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ABSTRACT

Background: Organohalogen compounds (OHCs), i.e. polychlorinated biphenyls (PCBs, are wide-spread environmental pollutants known to be neurotoxic for the developing brain. The hydroxylated metabolites of PCBs, OH-PCBs, might be even more toxic due to their structure and interference with thyroid hormone metabolism. We found that prenatal exposure to OH-PCBs was associated with thyroid hormone metabolism at toddler age. Little, however, is known about the neurotoxicity of OH-PCBs in humans.

Objectives: To determine whether prenatal background exposure to OHCs has an effect on mental and motor development in children at the age of 18 and 30 months.

Methods: One hundred and eighty-one healthy mother-infant pairs were included in this observational study performed in the Netherlands. We measured maternal pregnancy levels of PCB-153 and three OH-PCBs. In one part of the cohort we measured another nine PCBs and three OH-PCBs and in the other part we measured five brominated diphenyl ethers (BDEs), dichloro-diphenyldichloroethylene (p,p'-DDE), pentachlorophenol (PCP), and hexabromocyclododecane (HBCDD). We used the mental development index (MDI) and the motor development index (PDI) of the Bayley Scales of Infant Development II (BSID-II) to assess children's mental and motor development (mean = 100; delayed score < 85).

Results: Higher prenatal PCB-153 levels were associated with a delayed MDI score at 18 months. None of the other compounds were associated with a delayed score, but several associations were found between OHC levels and BSID-II scores. The sum of all six OH-PCBs and three individual OH-PCBs, 4-OH-PCB-107, 3-OH-PCB-153, and 4′−OH-PCB-172, correlated positively with MDI at 30 months. The compound 3′−OH-PCB-138 showed a similar trend. A higher 4-OH-PCB-187 was associated with a lower MDI at 18 months. We found a similar trend for higher BDE-99. Higher BDE levels were associated with higher PDI at 18 months. The levels of p,p'-DDE-, PCP, and HBCDD were not associated with BSID-II scores at 18 months.

Conclusions: Higher prenatal levels of PCB-153 were associated with a delayed MDI score at 18 months. None of the other compounds were associated with a delayed score, but several associations were found between OHC levels and BSID-II scores. Prenatal OH-PCBs were positively associated with mental development at 30 months, whereas one OH-PCB was negatively associated at 18 months. BDE levels were positively associated with psychomotor development. Prenatal p,p'-DDE, PCP, and HBCDD levels were not associated with neurodevelopment at 18 months.

1. Introduction

Polychlorinated biphenyls (PCBs) are organohalogen compounds (OHCs). These chemical compounds were widely used in industry as fire retardants, hydraulic liquids, and lubricants, to name but a few applications. Although these compounds have been banned by law, their properties cause them to break down slowly and therefore they persist in the environment (McKinney and Waller, 1994). This raises concerns as studies have shown that PCBs have adverse effects, including neurotoxicity and endocrine disruption. Animal studies showed that endocrine disruption mainly involves the reproductive and thyroid systems. Developing organisms seem to be the most vulnerable (León-Olea et al., 2014).

Although to date several studies have been performed on the effects of exposure to PCBs on mental development in children, the outcomes are not consistent. Some studies reported negative associations,

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whereas others reported positive associations or none at all (reviewed by El Majidi and colleagues (El Majidi et al., 2013)). PCBs seem to have a greater effect on motor development than on mental development (Rogan and Gladen, 1991; Koopman-Esseboom et al., 1996; Daniels et al., 2003; Gladen et al., 1988; Walkowiak et al., 2001). In the present cohort, we found an association between several PCBs and impairment of early motor development in three-month-old children by assessing their movement repertoire (Berghuis et al., 2013).

Under stimulation of the P450 enzyme complex in the liver, PCBs can be converted into hydroxylated polychlorinated biphenyls (OH-PCBs). OH-PCBs are water soluble and have shown to pass the placental barrier in a higher ratio compared to PCBs (Soechitram et al., 2004). In vitro and animal studies showed that OH-PCBs interfere with thyroid hormone activity, an essential hormone for normal brain development (Schuur et al., 1998; Kitamura et al., 2005). In our study on thyroid hormone levels at toddler age we found more effects of prenatal exposure to OH-PCBs than to PCBs (Soechitram et al., 2017). These findings suggest that OH-PCBs might be more toxic than PCBs, but only a few studies are currently available on the effects of OH-PCBs in humans. In our cohort higher prenatal exposure to 4-OH-PCB-107 was associated with less than optimal early motor development in three-month-old children, whereas 4′-OH-PCB-172 showed the opposite effect (Berghuis et al., 2013). Park and colleagues studied the effects of six OH-PCBs on neurodevelopment at 16 months and found 4-OH-PCB-107 to be negatively associated with mental and motor development (Park et al., 2009).

Other OHCs were also found to be associated with poorer mental and motor development (reviewed by Berghuis and colleagues (Berghuis et al., 2015)). Higher prenatal exposure to brominated diphenyl ethers (PBDEs) was associated with poorer mental and psychomotor development and lower IQs at preschool age. In our cohort, prenatal exposure to PBDE levels correlated with poorer attention, poorer fine manipulative abilities, better coordination, better behavior, and better visual perception in children at school age (Roze et al., 2009). Regarding prenatal exposure to dichlorodiphenyldichloroethylene (DDE), a breakdown product of the insecticide dichlorodiphenyltrichloroethane (DDT), some studies reported inverse associations between exposure to DDE and neurodevelopmental outcome, while others found no associations. Exposure to DDE seems to interfere more with psychomotor development than with mental development (Berghuis et al., 2015).

A reliable and widely used instrument to assess the mental and motor development in children for both clinical and research purposes, is the Bayley Scales of Infant Development (BSID) (Van der Meulen et al., 2002; Bell and Allen, 2000).

Evidence on the negative health effects of prenatal exposure to PCBs is growing, but limited knowledge exists about the effects of prenatal exposure to OH-PCBs, PBDEs, and DDE (Berghuis et al., 2015). On account of the fact that in the Netherlands prenatal background PCB levels are estimated to be three times higher than in the USA and that, as a consequence, OH-PCB levels might also be higher, there is every reason to investigate whether Dutch background exposure exerts negative health effects (Longnecker et al., 2003). The present study was conducted because to date the possible relationship between prenatal Dutch OH-PCB levels and neurodevelopment at 18 and 30 months has not been assessed. Because we assessed development at a young age, thus minimizing the effects of postnatal exposure, the findings of this study contribute towards knowledge of the impact of prenatal background chemical exposure on early development.

The aim of this study was to determine whether prenatal background exposure to PCBs, OH-PCBs, and other OHCs is associated with the mental and motor development of children at the age of 18 and 30 months in the Netherlands. We hypothesize that exposure to higher levels of PCBs, OH-PCBs, and other OHCs have a negative effect on the mental and motor development of children.

