Title

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Journal

Chemosphere, 287(Pt 4)

ISSN

0045-6535

Authors

Simeone, Regina M
Howards, Penelope P
Anderson, Elizabeth
et al.

Publication Date

2022

DOI

10.1016/j.chemosphere.2021.132375

Peer reviewed

HHS Public Access

Author manuscript

Chemosphere. Author manuscript; available in PMC 2023 January 01.

Published in final edited form as:

Chemosphere. 2022 January ; 287(Pt 4): 132375. doi:10.1016/j.chemosphere.2021.132375.

Pre- and Postnatal Polychlorinated Biphenyl Exposure and Cognitive and Behavioral Development at age 45 Months in a cohort of Slovak Children

Regina M. Simeone[1], **Penelope P. Howards**[1], **Elizabeth Anderson**[2], **Todd A. Jusko**[2], **Beata Drobná**[3], **Anton Kočan**[4], **Kamil Čonka**[3], **Anna Fabišiková**[5], **L'ubica Palkovičová Murínová**[3], **Richard L. Canfield**[6], **Dean Sonneborn**[7], **Soňa Wimmerová**[3], **Kelly Thevenet-Morrison**[2], **Tomáš Trnovec**[3], **Irva Hertz-Picciotto**[7], **Eva Šovčíková**[3]

[1]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA

[2]Department of Public Health Sciences, University of Rochester School of Medicine and Dentistry, Rochester, NY

[3]Slovak Medical University, Bratislava, Slovakia

[4]Research Centre for Toxic Compounds in the Environment, Masaryk University, Brno, Czech Republic

[5]Department of Analytical Chemistry, University of Vienna, Vienna, Austria

[6]Division of Nutritional Sciences, Cornell University, Ithaca, NY

[7]Department of Public Health Sciences, University of California, Davis, CA

Abstract

Corresponding author: Elizabeth Anderson, University of Rochester School of Medicine and Dentistry: Department of Public Health Sciences: 265 Crittenden Drive, Rochester, NY, 14642, Phone: 815-382-5360, Elizabeth_Anderson@URMC.Rochester.edu.

Regina M. Simeone: Writing—Original Draft, Formal Analysis, Investigation, Writing—Review & Editing; **Penelope Howards:** Resources, Writing—Original Draft, Writing—Review & Editing, Supervision; **Elizabeth Anderson:** Writing—Review & Editing, Formal Analysis, Visualization; **Todd Jusko:** Investigation, Resources, Supervision, Project Administration, Writing—Original Draft, Writing—Review & Editing, Funding Acquisition; **Beata Drobná:** Writing—Original Draft, Writing—Review & Editing, Methodology, Validation, Investigation; **Anton Kočan:** Writing—Original Draft, Writing—Review & Editing, Methodology, Validation, Investigation, Supervision; **Kamil Čonka:** Writing—Original Draft, Writing—Review & Editing, Methodology, Validation, Investigation, Supervision; **Anna Fabišiková:** Methodology, Validation; **L'ubica Palkovičová Murínová:** Investigation, Resources, Supervision, Project Administration, Writing—Original Draft, Writing—Review & Editing, Funding Acquisition; **Richard L. Canfield:** Methodology, Writing—Original Draft, **Dean Sonneborn:** Software, Validation, Formal Analysis, Data Curation; **Soňa Wimmerová:** Software, Validation, Formal Analysis, Data Curation; **Kelly Thevenet-Morrison:** Software, Validation, Formal Analysis, Data Curation; **Tomáš Trnovec:** Investigation, Resources, Supervision, Project Administration, Writing—Review & Editing, Funding Acquisition; **Irva Hertz-Picciotto:** Investigation, Resources, Supervision, Project Administration, Writing—Original Draft, Writing—Review & Editing, Funding Acquisition, Conceptualization; **Eva Šovčíková:** Conceptualization, Methodology, Investigation, Writing—Review & Editing, Supervision, Funding Acquisition

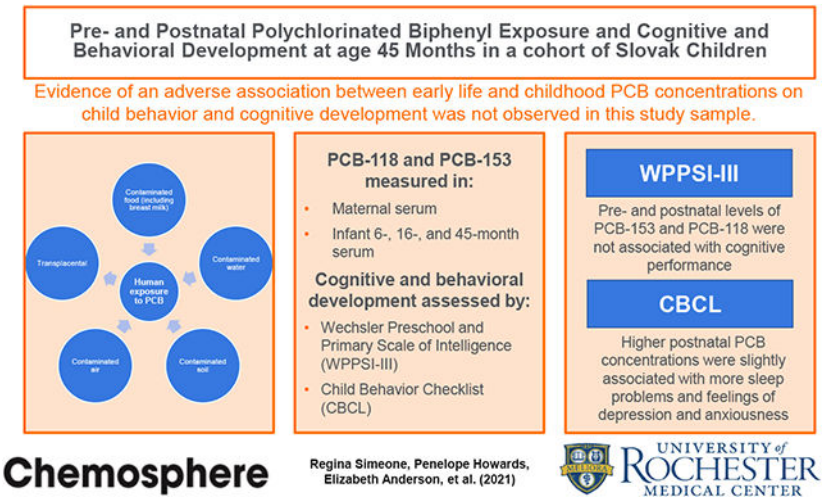
Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Financial Disclosure: The authors have no financial disclosures to declare.

Evidence of associations of pre- and postnatal exposure to polychlorinated biphenyls (PCBs) with cognitive development beyond early childhood is inconsistent. A previous report from this cohort observed adverse associations between early life PCB exposures and infant Bayley scores at age 16 months. The present study examines pre- and postnatal PCB exposures in relation to both behavior and cognitive development at age 45 months. Participants were 472 mother-child pairs residing in an area of eastern Slovakia characterized by environmental contamination with PCBs, which resulted in elevated blood serum concentrations. PCB-153 and PCB-118 concentrations were measured in maternal and in infant 6-, 16-, and 45-month serum samples. At age 45 months, children were administered five subtests of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III), and mothers completed the Child Behavior Checklist (CBCL). Negative binomial and multiple linear regressions were used to estimate PCB—CBCL and PCB—WPPSI-III subtest score associations, respectively. Pre- and postnatal levels of PCB-153 and PCB-118 were not associated with cognitive performance on the WPPSI-III in this cohort. There was some suggestion that higher postnatal PCB concentrations were associated with more sleep problems and feelings of depression and anxiousness.

