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Hydroxylated polychlorinated biphenyls in human sera from adolescents and their mothers living in two U.S. Midwestern communities

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Abstract

Hydroxylated polychlorinated biphenyls (OH-PCBs) have been detected in human specimens and some are suspected as being more toxic than their parent compounds. We compared 58 OH-PCB congeners (in 51 chromatographic peaks) in serum samples from participants in the AESOP Study, a longitudinal cohort study of adolescents and their mothers living in urban and rural areas in the United States. We hypothesized that adolescents would have lower levels of OH-PCBs than their mothers and that serum concentration of OH-PCBs would be stable over a 3-year period. We found statistically significant differences in Σ_{64} OH-PCBs between age groups in East Chicago ($p=0.001$) and Columbus Junction ($p<0.001$), with adolescents having lower concentrations than their mothers. We observed that lower-chlorinated OH-PCBs were rarely detected, suggesting that they are not retained in serum and/or rapidly biotransformed into other forms. Twelve OH-PCBs, including several that are rarely reported (4,4'-diOH-PCB 202, 4'-OH-PCB 208, and 4-OH-PCB 163) were detected in over 60% of participants. Lastly, from repeated measures within subject serum for three OH-PCBs, concentrations of 4-OH-PCB 107 and 4-OH-PCB 187 changed significantly over three years of the study.

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SUPPLEMENTARY MATERIAL

Figures of full chromatograms of standard solution and samples, and detection frequency; tables of OH-PCB column elution order, LOQ values and concentrations.

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Keywords

biomonitoring; longitudinal analysis; metabolism; hydroxylated PCB; polychlorinated biphenyl

INTRODUCTION

OH-PCBs, the major metabolites of PCBs in humans, have been detected in human tissues and fluids (Guvenius et al., 2002; Nomiyama et al., 2010; Fangstrom et al., 2002; 2005; Hovander et al., 2002; 2006; Sandanger et al., 2004; Weiss et al., 2006; Park et al., 2007; 2009; Hisada et al., 2013; Marek et al., 2013b; 2014). Recent studies also found OH-PCBs in sediments (Marek et al., 2013a) and human waste has been proposed as a source to surface waters (Ueno et al., 2007). Our group previously demonstrated that OH-PCBs are important metabolic products of PCB 11 and PCB 3 in rats and are excreted in urine and feces (Hu et al., 2013; 2014; Dhakal et al., 2014). OH-PCBs were present in the original Aroclors and this may have contributed OH-PCBs to sediments (Marek et al., 2013a). Thus, OH-PCBs are both metabolic products and environmental contaminants.

Some of the OH-PCB congeners mimic endogenous thyroxine (T4) and bind strongly to transthyretin (TTR) resulting in the alteration of thyroid hormone homeostasis (Rickenbacher et al., 1986; Darnerud et al., 1996; Meerts et al., 2002). OH-PCB congeners bearing a *para*-substituted hydroxyl group and adjacent chlorine on *meta* or *ortho* position of the biphenyl rings are more likely to cause alteration of thyroid hormone levels (Quinete et al., 2014; Tehrani and Van Aken, 2014). Some OH-PCBs decrease serum retinol transport (Brouwer and Vandenberg, 1986) and are potential endocrine disruptors (Meerts et al., 2004) and neurotoxins (Shimokawa et al., 2006; Londono et al., 2010; Lesmana et al., 2014; Kimura-Kuroda et al., 2007).

We measured these potentially toxic compounds in a large cohort of individuals as part of the Airborne Exposure to Semi-volatile Organic Pollutants (AESOP) Study (Ampleman et al., 2015). Blood samples have been collected annually since 2008 from participants, most of whom are mother-child dyads. Several households have more than one enrolled child. Participants live in East Chicago, Indiana or within Columbus Community School District, Iowa. East Chicago is a highly industrialized urban area with known high PCB contamination. Each year, about 7.5 kg PCBs volatilize from the Indiana Harbor and Ship Canal in East Chicago (Martinez et al., 2010). In contrast, the Columbus Community School District is rural with no industrial PCB contamination.

