The effects of exposure to environmental chemicals on child development

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PART 1

The neurotoxic effects of exposure to environmental chemicals during childhood: an overview

CHAPTER 2

Developmental neurotoxicity of persistent organic pollutants: an update on childhood outcome

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ABSTRACT

Organohalogens are persistent organic pollutants that have a wide range of chemical application. There is growing evidence that several of these chemical compounds interfere with human development in various ways.

The aim of this review is to provide an update on the relationship between various persistent organic pollutants and childhood neurodevelopmental outcome from studies from the past 10 years. This review focuses on exposure to polychlorinated biphenyls (PCBs), hydroxylated PCBs (OH-PCBs), polybrominated diphenyl ethers (PBDEs) and dichlorodiphenyldichloroethylene (DDE), and in addition on exposure to phthalates, bisphenol A (BPA), and perfluorinated compounds (PFCs) and their associations with neurodevelopmental outcome in childhood, up to 18 years of age.

This review shows that exposure to environmental chemicals affects neurodevelopmental outcome in children. Regarding exposure to PCBs and OH-PCBs, most studies report no or inverse associations with neurodevelopmental outcomes. Regarding exposure to PBDEs, lower mental development, psychomotor development and IQ were found at pre-school age, and poorer attention at school age. Regarding exposure to DDE, most studies reported inverse associations with outcome, while others found no associations. Significant relations were particularly found at early infancy on psychomotor development, on attention and ADHD, whereas at school age no adverse relationships were described. Additionally, several studies report gender related vulnerability.

Future research should focus on the long-term effects of prenatal and childhood exposure to these environmental chemicals, on sex-specific and combined exposure effects of environmental chemicals, and on possible mechanisms by which these chemicals have their effects on neurodevelopmental and behavioral outcomes.

INTRODUCTION

Organohalogens are persistent organic pollutants (POPs) that have a wide range of chemical applications. Particularly organochlorine compounds are used on a broad scale, such as in solvents and pesticides, in synthetic polymers and as intermediates in the preparation of dyes. In addition, brominated compounds, another type of organohalogen, have been widely used as flame retardants. There is growing evidence that several of these chemical compounds interfere with human development in various ways.

Organohalogens have specific characteristics that make them attractive for industrial use. They are more stable than other substances, not easily affected by acids or alkalis, and resistant to fire. However, their stability and bio-accumulation also make them persistent in the environment. This persistency in the environment potentiates their effect on human development.

Examples of organohalogen compounds

Polychlorinated biphenyls (PCBs) are synthetic organic chemical compounds composed of chlorine attached to biphenyl (a molecule composed of two benzene rings). Out of 209 different PCBs, 130 have been used for industrial application.[1] PCBs are stable compounds that do not easy decompose, due to their chemical inability to oxidize and reduce in the natural environment and the fact that they are insoluble in water. Their commercial application was, for example, in hydraulic fluids, adhesives, inks, lubricants, and as coolants in heat transfer systems. Although the production and use of PCBs has been banned by law since 1985, humans continue to be exposed to the contaminating effects of PCBs because these compounds still persist in the environment.[2] PCBs are metabolized by hepatic microsomal oxidases to form hydroxylated metabolites (OH-PCBs). In contrast to the relatively stable and highly lipophilic PCBs, OH-PCBs are readily conjugated and excreted. During the last decades, techniques have become available to detect these hydroxylated metabolites in human serum, allowing the effect of these metabolites on human health to be determined.

Polybrominated diphenyl ethers (PBDEs) have been used as flame retardants in a wide range of applications including furnishings, electronics and plastics. Although their industrial production is restricted around a decade ago,[3] they are still widely detectable in for example human blood.[2] In recent years, it has come to light that PBDEs also have the potential to interfere with human development.[4]

Dichlorodiphenyldichloroethylene (DDE) is a degradation product of the organochlorine compound dichlorodiphenyltrichloroethane (DDT). DDT has widely been used as an insecticide, in for example mosquito control, until the late 20th century, when the use was banned by law in most industrialized countries. There is a growing body of evidence that exposure to DDT and DDE is associated with adverse health outcomes such as spontaneous

abortion, impaired neurodevelopment in children, breast cancer, diabetes and decreased semen quality (for review see Eskenazi et al.[5])

Effects on neurodevelopment

Organohalogens are transferred from mother to fetus via the placenta, and can be detected in cord blood.[6] Breastmilk is an additional route of exposure to organohalogens in the young infant.[7] During this critical period of neurodevelopment in both fetal life and early infancy, important processes as synaptogenesis and myelination take place that form the basis of later neurodevelopmental outcome. Organohalogens act as endocrine disrupters that affect the central nervous system, reproductive system and immunological system. They have, for example, been related to reproductive problems in male and female, obesity, diabetes, endocrine related cancers and thyroid and neurotransmitter disruption.[5, 8, 9] Particularly thyroid and neurotransmitter disruption are of importance as a potential route for neurodevelopmental impairments in children exposed to high levels of organohalogens.

Other endocrine disruptors

Various other POPs have emerged as endocrine disruptors in recent human studies. Phthalates, which are used as plasticizers, have anti-androgenic effects, and have shown to interfere with sex steroid and thyroid hormone levels.[10, 11] Phthalate metabolites can be measured in urine in virtually all human beings.[12] Bisphenol A (BPA) is used in the manufacture of polycarbonate plastics. Exposure occurs mostly through diet.[13] From animal studies, it was reported that BPA interfered with reproductive organ development and had adverse neurobehavioral effects.[13] Finally, perfluorinated compounds (PFCs), are fluorinated organic compound, which can also be detected in humans worldwide. As a potential endocrine disruptor, PFCs have been linked to the development of obesity.[14]

The relationship between POP exposure and neurodevelopmental toxicity in humans has been studied in many different populations across the world. Although the use of PCBs has been abandoned since ~30 years now, their presence in the environment, and thus their potential adverse effect on human development, still continues. The neurotoxic effect of brominated flame retardants, which more recently became of interest, has less extensively been studied in humans.

The aim of the present review was to provide an update on the relationship between various POPs such as organohalogens and childhood neurodevelopmental outcome from studies from the past 10 years. This review focuses on exposure to PCBs, OH-PCBs, PBDEs and DDE, and in addition on exposure to phthalates, BPA, and PFCs and neurodevelopmental outcome in childhood, up to 18 years of age.

METHODS

We used PubMed for identifying studies that analyzed the association between exposure to organohalogens and neurodevelopmental outcomes in infants. Our search strategy included a combination of three general search terms: chemical terms (PCB, polychlorinated biphenyl, OH-PCB, hydroxylated polychlorinated biphenyl, hydroxy polychlorinated biphenyls, PBDE, polybrominated diphenyl ether, DDE, dichlorodiphenyl dichloroethylene, organohalogen, organo chlorine, POPs, persistent organic pollutant, flame retardant, phthalate, BPA, bisphenol A, perfluorinated compound), a search term for neurodevelopmental outcome (neuro, neurotoxic, neurodevelopment, neurologic, neurobehavioural, motor development, motor repertoire, cognitive development, cognition, IQ, intelligence quotient, intelligence, neuropsychological, behavior, ADHD, attention deficit hyperactivity disorder, ASD, autism spectrum disorder, autism, attention, inattention, hyperactivity), and a search term for the study population (child, children, infant, infants, toddler, toddlers, neonate, school age, adolescent, prenatal exposure, postnatal exposure). This review is restricted to human studies, published during the last 10 years, and of which a full text was available on PubMed on the 1st of October 2014.

In this review we will focus on the effects of exposure to the following organohalogens: polychlorinated biphenyls (PCBs), hydroxylated PCBs (OH-PCBs), and polybrominated diphenyl ethers (PBDEs). In addition, the effects of exposure to the following chemicals will be described: phthalates, bisphenol A (BPA), and perfluorinated compounds (PFCs). We excluded dental studies on specific exposure to BPA by dental composite restorations, because the main focus of this review is environmental exposure to these chemicals in the general population.

RESULTS

Study results were grouped by the specific organohalogens studied. First, studies with short-term outcome will be discussed such as early infancy and toddler's age. Then studies that aimed to investigate long-term relationships will be described.