2. Materials and methods

2.1. Cohort

For this observational longitudinal cohort study we included two cohorts from the northern part of the Netherlands. The first group of the study population stems from the Risk of Endocrine Contaminants on human health (RENCO) study (Soechitram et al., 2004). Pregnant women were approached by their midwife or obstetrician to participate in a study on the potential effects of PCB and OH-PCB exposure on the development of the child between September 1998 and December 2000. The second group stems from the Groningen Infant COMPARE (Comparison of Exposure-Effect Pathways to Improve the Assessment of Human Health Risks of Complex Environmental Mixtures of Organohalogens) study, known as the GIC study (Meijer et al., 2008). This study was launched as part of the European COMPARE study. These women were invited by their midwives between October 2001 and November 2002. Both cohorts only included women of western origin who spoke Dutch as their native language. We excluded women who experienced serious illnesses and/or complications during pregnancy and/or delivery. Further, only full-term children, born between 37 and 42 weeks of gestation, were included. We excluded children with congenital anomalies or diseases and if they had been admitted to a hospital for more than one day after birth. All parents gave their informed consent. The study was approved by medical ethics committee of the University of Groningen.

2.2. Chemical analysis

In both cohorts a blood sample was taken in the 35th week of pregnancy to determine organohalogens levels in the blood (Soechitram et al., 2004; Meijer et al., 2008). To determine the concentrations of PCBs and OH-PCBs the blood was collected in a vacuum system tube (EDTA) and centrifuged for ten minutes at 3600 rpm (RENCO cohort) or for five minutes at 4000 rpm (GIC cohort). Subsequently, the plasma was collected in separate glass tubes. These tubes were closed with a screw cap with Teflon inlayers and stored at −18 C° to −20 C° until analysis. Both studies used Hovander's clean-up and extraction procedure as is described by Hovander and colleagues (Hovander et al., 2000). A detailed description of the analyses of the OHCs can be found elsewhere (Soechitram et al., 2004; Meijer et al., 2008).

In the RENCO cohort ten PCBs and six OH-PCBs were measured to determine the effect of organohalogens on the development of children. We also calculated the values for the sum of all ten PCBs and all six OH-PCBs measured in the RENCO cohort, ΣPCBs and ΣOH-PCBs, respectively. In addition, we calculated the sum of all dioxin-like mono-ortho-substituted PCBs (105; 118; 156) and the sum of the other PCBs (138; 146; 153; 170; 180; 183; 187). The chemical activated luciferase gene expression (CALUX) essay was used to measure the total toxic equivalent quotient (TEQ) levels in maternal serum in the RENCO cohort. CALUX can be used to detect certain planar halogenated aromatic hydrocarbons including PCBs. After the compounds bind to the aryl hydrocarbon receptor (AhR), the PHAH-AhR complex is transported into the nucleus of the cell and subsequent binding to specific sequences in the DNA (BioDetection Systems) occurs. In the GIC cohort we measured PCB-153 and three hydroxylated PCB metabolites. We also measured the following organohalogen compounds in the GIC cohort: p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE), pentachlorophenol (PCP), five different brominated diphenyl ethers (BDEs) and hexabromocyclododecane (HBCDD). In Table 2 we show the maternal pregnancy serum levels of the OHC compounds we measured. The PCBs are numbered in accordance with Ballschmiter and colleagues and the OH-PCBs according to Letcher and colleagues (Ballschmiter et al., 1993; Letcher et al., 2000).

2.3. Assessment of neurodevelopment

To determine the children's neurodevelopment we used the Dutch version of the second edition of Bayley Scales of Infant Development (BSID-II-NL) at 18 months (both cohorts) and 30 months (RENCO cohort). This is a standardized test designed to assess the development of children aged between 1 and 42 months in the Netherlands. It assesses both mental and motor development and is widely used for both clinical and research purposes (Bell and Allen, 2000). The tests were conducted by trained examiners who were unaware of the child's organohalogen exposure levels. The BSID-II provides scores on the mental and motor development of the child. Mental development is expressed in the mental development index (MDI) and consists of 178 items. The mental scale assesses the age-appropriate level of cognitive functioning, personal and social development, and language development. Motor development is expressed in the psychomotor development index (PDI) and consists of 111 items. The motor scale assesses fine and gross motor skills. The test provides raw scores for mental and motor development that can be converted into standardized index scores of MDI and PDI, based on norms for the Dutch population. These index scores have a mean of 100, and a standard deviation of 15. A child with a test score below 85 is considered to have a mildly delayed development; a score below 70 indicates severe delay.

2.4. Statistics

To investigate whether prenatal exposure to OHCs is associated with neurodevelopment at 18 or 30 months of age, we used the Spearman partial correlation test to assess correlations between OHC levels and MDI and PDI scores at 18 and 30 months corrected age. To determine potential confounders we used the Spearman rank correlation and Mann Whitney tests. We considered sex, birth weight, maternal smoking during pregnancy, maternal alcohol use during pregnancy, parity, and maternal education as potential confounders. We entered these variables into the model if there was an association between OHC levels and these variables with $P < .15$.

Next, we performed univariate logistic regression analyses for compounds that correlated with BSID-II scores using the Spearman partial correlation test to calculate odds ratios (ORs) for obtaining a delayed MDI or PDI (< 85). We adjusted the results using multiple logistic regression analyses, entering confounders with $P < .15$ into the model. The tests were two-sided. We considered a P value of less than .05 to be statistically significant. A P value less than .10, but more than .05 is mentioned as a trend, as is usual for toxicological studies. We used the Statistical Package for the Social Sciences (SPSS), Version 23.0 for all the statistical analyses.

3. Results

3.1. Study group

The study group initially consisted of 194 mother-infants pairs (MI pairs). Initially, 104 MI pairs were included in the RENCO cohort and 90 MI pairs in the GIC cohort (Soechitram et al., 2004; Meijer et al., 2008). Four of the mother-infant pairs had to be excluded from the RENCO cohort because no OHC levels were obtained. Another nine MI pairs were excluded from the study because no BSID-II scores were available at 18 months. In total, 181 (95.3%) of the 190 MI pairs participated at the age of 18 months. At follow-up at 30 months of age, 63 (67.0%) of the 94 invited MI pairs of the RENCO cohort participated for assessment of BSID-II scores. Table 1 shows the characteristics of the study group. In the RENCO cohort a greater proportion of the mothers smoked, 23% versus 9% in the GIC cohort. Frequently, the level of education of mothers included in the GIC cohort was higher than that of the mothers of in the RENCO cohort (56% and 47%, respectively).

3.2. OHC levels

In Table 2 we present the levels of OHCs measured in maternal serum during pregnancy. PCB-153 had the highest mean concentration of the PCBs (83 ng/g lipid weight) and 4-OH-PCB-187 had the highest mean concentration of the OH-PCBs (87 ng/g fresh weight). As reported previously, the CALUX results correlated positively with the individual dioxin-like PCBs and the sum of the measured dioxin-like PCBs (Soechitram et al., 2017).

3.3. Bayley scales of infant development

The BSID-II scores of the children at 18 and 30 months were corrected for age and are presented in Table 1. The mean scores for MDI and PDI in the 181 children included at 18 months were 97.1 and 90.1, respectively. At 18 months, 13% of the children had a delayed score (< 85) on MDI and 31% on PDI. For the 63 children included at 30 months of age, the mean MDI and PDI scores were 98.5 and 94.2. At 30 months, 11% of the children had a delayed score (< 85) on MDI and 18% on PDI. There were no differences between children who switched from delayed to normal scores on PDI between 18 and 30 months (n = 14) and the children with a delayed score on PDI at both time points (n = 8) regarding maternal education level (MWU = 51.0, P = .673) and parity (MWU = 53.0, P = .810).