Graphical Abstract



Keywords

Polychlorinated biphenyls; Child Behavior Checklist; Wechsler Preschool and Primary Scale of Intelligence-III; Slovakia

Introduction

Polychlorinated biphenyls (PCBs) are a class of anthropogenic chemicals that were produced between 1929 and the late 1970s in the United States (1). Due to their distribution in the environment (2, 3), long half-lives (5-15 years) (4-6), and biomagnification up the food chain (2, 7), most individuals have detectable levels of PCBs in their bodies. Human exposure to PCBs occurs through consumption of contaminated food, including breast milk (8), from contact with environmental exposures in air, soil, and water due to improper

disposal of PCB waste (2, 3, 7, 10), and also transplacentally (11). Because *in utero* and lactational exposures occur during periods of rapid brain development, adverse effects of PCBs on behavior and cognition are a plausible consequence of exposure during these times (12). Increased prenatal PCB exposure has been associated with decreased cognitive ability in infants and young children (13-24).

The Michalovce district, in Slovakia, housed a PCB production plant from 1959-1984, which has been identified as a source of PCB environmental contamination mostly through liquid waste into a nearby river and lake, but also via landfill waste (10, 25, 26). Sources of exposure in this area may include fatty foods, soil, air, and water (10, 27). In 2002, a combined cohort from the Michalovce and nearby Svidnik district was established to study the effects of pre- and postnatal PCB exposure on child development, including neurodevelopment. In a previous report from this combined cohort, elevated prenatal PCB exposures were associated with lower scores on the Bayley Scales of Infant Development (BSID) at 16 months, specifically with dioxin-like mono-ortho congeners 118 and 156 (20). Cognitive development changes rapidly in infancy and early childhood; to determine whether this association persists beyond 16 months of age, and to evaluate behavior, the present study extends follow-up to 45 months in the Michalovce cohort and evaluates associations between pre- and postnatal concentrations of PCB congeners 153 and 118 and behavior on the Child Behavior Checklist (CBCL) and child cognition on subscales of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III).

Methods

Study Population

Between 2002 and 2004, 1134 mother-infant pairs were recruited from the Michalovce and Svidnik districts of Slovakia. Follow-up in both districts continued through age 16 months; thereafter, follow-up was limited to the Michalovce cohort (n=811). Mothers were screened as they entered the hospital for delivery; Michalovce has one main hospital, and this method likely captured most deliveries during the study period. Women were invited to participate if they were at least 18 years of age, had lived in their districts for at least five years, and had not had a major illness during pregnancy. Women with more than four previous pregnancies were excluded in order to reduce the effects of parity on maternal PCB concentrations. Women with multiple births and infants with major birth defects were not invited to participate (28). At the 45-month assessment, all mother-child pairs with at least one PCB-153 or 118 measurement and at least one outcome (CBCL or WPPSI-III) measurement were included.

Data Collection

When the child was approximately 45-months old, mothers were contacted to schedule a follow-up visit. At this visit, 472 mother-child pairs participated in the study (58% of the original 811 mother-child pairs), at which time mothers completed the CBCL (28) and children completed the WPPSI-III (29). The study protocol was approved by the Institutional Review Boards at the University of California, Davis and the Slovak Medical

University. Detailed descriptions of population selection, consent protocols, and data and specimen collection are described in previous reports (20, 21).

Mothers completed the Raven's Progressive Matrices, a non-verbal IQ test (31), and provided demographic information after their child's birth, during their 5-day hospitalization for delivery (32). Maternal reproductive and infant birth data were abstracted from medical records. Romani ethnicity was assigned if the ethnic origin of either of the mother's parents was Romani, the Romani language was spoken at home, or the mother was planning to raise her child with the Romani language. Otherwise, ethnicity was assigned as Slovak/other European. At the 16-month follow-up visit, a modified version of the Home Observation for Measurement of the Environment (HOME), an assessment designed to evaluate the amount of stimulation provided to a child in the home, was completed (33, 34). A modified HOME was used because follow-up occurred at the outpatient Department of Pediatrics; three items from the original version that required direct observations of play materials in the home had to be omitted. Based on sensitivity analysis in a birth cohort study from Düsseldorf, scores from this modified version were highly correlated with scores from the full scale (Winneke G, Walkowiak J, personal communication) (20).

PCB/Lipid Measurement

Two 9-mL vacutainer tubes (S-Monovette, Sarstedt, Germany) were used to collect a maternal blood specimen at delivery and up to 9 mL of blood was collected from children at 6, 16, and 45 months. Study staff transported samples on dry ice to the Slovak Medical University in Bratislava for storage at −20°C until analysis. Fifteen PCB congeners in maternal, infant, and child serum were measured: International Union of Pure and Applied Chemistry (IUPAC) numbers 28, 52, 101, 105, 114, 118, 123^{+149}, 138^{+163}, 153, 156^{+m}, 157, 167, 170, 180, and 189. All samples were analyzed by the Department of Toxic Organic Pollutants at the Slovak Medical University in Bratislava. This laboratory serves as the National Reference Laboratory for Dioxins and Related Compounds for the Slovak Republic. The procedure for determination of PCB concentrations involved extraction, cleanup, and quantitation by gas chromatography with electron capture detection (GC-ECD) (8, 9). Fasting, whole blood samples were collected from participants and allowed to clot and were then centrifuged at 3000 rpm for 15 min. Solid phase extraction (SPE) was used to prepare samples for PCB congener determination (9). The serum samples were spiked with extraction standard solution (PCB174, 500 ng/mL in n-heptane) and equivalent amounts of a water : 1-propanol (85:15, v/v) mixture were added to each sample. After sonication, the sample was applied on a conditioned SPE column (Alltech Extract Clean High Capacity C18 endcapped, Alltech, Associates Inc., Lokeren, Belgium) aspirating twice repeatedly through the column. The matrix residues were washed out with water : 1-propanol (85:15, v/v) and the SPE column was dried. The analytes were eluted from the SPE column with n-hexane : DCM (1:1, v/v) into a vial. The SPE hexane extract was purified using a silica/H_2SO_4 column and injected (Splitless mode, injection volume 2 μl) onto a 60 m × 0.25 mm ID × 0.25 μm FT DB-5 (J&W Scientific, USA) capillary column installed in a Gas Chromatograph 6890 N (Agilent Technologies, USA) equipped with micro electron capture detector, and Agilent Chemstation software. The following temperature program was used: from initial temperature 110 °C (1.5 min) to 200 °C (0.2 min) at a rate of 30 °C/min

and then 2.5 °C/min to final temperature 305 °C (5 min). Five standard congener mixtures for 15 PCB congeners established multilevel calibration curves. The calibration levels of PCBs ranged from 0.5 to 200 ng/mL. The method recovery was checked using PCB-174 as an internal standard. PCB-103 served as a syringe standard to correct volume of samples analyzed. The reported concentrations were all blank corrected and adjusted by recovery rates.