Effects of PCB and OH-PCB exposure

Table 1 gives an overview of the studies on the relationship between PCB and OH-PCB exposure on neurodevelopmental outcome and behavior in childhood.

Table 1. Studies on the effect of exposure to PCBs and OH-PCBs on neuro and behavioral development in infants

Reference	Location	Age at evaluation	Population	Number of infants	Outcome measure	Results	No(X), negative (-) or positive (+) effects on child-outcome [a]	Levels of compounds
Engel et al. 2007[15]	USA, New York City	1-5 days	General community	194	Brazelton Neonatal Behavioral Assessment Scale (NBAS)	- No adverse associations with prenatal Σ4PCB and any behavior, including habituation, orientation, motor development, range of state, autonomic stability and primitive reflexes.	X	Median (IQR) in µg/liter maternal serum Σ4PCBs: 0.8 (0.6-1.3) Σ4PCBs: 118, 153, 138 and 180
Sagiv et al. 2008[16]	USA, New Bedford, Massachusetts	2 weeks	Mothers residing near a PCB-contaminated harbor	542	NBAS	- Inverse associations between prenatal ΣPCB, Toxic Equivalency Quotient (TEQ)-PCB levels and quality of alert responsiveness and cost of attention ($p<0.10$); - Inverse associations between prenatal TEQ-PCB and consolability; - Inverse associations between ΣPCB, TEQ-PCB levels and self-quieting; - Positive association with TEQ-PCB and irritability; - Positive association with TEQ-PCB and spontaneous activity ($p=0.07$); - Inverse association ΣPCB and motor maturity ($p=0.06$);	- & +	Median (range) in ng/g cord serum Σ4PCBs: 0.19 (0.01-4.41) TEQ-PCB: Median (range) in pg/g lipid cord serum Mean ± SD: 6.75 ± 9.73 Range: 0-151.49 Σ4PCBs: 118, 153, 138 and 180 TEQ-PCB: TEF-weighted sum of mono-ortho PCB congeners 105, 118, 153, 167, and 189
Berghuis et al. 2013[17]	The Netherlands, northern part	3 months	General community	97	General movement assessment-Motor development by assessing the presence and performance of spontaneous movement patterns	- Inverse associations with prenatal 4-OH-PCB-107 levels and motor optimality score; - Inverse associations with prenatal PCB-187 levels and midline movements of arms and legs; - Positive associations with prenatal 4'-OH-PCB-172 levels and manipulation.	- & +	Median (IQR) in ng/g maternal serum 4-OH-PCB-107: 0.067 (0.039-0.102) (fresh weight) PCB-187: 11.8 (8.5-17.4) (lipid weight) 4'-OH-PCB-172: 0.017 (0.010-0.022) (fresh weight)

Table 1 continued

Reference	Location	Age at evaluation	Population	Number of infants	Outcome measure	Results	No(X), negative (-) or positive (+) effects on child-outcome [a]	Levels of compounds
Berghuis et al. 2014[18]	The Netherlands, northern part	3 months	General community	98	Touwen examination	- Positive correlations with prenatal PCB-146 and Optimality Score; - In boys, inverse correlations with 4-OH-PCB-107 and Optimality Score; - Positive associations with 9 PCBs and the sum of all PCBs and visuomotor and/or sensorimotor function; - Infants classified as 'non-optimal' had significantly lower prenatal exposure to PCB-105, PCB-118, PCB-138, PCB-146, PCB-153, PCB-156, PCB-187 and the sum of all the measured PCBs compared with infants classified as 'normal'.	- & +	Median (IQR) in ng/g in maternal serum; Two groups: 'normal' (n=62) versus 'non-optimal' scoring infants (n=36) PCB-146: normal: 9.0 (6.8–15.7) non-optimal: 5.2 (3.9–12.5) 4-OH-PCB-107 in boys: normal: 0.050 (0.030–0.085) non-optimal: 0.079 (0.045–0.113) ΣPCBs: normal: 318.8 (253.8–403.6) non-optimal: 244.0 (170.1–366.1) PCB-153: normal: 96.3 (77.7–126.1) non-optimal: 71.0 (47.9–110.0) ΣPCBs: 105, 118, 138, 146, 153, 156, 170, 180, 183 and 187
Doi et al. 2013[19]	Japan, Nagasaki	4 months	General community	29	Fixation patterns by observing upright and inverted biological motion (BM)	- Infants with a low-level of prenatal exposure to PCB-118 exhibited a preference for the upright BM over inverted BM, whereas those with a relatively high-level of exposure did not.	-	Mean ± SD in pg/g wet weight umbilical cord blood PCB-118: 3.9 ± 1.7
Nakajima et al. 2006[20]	Japan	6 months	General community	134	Bayley Scales of Infant Development (BSID-II)	- No negative associations between the total levels of PCBs and mental or motor development.	X	Median (range) in pg/g lipid in maternal blood Σ4Non-ortho PCBs: 85.5 (27.4-269.9) Σ8Mono-ortho PCBs: 11471.6 (2832.8-36382.2) Σ2Coplanar PCBs: 11554.7 (2860.2-36536.1) Σ4Non-ortho PCBs:77, 81, 126, 169 Σ8Mono-ortho PCBs:105, 114, 118, 123, 156, 157, 167, 189); Σ2Coplanar PCBs:170 en 180

Table 1 continued

Reference	Location	Age at evaluation	Population	Number of infants	Outcome measure	Results	No(X), negative (-) or positive (+) effects on child-outcome [a]	Levels of compounds
Pan et al. 2009[21]	USA, North Carolina	12 months	General community	231 Mullen; 218 CDI	- Mullen Scales of Early Learning; - Short Form: Level I (infant) of the MacArthur-Bates Communicative Development Indices.	- No consistent associations between lactational exposure to PCBs and the measures of infant development.	X	Median (range) in ng/g lipid in breast milk PCB-153: Milk: 17 (2–199) Mullen: 18 (2–199) CDI: 17 (2–199) ΣPCBs: Milk: 77 (9–708) Mullen: 79 (12–708) CDI: 79 (12–708) ΣPCBs: 66, 74, 99, 105, 118, 138–158, 146, 153, 156, 170, 177, 178, 180, 183, 187, 194, 196–203, and 199
Park et al. 2010[22]	Eastern Slovakia	16 months	Mother-infant pairs from two regions: Michalovce with high PCB contamination from a chemical manufacturing plant, and Svidnik with lower levels of PCBs	760 with maternal and 258 with cord samples	BSID-II	- Inverse associations maternal mono-ortho-substituted PCBs and scores on PDI and MDI; - Inverse associations cord mono-ortho-substituted PCBs and PDI; - inverse associations cord mono-ortho-substituted PCBs and MDI ($p = 0.05$); - No associations anti-estrogenic and di-ortho-substituted PCBs and cognitive scores; - Suggestive inverse association between cord di-ortho-substituted PCBs and PDI.	-	Median (IQR) in ng/mg lipids ΣMaternal dioxin-like mono-ortho-substituded PCBs: 0.021 (0.012-0.036) ΣCord dioxin-like substituted PCBs: 0.011 (0.005-0.028) ΣCord non-dioxin-like di-ortho-substituted PCBs: 0.380 (0.228-0.666) ΣDioxin-like mono-ortho-substituted PCBs: 118, and PCB-156 ΣNon-dioxin-like di-ortho-substituted PCBs: 138, 153, 170, and 180