3.3.1. Prenatal OHCs exposure to OHCs and neurodevelopment

In Table 3 we present the Spearman partial correlation coefficients of the relations between prenatal exposure to OHCs and BSID scores at 18 and 30 months corrected age. Higher maternal education was included in all models because it was associated with higher MDI and PDI scores at both time points (18 months: MWU = 3391.0, P = .046; MWU = 3274.0, P = .019; and 30 months: MWU = 369.0, P = .094, MWU = 329.0, P = .041, respectively). Parity was associated with MDI at both time points, with a higher rank for first-born children (MWU = 2778.5, P = .005 and MWU = 309.0, P = .024). Maternal alcohol use during pregnancy was associated with higher PDI at 30 months (MWU = 289.5, P = .141). Finally, we dichotomized the scores into normal and delayed scores and calculated the ORs for obtaining a delayed score. In Table 4 we present the ORs for the compounds that correlated significantly or showed a trend with BSID scores using the Spearman partial correlation test (Tables 3 and 4).

3.3.2. Prenatal exposure to PCBs and neurodevelopment

Higher exposure to PCB-153 was associated with delayed MDI scores at 18 months in the GIC cohort, but not in the combined cohort (Table 4). None of the other PCBs were associated with a delayed score. We did not find any associations between exposure to PCBs and MDI scores at 30 months or with PDI -scores at 18 or 30 months. The sum of the mono-ortho-substituted dioxin-like PCBs, the sum of the other measured PCBs, nor the CALUX-TEQ values were associated with BSID-II scores.

3.3.3. Prenatal exposure to OH-PCB

Regarding OH-PCB exposure and mental development we found both positive and negative associations (Table 3). At 18 months higher exposure to 4-OH-PCB-187 in the GIC cohort correlated with a lower MDI score. At 30 months of age higher exposure to four individual OH-PCBs and the ΣOH-PCBs correlated with a higher MDI in the RENCO cohort and a trend was seen for one OH-PCB (Table 3). After dichotomizing the scores into normal and delayed scores and correcting for confounders, none of the OH-PCBs were either positively or negatively associated with a delayed score (Table 4).

3.3.4. Prenatal exposure to other OHCs and neurodevelopment

Regarding exposure to the other measured OHCs and mental development we found a trend between higher exposure to BDE-99 and

Table 1
Characteristics of the study group.

Characteristic	18 months			30 months
	Both cohorts (n = 181)	RENCO (n = 94)	GIC (n = 87)	RENCO (n = 63)
Child				
Gender (male/female)	105/76 (58%)	50/44 (53%)	55/32 (63%)	36/27 (57%)
Gestational age (weeks, mean ± SD)	40 ± 1	40 ± 1	40 ± 1	40 ± 1
Apgar score 1 min [median (range)]	9 (2-10)	9 (2-10)	9 (3-10)	(6-10)
Apgar score 3 min [median (range)]	10 (6-10)	10 (6-10)	10 (7-10)	(6-10)
Age at examination (months; mean ± SD)	18 ± 0.5	18 ± 0.5	18 ± 0.5	30 ± 0.5
Mother				
Maternal age (years; mean ± SD)	32 ± 4	32 ± 4	32 ± 4	32 ± 4
Maternal smoking, yes/no (%)	30/150 (17%)	22/72 (23%)	8/78 (9%)	19/44 (30%)
Maternal alcohol consumption, yes/no (%)	46/134 (25%)	23/71 (24%)	23/63 (26%)	18/45 (29%)
Parity, first-born/second-, or third-born (%)	63/118 (35%)	34/60 (36%)	29/58 (33%)	24/39 (38%)
Maternal education level (%)				
Below average (≤ 11 years of education)	16 (9%)	12 (13%)	4 (5%)	8 (13%)
Average (12-13 years of education)	72 (40%)	38 (40%)	34 (39%)	27 (43%)
Above average (≥ 14 years of education)	93 (51%)	44 (47%)	49 (56%)	28 (44%)
MDI				
Mean ± SD	97.1 ± 13.3	97.6 ± 13.8	96.7 ± 12.7	98.5 ± 10.7
Normal (≥ 85)	157 (87%)	84 (89%)	73 (84%)	56 (89%)
Mildly delayed (70-85)	21 (12%)	8 (9%)	13 (15%)	7 (11%)
Severely delayed (< 70)	3 (2%)	2 (2%)	1 (1%)	0 (0%)
PDI				
Mean ± SD	90.1 ± 10.2	89.3 ± 10.5	91.1 ± 9.9	94.2 ± 15.1
Normal (≥ 85)	124 (69%)	61 (65%)	63 (72%)	51 (82%)
Mildly delayed (70-85)	51 (28%)	29 (31%)	22 (25%)	7 (11%)
Severely delayed (< 70)	6 (3%)	4 (4%)	2 (2%)	4 (6%)

lower MDI scores at 18 months (Table 3). Regarding psychomotor development we found a positive correlation between exposure to BDE-100 and PDI scores at 18 months, a similar trend was seen with exposure to BDE-47 (Table 3). After dichotomizing the scores into normal and delayed scores and correcting for confounders, none of the other OHCs were either positively or negatively associated with a delayed score (Table 4).

4. Discussion

In the present study, which was performed in the Netherlands, we found that higher prenatal background exposure to several OHCs was associated with mental and/or motor development at 18 or 30 months of age. We found both positive and negative associations. Our most important finding was that OH-PCBs were positively associated with mental development at 30 months. PCB-153, BDE-99, and 4-OH-PCB-187 were negatively associated with mental development at 18 months. Two PBDEs were positively associated with motor development at 18 months.

4.1. Prenatal exposure to OH-PCBs and neurodevelopment

Our most important finding was that prenatal exposure to OH-PCBs was associated with more optimal mental development at 30 months of age. We found a positive association between the sum of all OH-PCBs and four individual OH-PCBs (4-OH-PCB-107, 3′-OH-PCB-138, 3-OH-PCB-153, 4′-OH-PCB-172) and mental development at 30 months. The finding that 4′-OH-PCB-172 was positively associated with development at 30 months is consistent with our previous finding that the compound was positively associated with neurodevelopment at three months of age (Berghuis et al., 2013). The compound 4-OH-PCB-107 is a metabolite of PCB-105 and PCB-118, both of which are dioxin-like PCBs. Enhanced neurodevelopment was found after higher prenatal exposure to dioxin-like PCBs in our cohort at the age of three months (Berghuis et al., 2014) and also after higher perinatal dioxin exposure in another Dutch cohort of children at the age of two years and seven months (Ilsen et al., 1996). A possible explanation for such enhanced development could be agonistic effects on thyroid hormone functions. In our cohort we found higher levels of T4 and T4 sulfate at three and 18 months after higher prenatal OH-PCB exposure (Soechitram et al., 2017) and in Ilsen and colleagues' cohort a relatively high thyroid function during the first 11 weeks after birth was observed in children with high perinatal dioxin exposure (Pluim et al., 1993).