Quality control activities consisted of analyses of samples in batches of 10 run simultaneously with a blank sample and in-house reference material (spiked porcine serum). The response for a particular congener during daily analysis of a standard solution had to be in the range of 90–110% using the concentration at the midpoint of the calibration curves for that congener. The limit of detection (LOD) for each analyte was calculated by considering the ratio of background to noise (multiplied by three), the peak height of the analyte in standard solution of the lowest concentration, and the sample volume used for analysis. The laboratory of the Department of Toxic Organic Compounds has been certified by the Slovak National Accreditation Service (Certificate No. S 111) and regularly participates in international laboratory evaluations and comparisons in PCB analyses of serum (German External Quality Assessment Scheme, External quality assessment scheme for toxicological analyses in biological materials, University Erlangen, Germany).

PCB-153 was used as a proxy for total PCB exposure, as it is correlated with the sum of all measured PCBs in women and children (maternal PCB-153 and Σ maternal PCB $r_{spearman}$=0.993, p<0.001; month 16 PCB-153 and Σ month 16 PCB $r_{spearman}$=0.998, p<0.001; month 45 PCB-153 and Σ month 45 PCB $r_{spearman}$=0.998, p<0.001) as well as with other prevalent congeners (e.g., maternal PCB-138: $r_{spearman}$=0.987, p<0.001; month 16 PCB-138: $r_{spearman}$=0.996, p<0.001; month 45 PCB-138: 0.996, p<0.001) (21, 35-37) and because it is often used as a congener for comparison across populations (39). PCB-118, a dioxin-like, mono-ortho substituted congener, was examined because of previously reported associations suggesting deficits on the BSID at 16 months of age with greater exposure to dioxin-like, mono-ortho congeners in this cohort (20). PCB concentrations measured in maternal serum were regarded as representing prenatal, in utero exposure. Postnatal exposure was estimated by infant and child serum concentrations at 6-, 16-, and 45-months. Total maternal and child serum lipids were estimated using the enzymatic summation formula of Akins and Takayama (40, 41). Laboratory methods are described in detail elsewhere (20, 32).

Behavioral and Cognitive Assessment

The CBCL is comprised of 100 items for which parents report their child's behavior during the previous two months on a three-level scale: 0 (not true), 1 (somewhat or sometimes true), or 2 (very or often true) (29, 42). This assessment was a version for infants and children aged 1.5-5 years. Subscale scores are computed by summing scores on select subsets of items. Seven subscales are calculated: Emotionally Reactive, Anxious/Depressed, Somatic Complaints, Withdrawn, Sleep Problems, Attention Problems, and Aggressive Behavior. Externalizing behavior scores are obtained by summing the scores from the Attention Problems and Aggressive Behavior subscales; Internalizing behavior scores are

obtained by summing the Emotionally Reactive, Anxious/Depressed, Somatic Complaints, and Withdrawn subscale scores (42). Higher scores indicate a greater number of behavioral problems. All CBCL subscales were examined, as well as Internalizing and Externalizing behavior scores. The CBCL has not been standardized in the Slovak population, thus raw CBCL scores were used in all analyses (42).

The WPPSI-III is a test of intelligence designed for children from age 2.5 to 7.25 years (30). Five subtests of the WPPSI-III were administered at the 45-month follow-up: Receptive Vocabulary, Information, Block Design, Object Assembly, and Picture Naming. Because of a lack of normative data on WPPSI-III in this population, scaled scores for the subtests were not computed; instead, results on the five subtests were left as raw scores in order to avoid cross-cultural biases from non-Slovak standardization schemes. Each of the five subtests were analyzed separately.

All items from the CBCL and the WPPSI-III were translated from English into Slovak by a native Slovak speaker with 5 years of university study in English language and 40 years of experience in English-Slovak translation, in collaboration with the study psychologist (ES). All CBCL and WPPSI-III evaluations were administered by a doctoral-level clinical psychologist (ES) with 15 years of experience in child assessment who was unaware of maternal and child PCB concentrations.

Data Analysis

Differences in median maternal, 6-month, and 45-month serum PCB-153 and −118 concentrations by characteristics of the mother-child pairs were examined using Kruskal-Wallis tests. Potential confounders were identified using directed acyclic graphs (DAGs) and a literature review. Child's sex and age, ethnicity, maternal parity, maternal age, education, smoking during pregnancy, alcohol consumption during pregnancy, and Raven score were evaluated as potential confounders for all models. For prenatal PCB models, child's birth weight and breastfeeding duration were considered causal intermediates potentially influenced by maternal PCB levels and therefore not considered as potential confounders. Breastfeeding duration was considered part of the postnatal exposure for the 16- and 45-month exposures and was not considered as a potential confounder; birthweight was considered a potential confounder for the 6-, 16-, and 45-month models. HOME score was determined to be collinear with maternal Raven score. Potential confounders based on the DAGs were entered into the initial model. The final models for each cognitive outcome included all covariates whose removal changed the effect estimate for PCB exposure by ≥10% (parity and child's sex) when compared with a model adjusted for all potential confounders. Maternal Raven score, ethnicity, age-specific serum lipids, and child's age at assessment were retained in all models.

Of the children included in the analysis, 25 were evaluated when they were older than 48 months (range 43-53 months); the analysis was repeated excluding these children to examine whether these observations influenced interpretation of results. As an additional analysis, the PCB-BSID association (20) was re-estimated among the subset of children participating at the 45-month follow-up, to assess potential selection over time.