Table 1 continued

Reference	Location	Age at evaluation	Population	Number of infants	Outcome measure	Results	No(X), negative (-) or positive (+) effects on child-outcome [a]	Levels of compounds
Park et al. 2009[23]	Eastern Slovakia	16 months	Mother-infant pairs from two regions: Michalovce with high PCB contamination from a chemical manufacturing plant, and Svidnik with lower levels of PCBs	147 with maternal and 80 with cord samples	BSID-II	- Inverse associations between cord 4-OH-CB-107 and MDI and PDI; - Inverse associations between maternal 4-OH-CB-107 and MDI but not PDI; - No inverse associations between other OH-PCB metabolites and PDI or MDI.	-	Median (IQR) in ng/g wet weight maternal/cord blood Cord 4-OH-CB-107: 0.012 (0.008-0.033) Maternal 4-OH-CB-107: 0.023 (0.014-0.041)
Roze et al. 2009[24]	The Netherlands, northern part	5-6 years	General community	62	- Movement-ABC; - Touwen's age-specific neurologic examination; - Developmental Coordination Disorder Questionnaire (DCD-Q); - Wechsler Preschool and Primary Scale of Intelligence, revised (WPPSI-R); - Subtests of the Neuropsychological Assessment (NEPSY-II); - Dutch version of the Rey's Auditory Verbal Learning Test (AVLT); - Subtests of Test of Everyday Attention for Children (TEACh) - Child Behavior Checklist (CBCL); - Teacher's Report Form; - an ADHD questionnaire	- PCB-153 correlated with less choreiform dyskinesia; - 4-OH-PCB-107 correlated with poorer fine manipulative abilities, better attention and better visual perception; - 4-OH-PCB-187 correlated with better attention.	+ & -	Median (range), PCB in ng/g lipid and OH-PCBs in pg/g fresh-weight maternal serum PCB-153: 63.0 (34.0–162.2) 4-OH-CB-107: 26.0 (5.4–102.3) 4-OH-CB-146: 103.3 (36.3–290.1) 4-OH-CB-187: 79.3 (35.8–180.5)

Table 1 continued

Reference	Location	Age at evaluation	Population	Number of infants	Outcome measure	Results	No(X), negative (-) or positive (+) effects on child-outcome [a]	Levels of compounds
Grandjean et al. 2012[25]	Faroe Islands	7 years	Mothers living in areas with suggested increased exposure to methylmercury and PCBs by the traditional habit of eating pilot whales and whale blubber.	917	- Subtests of Neurobehavioral Evaluation System (NES2); - Bender Visual Motor Gestalt Test; - Subtests of Wechsler Intelligence Scale for Children-Revised (WISC-R); - California Verbal Learning Test; - Boston Naming Test	- Prenatal exposure to the sum of major PCB congeners (118, 138, 153, and 180) was negatively associated with the Boston Naming test.; - Major PCB congeners (118, 138, 153, and 180), the calculated total PCB concentration, and the PCB exposure estimated in a structural equation model showed weak associations with test deficits; - No or weak effects between PCBs and joined motor and verbally mediated functions after adjustment for methylmercury, while mercury remained significant; - None of the outcomes were associated with the concurrent PCB concentration at 7 years.	-	Geometric mean (IQR) in µg/L in cord and in µg/g lipid in age-7 serum samples Cord-blood PCB: 1.86 (1.16–3.16) Age-7 serum-PCB: 1.71 (1.06–2.64) The sum of the three major congeners PCB-138, PCB-153, and PCB-180 multiplied by 2.0 was used as a surrogate for the total concentration of PCBs
Gray et al. 2005[26]	USA, 12 US study centers	7 years	Mothers from 12 different areas of the USA	894 (high versus low IQ groups)	WISC	- No inverse associations between prenatal PCB levels and IQ.	X	Mean (IQR) µg/liter in maternal PCB serum ∑11PCBs: 2.85 (2.00-4.02) ∑11PCBs: 28, 52, 74, 105, 118, 138, 153, 170, 180, 194, and 203
Sagiv et al. 2010[27]	USA, New Bedford, Massachusetts	7-11 years	Mothers residing near a PCB-contaminated harbor	573	Conners' Rating Scale for Teachers (CRS-T)	- A higher risk for ADHD-like behaviors at higher levels of PCBs; - The authors found higher risk of atypical behavior on the Conners' ADHD Index for the highest quartile of the sum of 4 PCB congeners versus the lowest quartile.	-	Median (range) in ng/g cord serum ∑4PCBs: 0.19 (0.01–4.41) ∑4PCBs: 118, 138, 153, and 180

Table 1 continued

Reference	Location	Age at evaluation	Population	Number of infants	Outcome measure	Results	No(X), negative (-) or positive (+) effects on child-outcome [a]	Levels of compounds
Sagiv et al. 2012[28]	USA, New Bedford, Massachusetts	8 years	Mothers residing near a PCB-contaminated harbor	578 CPT; 584 WISC-III	- NES2 Continuous Performance Test (CPT) - Components of WISC-III	- No or very weak associations between ΣPCB, mono-ortho PCB TEQ, and CPT and WISC-III outcomes; - Boys with higher exposure to ΣPCB had a higher rate of errors of omission and slower WISC-III Processing Speed; - For girls, associations were in the opposite direction for the CPT and null for the WISC-III; - Boys had considerably longer mean reaction time with increasing exposure, particularly for the ΣPCB and the opposite was observed in females; - Higher variability in reaction time in males with increasing exposure to Σ4PCB, mono-*ortho*PCB TEQ.	-	Median (range) in ng/g cord blood Σ4PCB: 0.19 (0.01-2.59) PCB TEQ (pg/g lipid): 0.89 (0.00-26.56) Σ4PCB: 118, 138, 153, and 180
Stewart et al. 2008[29]	USA, Great Lakes region of the northeastern	9 years	Infants living in the Great Lakes region of the northeastern United States	156	WISC-III	- Inverse associations between prenatal PCB levels and Full Scale IQ and Verbal IQ.	-	Median (IQR)in ng/g wet weight placental tissue PCB: 1.50 (1.00-2.06)
Boucher et al. 2012[30]	Arctic Québec, Canada	8.5-14.5 years	Population with high consumption of fish and sea mammals because of traditional Inuit diet	279	- Teacher Report Form (TRF) from the CBCL - Disruptive Behavior Disorders Rating Scale (DBD)	- No associations between cord and child blood PCB levels and behavioral problems reported by teachers.	X	Median (range) in µg/kg fat cord or child blood Cord PCB-153: 93.6 (9.7-653.6) Current PCB-153: 45.9 (3.5-809.5)

Table 1 continued

Reference	Location	Age at evaluation	Population	Number of infants	Outcome measure	Results	No(X), negative (-) or positive (+) effects on child-outcome [a]	Levels of compounds
Boucher et al. 2012[31]	Arctic Québec, Canada	9.8-12.9 years	Population with high consumption of fish and sea mammals because of traditional Inuit diet	196	Visual go/no-go response inhibition paradigm	- Current plasma PCB-153 levels were associated with slower reaction times to go trials and with reduced amplitudes of the Pe/Pc components on EEG; - Cord plasma PCB-153 levels were not associated with any of the behavioral measures.	-	Median (range) in µg/kg fat cord/ plasma Cord plasma PCB-153: 93.3 (9.7-653.6) Current plasma PCB-153: 45.7 (3.5-431.4)
Newman et al. 2009[32]	St. Lawrence River and spanning the boundaries of New York State, and Ontario and Quebec, Canada	10-17 years	Living in an area lying on both sides of the St. Lawrence River and spanning the boundaries of New York State, and Ontario and Quebec, Canada. Several industrial complexes are lying close to the area.	271	- Non-verbal Ravens Progressive Matrices; - Test of Memory and Learning; - Woodcock Johnson-Revised	- Dioxine-like congeners were negatively associated with scores on the Ravens test - All four congener groupings were negatively associated with two measures of long-term memory - The persistent congener group was negatively associated with Auditory Processing - Almost all congeners associated with cognitive outcomes were non-dioxin-like and ortho-substituted - The low-persistent congener group was associated with Comprehension-Knowledge	-	Median (range)in parts per billion in blood of adolescents ∑Dioxin-like PCBs: 0.10 (0.05-0.45) ∑Non-dioxin-like PCBs: 0.52 (0.24-2.52) ∑Persistent PCBs: 0.36 (0.15-2.45) ∑Low-persistent PCBs: 0.22 (0.11-1.22) ∑Dioxin-like PCBs: in >50% of the sample, 105, 118, and 149[+123] ∑Non-dioxin-like PCBs: in >50% of the sample, 52, 70, 84, 74, 87, 95, 99, 101[+90], 110, 138[+163+164], 153, 180 ,and 187 ∑Persistent PCBs: in >50% of the sample, 74, 99, 105, 118, 138[+163+164], 153, 180, and 187 ∑Low-persistent PCBs: in > 50% of the sample, 52, 70, 84, 95, 110, 101[+90], and 87

Table 1 continued

Reference	Location	Age at evaluation	Population	Number of infants	Outcome measure	Results	No(X), negative (-) or positive (+) effects on child-outcome [a]	Levels of compounds
Lee et al. 2007[33]	USA	12-15 years	US civilian population, participants of National Health and Nutrition Examination Survey (NHANES)	278	Learning disability or attention deficit disorder	- No associations between PCB-126 and learning disability or attention deficit disorder.	X	Median (IQR) in ng/g of lipid child serum PCB-126: 9.1 (6.7-20.6)

[a] Negative effects on child outcome indicates poorer outcome, whereas positive effects indicates better outcome.