We hypothesized that many OH-PCBs are detectable in serum and that adolescents have lower concentrations than their mothers. We tested our hypothesis using an analytical method that allowed for detection of a much larger suite of OH-PCBs than has been previously examined. Most prior studies of OH-PCBs in humans have reported only a few OH-PCB congeners (Soechitram et al., 2004; Fangstrom et al., 2005; Hovander et al., 2006; Weiss et al., 2006; Park et al., 2008) including our laboratory (Marek et al., 2013b; 2014). Two exceptions are a study that measured 90 OH-PCB congeners and detected 35 in serum of Japanese women (Nomiyama et al., 2010) and another that identified 38 OH-PCBs in plasma (Hovander et al., 2002). The significant improvement of this study compared to our

previous studies is our current methodology enables us to identify as many as 64 OH-PCB congeners in human serum. To our knowledge, this is the first report to compare a large number of OH-PCB congeners in adolescents and their mothers from both urban and rural areas. Several studies have investigated a specific population such as mothers, pregnant women, or residents in highly contaminated areas (Fangstrom et al., 2002; Hovander et al., 2006; Park et al., 2009; Nomiyama et al., 2010; Hisada et al., 2013). Our study advances understanding of the distribution and levels of OH-PCBs in two communities (urban vs. rural), with each community having two age groups (adolescents and their mothers). We are also able to evaluate changes in serum levels of three OH-PCB congeners over three sequential years.

MATERIALS AND METHODS

Sample Collection

Serum samples collected between April 1, 2010 and March 31, 2011 from 97 adolescents (ages 14–18 years) and 86 mothers (ages 29–58 years) were available from East Chicago and Columbus Community School District. Sixteen instances of poor surrogate standard recovery resulted in the exclusion of 12 households from this analysis (25 participants). We report OH-PCB data from the remaining 33 adolescents and 30 mothers from East Chicago and 52 adolescents and 44 mothers from Columbus Junction (N=159).

Bilingual AESOP staff from each community collected blood samples at the subjects' homes. Blood was drawn into six 5 mL Vacutainer glass tubes and allowed to clot for 30 min while capped before centrifuging to isolate serum. Samples were stored in glass vials with Teflon caps at –25°C. Questionnaires were administered by field staff in English or Spanish as previously described (Ampleman et al., 2015). All protocols were approved by our Institutional Review Board. Written consent and assent were obtained in English or in Spanish from all participants.

Chemicals

Sixty-four calibration standards were purchased from AccuStandard (New Haven, CT) and Wellington Laboratories (Guelph, ON). 4'-OH-2,3,3',4,5,5'-hexachlorobiphenyl (4'-OH-PCB 159) was used as a surrogate standard and 2,4,6-trichlorobiphenyl (PCB 30) and 2,2',3,4,4',5,6,6'-octachlorobiphenyl (PCB 204) as internal standards. Diazomethane was provided by Dr. Hans-Joachim Lehmler (University of Iowa). All solvents used in this study were pesticide grade.

Analytical

OH-PCBs in human sera were extracted and separated from PCBs using a method described previously (Hovander et al., 2000; Marek et al., 2013b; Marek et al., 2014). Four grams of serum from each participant were spiked with 0.65 ng of ¹³C-labeled PCB surrogate standards and 10 ng of 4'-OH-PCB 159 just before extraction. Extraction and separation of OH-PCBs are described in Supplementary Material (SM). PCB fractions were spiked with 0.6 ng of ¹³C-labeled PCB surrogate standards and internal standards were added before

instrument analysis. Samples were analyzed using gas chromatography-tandem mass spectrometry (GC-MS/MS) (Marek et al., 2013a).

Instrument

Methods for instrumental analysis of PCBs and OH-PCBs were previously published (Marek et al., 2013b; Marek et al., 2014). Briefly, PCBs and OH-PCBs (as MeO-PCBs) were analyzed and quantified using an Agilent 7000 GC-MS/MS under multiple reaction monitoring mode (MRM). Sixty-four OH-PCB standards were quantified as single or co-eluting MeO-PCBs in 57 chromatographic peaks eluting on an SPB-Octyl column. A full MeO-PCB chromatogram (Figure S1) and full details of the precursor and product ions (Table S1) and retention times (Table S2) are presented in SM. Congener identity was confirmed using DB-5 and DB-1701 columns in a subset of 20 pooled samples.

Quality control

A quality control protocol was used during extraction and analysis. A method blank (4mL 1% KCl) was included in each batch of 10 serum samples and underwent the same extraction, analysis and quantification processes as the serum samples. Method blanks had significantly lower levels of Σ OH-PCBs than samples ($p < 0.001$) and each OH-PCB congener in the blank was consistently low (mean 0.0023 ± 0.0031 ng). A limit of quantification (LOQ) for each congener was generated based on the method blank mean plus twice the standard deviation. A list of the LOQ values for the analyzed congeners is provided in SM (Table S3). Each congener mass in a sample was assigned a value of 0 if the detected mass was $< \text{LOQ}$. Recovery of the surrogate standard ($72\% \pm 13\%$) was used to adjust for extraction efficiency.