Statistical model

The CBCL scores were right skewed, with clusters of children having scores of zero for each subscale (9.1% to 30.4% depending on the scale). Data transformation did not yield normal conditional distributions, thus negative binomial regression models were fit to analyze the association between PCB concentration and CBCL subscale scores. WPPSI-III did not violate normality assumptions and multiple linear regression models were fit to estimate the association between PCB concentration and WPPSI-III scores. All analyses were conducted in SAS (Version 9.4, SAS Institute, Cary, NC).

Results

In total, 472 mother-child pairs had PCB exposure measurements (maternal, child 6-month, child 16-month, or child 45-month PCB-153 or −118 measurements). There were 396 mother-child pairs of European descent and 77 mother-child pairs of Romani descent. Mothers older than 30 years of age at delivery were more likely to have higher levels of PCB-153 (compared with younger mothers, $p<0.01$) and at 6 and 45 months, their children were also more likely to have higher PCB-153 concentrations ($p<0.01$) (Table 1). Children who were breastfed more than six months had greater PCB-153 levels at 6 and 45 months (medians 2.2 ng/mL and 1.4 ng/mL, respectively), compared with children who were breastfed less than six months or not at all (0.6 mg/mL and 0.3 ng/mL, respectively) ($p<0.01$).

The Spearman correlations between the two congeners 153 and 118 (on a wet-weight basis) in each of maternal, child 6-, child 16-, and child 45-month sera were 0.80, 0.92, 0.92, and 0.86, respectively ($p<0.001$ for all). Maternal PCB-153 was moderately correlated with child's 6-month PCB-153 ($r_{spearman}=0.38$, $p<0.001$), child's 16-month PCB-153 ($r_{spearman}=0.31$, $p<0.001$) and child's 45-month PCB-153 ($r_{spearman}=0.34$, $p<0.001$). The strongest correlation among children sera was observed between 16-month and 45-month PCB-153 congener levels ($r_{spearman}=0.91$, $p<0.001$). Overall, maternal, 6-month, 16-month, and 45-month concentrations of PCB-153 were higher at each time point compared with PCB-118 (Figure 1). Distributions of measured congeners are provided in Table 2.

In this same subset of complete PCB and cognitive data, PCB-153 concentrations were detectable in ≥99% of individuals at any time point, and for PCB-118, concentrations were above a limit of detection in 89% of maternal samples, 82% of 16-month infant samples, and 86% of 45-month child samples. The LOD for PCB-118 varied across analytic batches and ranged from 0.009 to 0.279 ng/mL in maternal serum and 0.002 to 0.074 ng/mL in 16- and 45-month serum. Among those with completed assessments and maternal PCB measurements, two mother-child pairs were missing maternal Raven score.

Table 3a presents results from negative binomial regression models predicting CBCL subscale scores for an IQR increase in PCB-153 and Table 3b for PCB-118. Each model included the mother-child pairs with complete data for all covariates (total serum lipids, maternal Raven score, ethnicity, child's sex, child's age, parity, and age at assessment). Negative binomial regression is performed on the natural-log-scale, and coefficients have been multiplied by the IQR and exponentiated. Generally, maternal, 6-, 16-, and 45-month

exposures to PCB were not associated with CBCL performance with most estimates around the null value of 1.00. However, child 16- and 45-month PCB-153 and −118 exposures were most strongly associated with increased maternal report of sleep problems and feelings of anxiousness and depression. A one-IQR difference in 16-month PCB-153 increased reported Sleep Problem score by a factor of 1.07 (95% CI: 1.01, 1.14) and a one-IQR increase in 16-month PCB-118 increased reported Sleep Problem scores by a factor of 1.04 (95% CI: 1.00, 1.08). For feelings of Anxiousness and Depression, a one-IQR increase in 16-month PCB-153 increased reported Anxious/Depression score by a factor of 1.05 (95% CI: 1.0-1.10) and a one-IQR increase in 16-month PCB-118 increased reported Anxious/Depression score by a factor of 1.03 (95% CI: 1.00-1.06).

Table 4a presents the results for linear regression predicting WPPSI-III subtest scores for an IQR increase in PCB-153 and Table 4b for PCB-118 and WPPSI-III subtests. Although the majority of the observed associations were close to the null, increased 6-month, 16-month, and 45-month PCB-153 levels were associated with improved Picture Naming performance.

When 25 observations of children tested when they were older than 48 months were removed, results remained approximately null for the CBCL or WPPSI-III evaluations (data not shown). Similar to the associations observed in this analysis, results from the PCB-Bayley Scales of Infant Development scores in the 45-month subset were small and not significant (data now shown in tabular form).

Discussion

The present study examined whether increased prenatal and early childhood exposure to PCBs is associated with lower intelligence scores and increased behavioral problems at age 45 months. For the most part, despite cognitive deficits observed at 16 months using the BSID, evidence of a meaningful association between prenatal or postnatal PCB exposures and children's behavior or intelligence measures at 45 months of age was not observed. Furthermore, in the subset of 45-month participants who also completed the 16-month BSID, there was no evidence of adverse effects on child behavior or cognition at age 45 months.

Studies examining the impact of prenatal exposure to PCBs on cognitive outcomes have shown adverse effects at the youngest ages that tended to not be replicated as children age. In a cohort of Dutch children, reduced neurologic performance was observed at 18 months for infants with higher prenatal PCB exposure (44); at 42 months, poorer performance on the Kaufman Battery was associated with PCB exposure (18). However, at six-and-a-half years, children from this cohort who were more highly exposed prenatally performed better on the McCarthy Scales of Children's abilities (45). In a cohort from North Carolina, investigators observed negative associations with increased PCB exposure and newborn reflexes (46) and scores on the BSID Psychomotor Development Index (PDI) at six- and 12-months (14); however, at three-, four-, and five-years, no effect of prenatal PCB exposure on performance on the McCarthy scales was observed (47). Similarly, in a German cohort, poorer performance on the BSID and Kaufman Battery was observed among children more highly exposed through 42 months of age (19, 48); by 72 months of age, there was no

association between PCB exposure and mental development (49). Thus, our results are in concordance with a pattern of cognitive deficits in children who were exposed to higher concentrations of PCBs during the prenatal period, and the reduction of those associations as the child matures.

