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Hydroxylated Polychlorinated Biphenyl Metabolites (OH-PCBs), Maternal Smoking and Size at Birth

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Abstract

In a sample of 442 births from the Child Health and Development Studies cohort, we examined associations between maternal prenatal exposure to hydroxylated polychlorinated biphenyl metabolites (OH-PCBs) and pregnancy outcomes, and whether associations were mediated by maternal thyroid hormone levels and/or modified by maternal smoking. Compared to nonsmokers, smokers had twice the mean concentration of 4-OH-CB107 ($p < 0.001$) and lower levels of its parent compound, PCB118 ($p = 0.001$). Among mothers who smoked, the birth weight of newborns with maternal concentrations of 4-OH-CB107 in the upper quartile was 316 grams lighter (95% confidence interval (CI) 566, 65) compared to those with maternal concentrations in the lowest quartile, after control for PCB118 and other potential confounders. This association was not observed for non-smoking mothers and was not mediated by maternal thyroid hormone levels. Maternal prenatal 4-OH-CB107 levels appear to be influenced by maternal smoking and contribute to lower birth weight among smokers.

Keywords

Polychlorinated biphenyls; Hydroxylated PCB metabolites; Maternal smoking; Maternal thyroid hormone; Birth outcomes; Birth weight; Gestational length

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1. Introduction

Although polychlorinated biphenyl (PCB) production was banned in the 1970s, these compounds remain important environmental contaminants due to their persistence in the environment and their toxic effects on wildlife and humans. Hydroxylated polychlorinated biphenyls (OH-PCBs) are secondary contaminants that are produced by oxidative transformation of PCBs [1]. Compared with PCBs, most OH-PCBs are water soluble and are readily excreted from the body. Nonetheless, a few highly hydrophobic OH-PCBs, including 4-OH-CB107, can be retained in mammalian blood by binding to plasma proteins [2–4] and thus have been detected in blood samples from wildlife and multiple human populations [5–8]. These OH-PCB congeners are suspected to be more toxic than their parent compounds [9, 10] as they have been found to exert a wide range of toxic effects on the endocrine system [1].

Prenatal exposure to chlorinated compounds such as PCBs has been associated with adverse birth and neurodevelopmental outcomes in both animal experiments and epidemiologic studies [11–13]. There is growing evidence suggesting that OH-PCB exposure may have similar adverse effects on fetuses. OH-PCBs can cross the placenta [14–17], and OH-PCB levels in maternal plasma are highly correlated with levels in umbilical cord plasma [17–20]. Prenatal exposure to OH-PCBs, primarily to 4-OH-CB107, has been related to unfavorable neurodevelopment [21–24]; however, only one study has reported on the relationship between OH-PCBs and newborn anthropometrics [25]. That study, which found no associations, is based on a sample size of 79 maternal-newborn pairs. It is important to examine the effect of chlorinated compounds on birth outcomes as fetal growth is recognized as a vital indicator of offspring health, and predicts adult health outcomes such as lung function [26], obesity, and cardiovascular disease [27].

Adverse effects of OH-PCBs and PCBs on fetuses have been hypothesized to operate through disruption of maternal thyroid function, especially by reducing concentrations of thyroid hormones triiodothyronine (T3) and thyroxine (T4). This hypothesis is supported by evidence that in both the brain and the placenta, OH-PCBs can compete for binding transthyretin (TTR), one of the major carrier proteins of thyroid hormone in blood circulation [14, 28, 29]. Studies of the effect of OH-PCBs on thyroid function yield inconsistent results, but in those studies where an association is found it is strongest for 4-OH-CB107 [30]. In animal studies, exposure to 4-OH-CB107 is associated with reduced maternal total and free T4 (FT4) and increased thyroid stimulating hormone (TSH) levels in pregnant rats [14, 31], and a reduced total T3:free T3 ratio in hooded seals [32]. Other animal studies report no associations [33, 34].

