8–10) [27]. There were no

postnatal PCB exposure effects. Higher prenatal DDE levels were associated with neonatal hyporeflexia [24]; otherwise, there were no effects of DDE on developmental outcomes.

Michigan Birth Cohort

242 pregnant women who consumed moderate amounts of PCB-contaminated Lake Michigan fish and 71 women who did not consume the fish were enrolled in 1980–1981 [28]. PCB associations with neuromuscular development were not seen in infancy [29, 30]. Higher cord serum PCB levels were associated with poorer performance on the Fagan Test of Infant Intelligence (FTII) at 7 months, a measure of cognition and visual memory [31]. Cognitive decrements persisted with adverse PCB associations on the McCarthy general cognitive index, verbal, and memory scales at age 4 [32, 33], and lower full scale and verbal IQ on Wechsler Intelligence Scales for Children (WISC-R) at age 11 [34]. Eleven-year-olds also had prenatal PCB exposure-associated decrements in executive function, focused attention, and word comprehension [34, 35]. This is the oldest group in which persistent prenatal PCB effects have been described.

This study by Jacobson et al. was among the first to test the relationship between PCBs and behavioral outcomes. At both ages 4 and 11 prenatal exposures were associated with measures of poor attention and impulse control [35, 36], though both were generally only seen among children who were not breastfed. Excepting an association of decreased activity at age 4 with concurrent PCB levels, no postnatal PCB exposure effects were seen [33].

Faroe Islands Birth Cohorts

Several birth cohort studies of methylmercury and PCB exposures and neurodevelopment are being conducted in the Faroe Islands. These are North Atlantic Danish islands where the traditional diet includes whale meat and blubber [37]. Whale meat is high in methylmercury, and blubber is high in PCBs [38]. Indeed, serum and milk PCB levels were the highest of the studies reviewed [39]. The first of these cohorts included 1,022 children born 1986–87 with neurodevelopmental assessments and prenatal PCB exposure measures for 435 children at age 7 [40, 41]. As reviewed elsewhere in this volume (see Oken and Bellinger), the predominant findings relate to neurodevelopmental toxicities of methylmercury exposures. Despite high PCB exposures, PCB effects have been confounded by methylmercury. For example, higher prenatal PCB exposure measures were associated with poorer performance on the Boston Naming Test (verbal ability) and longer reaction times on a continuous performance test (an indicator of poor attention) at age 7 but these associations were no longer significant after adjustment for methylmercury exposure [41]. Of note, there was evidence of effect modification by joint exposure. Specifically, the association of PCBs with these outcomes was strongest among children with the highest methylmercury exposure, though the interaction was not significant. In neurophysiologic testing at age 7, possible adverse PCB effects on visual evoked potentials (VEPs) and brain stem auditory evoked potentials (BAEPs), reflecting integrity of sensory afferent neural pathways, were also no longer significant after adjustment for methylmercury [41].

Dutch Birth Cohort

209 breastfed and 209 formula-fed infants born between 1990 and 1992 in Rotterdam and Groningen were enrolled [42]. Prenatal PCB exposure was associated with neonatal hypotonia [42] and decrements in psychomotor development (BSID PDI) at 3 months [43]. Prenatal PCB neuromotor effects were no longer discernible at 7 and 18 months, but postnatal PCB exposure was associated with lower BSID PDI at 7 months [43]. Early-life PCB exposures were not associated with delayed general cognitive development between 3 and 18 months [43], but cognitive effects were seen at older ages, with poorer overall cognition on the Kaufman Assessment Battery for Children (K-ABC) and poorer verbal

comprehension on the Reynell Developmental Language Scales (RDLs) at 42 months [44]. These associations were specific to formula-fed infants and were not found with postnatal or current exposure. In addition, prenatal PCB exposure was correlated with poorer general cognition, memory, and motor skills on the McCarthy at age 6.5 years but only among children with suboptimal home environments and parenting [45]. In a small subset of the children (n=83) assessed at 9 years, higher prenatal PCB exposures were associated with decrements in attention (longer and more varied reaction times), executive function (lower scores on the Tower of London) [46], and neurophysiologic measures reflecting underlying attention and memory processes (longer latency of auditory event-related brain potentials or ERPs) assessed in 60 children [47]. There was some evidence that postnatal PCB exposures via breastfeeding diminished executive function at age 9.