In contrast to previous studies and to findings in our cohort at the age of three months, we did not find negative effects of the metabolite 4-OH-PCB-107 on motor development. An animal study in rats indicated that exposure to 4-OH-PCB-107 had a long-term effect on development and behavior (Meerts et al., 2004). In the children included in the RENCO cohort, background exposure to 4-OH-PCB-107 was associated with impairment of motor development at the age of three months (Berghuis et al., 2013) and a negative association between 4-OH-PCB-107 and neurological function was found in boys at three months of age (Berghuis et al., 2014). A Slovakian study found a negative association between prenatal exposure to 4-OH-PCB-107 and motor development in 16-month-old children who were assessed by using BSID-II (Park et al., 2009). A possible explanation for the fact that we did not find similar associations with 4-OH-PCB-107 levels might be differences in OH-PCB levels. We found higher 4-OH-PCB-107 levels than Park and colleagues: 52 versus 37 pg/g wet weight (Park et al., 2009). Unlike the 4-OH-PCB-107 levels, we found lower levels of the other OH-PCB congeners in comparison to the Slovakian study: for 4-OH-PCB-146 99 versus 147 pg/g fresh weight and for 4-OH-PCB-187 117 versus 273 pg/g fresh weight. However, the mean PDI found by Park and colleagues was much higher than in our study: 99.8 versus 90.1. Another difference between our study and the Slovakian study is that we used the BSID-II version, which is standardized for the Dutch population, whereas they did not use a version that had been standardized for their population. Instead, they used a modification of the American version. This might also contribute to the explanation for the differences in the findings between the two populations. The Slovakian study also investigated other OH-PCB congeners, but these congeners show no significant associations with mental or motor development at 16 months of age (Park et al., 2009). This is partly in line with our result of finding only one OH-PCB congener to be associated with

Table 2
Organohalogen levels in maternal serum samples during pregnancy.

Compound	Median (IQR)	n
PCB-105[a]	4.2 (2.1–11.3)	94
PCB-118[a]	21.0 (14.6–33.9)	94
PCB-138[a]	68.7 (48.9–86.2)	94
PCB-146[a]	8.2 (5.0–13.7)	94
PCB-153	88.0 (68.8–144.0)	181
-RENCO	91.9 (63.2–123.2)	94
-GIC	62.9 (43.2–80.4)	87
PCB-156[a]	11.1 (7.8–14.7)	92
PCB-170[a]	19.0 (13.5–25.4)	92
PCB-180[a]	45.2 (31.7–58.5)	92
PCB-183[a]	8.2 (5.6–10.4)	94
PCB-187[a]	12.3 (8.6–17.8)	94
Σ dl-PCBs[a,b]	38.7 (24.1–60.8)	92
Σ non-dl-PCBs[a,c]	259.3 (181.4-334.3)	92
Σ 10 PCBs[a]	296.8 (217.5–391.1)	92
CALUX-TEQ	19.5 (13.8–60.4)	92
4-OH-PCB-107	42.0 (23.0–76.6)	175
-RENCO	69.0 (42.0–100.0)	91
-GIC	26.1 (17.8–38.6)	84
3'-OH-PCB-138[a]	46.0 (31.0–66.0)	91
4-OH-PCB-146	80.3 (61.0–128.4)	178
-RENCO	70.0 (53.0–100.0)	91
-GIC	102.4 (72.4–140.0)	87
3-OH-PCB-153[a]	38.0 (24.0–54.0)	91
4'-OH-PCB-172[a]	16.0 (10.0–22.0)	72
4-OH-PCB-187	105.0 (78.6–148.0)	178
-RENCO	136.0 (105.0–172.0)	91
-GIC	79.8 (59.3–100.6)	87
Σ 6 OH-PCBs[a]	388.5 (275.8–546.3)	72
p,p'-DDE[d]	88.0 (68.8–144.0)	87
PCP[d]	972.5 (686.3–1641.2)	87
BDE-47[d]	0.85 (0.53–1.30)	60
BDE-99[d]	0.20 (0.10–0.40)	57
BDE-100[d]	0.20 (0.10–0.30)	60
BDE-153[d]	1.55 (1.20–2.20)	60
BDE-154[d]	0.50 (0.40–0.78)	60
HBCDD[d]	0.82 (0.47–1.26)	59

PCBs, DDE, PCP, BDEs, and HBCDD in ng/g lipid weight; OH-PCBs in ng/g fresh weight; CALUX levels in pg TEQ/g lipid.

[a] RENCO cohort.

[b] sum of dioxin-like PCBs (105; 118; 156).

[c] sum of non-dioxin-like PCBs (138; 146; 153; 170; 180; 183; 187).

[d] GIC cohort.

mental development at the age of 18 months. We mainly found associations between prenatal OH-PCB levels and mental development at 30 months of age, whereas these OH-PCBs were not found to be associated with development at the age of 18 months. A possible explanation for the fact that we did not observe effects at 18 months of age could be that the effects might appear more subtle at younger ages and might therefore not result in significant changes in MDI scores. Another explanation for the positive and earlier negative effects might be that the tests were performed during toddler age, an age during which major transformation of neural functions take place and the quality rather than the quantity of the motor repertoire changes (Hempel, 1993). We speculate that in later life the effects of prenatal exposure on developmental outcomes might become more apparent. At the age of 30 months we found a positive association between MDI scores and the sum of the OH-PCBs and four separate OH-PCBs. However, after subdividing the group into children with normal and delayed MDI, we did not find significant differences with regard to prenatal OH-PCB levels. This might suggest a more general effect of exposure positively affecting the mental development without resulting in a lower risk of obtaining a delayed score.

4.2. Prenatal exposure to PCBs and neurodevelopment

We found higher exposure to PCB-153 to be associated with a higher risk of obtaining a delayed MDI score (< 85) at 18 months. Other studies on the effects of PCBs showed different outcomes for mental than for motor development, as reviewed by El Majidi and colleagues and by Faroon and colleagues (El Majidi et al., 2013; Faroon et al., 2000). The results of the previous studies point to a relation between prenatal exposure to PCBs and a less than optimal performance on motor skills during first months of life. Later effects seem to involve mainly cognitive areas (Ribas-Fito et al., 2001). Exposure to PCB-153, in particular, is often found to be associated with developmental outcomes in children (Casas et al., 2015; Gascon et al., 2013; Verner et al., 2010). PCB-153 is the most abundant congener in humans. This could be an explanation for finding an effect of PCB-153 only. An animal study found that PCB-153 affects the regulation of the intracellular signaling systems in the brain (Bemis and Seegal, 2004). Moreover, PCB-153 alters neurotransmitter functions in rats, causing a decrease in brain serotonin and dopamine that are essential for the proper development of the brain (Castoldi et al., 2006).