Statistical Analysis

Concentrations of OH-PCBs are reported as ng/g fresh weight (f.w.). All OH-PCB data, even after log, square root and cube root transformation, were not distributed normally (Shapiro-Wilk, $p < 0.05$). Total OH-PCB concentrations between adolescents and their mothers were tested in mother-child dyads using the Wilcoxon signed rank test. Mann-Whitney rank sum test was used to compare OH-PCB levels between locations. Spearman's rank correlation was used to determine the strength of association between OH-PCB levels and their possible precursor PCBs. The level of significance was set to $\alpha = 0.05$ and analyses were performed using SPSS (IBM, Inc., Armonk, NY). Comparison of OH-PCB congener profiles between age groups (not in dyads) were calculated using cosine theta ($\cos\theta$) where $\cos\theta = 0$ defines no similarity between two profiles and $\cos\theta = 1$ defines a perfect match between two profiles (Marek et al., 2013a). Year effect longitudinal analysis (AESOP Study 2008–2011) was conducted using a proportional odds mixed effects model implemented in the R package ordinal (see SM). Participants were included in the analysis if they had all 3 years of data ($n = 102$). Only 4-OH-PCB 107, 4-OH-PCB 146 and 4-OH-PCB 187 were investigated as they were measured in all three years.

RESULTS

MRM chromatograms from standards and a participant exemplar are displayed in Figure 1. To identify each detected OH-PCB congener, peaks that were present in the chromatogram were matched to peaks present in our standard based on MRM transition and retention time. Several rarely reported congeners and unknown peaks were detected in our samples. As many as 58 OH-PCB congeners (in 51 chromatographic peaks) were detected in samples and 24 were identified in 30% of our participants (Figure S2). The six most frequently detected OH-PCBs were 4-OH-PCB 146, 4,4'-diOH-PCB 202, 4-OH-PCB 107, 5-OH-PCB 183 + 4-OH-PCB 187 and 4'-OH-PCB 199. The first two congeners were detected in all participants and all six congeners were identified in every East Chicago participant.

Serum concentrations of Σ_{64} OH-PCBs in adolescents ranged from 0.017–0.160 ng/g f.w. (median 0.0369 ng/g f.w.) while mothers ranged from 0.0204–0.314 ng/g f.w. (median 0.0633 ng/g f.w.) (Figure 2, Table S4, Table S5). OH-PCBs with fewer than four chlorines were either not detected or were detected in extremely low concentrations in all our participants when compared to higher-chlorinated OH-PCBs (Figure 3a–d). Median levels of most OH-PCBs were lower in adolescents compared to mothers (Figure 3a–d). The OH-PCB congener profiles between age groups in East Chicago ($\cos\theta=0.85\pm0.18$) and Columbus Junction ($\cos\theta=0.76\pm0.20$) were comparable, suggesting that adolescents have different profiles than mothers. OH-PCB metabolites in age groups between locations were also similar.

Selection of the possible precursor PCB congeners of each OH-PCB congener are based on direct metabolic insertion of hydroxyl group and/or NIH shift of hydroxyl group with the adjacent chlorines in the biphenyl rings (Table 1). The concentration of 5-OH-PCB 183+4-OH-PCB 187 correlated more strongly with that of PCB 193+180 whereas the concentration of PCB 187 was more strongly associated with these PCBs than with PCB 183. The concentrations of PCB 105 and PCB 118 had comparable moderate correlation with that of 4-OH-PCB 107. The 4-OH-PCB 162 concentration was comparably correlated with PCB 156+157 and PCB 167. No test for correlation between 4-OH-PCB 162 and the concentration of its precursor compound, PCB 162, was carried out due to its low detection frequency (5%). The concentration of 4'-OH-PCB 199 correlated weakly with that PCB 198+199 while 4-OH-PCB 146 correlated strongly with PCB 146, PCB 153+168 and PCB 138+163+129 levels. We investigated the association of the concentration of Σ_6 major OH-PCBs and the sum of their likely parent PCBs and observed a significant and moderate correlation in participants in East Chicago ($\rho=0.64$, $p<0.0001$) and Columbus Junction ($\rho=0.65$, $p<0.0001$).