Exposure to PCBs and OH-PCBs and outcome in young infants

Studies on the exposure to PCBs and OH-PCBs and outcome in young infants show a wide variety of findings: some report no associations, others inverse and positive associations. In a cohort study performed in New York City, no associations were found between prenatal PCB levels and behavioral outcomes including habituation, orientation, motor development, range and regulation of state, autonomic stability and primitive reflexes at the age of 1-5 days.[15] A cohort study which included pregnant women near a PCB-contaminated harbor in the USA, reported inverse associations between prenatal PCB levels and quality of alertness, cost of attention, consolability, and self-quieting.[16] In this cohort, positive associations were reported for exposure to PCBs and irritability and spontaneous activity. Motor maturity of the infants appeared to decline with increasing prenatal PCB levels.

In three-month-old infants in a Dutch cohort, inverse associations were found between prenatal 4-OH-PCB-107 and motor development by assessing spontaneous movement patterns.[17] Also inverse associations were observed between prenatal PCB-187 levels and midline movements of arms and legs. In contrast, positive associations were found between prenatal 4'-OH-PCB-172 and manipulation. Regarding neurological functioning at three months, positive associations were found between prenatal PCB exposure and neurological functioning, especially on visuomotor and sensorimotor functions.[18] An inverse correlation was observed between 4-OH-PCB-107 levels and neurological functioning in boys. This suggests that boys might be more susceptible for exposure to these chemicals compared to girls.

In four-month-old Japanese infants, included in a cohort of 29 infants, prenatal exposure to PCB-118 was related to fixation duration on biological motion stimuli.[19] Preferential looking patterns towards biological motion stimuli were observed as a hallmark of socio-cognitive development, and the results suggest that prenatal PCB-118 exposure may have an adverse effect on early social development. In 6-month-old infants of another Japanese cohort, no associations were found between exposure to PCBs and mental and motor development.[20] In 12-month-old infants living in the USA, no consistent associations were observed between lactational exposure to PCBs and the cognitive and motor development and parental reported language comprehension and production.[21]

In a large cohort study in Eastern Slovakia, inverse associations were found between prenatal exposure to PCBs and scores on psychomotor and mental development at the age of 16 months.[22] Dioxin-like mono-ortho-substituted PCBs, measured in maternal and cord blood samples, were negatively associated with psychomotor developmental index (PDI) and mental developmental index (MDI). Regarding anti-estrogenic and non-dioxine-like di-ortho-substituted PCBs, no associations were found with cognitive scores. Nearly significant inverse associations were observed between cord blood di-ortho-substituted PCBs and PDI. In the same cohort, the authors reported negative associations between cord blood 4-OH-

PCB-107 levels and a lower MDI and PDI at the age of 16 months.[23] Maternal 4-OH-PCB-107 was associated with a lower MDI, but not with a lower PDI. No other measured OH-PCBs were associated with a decreased MDI or PDI.

Exposure to PCB and OH-PCBs and outcomes during school age

Several studies have been performed on the effects of PCB-exposure during school-age. At the age of 5-6 years, Roze et al reported in a Dutch cohort that prenatal exposure to PCB-153 correlated with less choreiform dyskinesia and poorer behavioral outcome, particularly externalizing behavior.[24] Regarding effects of hydroxylated compounds in the same cohort, prenatal exposure to 4-OH-PCB-107 correlated with poorer fine manipulative abilities, better attention and better visual perception, and exposure to 4-OH-PCB-187 also correlated with better attention at the age of 5-6 years. A the age of 7 years, in a Faroese birth cohort with relatively high PCB and methylmercury exposure by the traditional habit of eating pilot whales and whale blubber, negative associations were found between prenatal exposure to PCBs and the Boston Naming test.[25] After adjustment for methylmercury exposure, the significance disappeared, while the effect of methylmercury remained significant. These results would suggest that PCB neurotoxicity may be difficult to detect in the presence of elevated methylmercury exposure.

In a collaborative perinatal project in the USA, analyses on 894 infants showed no inverse associations between prenatal exposure to PCBs and Intelligence quotient (IQ) at the age of 7 years.[26] A study performed in a cohort residing near a PCB-contaminated harbor in the USA, showed a higher risk for attention deficit hyperactivity disorder (ADHD)-like behavior at the age of 7-11 years after exposure to higher prenatal PCB levels.[27] In the same cohort, no or very weak associations were found between PCB exposure and attention and impulse control for all children at the age of 8 years.[28] Among boys only, higher exposure to PCB had a higher rate of errors of omission, longer mean reaction time and higher variability in reaction time and slower processing speed on Wechsler Intelligence Scale for Children (WISC). For girls, associations were in the opposite direction for outcomes on the Continuous Performance Test (CPT) and PCB exposure was not associated with the WISC-III. These findings suggest more susceptibility for boys compared to girls regarding the impact of prenatal exposure to PCBs.

Inverse associations between prenatal PCB levels and full scale IQ and verbal IQ at the age of 9 years were observed in an American cohort.[29] In a cohort of Inuit children living in Arctic Quebec, Canada, no associations were found between cord and child blood PCB levels and behavioral problems in children at the age of 8-14 years reported by teachers.[30] In the same cohort, the current plasma levels of PCB-153 were associated with slower reaction times and with reduced amplitudes of the Pe/Pc response-related potentials.[31] These findings suggest that postnatal PCB exposure can affect processes associated with

error monitoring, an aspect of behavioral regulation required for adequately adapting to the changing demands of the environment.

In a cohort of children at the age of 10-17 years, PCB levels measured in blood samples during infancy were associated with cognitive functioning.[32] In this study, almost all congeners associated with cognitive outcomes were non-dioxin-like and ortho-substituted. All four PCB congener groups (dioxin-like, nondioxin-like, persistent, and non-persistent) were negatively associated with long-term memory. Scores on the Ravens test were negatively associated only with dioxin-like congeners, and auditory processing was related only to the persistent congener group. The non-persistent group of compounds was associated with three cognitive test scores (Delayed Recall, Long Term Retrieval and Comprehension-Knowledge). In an American cohort, however, no associations were found between exposure to PCB-126 and learning disability or attention deficit disorders at the age of 12-15 years.[33]

In conclusion, several studies have been performed on the effects of PCBs and OH-PCBs on developmental outcome in children. Most studies reported mainly negative effects of exposure to these compounds, whereas a few others reported no or positive effects. It appears from some studies that boys may be more vulnerable than girls to the effects of PCB exposure.

Effects of exposure to PBDEs

Exposure to PBDEs and outcome in young infants

Several studies have been performed on the effects of PBDEs on neurodevelopment in young infants as shown in Table 2. Increasing PBDE concentrations were nearly significantly associated with decreasing MDI in 12-18 month old Spanish infants, but there was little evidence for an association with PDI.[34] In a cohort recruited to measure the extent and effects of prenatal exposure to contaminants (including PBDEs) that were potentially released by the destruction of the World Trade Centre towers in the United States, inverse associations were found between prenatal exposure to BDE-47, BDE-99 and BDE-100 and mental and psychomotor development at the age of 12-48 months.[35] At the age of 48 months, BDE-47, BDE-99 and BDE-100 were inversely associated with full-scale and verbal IQ. Prenatal exposure to BDE-100 was also inversely associated with performance IQ at the age of 48 and 72 months. In another American cohort, higher lactational exposure to BDEs 47, 99, and 100 was associated with increased externalizing behavior problems, specifically activity/impulsivity behaviors at the age of 30 months.[36] In another study, however, no differences in PBDE levels were found between children with autism/autism spectrum disorder (ASD) and developmental delay, and controls with typical development at the age of 24-60 months.[37] In a cohort study on the effects of prenatal exposure to PBDEs on mental, psychomotor, intelligence and behavior in toddlers, BDE-47 was not associated with mental or psychomotor development at the age of 1-3 years.[38] At the age of 5 years, prenatal BDE-47 was inversely associated with intelligence, and positively associated with hyperactivity.