Oswego, New York Birth Cohort

This population was enrolled in 1991–1994 and consisted of 316 mother-infant pairs comprised of those consuming high levels of contaminated Lake Ontario fish (n=152) and non-fish consumers (n=164). Although this population was born over a decade later, findings paralleled Michigan findings, notable since both cohorts include a large proportion of mothers who consumed contaminated Great Lakes fish. Abnormal neonatal reflexes were associated with maternal consumption of contaminated fish, but not with prenatal serum PCB, DDE, or HCB [48, 49]. Decrements in infant intelligence (FTII) at 6 months (n=230) and 12 months (n=216) were associated with prenatal PCBs, though not with postnatal PCB or prenatal DDE exposures [50]. In early childhood, prenatal PCB exposures were associated with poorer general cognition on the McCarthy at 38, but not 54, months with evidence of “catch-up” for the more exposed children in the interval between exams [51]. Behavioral assessments demonstrated consistent PCB associations with poor impulse control. In particular, there were associations of prenatal PCB exposures with errors of commission on various continuous performance tasks (CPT) at ages 4.5, 8, and 9.5 years [52, *53]. Prenatal PCB exposure was associated with poor response inhibition at 9.5 years, measured with an experimental technique (Differential Reinforcement of Low Rates, DRL) in which the child must withhold response for a fixed time [54]. DDE and HCB were not associated with performance on any of these behavioral tests.

Duesseldorf (Germany) Birth Cohort

In this study 171 mothers from three Duesseldorf hospitals were recruited in 1993–1995 [55]. Findings include an inverse association of prenatal PCB levels with BSID PDI and Mental Developmental Index (MDI) at age 30 months (n=104), with marginally non-significant findings at 7 and 18 months and no relation with the FTII at age 7 months [55, 56]. In addition, both pre- and postnatal PCB exposure measures were associated with decrements in general cognition on the K-ABC at 42 months [56].

Canadian Inuit Cohorts

There are several studies among Inuit families living in Northern Quebec (Canada). First, the Cord Blood Monitoring Program, a study of 483 participants which took place from 1993–96 and a second study of approximately 200 mothers and their infants enrolled between 1995–2001 to assess Inuit infant health and development [57, 58]. The traditional Inuit diet includes marine mammals, substantial sources of organochlorines [59].

Among 4- to 6-year-old participants in the Cord Blood Monitoring Program (n=110), there was no relation of pre- or postnatal PCB or organochlorine pesticide exposures (including DDT/DDE and HCB) with multiple quantitative neuromotor assessments [58]. Neurophysiologic assessments of 78 of these children at 5 to 6 years demonstrated an association of current blood PCB levels with increased latency and decreased amplitude of

Visual Evoked Potentials (VEPs), reflecting presumed perturbations in brain visual processing [60]. Similar associations were seen for current blood HCB levels.

The Collaborative Perinatal Project (CPP)

Between 1959–1965, over 42,000 pregnant women from 12 study centers (in 11 U.S. cities) were recruited for this study of determinants of adverse neurodevelopment. Using archived maternal pregnancy serum samples from a random sample of approximately 1,200 of these children, no discernible adverse cognitive effects of prenatal PCB exposure were found. Prenatal PCB exposures were not associated with either PDI or MDI indices at 8 months [61]; with performance on the Stanford-Binet IQ test at age 4 years; with WISC IQ assessments at age 7 years (n=874); nor with spelling, reading, or arithmetic skills on the Wide Range Achievement Test [**62]. In fact, higher PCBs were associated with higher IQ at age 4, possibly reflecting residual confounding by socioeconomic status (SES), as higher PCB levels were associated with higher SES in this population [**62].

Spanish Cohorts

Organochlorine emissions from a rural electrochemical factory in Flix, Spain produced unusually high ambient air and serum HCB levels [63]. HCB exposure and child development is being studied among 102 mother-infant pairs recruited between 1997–1999 in Flix and 5 neighboring villages [64]. Among 92 of these infants assessed at age 13 months, prenatal DDE exposure, but not HCB exposure, was associated with significant decrements in BSID MDI, PDI, and the Griffiths Scales of Infant Development, whereas prenatal PCBs were marginally associated ($p<0.10$) with psychomotor development [64].

A second cohort of 482 children was recruited from pregnant women seeking prenatal care in 1997–1998 in Menorca, Spain, where high concentrations of organochlorines have been reported [65]. In assessments of the combined Menorca and Flix cohorts (n=475) at age 4 years, prenatal DDT exposure was associated with cognitive decrements on the McCarthy, especially in memory and verbal skills, with a stronger association in girls than boys [65]. Among these 4-year-olds, higher cord blood HCB levels were associated with poorer Social Competence and more Attention-Deficit Hyperactivity (ADHD) behaviors [*66] using the California Preschool Social Competence Scale and an ADHD symptom check list [67] completed by each child's teacher. Four-year serum HCB as well as prenatal PCB and DDT/DDE levels were unrelated to these behavioral measures.

Recent Studies

A number of recently initiated birth cohort studies of organochlorines and child development are underway with results limited to infant and early childhood. In a multiethnic cohort of 130 New York City infants (born 1998–2001), maternal pregnancy blood PCB and DDE levels were not associated with abnormal neonatal reflexes or tone [68]. Similarly, no associations of prenatal DDE/DDT, PCB, or HCB exposure with neonatal reflexes or tone were observed among 303 Mexican American infants in an agricultural region of California (pregnant 1999–2000) despite relatively high DDE/DDT levels [69]. In follow-up assessments of 360 of these children through age 2, prenatal DDT levels were associated with lower BSID PDI scores at 6 and 12 months and lower MDI scores at 12 and 24 months [70]. DDE was also associated with lower PDI scores at 6 months.