Few epidemiologic studies have detected an association between cognitive development in early childhood and PCB exposure in the postnatal period (13-15). Postnatal exposure measured through breast milk collected two weeks post-partum in a German cohort, however, was negatively associated with performance on the Kaufman Battery at up to and including 42 months (48). This exposure, however, likely reflects prenatal, rather than postnatal exposure, given the short time between birth and breastmilk collection. A second German birth cohort found no effect on the BSID MDI and a non-significant but slight decrease in PDI scores when examining associations with postnatal PCB exposure at 12 and 24 months (50). Again, the postnatal PCB exposure may reflect prenatal levels of PCB, though the prenatal contribution would be reduced by 24 months for many congeners; moreover, the exposure concentrations of PCB in the second German birth cohort were substantially less than those observed in the initial cohort, possibly explaining the null results. In a small cohort of children from New York, postnatal PCB exposure, measured in breast milk at four weeks postpartum, a negative, though not statistically significant, association was observed between the highest levels of PCB exposure and performance on the BSID at 24 months of age (22). Both pre- and postnatal exposures to PCB have also been associated with behavioral changes in children (51, 52), as well as in animal studies (53). Our study detected a trend between 16- and 45-month PCB serum levels, Sleep Problem CBCL subscales, and Anxiousness/Depression CBCL subscales. Additionally, there was a small but positive trend identified between 6-, 16-, and 45- month PCB-153 levels and picture naming WPPSI-III performance.

There were several limitations to our study. First, the small 6-month sample size and reduction in sample size from the 16-month to the 45-month evaluation could have reduced the ability to detect small differences in CBCL and WPPSI-III outcomes or biased the results due to loss to follow up. However, measured levels of PCB-153 and 118 were similar in those who were lost to follow up compared with those who participated at 6-, 16-, and 45 months (data not shown); additionally, there were no significant differences in performance on the Bayley Scales MDI and PDI scores at 16 months comparing those lost to follow up with those who participated at 6-, 16-, and 45-months (data not shown), thus a large effect due to selection is unlikely. Second, CBCL and WPPSI-III measures have not been standardized in the Slovak population. Studies of the CBCL and Wechsler scales in various countries suggest that the assessments exhibit cross-cultural validity and can be used for assessing behavioral problems and intelligence (54-56). However, cultural differences or translation discrepancies may weaken the ability of these evaluations to detect problems with cognitive development by introducing non-differential misclassification; with the CBCL, for example, parents may be reluctant to report on behavioral problems. Also, this assessment occurred when children were approximately 45 months of age; young children can be difficult to assess, and their scores even on standardized instruments are often sensitive to minor variations in, e.g., the child’s mood, the environment and the time of day, which can introduce additional non-differential misclassification. Third, in this

population, women with the highest measured PCB exposure tended to be older, better educated, and have higher Raven scores. Thus, positive associations indicating a protective effect of PCB exposure may be the result of residual and/or negative confounding. In models that adjusted for some of these covariates during the confounding assessment, however, results did not meaningfully change.

The present study had several strengths. PCB exposure was based on measured concentrations rather than a proxy measure such as fish consumption, or duration of breastfeeding. This is one of the few studies with childhood measures of PCB exposure. Despite attrition from the original cohort, the sample at 45 months is larger than many previous studies of PCB and neurobehavioral development and included a considerable range of PCB exposure. We were also able to measure and adjust for several potentially important confounders, including maternal intelligence. Finally, both cognitive function and behavior problems were assessed, allowing for examination of different types of neurodevelopmental outcomes.

Findings from this study add insight to the impact of prenatal and postnatal PCB exposure on neurodevelopment and whether adverse associations seen in infancy continue into early childhood. Additionally, this study incorporates childhood measures of PCB exposure. In this population of Slovak children, postnatal exposure to both of the PCB congeners we examined was associated with reports of sleep problems and feelings of anxiousness/depression on the CBCL. Results from this investigation following a birth cohort in eastern Slovakia with environmental PCB exposures, relative to other cohorts of the last 15 years, could mean that that possible early cognitive deficits in children exposed prenatally and postnatally to PCBs may be transient and may decrease as the children mature. This pattern, previously observed in three other cohorts, may be due to a restricted range of exposure, external factors that might attenuate PCB exposures, residual or unmeasured confounding, or the age of the children. Additional studies will be critical in better understanding the role of both prenatal and postnatal PCB exposure in later childhood development, as well as the role of potential mitigating factors that could attenuate possible adverse effects.

Acknowledgements:

This work was supported by NIH grants R01-CA096525, R01-ES030300, R03-TW007152, K12-ES019852, and P30-ES001247, grants from the Slovak Ministry of Health 2007/9-SZU-05 and 2012/47-SZU-11, and a grant from the Slovak Research and Development Agency APVV-0571-12. Support was also provided by a Fulbright Grants from the US State Department and in part by Center of Excellence of Environmental Health, IMS No. 26240120033, based on the supporting operational Research and Development program financed from the European Regional Development Fund.

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- Prenatal PCB-associated cognitive deficits are generally well-documented
- There is mixed evidence as to whether these effects persist into childhood
- This association was examined in a cohort with varied PCB exposures
- Evidence of an adverse association was not observed in this study