Table 2. Studies on the effect of exposure to PBDEs on neuro and behavioral development in infants

Reference	Location	Age at evaluation	Population	Number of infants	Outcome measure	Results	No(X), negative (-) or positive (+) effects on child-outcome [a]	Levels of compounds
Gascon et al. 2012[34]	Spain	12-18 months	General community	290	- Bayley Scales of Infant Development (BSID)	- Increasing Σ7PBDEs concentrations showed an association of borderline statistical significance with decreasing MDI; -BDE-209 appeared to be the main congener responsible for this association, after adjustment for other POPs, this association became slightly weaker; - Little evidence for an association with PDI.	-	Median (range) in ng/g lipid colostrum Σ7PBDEs: 4.05 (0.31-32.66) BDE-209: 1.02 (0.04 6.49) Σ7PBDEs: 47, 99, 100, 153, 154, 183, 209
Herbstman et al. 2010[35]	USA, lower Manhattan, New York	12, 24, 36, 48 and 72 months	Mothers pregnant on 11 September 2001, and delivered at a hospital approximately 2 miles or within a half-mile from the World Trade Centre site.	118, 117, 114, 104, and 96 infants	- BSID-II; - Wechsler Preschool and Primary Scale of Intelligence, Revised Edition (WPPSI-R);	- Inverse associations BDE-47 and PDI at 12 months; - Inverse associations BDE-47, 99, and 100 and MDI at 24 months; - Inverse associations BDE-100 and MDI at 36 months; - Inverse associations BDE-47, 99, and 100 and full-scale and verbal IQ at 48 months; - Inverse associations BDE-100 and performance IQ at 48 months; - Inverse associations BDE-100 and performance IQ at 72 months.	-	Median, in ng/g lipid cord blood BDE-47: 11.2 BDE-99: 3.2 BDE-100: 1.4
Hoffman et al. 2012[36]	USA, North Carolina	30 months	General community	222	- Infant-Toddler Social and Emotional Assessment (ITSEA)	- BDEs 47, 99, and 100 positively associated with externalizing behaviors, specifically activity/impulsivity behaviors; - PBDEs were not associated with other social and emotional developmental domains.	-	Median (range) in ng/g lipid breastmilk BDE-28: 2.2 (ND-49.6) BDE-47: 28.7(4.0-1430.0) BDE-99: 5.5 (ND-299.0) BDE-100: 5.3 (ND-188.0) BDE-153: 5.6 (ND-229.0)

Table 2 continued

Reference	Location	Age at evaluation	Population	Number of infants	Outcome measure	Results	No(X), negative (-) or positive (+) effects on child-outcome [a]	Levels of compounds
Hertz-Picciotto et al. 2011[37]	USA, California	24-60 months	Infants included in a cohort study on Childhood Autism Risk from Genetics and the Environment	94	- Diagnoses of autism using the Autism Diagnostic Observation Schedule and Autism Diagnostic Inventory-Revised; - Mullen's Scales of Early Learning; - Vineland Adaptive Behavior Scales	- No differences in PBDE exposure between children with autism/ autism spectrum disorder and developmental delay, and typically developing controls.	X	Median (IQR) in ng/g lipids blood samples of the infants after diagnosis *AU/ASD (n=49)* BDE-28: 1.11 (0.61-2.13); BDE-47: 63.39 (34.36-117.18); BDE-66: 0.45 (0.23-0.87); BDE-85: 2.60 (1.54-4.75); BDE-99: 20.38 (12.90-39.40); BDE-100: 20.86 (11.14-39.78); BDE-153: 17.55 (8.60-34.20); BDE-183: 0.63 (0.45-0.84); BDE-197: 1.26 (0.71-2.60); BDE-207: 2.15 (1.71-2.80); BDE-209: 2.96 (1.88-4.84)
Chen et al. 2014[38]	USA, Cincinnati, Ohio	1-5 years	General community	119 BSID-II; 190 WPPSI; 194 BASC-II	- Bayley Scales for Infant Development (BSID-II); - Wechsler Intelligence Scale for Children (WISC-III); - Behavior Assessment System for Children (BASC-II)	- No associations between prenatal BDE-47 and MDI or PDI at 1-3 years; - Inverse association between prenatal BDE-47 and Full-Scale IQ at 5 years; - Positive association between prenatal BDE-47 and hyperactivity score at 5 years.	-	Geometric mean (geometric SD) in ng/g lipid maternal serum BDE-47: 20.1 (2.61)

Table 2 continued

Reference	Location	Age at evaluation	Population	Number of infants	Outcome measure	Results	No(X), negative (-) or positive (+) effects on child-outcome [a]	Levels of compounds
Roze et al. 2009[24]	The Netherlands, northern part	5-6 years	General community	62	- Movement-ABC; - Touwen's age-specific neurologic examination; - Developmental Coordination Disorder Questionnaire (DCD-Q); - Wechsler Preschool and Primary Scale of Intelligence, revised (WPPSI-R); - Subtests of the Neuropsychological Assessment (NEPSY-II); - Dutch version of the Rey's Auditory Verbal Learning Test (AVLT) - Subtests of Test of Everyday Attention for Children - Child Behavior Checklist (CBCL); - Teacher's Report Form; - an ADHD questionnaire	- PBDE correlated with poorer fine manipulative abilities, poorer attention, and with better coordination, better visual perception, and better behavior.	+ & -	Median (range) in ng/g lipid maternal serum BDE-47: 0.9 (< LOD-6.1) BDE-99: 0.2 (< LOD-2.1) BDE-100: 0.2 (< LOD-1.4) BDE-153: 1.6 (0.3-19.7) BDE-154: 0.5 (0.1-3.5)

Table 2 continued

Reference	Location	Age at evaluation	Population	Number of infants	Outcome measure	Results	No(X), negative (-) or positive (+) effects on child-outcome [a]	Levels of compounds
Eskenazi et al. 2013[39]	USA, California	5 and 7 years	Predominantly Mexican-American families in California's Salinas Valley, participants of the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS)	310 (5 y) and 323 (7 y)	At 5 years: - CBCL - Conners' Kiddie Continuous Performance Test (K-CPT) At 7 years: - Conners' ADHD/ DSM-IV Scales (CADS); - BASC-II.	- Maternal prenatal PBDE levels were associated with impaired attention as measured by a CPT at 5 years and maternal report at 5 and 7 years of age, with poorer fine motor coordination at both age points, and with decrements in Verbal and Full-Scale IQ at 7 years; - PBDE levels in 7-year-old infants were (nearly) significantly associated with concurrent teacher reports of attention problems and decrements in Processing Speed, Perceptual Reasoning, Verbal Comprehension, and Full-Scale IQ.	-	Median (range)in ng/g lipids maternal or infant serum Maternal ∑4PBDE: 24.9 (2.6-1293.7) Infant ∑4PBDE: 84.6 (5.8-1308.5) ∑4PBDE: 47, 99, 100, and 153
Kicinski et al. 2012[40]	Belgium	13.6-17 years	Living in two industrial areas (Genk and Menen) and from the general Flemish population	515	Neurobehavioral Evaluation System (NES-3)	- Sum of PBDEs was associated with a decrease of the number of taps with the preferred-hand in the Finger Tapping test; - The effects of the individual PBDE congeners on the motor speed were consistent.	-	Median (max) in ng/L serum ∑4PBDE: 7 (125) ∑PBDE: 47, 99, 100, and 153

[a] Negative effects on child outcome indicates poorer outcome, whereas positive effects indicates better outcome.