Studies of OH-PCBs and thyroid function in human populations are scarce. Dallaire et al. (2009) reported a negative association between serum levels of the sum of ten OH-PCBs (Σ OH-PCBs) and total T3 in Inuit adults [35]; that group later found a positive association between serum Σ OH-PCBs and total T3 in another study on pregnant Inuit women [36]. In a pilot study of 23 mother-newborn pairs, Otake et al. (2007) found a significant positive correlation between the sum of 6 OH-PCBs and FT4 and a non-significant negative correlation between total PCBs and FT4; the correlation for OH-PCBs was predominantly

driven by 4-OH-CB107 and 4-OH-CB187 [30]. In contrast, two studies by Hisada et al. in a cohort of pregnant Japanese women found little or no evidence of associations between maternal serum levels of OH-PCBs and thyroid hormones [25, 37]; however, these studies had limited sample size and relatively low exposure to OH-PCBs (e.g. 4-OH-CB107 range: 4.8–77 pg/g serum [25]).

Because OH-PCBs may influence maternal thyroid hormone levels, and because maternal thyroid dysfunction during pregnancy may result in adverse pregnancy outcomes [38], it is important to examine whether this is a mechanism through which OH-PCBs operate. Here, we examine the associations between maternal OH-PCBs and four pregnancy outcomes (birth weight, gestational length, birth length and head circumference) in a large population sample. We also examine whether associations are mediated by maternal serum levels of thyroid hormones during pregnancy. Additionally, because both infant sex and maternal smoking during pregnancy are strong independent predictors of adverse pregnancy outcomes, and because previous research examining PCBs and pregnancy and early-life growth outcomes observed sex-specific effects [39, 40] and differences by maternal smoking status [41], we also examine effect modification of the associations by these risk factors.

2. Materials and methods

2.1 Data sources

The Child Health and Development Studies (CHDS) is a prospective birth cohort based on women who resided in Oakland, California between 1959 and 1967, their pregnancies, and their offspring [42]. The CHDS was designed and initiated by Dr. Jacob Yerushalmy from the University of California at Berkeley School of Public Health in collaboration with the Kaiser Foundation Health Plan in Oakland, California. The cohort includes data on 20,754 pregnancies and 19,044 live births. It enrolled pregnant women who were Kaiser Permanente members and received obstetric care between 1959 and 1967 (nearly 100% of eligible women were enrolled). Women were followed throughout their pregnancies and their offspring were followed for at least 5 years. The loss to follow up was 0.2% at 12 months and 7.4% at 5 years.

2.2 Study population

The study on prenatal organochlorine metabolites, thyroid function, and development consisted of a subset of participants in the CHDS cohort. Participants in this study were born between the years 1960–1963 and participated in follow up examinations at ages 5, 9–11, and 15–17. A total of 953 participants with an adequate amount of maternal sera and information on outcomes of interest were eligible [11]. We randomly selected 600 participants (300 males, 300 females) to be included in the study. PCBs congeners were assayed for nearly all participants (N=579). Maternal serum samples for a number of the selected female participants (N=80) had already been assayed for PCB congeners (but not OH-PCBs) in a prior study which had selection criteria very similar to the present study and in addition required participants to be female. To conserve serum and budget these samples were not re-assayed and thus have missing measures for OH-PCBs. This analysis sample is based on the remaining 442 participants who had a sufficient amount of sera available to

measure OH-PCBs. There is a deficit of female participants in this sample due to the overlap between the current and the prior study discussed above, thus findings are based on 258 males and 184 females. Gestational length, birth weight, levels of PCB118 and prevalence of maternal smoking were not different for females with missing and non-missing OH-PCBs.