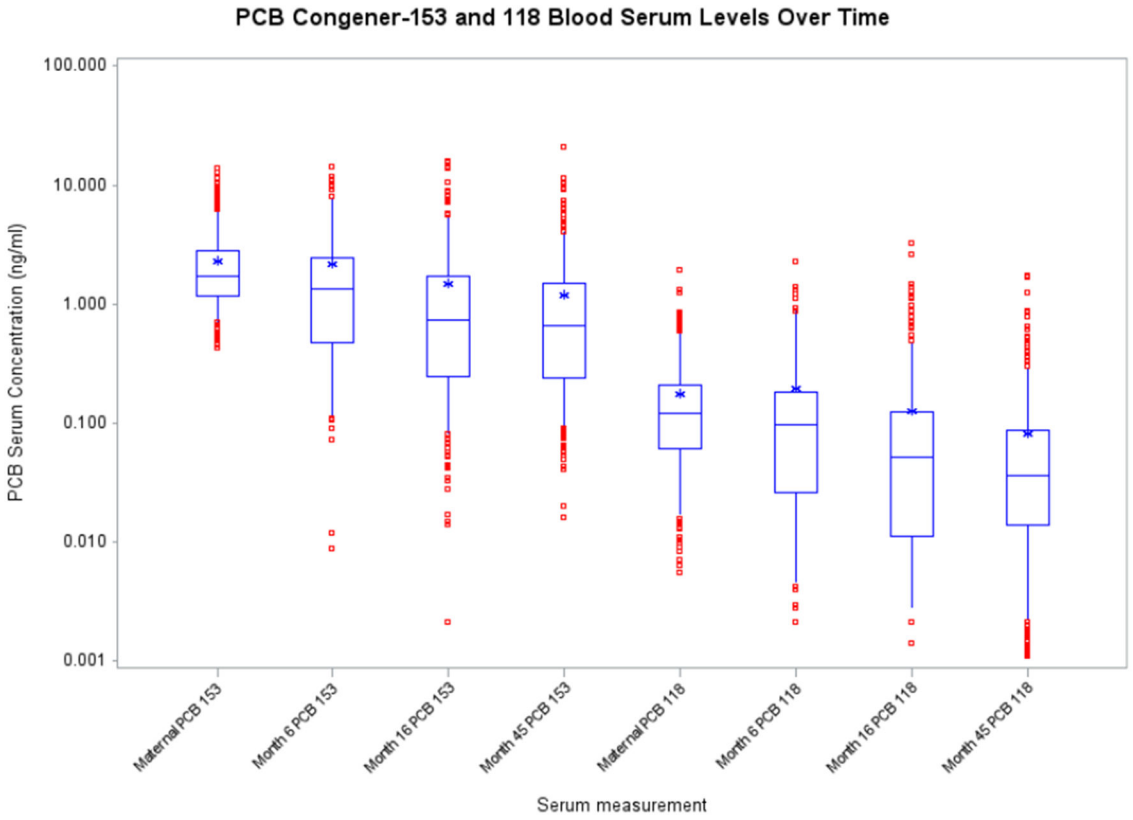

Figure 1.

Boxplots of blood serum PCB congeners 153 and 118, measured in the mother and in the child at 6, 16, and 45 months among those with PCB measurements at least one time point. Concentrations are presented on the natural-log-scale. The boxplot represents the median and interquartile range of each congener at each time-point; the asterisk represents the mean of each congener; whiskers extend to the 5th and 95th percentiles.

Table 1.

Median (IQR[a]) maternal serum polychlorinated biphenyl (PCB) congener 153 (ng/mL), child 6-month serum PCB congener 153 (ng/mL), and child 45-month serum PCB congener 153 (ng/mL) by population characteristics of a cohort of mother-child pairs from Michalovce, Slovakia.

Characteristic	N=472	%	Maternal PCB-153 (ng/mL) Median (IQR[a])		6-month PCB-153 (ng/mL) Median (IQR[a])		45-month PCB-153 (ng/mL) Median (IQR[a])	
Maternal age at delivery (years)								
18-24	188	39.8	1.3	(0.96, 2.2)[§]	1.3	(0.5, 2.5)[§]	0.6	(0.2, 1.3)[§]
25-29	180	38.1	1.8	(1.3, 2.8)	1.0	(0.3, 2.0)	0.6	(0.2, 1.2)
≥30	104	22.0	2.5	(1.6, 4.1)	2.1	(0.6, 2.4)	1.0	(0.4, 1.8)
Maternal education								
Basic Schooling	98	21.1	1.3	(0.8, 2.1)[§]	1.4	(0.4, 3.5)	0.8	(0.2, 1.5)
Some High School	115	24.8	2.0	(1.2, 3.0)	1.2	(0.4, 2.7)	0.5	(0.2, 1.0)
High School Graduate	223	48.1	1.7	(1.3, 2.8)	1.2	(0.5, 2.2)	0.7	(0.2, 1.6)
College or Higher	28	6.0	2.0	(1.3, 2.8)	2.3	(1.0, 3.9)	0.9	(0.5, 1.9)
Missing	8							
Maternal smoking during pregnancy								
Yes	74	16.2	1.8	(1.1, 3.2)	1.3	(0.5, 2.4)	0.6	(0.2, 1.1)
No	382	83.8	1.7	(1.2, 2.7)	1.4	(0.5, 3.1)	0.7	(0.3, 1.5)
Missing	16							
Maternal alcohol consumption during pregnancy								
Yes	60	13.4	1.8	(1.1, 2.7)	1.4	(0.6, 2.7)	0.5	(0.2, 1.0)
No	389	86.6	1.8	(1.2, 2.8)	1.1	(0.3, 1.9)	0.7	(0.2, 1.5)
Missing	23							
Breastfeeding								
< 6 months	228	52.7	1.7	(1.2, 2.8)	0.6	(0.2, 1.0)[§]	0.3	(0.1, 0.6)[§]
≥ 6 months	205	47.3	1.7	(1.1, 2.7)	2.2	(1.5, 4.8)	1.4	(0.8, 2.3)
Missing	39							
Birthweight								
< 2500 grams	21	4.4	1.5	(1.1. 2.5)	0.4	(0.2, 1.2)	0.5	(0.2, 1.0)[§]
≥ 2500 grams	447	94.7	1.7	(1.2, 2.8)	1.4	(0.5, 2.7)	0.7	(0.2, 1.5)
Missing	4							
Marital status								
Living with partner	426	93.2	1.7	(1.2, 2.8)	1.3	(0.5, 2.3)	0.7	(0.2, 1.5)
Not living with partner	31	6.8	1.7	(1.1, 2.4)	3.7	(1.5, 5.4)	0.5	(0.2, 0.9)
Missing	15							
Child's sex								
Male	232	49.2	1.7	(1.1, 2.7)	1.5	(0.4, 2.8)	0.7	(0.2, 1.6)
Female	240	50.9	1.7	(1.2, 2.9)	1.3	(0.5, 2.3)	0.6	(0.2, 1.3)
Parity								