4.3. Prenatal exposure to PBDE and neurodevelopment

We found a negative trend between prenatal levels of BDE-99 and mental development at 18 months. Regarding motor development BDE-100 and BDE-47 showed a positive trend with outcomes at 18 months. Regarding exposure to PBDEs most studies demonstrated strong inverse effects on mental development. Inconsistent effects were found for motor development (reviewed by Roth and Wilks (Roth and Wilks, 2014)). Animal studies seem to confirm the impact on mental development. They revealed that exposure to PBDEs can alter spontaneous behavior resulting in increased impulsivity, hyperactivity, and disrupted habituation. Moreover, attention, learning, and memory functions were impaired (reviewed by Dingemans and colleagues (Dingemans et al., 2011)). In our cohort prenatal exposure to PBDE levels was correlated with poorer attention, poorer fine manipulative abilities, better coordination, better behavior, and better visual perception in children at school age (Roze et al., 2009). It might well be that effects of prenatal exposure to PBDEs become more apparent at a later age. More studies are needed on the potential effects of prenatal exposure to PBDEs on psychomotor development.

4.4. Prenatal exposure to DDE, PCP, and HBCDD and neurodevelopment

We did not find associations between prenatal exposure to p,p'-DDE, PCP, or HBCDD and mental or motor development at 18 months of age. Several studies on the effects of p,p'-DDE showed impairment of mental and motor development in children aged between three and 24 months (reviewed by Eskenazi and colleagues (Eskenazi et al., 2009)). In later life, studies predominantly reported no associations between exposure to p,p'-DDE and neurodevelopment. A possible explanation for the fact that we found no associations might be that the levels measured in our study were too low to exert effects in the children.

4.5. Mechanisms of neurotoxicity

A possible explanation for the neurotoxicity of OHCs might involve the interactions of OHCs with the endocrine system, particularly the thyroid hormone system (Brouwer et al., 1998). The thyroid hormone system is hugely important for the normal maturation of the brain. It influences neuronal proliferation and migration in the brain, as well as synapse formation (Williams, 2008). The thyroid hormone system is also essential for timing these processes. Studies in animals and humans showed that OHC exposure can lead to disturbances of the thyroid hormone system (for review see Brouwer and colleagues (Brouwer et al., 1998)) (Soechitram et al., 2017; Koopman-Esseboom et al., 1994). Disruption of the endocrine system can be the result of an agonistic or antagonistic action of the chemicals. The structures of several OHCs are highly similar to the chemical structures of thyroid

Table 3
Spearman's partial correlation coefficients of organohalogen compounds and Bayley Scale of Infant Development scores at age of 18 and 30 months.

	18 months					30 months					
	MDI			PDI		MDI			PDI		
Compound	*n*	Rho[a]	*P* value	Rho[b]	*P* value	*n*	Rho[a]	*P* value	*n*	Rho[c]	*P* value
PCB-105[d]	94	.000	.998	.005	.961	63	−.105	.419	62	−.103	.434
PCB-118[d]	94	.072	.495	.044	.676	63	−.037	.780	62	−.147	.262
PCB-138[d]	94	.090	.395	.132	.209	63	.120	.358	62	.007	.959
PCB-146[d]	94	.020	.851	.037	.724	63	.043	.744	62	−.031	.816
PCB-153	181	−.025	.742	.016	.826						
-RENCO	94	.077	.466	.111	.288	63	.077	.555	62	−.025	.850
-GIC	87	−.206	.059#	−.040	.712		n.a.			n.a.	
PCB-156[d]	92	.060	.572	.111	.295	61	.111	.402	60	.026	.847
PCB-170[d]	92	.137	.199	.096	.364	61	.205	.119	60	.086	.522
PCB-180[d]	92	.118	.270	.084	.427	61	.198	.133	60	.084	.529
PCB-183[d]	94	.004	.972	.058	.581	63	−.050	.702	62	.038	.771
PCB-187[d]	94	.076	.471	.050	.633	63	.067	.610	62	.034	.799
Σ dl-PCBs[d,e]	92	.067	.532	.052	.622	61	−.006	.962	60	−.108	.420
Σ non-dl-PCBs[d,f]	92	.083	.436	.098	.353	61	.112	.398	60	−.029	.832
Σ 10 PCBs[d]	92	.075	.483	.097	.361	61	.101	.444	60	−.037	.781
CALUX-TEQ[d]	92	.016	.884	-.083	.433	63	.035	.788	62	.169	.197
4-OH-PCB-107	175	.043	.573	.029	.705						
-RENCO	91	.074	.492	.125	.239	61	.298	.022*	60	.151	.257
-GIC	84	−.101	.365	.065	.560		n.a.			n.a.	
3'-OH-PCB-138[d]	91	−.030	.777	.014	.893	61	.225	.086#	60	.106	.426
4-OH-PCB-146	178	−.105	.167	.045	.555						
-RENCO	91	.015	.887	.107	.314	61	.201	.127	60	.098	.465
-GIC	87	−.178	.103	−.088	.418		n.a.			n.a.	
3-OH-PCB-153[d]	91	.069	.519	.006	.958	61	.295	.023*	60	.065	.630
4'-OH-PCB-172[d]	72	.089	.465	−.023	.847	48	.396	.006**	47	.218	.150
4-OH-PCB-187	178	−.113	.137	−.111	.140						
-RENCO	91	−.020	.849	−.007	.946	61	.039	.768	60	−.081	.547
-GIC	87	−.253	.019*	−.178	.100		n.a.			n.a.	
Σ 6 OH-PCBs[d]	72	.025	.835	−.063	.599	48	.367	.012*	47	.133	.383
p,p'-DDE[g]	87	−.058	.601	.076	.485		n.a.			n.a.	
PCP[g]	87	−.039	.725	.068	.532		n.a.			n.a.	
BDE-47[g]	60	−.193	.147	.237	.071#		n.a.			n.a.	
BDE-99[g]	57	−.232	.089#	.185	.172		n.a.			n.a.	
BDE-100[g]	60	−.096	.473	.273	.036*		n.a.			n.a.	
BDE-153[g]	60	−.025	.854	.183	.165		n.a.			n.a.	
BDE-154[g]	60	−.136	.308	−.098	.460		n.a.			n.a.	
HBCDD[g]	59	−.133	.324	.004	.979		n.a.			n.a.	