Between 2001–2005, 722 Mexican women living in the state of Morelos (where DDT was used until 1998 and DDT/DDE levels are high) were recruited at their state-mandated premarital counseling and followed through pregnancy. In assessments of 244 resulting children, higher maternal serum DDE levels in the first trimester of pregnancy were

associated with reduced BSID PDI scores in the first year of life [71]. There was no association of prenatal DDE levels with MDI scores.

Among 134 pregnant women recruited in 2002–2004 from Hokkaido, Japan prenatal PCBs were unrelated to 6-month BSID performance [72].

Discussion

Most studies identified at least one neurodevelopmental effect of early-life PCB exposure, with more limited data available for DDT/DDE and HCB. However, study findings differ with respect to observed effects and their persistence. Thus, despite compelling findings in animals [6, 73], there is still uncertainty in the epidemiologic literature regarding the long-term neurodevelopmental risks associated with low-level early-life exposures to PCBs, DDT/DDE, and HCB.

There are a number of possible explanations for variable findings. Study populations vary in sociodemographic features that may confound or modify effects. For example, the association of PCBs with higher IQ among 4-year-olds in the CPP is unlikely to represent “true” PCB risk but is consistent with residual confounding. In this population higher exposures were associated with sociodemographic advantage, a correlate of higher IQ [**62]. The study populations also differ in both source and rate of exposure, and there is variability in co-occurring exposures that may confound or modify effects. A good example of this is in the Faroe Islands, where despite high PCB and mercury exposures, no strong independent PCB effects have been ascertained [37, 74, 75].

Still, taken in the aggregate, these studies support the conclusions that: prenatal are more deleterious than postnatal organochlorine exposures; sociodemographic disadvantage may enhance, and advantage mitigate, PCB toxicity; co-occurring neurotoxicants (e.g., methylmercury) can modify effects; and early-life PCB exposure likely interferes with neuromotor development in infancy and, in certain populations, adversely affects childhood cognition and behavior.

There are limited human data regarding neurodevelopmental toxicities of DDE, DDT, or HCB. Findings thus far do not support an association of prenatal DDE exposures with neonatal neuromuscular development [24, 49, 68, 69], childhood cognition, or childhood behavior [26, 27, *53, 54]. Studies have demonstrated associations of prenatal DDE and DDT exposures with decrements in later infant neuromuscular and cognitive development [64, 70] and, for DDT, subsequent childhood cognition through age 4 [65, 70]. Prenatal HCB exposures have been associated with adverse behaviors, including ADHD-related symptoms, in heavily exposed Spanish [*66] but not U.S. children [*53, 54]. However, conclusive inferences regarding the neurodevelopmental effects of these organochlorine pesticides will not be possible until more epidemiologic data are available.

Conclusions

The prospective birth cohort studies here focused on subtle neurodevelopmental consequences of PCB, DDT/DDE, and HCB exposures. Studies were performed among generally healthy children, with effects measured as continuous outcomes rather than clinically defined abnormalities. It is important not to underestimate the implications for population health of neurobehavioral differences noted with continuous outcomes [76, 77]. Small changes in the mean value of health indicators such as IQ can indicate substantial changes in the prevalence of clinically evident cognitive impairment within a population [78].

Therefore, limiting early-life exposures to these organochlorines is generally desirable. Applying the U.S. Environmental Protection Agency (EPA)'s presumed safe levels (reference dose, RfD) for chronic oral intake of these compounds [79–81] is difficult. Although contaminated fish is a key source of PCB exposure, in contrast to methylmercury, there are a number of other foods and environmental exposure sources for organochlorines. Indeed, excepting age and regional differences [82], individual determinants of organochlorine exposures are variable [83]. Because these compounds bioconcentrate in breastmilk, early-life exposures via nursing can be substantial. However, absent acute toxicities in the mother, in essentially all studies, the beneficial effects of breastfeeding consistently outweigh any potential adverse effect associated with milk organochlorine contaminants. Among other dietary exposure sources, PCB levels for example can vary widely even for a single species of fish [12]. Furthermore, fish sources of organochlorine exposure are often excellent sources of nutrients beneficial to neurodevelopment [84, 85]. Where contamination is severe, local advisories exist for sports fishermen (see <http://epa.gov/waterscience/fish/states.htm>). However, such advisories are not applicable to the majority of consumers, whose fish comes from markets and restaurants.

Findings from a number of ongoing studies are not yet available. Therefore, the interpretation of this body of literature may soon change, and updated findings will better elucidate neurodevelopmental risks of PCBs and persistent organochlorine pesticides and inform exposure prevention efforts.

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