Characteristic	N=472	%	Maternal PCB-153 (ng/mL) Median (IQR[a])		6-month PCB-153 (ng/mL) Median (IQR[a])		45-month PCB-153 (ng/mL) Median (IQR[a])	
0	187	39.6	1.7	(1.2, 2.7)	1.3	(0.4, 3.1)	0.5	(0.2, 1.2)[§]
≥ 1	285	60.4	1.7	(1.2, 2.9)	1.3	(0.5, 2.2)	0.7	(0.4, 1.5)
Maternal raven score [b]								
≤ Median	244	51.9	1.6	(1.1, 2.8)[†]	1.4	(0.4, 3.1)	0.7	(0.2, 1.5)
> Median	226	48.1	1.9	(1.2, 2.8)	1.3	(0.5, 2.2)	0.7	(0.3, 1.5)
Missing	2							
HOME score [b]								
≤ Median	223	51.9	1.7	(1.1, 2.7)	1.3	(0.5, 2.2)	0.7	(0.2, 1.3)
> Median	207	48.1	1.7	(1.2, 2.9)	1.4	(0.5, 2.7)	0.7	(0.3, 1.6)
Missing	42							

[a] Interquartile Range

[b] Median Raven score: 47.5; median HOME score: 30

[§] $p<0.01$;

[†] $p<0.05$; Kruskal-Wallis comparison of differences across the levels of the covariates in distribution of maternal, 6-month, and 45-month PCB 153 concentrations

Table 2.

Measured PCB congeners (ng/mL) in maternal, child 6-month, child 16-month, and child 45-month serum, among a cohort of Slovak mother-child pairs evaluated at 45-months of age. These values are not based on the imputation of any values < LOD.

PCB Congener	N	Mean	Minimum	25th Percentile	50th Percentile	75th Percentile	Maximum
Maternal sum measured PCBs	436	7.42	1.33	3.61	5.37	8.88	50.0
Maternal PCB 153	436	2.34	0.43	1.17	1.70	2.78	14.3
Maternal PCB 118	436	0.18	0.01	0.06	0.12	0.21	1.96
Child 6-month sum measured PCB	140	6.6	0.03	1.3	4.0	7.62	43.2
Child 6-month PCB 153	141	2.16	0.01	0.47	1.35	2.46	14.5
Child 6-month PCB 118	140	0.20	0.00	0.03	0.10	0.18	2.29
Child 16-month sum measured PCB	437	4.43	0.01	0.69	2.18	5.15	49.3
Child 16-month PCB 153	437	1.49	0.00	0.25	0.73	1.73	16.2
Child 16-month PCB 118	437	0.13	0.00	0.01	0.05	0.13	3.26
Child 45-month sum measured PCB	466	3.51	0.06	0.67	1.86	4.20	58.0
Child 45-month PCB 153	467	1.21	0.02	0.24	0.66	1.47	21.4
Child 45-month PCB 118	466	0.08	0.00	0.01	0.036	0.09	1.76

Table 3a.

Proportion difference in 45-month Child Behavior Checklist subscales for an interquartile range difference in maternal, child 6-month, child 16-month, and child 45-month serum concentration of PCB congener 153 in a birth cohort of children from, Michalovce, Slovakia, 2002-2004

	Maternal Serum PCB-153[b]	Child's 6 Month Serum PCB-153[b]	Child's 16 Month Serum PCB-153[b]	Child's 45 Month Serum PCB-153[b]
Subscale	**Proportion change[c] (95% Confidence Interval)**	**Proportion change[c] (95% Confidence Interval)**	**Proportion change[c] (95% Confidence Interval)**	**Proportion change[c] (95% Confidence Interval)**
Attention Problems	1.00 (0.94, 1.07)	1.02 (0.95, 1.10)	1.01 (0.96, 1.06)	1.00 (0.96, 1.05)
Aggressive Behavior	1.00 (0.94, 1.07)	1.00 (0.93, 1.08)	1.00 (0.95, 1.05)	0.99 (0.95, 1.04)
Sleep Problems	1.00 (0.92, 1.08)	1.09 (0.98, 1.21)	1.07 (1.01, 1.14)	1.05 (0.98, 1.11)
Emotionally Reactive	0.99 (0.91, 1.89)	0.95 (0.85, 1.06)	1.00 (0.94, 1.07)	0.98 (0.92, 1.05)
Anxious Depressed	1.02 (0.96, 1.09)	1.04 (0.96, 1.12)	1.05 (1.00, 1.10)	1.02 (0.97, 1.07)
Somatic Complaints	0.98 (0.91, 1.04)	0.97 (0.88, 1.06)	0.96 (0.91, 1.02)	0.96 (0.91, 1.02)
Withdrawn	0.97 (0.90, 1.04)	0.99 (0.90, 1.09)	0.99 (0.94, 1.05)	0.97 (0.92, 1.03)
Externalizing	1.00 (0.94, 1.07)	1.01 (0.94, 1.09)	1.00 (0.65, 1.05)	1.00 (0.95, 1.04)
Internalizing	0.99 (0.93, 1.05)	1.00 (0.93, 1.07)	1.01 (0.96, 1.05)	0.99 (0.94, 1.03)

[a]Models adjusted for total serum lipids, maternal Raven Score, ethnicity, child's sex, parity, and child's age at assessment

[b]The maternal PCB model used 433 observations; the 6-month model used 132 observations; the 16-month model used 432 observations; the 45-month model used 462 observations

[c]Expected proportional increase associated with an interquartile change in PCB-153 serum levels: maternal: (1.66 ng/mL), 6-month PCB-153 serum levels (1.63 ng/mL), 16-month PCB-153 serum levels (1.47 ng/mL), and 45-month PCB-153 serum levels (1.22 ng/mL)

Table 3b.

Proportion difference in 45-month Child Behavior Checklist subscales for an interquartile range difference in maternal, child-6 month, child 16-month, and child 45-month PCB congener 118 in a birth cohort of Slovak children from Michalovce, Slovakia, 2002-2004