[a] corrected for parity and maternal education level.
[b] corrected for maternal education level.
[c] corrected for maternal alcohol use during pregnancy and maternal education level.
[d] RENCO cohort.
[e] sum of dioxin-like PCBs (105; 118; 156).
[f] sum of non-dioxin-like PCBs (138; 146; 153; 170; 180; 183; 187).
[g] GIC cohort.
** $P < .01$.
* $P < .05$; # $P < .10$. Abbreviations: MDI - mental development index, PDI - psychomotor development index, n.a.- not assessed.

hormones and therefore might interact with their receptors (McKinney and Waller, 1994; McDonald, 2002). According to an animal study, OH-PCBs exhibit agonistic thyroid hormone activity as a result of interaction with thyroid hormone receptors (TR) (Kitamura et al., 2005). Interaction with these TRs disrupts normal thyroid homeostasis, potentially resulting in abnormalities in brain development. The study demonstrated that a 4-hydroxyl group and 3,5-chlorine substituent on the phenyl group were required for this interaction with TR. This is a possible explanation for our finding that OH-PCBs with a 4-hydroxyl group were associated with neurodevelopment. And it is in accordance with our earlier findings in which we describe associations between prenatal OH-PCB exposure and thyroid hormone metabolism at three and 18 months (Soechitram et al., 2017). Studies in animals and in vitro studies showed that OHCs can bind to the transthyretin receptor (TTR), a transport protein in the blood and cerebral fluid for T4 (Lans et al., 1994; Meerts et al., 2002). In vitro studies showed that both PCBs and OH-PCBs were able to bind to TTR, although only the affinity of OH-PCBs to TTR was able to compete with T4 binding (Lans et al., 1994; Meerts et al., 2002). A study in rats showed an affinity of 4-OH-PCB-107 with the thyroid transport protein TTR (Meerts et al., 2004). Binding of 4-OH-PCB-107 to TTR could be a reason for lower circulating T4 levels in animals, found in both fetal plasma and brains, as seen by Morse and colleagues (Morse et al., 1996). The presence of OH-PCBs in the fetal animal may result in a decrease in circulating plasma T4 levels and brain T4 levels. A similar mechanism is seen for metabolites of PBDEs (Brouwer et al., 1998). In humans, however, most T4 transport depends on the thyroxin-binding globulin (TBG) (Brouwer et al., 1998). Nevertheless, binding of T4 to TTR might be important in humans for transport across the blood-brain barrier. PCBs and OH-PCBs therefore might influence brain levels of thyroid hormones in humans. In the current study, we found most effects to be associated with prenatal exposure to OH-PCBs, which suggest OH-PCBs to be more toxic than PCBs and other OHCs. This is similar to the findings in animal studies and in our study on thyroid hormone levels at toddler age (Kitamura et al., 2005; Soechitram et al., 2017; Kimura-Kuroda et al., 2007).

Table 4
Odds ratios for associations between prenatal organohalogen compound levels and delayed mental or motor development at 18 and 30 months of age.

Compound	Outcome	Age in months	OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
PCB-153[a],[*]	MDI	18	1.02 (1.00-1.04)	**.030**	1.02 (1.00–1.04)[b]	**.023**
4-OH-PCB-107[c],[#]	MDI	30	0.98 (0.95-1.01)	.110	0.98 (0.95–1.01)[b]	.126
3'-OH-PCB-138[c],[#]	MDI	30	0.99 (0.96-1.02)	.443	0.99 (0.97–1.02)[b]	.459
3-OH-PCB-153[c],[#]	MDI	30	0.98 (0.94-1.02)	.264	0.98 (0.94–1.02)[b]	.283
4'-OH-PCB-172[c],[#]	MDI	30	0.87 (0.72-1.05)	.153	0.87 (0.72–1.05)[b]	.142
4-OH-PCB-187[c],[#]	MDI	18	1.39 (1.15-1.69)	**.001**	1.01 (1.00–1.02)[b]	.150
Σ 6 OH-PCBs[c],[#]	MDI	30	0.99 (0.99-1.00)	.153	0.99 (0.99–1.00)[b]	.166
BDE-47[a],[*]	PDI	18	0.80 (0.44-1.46)	.464	0.79 (0.44–1.45)[d]	.453
BDE-99[a],[**]	MDI	18	1.14 (0.98-1.33)	**.089**	1.13 (0.97–1.33)[b]	.127
BDE-100[a],[**]	PDI	18	0.88 (0.67-1.17)	.379	0.88 (0.66–1.16)[d]	.369

Associations are only shown for the compounds that were associated with a $P < .10$ in the Spearman partial analyses.
Abbreviations: OR - odds ratio, CI - confidence interval, MDI - mental development index, PDI - psychomotor development index.
[a] GIC cohort.
[b] adjusted for parity and maternal education level.
[c] RENCO cohort.
[d] adjusted for maternal education level.
[*] per ng/g lipid weight.
[**] per 0.1 ng/g lipid weight.
[#] per pg/g fresh weight.

4.6. Strengths and limitations

A strength of our study is the measurement of prenatal background exposure of individual OHCs in healthy children, in which we also investigated the effects of OH-PCBs. Only a few studies have been performed on the impact of OH-PCBs on neurodevelopment. Although the levels of OH-PCB are generally lower in comparison to other studies, we did find associations. This suggests that even lower levels seem to affect the child's development. A second strength is that we assessed the development in one part of the cohort at two different ages. Although the sample size is smaller for the analyses at 30 months of age, we were able to obtain more insight into consistency between the outcomes at 18 and 30 months.

Our study also has limitations. The first limitation we address is the possibility of Type 1 errors due to the explorative nature of the study. Nevertheless, we believe that our analyses were justified as part of a careful evaluation of a rich data set in hypothesis-driven research (Rothman, 1990). A second limitation is the relatively small sample size. We only found significant results in one of the two cohorts, but not in the cohorts combined. This limits definite conclusion about whether our findings, especially negative ones, are valid. In our opinion, these sizes are appropriate for such complicated studies that involve, involving the assessment of multiple OHCs. Nevertheless, our results need to be interpreted with caution. A third limitation is that we included children from two cohorts. This might have led to differences in inclusion and characteristics of the two study groups. Although the GIC cohort included higher educated women, other characteristics of the two cohorts were comparable, for example demographics and methods used. Because we noticed differences between the cohorts, we decided to also report on the sub analyses for both cohorts separately for those compounds which were measured in both cohorts. A fourth limitation is that we found relatively low scores for both MDI and PDI at 18 months. Meta-analyses already showed that findings of the BSID-II might underestimate mental and motor development resulting, more frequently, in lower scores (Santos et al., 2013). Another explanation for the relatively low scores could be the relatively young age at examination. The children were seen at the age of 18 months. At this age, the range in development is considerable as far as the achievement of various milestones in both mental and motor development is concerned. Additionally, rapid development is characteristic of this age, making it difficult to obtain a good impression of the development at that moment. Testing a few weeks later could result in essential differences in scores if the child had obtained certain milestones in the meantime. Moreover, especially the evaluation of the motor development depends to a large extent on the children's behavior and their willingness to perform the tests, which requires experience of the examiner. Even so, the BSID-II is a standardized test, administered by experienced examiners, and we kept close to 18 months as the age of assessment, resulting in a SD for age of assessment of two weeks. Another limitation is a potential selection bias due to voluntary participation of the women to our study. The women who agreed to participate might be interested in the effects of environmental compounds and therefore might show more awareness regarding their life style and eating habits. Such awareness, however, does not mean that these women did indeed change their habits. Perhaps they did not possess the means to do so, or they lacked the knowledge on how to avoid exposure to these pollutants. As regards inclusion, we did include many highly educated women. This could have affected the general development of the children. Nevertheless, we did correct for the level of maternal education, which had no significant effect on our outcome. A final limitation is that we cannot exclude the possibility that co-exposure to other OHCs confounded our findings, because all children are exposed to a mixture of chemicals. On account of these limitations the results of our study should be considered as exploratory, and our results should be interpreted with caution.