2.3 Outcomes

Data on all pregnancy outcomes were obtained from maternal and pediatric medical records. The primary outcomes are birth weight in grams (g), gestational length in days, birth length in centimeters (cm) and head circumference (cm). Gestational length was determined by mothers' self-reported last menstrual period and recorded delivery date. Birth weight, birth length and head circumference were recorded at delivery. We also analyzed birth weight percentiles for gestational age which were calculated using race stratified tables [28]. Nine women with implausible gestational lengths (those greater than 308 days) were removed from the analysis; removal of these women did not impact our findings.

2.4 Exposures

The primary exposures for this analysis are concentrations of PCBs and their OH-PCB metabolites in non-fasting maternal sera collected within 3 days post-partum. Blood samples were aliquoted and stored at -20°C at the National Institutes of Health until analyzed in 2007/2008.

We measured 11 PCBs (PCB66, PCB74, PCB99, PCB118, PCB138, PCB153, PCB170, PCB180, PCB187, PCB194, PCB203) in this sample in the Environmental Chemistry Laboratory (ECL), a division of the California Department of Toxic Substances Control [11, 43] and five OH-PCB metabolites (4-OH-CB107, 4-OH-CB146, 3'-OH-CB138, 4-OH-CB153, 4-OH-CB187) by using a gas chromatograph with electron capture detector (Varian, Inc. Walnut Creek, CA). Thus, we were able to examine the effect of OH-PCBs in relation to their parent PCB congeners [44]. OH-PCBs were separated from the serum samples and quantified according to Park et al. (2009) [45]. For the analysis of both PCBs and OH-PCBs, each batch contained a method blank (bovine serum), a Standard Reference Material for the PCB analysis (1589a, National Institute for Standards and Technology, Gaithersburg, MD), an in-house control sample of pooled human serum for OH-PCB analysis, an in-house control sample of bovine serum for PCB and OH-PCB analysis, and ten serum samples. The external calibration curves for OH-PCB standards ranged from 0.1 to 48 pg/ μL with $R^2 > 0.99$. Reasonable analytical errors ($\pm 25\%$) were obtained for the precision and accuracy of both PCBs and OH-PCBs from the internal surrogate spikes, reference material, and control samples. The limits of detection (LOD) were 0.010, 0.027, 0.010, 0.033, and 0.023 ng/mL wet weight for 4-OH-CB107, 3'-OH-CB138, 4-OH-CB146, 4-OH-CB153, and 4-OH-CB187, respectively. Values below the LOD were given the value as measured. Where possible (i.e. 4-OH-CB107, 4-OH-CB187) we categorized exposure into quartiles with the lowest quartile as the reference category; otherwise, we used $<\text{LOD}$ as the reference category and grouped the remaining observations into approximate tertiles. PCBs were lipid standardized ($\mu\text{g/g}$ lipid) by dividing their serum concentrations in ng/mL by total serum lipids; total lipids (g/L) were calculated from total serum cholesterol and triglycerides using Equation 2 in Phillips et al. (1989) [46].

2.5 Covariates

Potential covariates were those identified in previous work relating environmental exposures to pregnancy outcomes, including maternal age, BMI, race, parity, education, occupation, smoking status, alcohol consumption, and infant sex. Detailed information on these covariates was obtained from maternal interviews and medical records. We used maternal BMI at the first prenatal visit as 200 participants were missing data for pre-pregnancy BMI; however, pre-pregnancy and first visit BMIs were highly correlated (correlation coefficient = 0.94, $p < 0.0001$). Maternal alcohol consumption (ever/never) was only considered in sensitivity analyses due to the number of missing data ($N_{\text{miss}} = 96$). Maternal age, BMI, and parity were analyzed as continuous (age and BMI) or grouped-linear (parity) variables in regression models, but were categorized for variable description. Maternal smoking (never/former and current) and infant sex were examined as potential effect modifiers, as has been done in studies relating the parent PCBs to these outcomes [47].