Non-parametric pairwise analysis of serum OH-PCBs for mother-child dyads showed that adolescents had significantly lower levels of Σ_{64} OH-PCBs than their own mothers for those residing in both East Chicago ($p=0.001$) and Columbus Junction ($p<0.001$) (Table 2).

A longitudinal analysis using a proportional odds mixed effects model was performed for three OH-PCBs measured across the first three years of the AESOP Study (Table 2). The concentrations of 4-OH-PCB 107 ($p<0.001$) and 4-OH-PCB 187 ($p<0.001$) changed

significantly within individuals across the three years (Table 2b) while 4-OH-PCB 146 showed no significant change over time ($p=0.30$). There was no significant concentration change of 4-OH-PCB 107 in our first two study years ($p=0.95$); however, the concentration of 4-OH-PCB 187 in the first year was significantly different from the second year ($p=0.004$). There was no difference in the concentration of OH-PCBs by location but these OH-PCBs levels were consistently higher in mothers than adolescents (Table 2).

DISCUSSION

We assessed as many as 58 OH-PCB congeners in human serum from adolescents and their mothers in urban and rural communities. We detected 5-OH-PCB 183 + 4-OH-PCB 187, 4-OH-PCB 107, and 4-OH-PCB 146 in nearly all samples. In addition, a few uncommonly-measured congeners including 4,4'-diOH-PCB 202, 4'-OH-PCB 208, and 4-OH-PCB 163, were detected in at least half of the participants. Of those detected, 4-OH-PCB 163 is present in original Aroclor mixtures (Marek et al., 2013a).

Although the lower-chlorinated OH-PCBs are the most prevalent in Aroclor mixtures, they were rarely detected in AESOP Study serum samples. Analytical artifacts cannot explain the low levels of these congeners because our laboratory was successful in measuring them in the Aroclors (Marek et al., 2013a) and our mono-tri homolog PCB standards showed good recoveries in our serum samples. Our animal inhalation studies have shown that these lower-chlorinated OH-PCBs are rapidly biotransformed to phase II metabolites (e.g., sulfated and glucuronidated conjugates) (Hu et al., 2013; Hu et al., 2014; Dhakal et al., 2012; Grimm et al., 2015). This suggests that other PCB metabolites may be better biomarkers for lower-chlorinated metabolites.

Our OH-PCBs levels are comparable to other studies that have measured OH-PCBs in serum including pregnant Japanese women, breast cancer patients in Belgium and Romania, and 1950–60s California mothers (Park et al., 2009; Dirtu et al., 2010; Nomiya et al., 2010; Hisada et al., 2013). The levels of OH-PCBs in this study are about an order of magnitude lower than populations with high seafood diets in contaminated areas such as the Faroe Islands and Eastern Slovakia (Fangstrom et al., 2002; Hovander et al., 2006). AESOP Study participants consume relatively low amounts of seafood (Ampleman et al., 2015). The concentration range of Σ OH-PCBs in this study was similar to our previous studies which analyzed AESOP Study serum samples collected between 2008 and 2010 for a limited set of 4 or 12 OH-PCBs (Marek et al., 2013b; Marek et al., 2014).

Our study showed no significant difference in Σ OH-PCBs levels between locations. Although Columbus Junction has no previously recognized PCB contamination from industrial sources, legacy and non-legacy PCBs from other sources such as caulk and paint pigments, may contribute to PCB exposure resulting in similar levels of OH-PCBs as our cohort in East Chicago. On the other hand, we found that OH-PCB concentrations in adolescents were half those of their mothers. Due to the bioaccumulation of highly chlorinated PCBs, older participants would be expected to have higher levels of PCBs and this suggests they would also have higher levels of PCB metabolites. In addition, older people generally have lower metabolism rates than the young (Quinete et al., 2014).