4.7. Implications

Our findings suggest that prenatal background exposure to OHCs is associated with the children's neurodevelopment at toddler age. Less is known about the effects of prenatal exposure, of OH-PCBs in particular. Our study seems to suggest that it has subtle effects early in life. Although the effects might be subtle for the individual, it may still have a great impact at population level. The effects found could be temporary or evolve over years. Behavioral problems seem to be increasing in the population, with the exposure to environmental pollutants as a potential explanation. Even though, some of the compounds were positively associated with mental development, chemical compounds are not supposed to interfere with children's development, and an enhanced development might possibly occur at the expense of the formation of stable neural networks. Less is known about the long-term effects of prenatal exposure to OH-PCBs. Further research is required to determine the consequences of prenatal exposure to OHCs later in life. Further knowledge is also needed on the biological and biochemical actions of these compounds to prevent the production of chemical compounds with similar effects.

5. Conclusions

In one cohort higher prenatal levels of PCB-153 were associated with delayed MDI scores at 18 months. None of the other compounds were associated with a delayed score, but several associations were found between OHC levels and BSID-II scores. In our study, higher prenatal background OH-PCB exposure in the Netherlands was associated with neurodevelopment at 18 and 30 months of age, both adversely and positively. Our data suggest that OH-PCBs exert more effects on mental development than on motor development, and that OH-PCBs exert more effects than PCBs. Four OH-PCBs and the sum of 6 OH-PCBs were positively associated with mental development at 30 months, whereas one OH-PCB was negatively associated at 18 months. Prenatal exposure to BDE-99 was negatively associated with mental development at 18 months, BDE-47 and BDE-100 were positively associated with motor development. Prenatal p,p'-DDE-, PCP, or HBCDD levels were not associated with mental or motor development at 18 months of age. Larger studies are needed to confirm our data.

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Transparency document

The Transparency document associated with this article can be found in the online version.

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References

Ballschmiter, K., Mennel, A., Buyten, J., 1993. Long chain alkyl-polysiloxanes as non-polar stationary phases in capillary gas chromatography. Fresenius J. Anal. Chem. 346, 396–402.
Bell, S., Allen, B., 2000. Book review: bayley scales of infant development, second edition: manual. J. Psychoeduc. Assess. 18, 185–195.
Bemis, J.C., Seegal, R.F., 2004. PCB-induced inhibition of the vesicular monoamine transporter predicts reductions in synaptosomal dopamine content. Toxicol. Sci. 80, 288–295.
Berghuis, S.A., Soechitram, S.D., Hitzert, M.M., Sauer, P.J., Bos, A.F., 2013. Prenatal exposure to polychlorinated biphenyls and their hydroxylated metabolites is associated with motor development of three-month-old infants. Neurotoxicology 38, 124–130.
Berghuis, S.A., Soechitram, S.D., Sauer, P.J., Bos, A.F., 2014. Prenatal exposure to polychlorinated biphenyls and their hydroxylated metabolites is associated with neurological functioning in 3-month-old infants. Toxicol. Sci. 142, 455–462.
Berghuis, S.A., Bos, A.F., Sauer, P.J., Roze, E., 2015. Developmental neurotoxicity of persistent organic pollutants: an update on childhood outcome. Arch. Toxicol. 1–23.
Brouwer, A., Morse, D.C., Lans, M.C., Schuur, A.G., Murk, A.J., Klasson-Wehler, E., et al., 1998. Interactions of persistent environmental organohalogens with the thyroid hormone system: mechanisms and possible consequences for animal and human health. Toxicol. Ind. Health 14, 59–84.
Casas, M., Nieuwenhuijsen, M., Martínez, D., Ballester, F., Basagaña, X., Basterrechea, M., et al., 2015. Prenatal exposure to PCB-153, p, p′-DDE and birth outcomes in 9000 mother–child pairs: exposure–response relationship and effect modifiers. Environ. Int. 74, 23–31.
Castoldi, A.F., Blandini, F., Randine, G., Samuele, A., Manzo, L., Coccini, T., 2006. Brain monoaminergic neurotransmission parameters in weanling rats after perinatal exposure to methylmercury and 2, 2′, 4, 4′, 5, 5′-hexachlorobiphenyl (PCB153). Brain Res. 1112, 91–98.
Daniels, J.L., Longnecker, M.P., Klebanoff, M.A., Gray, K.A., Brock, J.W., Zhou, H., et al., 2003. Prenatal exposure to low-level polychlorinated biphenyls in relation to mental and motor development at 8 months. Am. J. Epidemiol. 157, 485–492.
Dingemans, M.M., van den Berg, M., Westerink, R.H., 2011. Neurotoxicity of brominated flame retardants: (in)direct effects of parent and hydroxylated polybrominated diphenyl ethers on the (developing) nervous system. Environ. Health Perspect. 119, 900–907.
El Majidi, N., Bouchard, M., Carrier, G., 2013. Systematic analysis of the relationship between standardized prenatal exposure to polychlorinated biphenyls and mental and motor development during follow-up of nine children cohorts. Regul. Toxicol. Pharmacol. 66, 130–146.
Eskenazi, B., Chevrier, J., Rosas, L.G., Anderson, H.A., Bornman, M.S.R., Bouwman, H., et al., 2009. The Pine River Statement: Human Health Consequences of DDT Use. Environ. Health Perspect 117, 1359–1367.
Faroon, O., Jones, D., de Rosa, C., 2000. Effects of polychlorinated biphenyls on the nervous system. Toxicol. Ind. Health 16, 305–333.
Gascon, M., Verner, M., Guxens, M., Grimalt, J.O., Forns, J., Ibarluzea, J., et al., 2013. Evaluating the neurotoxic effects of lactational exposure to persistent organic pollutants (POPs) in Spanish children. Neurotoxicology 34, 9–15.
Gladen, B.C., Rogan, W.J., Hardy, P., Thullen, J., Tingelstad, J., Tully, M., 1988. Development after exposure to polychlorinated biphenyls and dichlorodiphenyl dichloroethene transplacentally and through human milk. J. Pediatr. 113, 991–995.
Hempel, M., 1993. Neurological development during toddling age in normal children and children at risk of developmental disorders. Early Hum. Dev. 34, 47–57.
Hovander, L., Athanasiadou, M., Asplund, L., Jensen, S., Wehler, E.K., 2000. Extraction and cleanup methods for analysis of phenolic and neutral organohalogens in plasma. J. Anal. Toxicol. 24, 696–703.
Ilsen, A., Briet, J., Koppe, J., Pluim, H., Oosting, J., 1996. Signs of enhanced neuromotor maturation in children due to perinatal load with background levels of dioxins: follow-up until age 2 years and 7 months. Chemosphere 33, 1317–1326.
Kimura-Kuroda, J., Nagata, I., Kuroda, Y., 2007. Disrupting effects of hydroxy-polychlorinated biphenyl (PCB) congeners on neuronal development of cerebellar Purkinje cells: a possible causal factor for developmental brain disorders? Chemosphere 67, S412–20.
Kitamura, S., Jinno, N., Suzuki, T., Sugihara, K., Ohta, S., Kuroki, H., et al., 2005. Thyroid hormone-like and estrogenic activity of hydroxylated PCBs in cell culture. Toxicology 208, 377–387.
Koopman-Esseboom, C., Morse, D.C., Weisglas-Kuperus, N., Lutkeschipholt, I.J., Van der Paauw, C.G., Tuinstra, L.G., et al., 1994. Effects of dioxins and polychlorinated biphenyls on thyroid hormone status of pregnant women and their infants. Pediatr. Res. 36, 468–473.
Koopman-Esseboom, C., Weisglas-Kuperus, N., de Ridder, M.A., Van der Paauw, C.G., Tuinstra, L.G., Sauer, P.J., 1996. Effects of polychlorinated biphenyl/dioxin exposure and feeding type on infants' mental and psychomotor development. Pediatrics 97, 700–706.
Lans, M.C., Spiertz, C., Brouwer, A., Koeman, J.H., 1994. Different competition of thyroxine binding to transthyretin and thyroxine-binding globulin by hydroxy-PCBs, PCDDs and PCDFs. Eur. J. Pharmacol. Environ. Toxicol. Pharmacol. 270, 129–136.
León-Olea, M., Martyniuk, C.J., Orlando, E.F., Ottinger, M.A., Rosenfeld, C.S., Wolstenholme, J.T., et al., 2014. Current concepts in neuroendocrine disruption. Gen. Comp. Endocrinol. 203, 158–173.
Letcher, R.J., Klasson-Wehler, E., Bergman, A., 2000. Methyl sulfone and hydroxylated metabolites of polychlorinated biphenyls. Anonymous Volume 3 Anthropogenic Compounds Part K. Springer, pp. 315–359.
Longnecker, M.P., Wolff, M.S., Gladen, B.C., Brock, J.W., Grandjean, P., Jacobson, J.L., et al., 2003. Comparison of polychlorinated biphenyl levels across studies of human neurodevelopment. Environ. Health Perspect. 111, 65–70.
McDonald, T.A., 2002. A perspective on the potential health risks of PBDEs. Chemosphere 46, 745–755.
McKinney, J.D., Waller, C.L., 1994. Polychlorinated biphenyls as hormonally active structural analogues. Environ. Health Perspect. 102, 290–297.
Meerts, I.A., Assink, Y., Cenijn, P.H., Van Den Berg, J.H., Weijers, B.M., Bergman, A., et al., 2002. Placental transfer of a hydroxylated polychlorinated biphenyl and effects on fetal and maternal thyroid hormone homeostasis in the rat. Toxicol. Sci. 68, 361–371.
Meerts, I.A., Lilienthal, H., Hoving, S., van den Berg, J.H., Weijers, B.M., Bergman, A., et al., 2004. Developmental exposure to 4-hydroxy-2,3,3',4',5-pentachlorobiphenyl (4-OH-CB107): long-term effects on brain development, behavior, and brain stem auditory evoked potentials in rats. Toxicol. Sci. 82, 207–218.
Meijer, L., Weiss, J., Van Velzen, M., Brouwer, A., Bergman, Å, Sauer, P.J., 2008. Serum concentrations of neutral and phenolic organohalogens in pregnant women and some of their infants in the Netherlands. Environ. Sci. Technol. 42, 3428–3433.
Morse, D.C., Wehler, E.K., Wesseling, W., Koeman, J.H., Brouwer, A., 1996. Alterations in rat brain thyroid hormone status following pre-and postnatal exposure to polychlorinated biphenyls (Aroclor 1254). Toxicol. Appl. Pharmacol. (136), 269–279.
Park, H.Y., Park, J.S., Sovcikova, E., Kocan, A., Linderholm, L., Bergman, A., et al., 2009. Exposure to hydroxylated polychlorinated biphenyls (OH-PCBs) in the prenatal period and subsequent neurodevelopment in eastern Slovakia. Environ. Health Perspect. 117, 1600–1606.
Pluim, H.J., de Vijlder, J.J., Olie, K., Kok, J.H., Vulsma, T., van Tijn, D.A., et al., 1993. Effects of pre- and postnatal exposure to chlorinated dioxins and furans on human neonatal thyroid hormone concentrations. Environ. Health Perspect. 101, 504–508.