	Maternal Serum PCB-118[b]	Child's 6 Month Serum PCB-118[b]	Child's 16 Month Serum PCB-118[b]	Child's 45 Month Serum PCB-118[b]
Subscale	**Proportion change[c] (95% Confidence Interval)**	**Proportion change[c] (95% Confidence Interval)**	**Proportion change[c] (95% Confidence Interval)**	**Proportion change[c] (95% Confidence Interval)**
Attention Problems	1.01 (0.97, 1.07)	1.03 (0.99, 1.07)	1.02 (0.99, 1.05)	1.01 (0.98, 1.04)
Aggressive Behavior	1.01 (0.96, 1.06)	1.02 (0.97, 1.06)	1.01 (0.98, 1.04)	1.00 (0.97, 1.03)
Sleep Problems	0.98 (0.92, 1.06)	1.06 (0.99, 1.12)	1.04(1.00, 1.08)	1.02 (0.99, 1.06)
Emotionally Reactive	1.00 (0.94, 1.07)	1.00 (0.94, 1.06)	1.02 (0.98, 1.06)	1.00 (0.96, 1.05)
Anxious Depressed	0.99 (0.94, 1.05)	1.02 (0.98, 1.07)	1.03 (1.00, 1.06)	1.01 (0.98, 1.04)
Somatic Complaints	0.94 (0.89, 1.00)	0.99 (0.94, 1.05)	0.99 (0.95, 1.02)	1.00 (0.96, 1.03)
Withdrawn	0.94 (0.88, 1.01)	0.98 (0.92, 1.04)	0.99 (0.95, 1.03)	0.98 (0.94, 1.02)
Externalizing	1.01 (0.96, 1.06)	1.02 (0.98, 1.06)	1.01 (0.98, 1.04)	1.00 (0.97, 1.03)
Internalizing	0.97 (0.93, 1.02)	1.00 (0.96, 1.05)	1.01 (0.98, 1.04)	1.00 (0.97, 1.03)

[a]Model adjusted for total serum lipids, maternal Raven Score, ethnicity, child's sex, parity, and child's age at assessment

[b]The maternal PCB model used 433 observations; the 6-month model used 132 observations; the 16-month model used 432 observations; the 45-month model used 462 observations

[c]Expected proportional increase associated with an interquartile change in PCB-153 serum levels: maternal (0.16 ng/mL), 6-month PCB-118 serum levels (0.15 ng/mL), 16-month PCB-118 serum levels (0.11 ng/mL), and 45-month PCB-118 serum levels (0.07 ng/mL)

Table 4a.

Association between an interquartile range change in maternal, child 6-month, child 16-month, and child 45-month PCB congeners 153 with 45-month WPPSI-III[a] subtests in a cohort of Slovak children[b] Michalovce, Slovakia, 2002-2008

	Maternal Serum PCB-153[c]	Child's 6 Month Serum PCB-153[c]	Child's 16 Month Serum PCB-153[c]	Child's 45 Month Serum PCB-153[c]
Subtest	**Mean[d] (95% Confidence Interval)**	**Mean[d] (95% Confidence Interval)**	**Mean[d] (95% Confidence Interval)**	**Mean[d] (95% Confidence Interval)**
Block Design	−0.06 (−0.34, 0.23)	0.25 (−0.14, 0.63)	−0.01 (−0.22, 0.21)	0.09 (−0.12, 0.31)
Information	−0.01 (−0.32, 0.29)	0.23 (−0.15, 0.61)	0.12 (−0.12, 0.36)	0.09 (−0.15, 0.32)
Object Assembly	0.05 (−0.35, 0.46)	0.36 (−0.16, 0.88)	0.19 (−0.13, 0.51)	0.14 (−0.17, 0.45)
Picture Naming	0.15 (−0.19, 0.48)	0.52 (0.07, 0.97)	0.34 (0.07, 0.61)	0.33 (0.07, 0.59)
Receptive Vocabulary	0.18 (−0.21, 0.57)	0.21 (−0.29, 0.71)	0.09 (−0.22, 0.40)	0.09 (−0.21, 0.40)

[a] Wechsler Preschool and Primary Scale of Intelligence

[b] Models adjusted for total serum lipids, maternal Raven Score, ethnicity, child's sex, parity, and child's age at assessment

[c] The maternal PCB model used 433 observations for all subtests except Picture Naming, which used 432; the 6-month models used 139 observations for all subtests except Picture Naming, which used 138, the 16-month models used 432 observations for all subtests except Picture Naming, which used 431; the 45-month models used 462 observations, except for Picture Naming, which used 461.

[d] Mean represents mean change in score associated with an interquartile range change in maternal PCB-153 serum levels (1.66 ng/mL), 16-month PCB-153 serum levels (1.47 ng/mL), and 45-month PCB-153 serum levels (1.22 ng/mL)

Table 4b.

Association between an interquartile range change in maternal, child 6-month, child 16-month, and child 45-month PCB congeners 118 with 45-month WPPSI-III[a] subtests in a cohort of Slovak children[b], Michalovce, Slovakia, 2002-2008

	Maternal Serum PCB-118	Child's 6-Month Serum PCB-118	Child's 16 Month Serum PCB-118	Child's 45 Month Serum PCB-118
Subtest	**Mean[c] (95% Confidence Interval)**	**Mean[c] (95% Confidence Interval)**	**Mean[c] (95% Confidence Interval)**	**Mean[c] (95% Confidence Interval)**
Block Design	−0.09 (−0.32, 0.14)	0.07 (−0.16, 0.30)	−0.02 (−0.16, 0.12)	0.06 (−0.08, 0.19)
Information	0.01 (−0.24, 0.25)	0.10 (−0.13, 0.32)	0.06 (−0.09, 0.21)	0.00 (−0.15, 0.15)
Object Assembly	0.11 (−0.22, 0.43)	0.19 (−0.13, 0.50)	0.07 (−0.13, 0.27)	0.07 (−0.13, 0.27)
Picture Naming	0.02 (−0.25, 0.29)	0.19 (−0.08, 0.46)	0.16 (−0.01, 0.33)	0.15 (−0.02, 0.32)
Receptive Vocabulary	−0.05 (−0.36, 0.27)	0.02 (−0.27, 0.31)	−0.02 (−0.21, 0.18)	−0.04 (−0.23, 0.16)

[a] Wechsler Preschool and Primary Scale of Intelligence

[b] Models adjusted for total serum lipids, maternal Raven Score, ethnicity, child's sex, parity, and child's age at assessment

[c] The maternal PCB model used 433 observations for all subtests except Picture Naming, which used 432; the 6-month models used 138 observations for all subtests except Picture Naming, which used 138; the 16-month models used 432 observations for all subtests except Picture Naming, which used 432; the 45-month models used 462 observations, except for Picture Naming, which used 461.

[d] Mean represents mean change in score associated with an interquartile range change in maternal PCB-118 serum levels (0.16 ng/mL), 16-month PCB-118 serum levels (0.11 ng/mL), and 45-month PCB-118 serum levels (0.07 ng/mL)