Because 4-OH-PCB 187, one of the most reported OH-PCB congeners, co-eluted with rarely-reported 5-OH-PCB 183 on all three columns, we compared their concentrations with those of their likely parent compounds (see Table S6 for structures). Direct insertion was the preferred hydroxylation mechanism in the formation 4-OH-PCB 187. This result was similar to previously-published studies (Park et al., 2009; Nomiyama et al., 2010; Marek et al., 2013b). Some studies have shown a strong relationship between concentrations of 4-OH-PCB 107 and PCB 118 instead of PCB 105 (Dirtu et al., 2010; Nomiyama et al., 2010). In contrast, our study showed concentrations of PCB 118 and PCB 105 are almost equally associated with 4-OH-PCB 107. The concentration of 4-OH-PCB 146 was strongly correlated with those of its possible parent PCBs including PCB 153 ($\rho = 0.83$), PCB 146 ($\rho = 0.79$) and PCB 138 ($\rho = 0.78$). Dirtu *et al* reported similar outcomes (Dirtu et al., 2010). Several studies showed a stronger relationship of PCB 153 and PCB 138 over PCB 146 in the formation of 4-OH-PCB 146 (Hovander et al., 2006; Park et al., 2007; Nomiyama et al., 2010; Hisada et al., 2013) whereas we showed 4-OH-PCB 146 correlated more strongly with PCB 146 (Marek et al., 2013b). Our data suggest that human variability and the complexity of PCB metabolism make it far from obvious which OH-PCBs are biotransformed from which PCBs.

The major dominating congeners in this study were similar to those reported in other studies (Park et al., 2007; Rylander et al., 2012; Hisada et al., 2013; Marek et al., 2013b) except that we also report 4-OH-PCB 162, 4'-OH-PCB 199 and 4,4'-di-OH-PCB 202, which were seldom assessed in prior studies. These congeners comprised 2–46% of the concentration of total OH-PCBs. This shows that additional OH-PCB congeners, other than the five most frequently reported OH-PCBs (4-OH-PCB 107, 4-OH-PCB 146, 3-OH-PCB 153, 4-OH-PCB 187 and 4'-OH-PCB 138) are present in high levels in humans. Some of these congeners have a *para*-substituted hydroxyl group with adjacent chlorine on *meta* or *ortho* position of the biphenyl rings. This structure was found to bind to transthyretin stronger than the thyroxine and may be more toxic (Rickenbacher et al., 1986; Darnerud et al., 1996; Meerts et al., 2002). Future toxicity studies should investigate not only those regularly reported OH-PCBs but also other OH-PCB congeners bearing such structures.

We found that adolescents and mothers share similar OH-PCB congener profiles which suggest that profiles are not age-dependent in the general population, even though concentrations are. Some studies have shown placental transfer of both PCBs and OH-PCBs from mothers to their infants during pregnancy (Soechitram et al., 2004; Park et al., 2008), however, it is unknown if placental transfer would have any effect on the OH-PCB distribution in AESOP Study adolescents since they were 14–18 years old. The short retention time of lower-chlorinated OH-PCBs in blood could also explain the similarity of congener profiles between age groups. Moreover, we also observed that OH-PCB congener profiles of both communities were comparable. This suggests that sources other than industrial PCB contamination, especially diet, may have accounted for the majority of the PCB exposure (Ampleman et al., 2015). Future studies should investigate the sources contributing to the OH-PCB congener profiles in adolescents and mothers.

In our non-parametric longitudinal analysis using a proportional odds mixed effect model, participants' serum concentration of 4-OH-PCB 107 and 4-OH-PCB 187 had significantly

changed over the three-year evaluation but 4-OH-PCB 146 concentration remained similar. PCB 153, one of the parent PCB compounds of 4-OH-PCB 146 with which it was strongly correlated, was reported having the longest half-life of congeners (Letcher et al., 2000) which may explain the stability of 4-OH-PCB 146. Concentrations of these OH-PCBs in adolescents differed significantly from mothers over the three-year evaluation likely due to bioaccumulation of higher-chlorinated congeners.

We are unable to quantify and identify some unknown OH-PCBs present in our samples due to the limited OH-PCB standards available. Further expansion of the OH-PCB standards would help to identify more OH-PCB congeners in human serum. PCB metabolism involves not only OH-PCBs but also MeSO₂-PCBs, especially for lower-chlorinated PCBs (Letcher et al., 2000). Study of other PCB metabolites in human serum such as MeSO₂-PCBs and phase II metabolites as biomarkers should be investigated especially when studying lower-chlorinated congeners. We applied only one surrogate standard to correct masses for all detected congeners, 4'-OH-PCB 159, a hexa-chlorinated OH-PCB. Thus, lower-chlorinated congeners may have less accurate mass correction than if a lower-chlorinated surrogate standard were used. However, this does not appreciably affect our overall results and conclusions since lower-chlorinated OH-PCB congeners were seldom detected in human serum (Figure S1b).