Exposure to PBDEs and outcomes during school age

At school age, prenatal PBDE levels correlated with poorer fine manipulative abilities, poorer attention, better coordination, better visual perception, and better behavior in a Dutch cohort.[24] In an American cohort, prenatal PBDE levels were associated with impaired attention at 5 and 7 years, with poorer fine motor coordination, and with decrements in intelligence at 7 years.[39] PBDE levels at the age of 7 years were significantly or marginally associated with teacher reported attention problems and decrements in processing speed, perceptual reasoning, verbal comprehension, and full-scale IQ. A Belgian study including 515 infants reported that PBDE exposure was associated with changes in the motor function, a decrease of the number of taps with the preferred-hand in the Finger Tapping test, at the age of 13-17 years.[40]

In conclusion, prenatal exposure to PBDEs, among other relationships, was associated with poorer mental development, poorer psychomotor development and lower IQ at pre-school age, and poorer attention at school age in multiple studies.

Effects of exposure to DDE

Regarding DDE exposure, several studies reported on the effects of exposure to DDE on neurological and behavioral outcomes as shown in Table 3.

In a cohort of 194 infants living in New York City, no inverse associations were observed between prenatal DDE-levels and behavioral outcomes including habituation, orientation, motor development, range and regulation of state, autonomic stability and primitive reflexes at the age of 1-5 days.[15] In another American cohort of 542 infants, higher prenatal DDE exposure was associated with more irritability, and with more frequently the situation that the infant is never in the state for assessment of the orientation items.[16] During follow-up of the infants at school age, the authors found a higher risk for ADHD-like behaviors assessed by their teachers.[27] No or very weak associations were found between prenatal DDE levels and neuropsychological measures of attention, impulse control, processing speed and freedom from distractibility in the infants at the age of 8 years.[28]

In a Mexican cohort of 244 infants aged 1-12 months, DDE-levels measured during the first trimester of pregnancy were found to be associated with a significant reduction in PDI during the first year of life.[41] The mothers were living in regions where DDT was used until 1998 to combat endemic malaria. No associations were observed between levels measured during the second and third trimester of pregnancy and PDI, suggesting that the critical window of exposure to DDE might be the first trimester of pregnancy. Prenatal exposure to DDE was not found to be related to MDI, suggesting that the compound DDE has mainly effects on psychomotor and not on mental development. During follow-up of the cohort at the age of 18, 24 and 30 months, the authors found no associations between prenatal DDE and PDI or MDI anymore.[42]

In an American cohort of 1142 infants aged 8 months, prenatal DDE-levels were not found to be related to MDI or PDI.[43] In another cohort of a Mexican-American population living in agricultural areas, inverse associations were found between DDE levels and PDI at the age of 6 months.[44] These associations were not observed at the age of 12 or 24 months, suggesting that it might be a temporarily effect which does not persist during later in life. No associations were observed between prenatal DDE-levels and MDI, again suggesting that DDE might have more effects on psychomotor than mental development.

In an American cohort, lactational exposure to DDE was not associated with measures of infant development at 12 months.[21] In boys, DDE exposure was inversely associated with gross motor function. These results suggest that DDE might affect motor development more than other functions, and also that DDE might affect especially the development in males. In a Dutch cohort, prenatal DDE levels correlated with less choreiform dyskinesia at school age. Prenatal DDE exposure was not related to other motor performances, or cognitive or behavioral outcomes.[24] In a study on the Faroese Islands on the effects of exposure to PCBs on neurobehavioral defects at school age, DDE levels have also been measured for analyses as independent exposure indicator.[25] Prenatal DDE levels were significantly associated with the continuous performance test and the naming test outcome at the age of 7 years. The DDE levels correlated closely with PCB levels, and did not reveal any clear indication of neurotoxicity independent of PCB-associated deficits. In 12-15 year old infants living in the USA, no associations were found between exposure to DDE and learning disabilities or attention deficit disorders.[33]

In conclusion, some of the studies reported inverse associations between DDE exposure and outcome, while others found no associations. Significant relations were particularly found at early infancy on psychomotor development and on attention and ADHD, whereas at school age no adverse relationships were reported.

Table 3. Studies on the effect of exposure to DDEs on neuro and behavioral development in infants

Reference	Location	Age at evaluation	Population	Number of infants	Outcome measure	Results	No(X), negative (-) or positive (+) effects on child-outcome [a]	Levels of compounds
Engel et al. 2007[15]	USA, New York City	1-5 days	General community	194	Brazelton Neonatal Behavioral Assessment Scale (NBAS)	- No adverse associations with prenatal DDE levels and any behavior, including habituation, orientation, motor development, range of state, autonomic stability and primitive reflexes.	X	Median (IQR) in µg/liter maternal serum DDE: 0.6 (0.4-1.3)
Sagiv et al. 2008[16]	USA, New Bedford, Massachusetts	2 weeks	Mothers residing near a PCB-contaminated harbor	542	NBAS	- Inverse associations between DDE levels and self-quieting; - Positive association with DDE and irritability; - Positive association with DDE and the state that the infants are never in the state for assessment of orientation items on the NBAS.	-	Median (range) in ng/g cord serum DDE: 0.30 (0-10.29)
Torres-Sanchez et al. 2007[41]	Mexico	1, 3, 6, and 12 months	Residents in regions where DDT was used until 1998 to combat endemic malaria.	244	Bayley Scales for Infant Development (BSID-II)	- Inverse associations only between DDE levels during the *first* trimester of pregnancy and PDI; - No associations between DDE and MDI.	-	Geometric mean (geometric SD) in ng/mL maternal serum DDE: 1st trimester: 6.4 (2.8) 2nd trimester: 6.8(2.9) 3th trimester: 7.8 (2.8)
Jusko et al. 2012[43]	USA, 12 US study centers	8 months	Mothers from 12 different areas of the USA	1142	BSID	- No associations between prenatal DDE levels and MDI or PDI.	X	Median (range) in µg/L wet weight maternal serum DDE: 24.5 (3.1 - 178.1)
Eskenazi et al. 2006[44]	USA, California	6, 12, and 24 months	Primarily Mexican farm-worker families, living in agricultural Salinas Valley	330 (6m); 327 (12m); 309 (24m)	BSID	- Inverse associations between DDE levels and PDI at 6 months; - No associations between DDE and PDI at 12 or 24 months; - No association with DDE levels and MDI.	-	Geometric mean (range) in ng/g lipid maternal serum DDE: 1436.9 (48.80–159)

Table 3 continued

Reference	Location	Age at evaluation	Population	Number of infants	Outcome measure	Results	No(X), negative (-) or positive (+) effects on child-outcome [a]	Levels of compounds
Pan et al. 2009[21]	USA, North Carolina	12 months	General community	231 Mullen and 218 CDI	- Mullen Scales of Early Learning; - Short Form: Level I (infant) of the MacArthur-Bates Communicative Development Indices.	- No consistent associations between lactational exposure to DDE and the measures of infant development. - In boys, inverse associations between DDE and scoring on the gross motor scale of the Mullen.	-	Median (range) in ng/g lipid breast milk DDE: 121 (1-2,140) Mullen: 117 (15-2,140) CDI: 117 (15-2,140)
Torres-Sanchez et al. 2009[42]	Mexico	12, 18, 24 and 30 months	General community	270	- BSID-II	- No associations between prenatal DDE and MDI or PDI at 18, 24 or 30 months.	X	Mean ± SD in ng/ml maternal serum DDE: 1st trimester (n=244) 6.3±3.1 2nd trimester (n=153) 6.5±3.0 3rd trimester (n=160) 7.9±2.8
Roze et al. 2009[24]	The Netherlands, northern part	5-6 years	General community	62	- Movement-ABC; - Touwen's age-specific neurologic examination; - Developmental Coordination Disorder Questionnaire (DCD-Q); - Wechsler Preschool and Primary Scale of Intelligence, revised (WPPSI-R); - Subtests of the Neuropsychological Assessment (NEPSY-II); - Dutch version of the Rey's Auditory Verbal Learning Test (AVLT) - Subtests of Test of Everyday Attention for Children - Child Behavior Checklist (CBCL); - Teacher's Report Form; - an ADHD questionnaire	- DDE correlated with less choreiform dyskinesia; - No associations between prenatal DDE and other motor, cognitive and behavioral outcomes.	+	Median (range) in ng/g lipid maternal serum DDE: 94.7 (17.5-323.8)