Ribas-Fito, N., Sala, M., Kogevinas, M., Sunyer, J., 2001. Polychlorinated biphenyls (PCBs) and neurological development in children: a systematic review. J. Epidemiol. Community Health 55, 537–546.
Rogan, W.J., Gladen, B.C., 1991. PCBs, DDE, and child development at 18 and 24 months. Ann. Epidemiol. 1, 407–413.
Roth, N., Wilks, M., 2014. Neurodevelopmental and neurobehavioural effects of polybrominated and perfluorinated chemicals: a systematic review of the epidemiological literature using a quality assessment scheme. Toxicol. Lett. 230, 271–281.
Rothman, K.J., 1990. No adjustments are needed for multiple comparisons. Epidemiology 43–46.
Roze, E., Meijer, L., Bakker, A., Van Braeckel, K.N., Sauer, P.J., Bos, A.F., 2009. Prenatal exposure to organohalogens, including brominated flame retardants, influences motor, cognitive, and behavioral performance at school age. Environ. Health Perspect. 117, 1953–1958.
Santos, Luttikhuizendos, Elsa, S., de Kieviet, J.F., Königs, M., van Elburg, R.M., Oosterlaan, J., 2013. Predictive value of the Bayley scales of infant development on development of very preterm/very low birth weight children: a meta-analysis. Early Hum. Dev. 89, 487–496.
Schuur, A.G., Brouwer, A., Bergman, Å, Coughtrie, M.W., Visser, T.J., 1998. Inhibition of thyroid hormone sulfation by hydroxylated metabolites of polychlorinated biphenyls. Chem. Biol. Interact. 109, 293–297.
Soechitram, S.D., Athanasiadou, M., Hovander, L., Bergman, A., Sauer, P.J., 2004. Fetal exposure to PCBs and their hydroxylated metabolites in a Dutch cohort. Environ. Health Perspect. 112, 1208–1212.
Soechitram, S.D., Berghuis, S.A., Visser, T.J., Sauer, P.J., 2017. Polychlorinated biphenyl exposure and deiodinase activity in young infants. Sci. Total Environ. 574, 1117–1124.
Van der Meulen, B., Ruiter, S., Spelberg, H.L., Smrkovsky, M., 2002. Bayley Scales of Infant Development-II. Dutch version. Swets, Lisse.
Verner, M., Plusquellec, P., Muckle, G., Ayotte, P., Dewailly, E., Jacobson, S., et al., 2010. Alteration of infant attention and activity by polychlorinated biphenyls: unravelling critical windows of susceptibility using physiologically based pharmacokinetic modeling. Neurotoxicology 31, 424–431.
Walkowiak, J., Wiener, J., Fastabend, A., Heinzow, B., Krämer, U., Schmidt, E., et al., 2001. Environmental exposure to polychlorinated biphenyls and quality of the home environment: effects on psychodevelopment in early childhood. Lancet 358, 1602–1607.
Williams, G., 2008. Neurodevelopmental and neurophysiological actions of thyroid hormone. J. Neuroendocrinol. 20, 784–794.