CONCLUSION

Adolescents had significantly lower levels of OH-PCBs than their mothers. Additional OH-PCB congeners were found at meaningful concentrations than those previously reported. Lower-chlorinated OH-PCB congeners were less commonly detected in our participants' serum and both age groups in our communities exhibited similar OH-PCB congener profiles. 4-OH-PCB 107 and 4-OH-PCB 187 levels changed significantly over three sequential years but 4-OH-PCB 146 concentration remained stable.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Fifty-eight OH-PCBs were assessed in serum of 85 adolescents and 74 their mothers.
- Lower-chlorinated OH-PCBs were rarely detected in serum.
- Mothers had significantly higher total OH-PCB concentrations than their children.
- 4-OH-PCB 107 and 4-OH-PCB 187 changed significantly within subject across 3 years.
- OH-PCBs did not differ between subjects from the urban vs. the rural community.

Figure 1.

Example chromatogram of the MRM transition 390.9→346.8 shows some of the rarely investigated and reported OH-PCB congeners in human serum in one of our participants (green peaks) and our standard solution (purple peaks).

Figure 2. Sum OH-PCBs of 85 adolescents, 74 mothers and 159 participants. Boxplot illustrates the median, 25th and 75th percentiles, 10th and 90th percentiles, and extreme values.

Figure 3.
OH-PCB congener profile of adolescents and their mothers in East Chicago, IN and
Columbus Junction, IA.

Table 1

Major dominating OH-PCBs, their possible parent PCB compounds, hydroxylation mechanism and Spearman's correlation.

OH-PCBs	Possible parent PCB compounds	Hydroxylation mechanism	Spearman's Correlation, ρ
5-OH-PCB 183 + 4-OH-PCB 187	PCB 187	Direct insertion/NIH shift ^a	0.58 ^{**}
	PCB 183	Direct insertion/NIH shift ^b	0.52 ^{**}
	PCB 193+180 [*]	NIH shift ^a	0.64 ^{**}
4-OH-PCB 107	PCB 107	Direct insertion	0.39 ^{**}
	PCB 105	NIH shift	0.46 ^{**}
	PCB 118	NIH shift	0.45 ^{**}
4-OH-PCB 162	PCB 162	Direct insertion	n.d.
	PCB 167	NIH shift	0.36 ^{**}
	PCB 156+157 [*]	NIH shift	0.38 ^{**}
4'-OH-PCB 199	PCB 199	Direct insertion	0.37 ^{**}
	PCB 204	NIH shift	n.d.
4-OH-PCB 146	PCB 146	Direct insertion	0.79 ^{**}
	PCB 153 [*] +168	NIH shift	0.83 ^{**}
	PCB 138 [*] +163+129	NIH shift	0.79 ^{**}

^a PCB 187 and PCB 180 are the possible parent PCB compounds of 5-OH-PCB 183 via NIH shift

^b PCB 183 is the possible parent PCB compound of 4-OH-PCB 187 via NIH shift

^{*} Corresponding possible parent PCB compounds when the PCB congener was co-eluting with other PCB congeners.

^{**} $p < 0.0001$ and N/A = Data not available

n.d. = Not done due to low detection frequency of the parent PCB compound.

Table 2

Analysis of OH-PCB serum concentrations comparing each mothers to their child (top) and comparing concentrations across three years (bottom). The mother-child pairwise analysis used a non-parametric analysis and demonstrated that mothers had significantly higher $\Sigma 64$ OH-PCBs than their children. Longitudinal analysis for the three congeners with data in all 3 years conducted using a proportional odds mixed effects model demonstrated significant differences between mothers and children and across years but no differences between East Chicago and Columbus Junction.

	Median (ng/g f.w.)	25 th –75 th percentile (ng/g f.w.)	P-value
East Chicago, IN			
Adolescent	0.0390	0.0308–0.0595	<u>0.001</u>
Mother	0.0622	0.0391–0.1060	
Columbus Junction, IA			
Adolescent	0.0365	0.0265–0.0514	<u><0.001</u>
Mother	0.0689	0.0445–0.0922	
P-value for Covariates (Across all 3 years)			
	4-OH-PCB 107	4-OH-PCB 187	4-OH-PCB 146
East Chicago vs. Columbus Junction	0.64	0.64	0.78
Adolescent vs. Mother	0.036	<0.001	<0.001
Study Year	<0.001	<0.001	0.30