Table 3 continued

Reference	Location	Age at evaluation	Population	Number of infants	Outcome measure	Results	No(X), negative (-) or positive (+) effects on child-outcome [a]	Levels of compounds
Grandjean et al. 2012[25]	Faroe Islands	7 years	Mothers living in areas with increased exposure to methylmercury by the traditional habit of eating pilot whales, the meat which contains high mercury concentrations. Mothers with suggested increased exposure to PCBs by eating whale blubber in which PCBs can accumulate.	917	- Subtests of the Neurobehavioral Evaluation System (NES2) - Bender Visual Motor Gestalt Test; - Subtests of Wechsler Intelligence Scale for Children-Revised (WISC-R); - California Verbal Learning Test ; - Boston Naming Test	- DDE was significantly associated with the CPT and the Naming test outcome; - Cord DDE levels correlated closely with PCB and did not reveal any clear indication of neurotoxicity independent of PCB-associated deficits (shown in Table 1)	-	Cord DDE: Data not available
Sagiv et al. 2010[27]	USA, New Bedford, Massachusetts	7-11 years	Mothers residing near a PCB-contaminated harbor	573	Conners' Rating Scale for Teachers (CRS-T)	- A higher risk for ADHD-like behaviors at higher levels of DDE; - Higher risk of atypical behavior on the Conners' ADHD Index for the highest quartile of DDE versus the lowest quartile.	-	Median (range) in ng/g cord serum DDE: 0.31 (0.00–14.93)

Table 3 continued

Reference	Location	Age at evaluation	Population	Number of infants	Outcome measure	Results	No(X), negative (-) or positive (+) effects on child-outcome [a]	Levels of compounds
Sagiv et al. 2012[28]	USA, New Bedford, Massachusetts	8 years	Mothers residing near a PCB-contaminated harbor	578 CPT; 584 WISC-III	- NES2 Continuous Performance Test (CPT); - Components of the WISC-III	- No or very weak associations between DDE and CPT and WISC-III outcomes; - Boys with higher exposure to DDE had a higher rate of errors of omission; - For girls, associations were in the opposite direction for the CPT and null for the WISC-III; - No associations between prenatal DDE and Processing Speed or Freedom from Distractibility; - Higher variability in reaction time in males with increasing exposure to DDE.	- & +	Median (range) in ng/g cord blood DDE: 0.31 (0.00–14.93)
Lee et al. 2007[33]	USA	12-15 years	US civilian population, participants of National Health and Nutrition Examination Survey (NHANES)	278	Learning disability or attention deficit disorder	- No associations between DDE and learning disability or attention deficit disorder.	X	Median (IQR)in ng/g of lipid child serum DDE: Group Non-detectable POPs (<50th): 75.3 (49.0–98.4) Group Detectable POPs (>50th): 278 (186–528)

[a] Negative effects on child outcome indicates poorer outcome, whereas positive effects indicates better outcome.

Effects of exposure to other chemical compounds

Effects of exposure to phthalates

During the last decade, several studies have been performed on the effects of exposure to phthalates and/or their metabolites on neurodevelopment. Many sex-specific effects have been observed. In boys, higher exposure to phthalates or their metabolites was found to be associated with improved motor performance,[45] more non-optimal reflexes,[46] lower MDI,[47] higher PDI,[47, 48] a decrease in masculine play score,[49] and lower vocabulary scores on the WISC.[50] In girls, higher exposure to phthalates or their metabolites were found to be associated with lower Orientation and Quality of Alertness scores,[45] and lower MDI.[48, 51]

Besides the previous mentioned sex-specific effects, higher exposure to phthalates and/or their metabolites were found to be associated with improved behavioral organization,[46] higher PDI and MDI at 6 months,[47] and lower PDI at 3 years.[51] Increased exposure to low molecular weight phthalate metabolites were found to be associated with poorer scores on the aggression, conduct problem, attention problems, and depression clinical scales, externalizing problems, and behavioral symptom index composite scales.[52] In addition, increased exposure to low molecular weight phthalates was found to be associated with poorer scores on global executive composite index, and the emotional control scale. Finally, increased exposure to phthalates is also found to be negatively associated with Full Scale IQ and Verbal IQ scores, and children's vocabulary subscores.[50] In children with ASD, significant increase in urinary levels of 5-OH-MEHP [mono-(2-ethyl-5-hydroxyhexyl) 1,2-benzenedicarboxylate] and 5-oxo-MEHP [mono-(2-ethyl-5-oxohexyl) 1,2-benzenedicarboxylate] were detected. Testa et al. reported that the metabolite 5-oxo-MEHP showed 91.1% specificity in identifying children with ASD.[53] These findings suggest a possible role for phthalates in the pathogenesis of ASD. Park et al. studied the effect of phthalate exposure on neuropsychological performance in children with ADHD, and whether this effect was affected by genotype-phthalate interaction.[54] In infants with the DRD4 4/4 genotype(dopamine receptor D4, a polymorphism on a major candidate gene for ADHD), associations were found between phthalate metabolite levels and the number of omission errors, the number of commission errors, and the response time variability scores on the Continuous Performance Test (CPT). Regarding their findings, the authors suggest a possible association between phthalate metabolite levels and poor attentional performances in children with ADHD, as well as a genetic influence on this association.

In conclusion, sex-specific effects have been reported after exposure to phthalates and their metabolites. Phthalates might possibly play a role in the pathogenesis of ASD. A genetic influence is suggested for the association between phthalate exposure and attentional problems in children with ADHD.

Effects of exposure to bisphenol A

Several studies have been performed to determine the possible effects of exposure to BPA on child development, paying special attention to sex-specific effects of this compound. Prenatal exposure to BPA was not found to be associated with neurobehavior at the age of 5 weeks.[46] Higher gestational BPA exposure was found to be associated with more anxious and more depressed behavior, poorer emotional control and inhibition of the children at the age of 3 years, especially in girls.[55] Conversely, Perera et al. reported more problems in boys than girls regarding behavior at the age of 3-5 years using the Child Behavior Checklist (CBCL).[56] Among boys, higher prenatal exposure to BPA was associated with higher scores, indicating more problems, on emotionally reactive and aggressive behavior syndrome scales. Among girls, higher exposure was found to be associated with lower scores on anxious or depressed and aggressive behavior. Harley et al. reported associations between higher prenatal urinary BPA levels and internalizing problems in boys, including anxiety and depression at the age of 7 years.[57] Among girls, no associations were found between prenatal BPA levels and behavior, but higher childhood urinary BPA levels were found to be associated with externalizing behavioral problems, including conduct problems. Childhood urinary BPA levels were also found to be associated with internalizing behavioral problems and inattention and hyperactivity in boys and girls. In conclusion, exposure to BPA was found to be associated with child behavior, affecting boys and girls differently.

Effects of exposure to perfluorinated compounds

PFCs such as perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) and its potential relationship with neurodevelopmental outcome in humans have not extensively been studied. A study in 7-year-old children found no associations between maternal levels of PFOS or PFOA and higher scores on the Strengths and Difficulties Questionnaire or Developmental Coordination Disorder Questionnaire.[58] Because exposure to perfluorinated compounds are suggested to induce attention problems during infancy, several studies have been performed on this subject recently. Stein et al. reported that children in the highest quartile as compared with the lowest quartile of estimated in utero PFOA had higher Full Scale IQ, and less characteristics of attention deficit/hyperactivity at the age of 6-12 years.[59] In a cohort of 10,546 children aged 5-18 years, Stein et al observed an inverted J-shaped association between PFOA and ADHD, with a small increase in prevalence for the second quartile of exposure compared with the lowest, and a decrease for the highest versus lowest quartile.[60] In contrast, Ode et al. reported no associations between exposure to perfluorinated compounds and ADHD.[61] In conclusion, the few studies performed so far found no or inverse associations between exposure to perfluorinated compounds and characteristics of attention deficit/hyperactivity at school age.

DISCUSSION

This review shows that exposure to POPs has effects on neurodevelopmental outcome in children. Regarding exposure to PCBs and OH-PCBs, most studies report inverse associations with neurodevelopmental outcomes. Regarding exposure to PBDEs, lower mental development, psychomotor development and IQ were found at pre-school age, and poorer attention at school age. Regarding exposure to DDE, some studies reported inverse associations with outcome, while others found no associations. The inverse associations were particularly found at early infancy on psychomotor development, and on attention and ADHD, whereas at school age no adverse relationships were reported anymore. Additionally, regarding PCB and DDE exposure, several studies report gender related vulnerability.

Regarding exposure to other environmental chemicals, sex-specific effects have been reported after exposure to phthalates and their metabolites. Phthalates possibly also play a role in the pathogenesis of ASD, and there might be a genetic influence on the association between phthalate exposure and attentional problems in children with ADHD. Exposure to BPA was found to be associated with child behavior, affecting boys and girls differently. No or inverse associations existed between exposure to perfluorinated compounds and characteristics of attention deficit/hyperactivity at school age.

When interpreting the relationship between environmental chemicals and neurodevelopmental outcome, certain aspects need to be taken into account.

Establishing neurodevelopmental outcome

To determine neurodevelopmental outcome and it relationship with POP exposure, a broad range of neurodevelopmental functions can be assessed. Examples are motor functioning, intellectual functioning, neuropsychological outcome and behavioral characteristics. For these different outcome measures, a wide range of age-adapted tests are available which can make comparison among studies difficult.

In the neonatal period, functioning of the central nervous system (CNS) was assessed by the neonatal behavioral assessment scale by Brazelton in two studies. This assessment involves autonomic functions of the central nervous system (such as color of the infant, breathing), primitive functions such as reflexes but also behavioral state.[15, 16] A more qualitative assessment of CNS functioning is the general movement assessment, that reports on fluency, variability and complexity of motor behavior, which has been used in for example the study of Berghuis et al.[17] At toddler's age, the Bayley Scales of Infant Development is a frequently used test to assess outcome. It differentiates mental from psychomotor development and reports with a quantitative measure on outcome (MDI and PDI). In addition, the third edition has subdivided scales for fine and gross motor functioning, expressive and receptive language, and cognition. At a young age however, it

remains difficult to isolate these functions because a certain level of motor functioning is a prerequisite for measuring cognitive function. In addition, during the first years after birth, results of neurodevelopmental tests depend strongly on the behavioral state. This indicates a key role for behavioral state, because test results are easily affected by differences in behavioral state. These aspects should be taken into account when interpreting the relationships of organohalogen exposure and early neurodevelopmental outcome.

Whilst some of the studies included in this review report on motor and cognitive outcome measured in a test-setting (such as the BSID, movement-ABC and IQ testing), others used screenings instruments such as questionnaires for developmental delay filled out by parents (i.e. the MacArthur-Bates Communicative Development Indices). These differences affect precision in assessing neurodevelopmental outcome and also play a role in the potential to detect relations between exposure and outcome.

Finally, effects of organohalogen exposure on certain functions may only come to light when children reach school age, because at school age functional demands are higher than at younger ages. Also, from 6 years of age onwards, a wider variety of tests are available and more precise assessment of attention and school achievement is possible. Previously existing problems, not apparent earlier, become evident at school age when functions involving these deficits are challenged.

Other factors influencing neurodevelopmental outcome

There are several well-known factors that are involved in neurodevelopmental outcome. Socio-economic status is a major determinant. In addition genetic predisposition for neurodevelopmental and behavioral impairments (such as intellectual development of parents, behavioral disorders within the family) should also be taken into account when examining the relation between organohalogen exposure and for example intellectual development, ASD and ADHD.

Bi-directional effects on neurodevelopment

It is striking that various studies report both positive and negative associations between POPs and outcome. Differences in tests may play a role, as outlined above. It is unknown if early positive relationships may lead to earlier maturation with a lower end-point outcome, or that performing multiple statistical analyses (and thus chance findings) can be responsible for these results.

Gender differences

Several studies reported sex-specific effects of exposure to environmental chemicals.[18, 21, 28] Boys are suggested to be more vulnerable to the effects of exposure to these compounds than girls. A possible explanation for this difference could be that these chemical compounds act

as androgen receptor antagonists, and thereby affect development of males differently. For example, in studies investigating effects of PCBs on male reproduction, inverse associations were found between PCBs and serum testosterone levels (for review see Meeker and Hauser[62]). Animal studies reported that several chemicals can disrupt androgen signaling in the foetal male rat, and that, for example, exposure to phthalates decreases mRNA expression of key steroidogenic enzymes and peptide hormone insulin-like peptide 3 from the foetal Leydig cells (for review see Wilson et al.[63]).

Differences in exposure levels

Differences in exposure levels could explain differences in effects observed among the mentioned studies. Some studies were performed in populations with relatively high exposure, i.e. through local eating habits or living near a contaminated harbor, whereas other studies were performed in areas with background exposure to the environmental chemicals. In addition, exposure levels differ among different countries and continents. For example PBDE levels in US breast milk are higher than in Europe,[64] whilst PCB serum concentrations were found to be higher in Europe when compared to the US.[65]

It is known that some POPs show a non-monotonic dose response relation with outcome.[66] Therefore, absolute exposure levels should be taken into account when interpreting effects on outcome. Finally, differences in sample material used for assessment of exposure levels, and differences in analytical methods could also explain differences in observed effects among the studies.

Collinearity

It is essential to realize that collinearity may exist regarding the associations between exposure and neurodevelopment. It is, therefore, important to investigate whether observed effects might be confounded by other chemicals or environmental factors. As reported by Grandjean et al., for example, effects of exposure to PCBs disappeared after adjustment for exposure to methylmercury, while the effect of mercury remained significant.[25] Future research should pay attention to combined exposures, and adjust for exposure to other chemicals and environmental factors which are suggested to influence the outcome.

Mechanisms of developmental interference

One of the potential mechanisms through which organohalogens have an adverse effect on neurodevelopment is through interference with thyroid hormone signaling in the developing brain. It is hypothesized that organohalogens affect thyroid hormone homeostasis by changing intracellular thyroid hormone availability, and by interacting directly at the level of the thyroid hormone receptors.[67] Thyroid hormone plays a role in synaptogenesis and myelination in the developing brain during the prenatal and postnatal period. In addition, an effect of organohalogens on neurotransmitter systems has been described.[68]

Future directions

Future studies should focus on exposure to combinations of several environmental chemicals, or even taken co-exposure with other chemicals into account. More research is also needed to clarify the presence and mechanisms of sex-specific effects of exposure to environmental chemicals. Because studies on the long-term follow-up after prenatal and childhood exposure to environmental chemicals are sparse, it is important to perform follow-up studies to investigate whether the observed effects of chemical exposure persist later on, for example in puberty and young adulthood.

CONCLUSIONS

Exposure to environmental chemicals affects neurodevelopmental and behavioral outcomes in children in several domains, including attention, motor development and mental development. Several studies suggest gender specific vulnerability to exposure to PCBs, OH-PCBs, DDE, phthalates and BPA. Boys are suggested to be more vulnerable for the harmful effect of exposure to environmental chemicals. Exposure to PCBs and OH-PCBs is predominantly found to be either not or inversely associated with attention, motor and mental development, whereas some studies reported positive associations. Most studies on exposure to PBDE reported negative effects on intelligence. Regarding DDE exposure, predominantly negative effects were reported on intelligence and attention, whereas one study reported positive effects on attention in girls.

Regarding other environmental chemicals, phthalates might possibly play a role in the pathogenesis of ASD, and there is possibly a genetic influence on the association between phthalate exposure and attentional problems in children with ADHD. Exposure to BPA was found to be associated with child behavior, affecting boys and girls differently. No or inverse associations existed between exposure to PFCs and attention at school age.

Future research should focus on the long-term effects of prenatal and childhood exposure to these environmental chemicals, on sex-specific and combined exposure effects of environmental chemicals, and on possible mechanisms by which these chemicals have their effects on developmental outcomes.

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