For maternal thyroid function, we measured levels of FT4 and TSH in second trimester serum samples. Thyroid assays were performed in Dr. Nadir Rafai's laboratory at Boston Children's Hospital, Harvard Medical School. The detection limits were 0.023 ng/dL for FT4 and 0.005 $\mu\text{IU/mL}$ for TSH. Details of the methods are available in a previous publication [11].

2.6 Statistical analysis

The sample of infants included in this analysis was previously compared to those who were not included for key characteristics [11]. For our current study, we compared the characteristics of the 442 participants who had OH-PCBs measures to the 158 participants without OH-PCB measures (but in the original subset selected for PCB analysis) using Chi-squared tests for categorical variables and two sample t-tests for continuous variables.

To examine the shape of the associations between exposure and outcomes, OH-PCBs were first considered as non-transformed, continuous variables for descriptive analyses. However, due to their skewed distributions, OH-PCBs were analyzed as quartiles in regression models. For consistency with OH-PCBs, we also categorized the lipid-standardized parent PCB congeners into quartiles. We created metabolite/parent PCB ratio variables by dividing OH-PCB concentrations in ng/mL serum by PCBs in ng/mL serum; where OH-PCBs had two parent compounds we summed the parent congeners in the denominator. These ratio variables were also grouped into quartiles. TSH levels were square root transformed to reduce the influence of outliers and to improve model fit while FT4 did not require transformation. In descriptive analyses, associations between potential covariates and OH-PCB exposure were examined using two-sided t-tests or ANOVA for categorical covariates. Correlations between OH-PCBs and their parent congeners were examined using Spearman's rank correlation coefficients (r_s).

We used multiple linear regression analysis to assess the associations between individual OH-PCB congeners and each outcome. First, bivariate analyses were conducted to examine the relationships between 1) OH-PCBs and each outcome, and 2) OH-PCBs and potential covariates. Next, potential covariates were included in the multiple regression models if they

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were associated with the outcome at $p < 0.20$ in a model not including the exposure of interest. After including the exposure variables, covariates were deleted from the final regression model if their exclusion did not result in a substantial change in the coefficient for the exposure (i.e. $< 10\%$ change in the estimated regression coefficient relating exposure to outcome). The final linear models for birth weight, birth length and head circumference were adjusted for maternal BMI, race, parity, infant sex, and a term for gestational length centered at its mean. The linear models for gestational length were adjusted for maternal age, race, BMI, and infant sex.

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We examined the effects of each individual OH-PCB congener on the outcomes separately, and then examined the joint effects of the OH-PCB exposure of interest and its parent PCB congener(s) by further adding lipid-standardized quartiles of the parent PCB(s) to the model. Given the potential bias that can result from lipid standardizing PCB measures [48] we performed sensitivity analyses in which we used in regression models i) unstandardized PCB measures with controls for serum lipids (lipid adjusted) and ii) unstandardized PCB measures and with no controls for serum lipids (lipid unadjusted); conclusions were consistent across all three methods. We decided to present results using lipid-standardized PCBs since in the final fully adjusted regression models that consider joint exposure to OH-PCBs and their parent compounds, only PCBs (not OH-PCBs) are lipophilic and should be considered for lipid adjustment. We also examined in quartiles the ratio of metabolite/parent PCB(s) in models additionally adjusted for total serum cholesterol and triglycerides.

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Missing data was addressed by conducting a complete case analysis. Of the 442 participants with available OH-PCB information, complete covariate information was available for 423 participants. With the additional exclusion of 9 women with implausible gestational lengths, the final analytic sample size was 414 for birth weight, birth length and head circumference and 413 for gestational length analyses (where one additional woman was missing data on age).

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We tested for the presence of mediation by maternal thyroid function by adding FT4 and TSH separately into the linear regression models. Mediation is suggested if 1) the exposure is associated with the outcome; 2) FT4 or TSH are associated with the exposure; 3) they are associated with the outcomes after adjusting for the exposure, and their inclusion reduces the magnitude of parameter estimates for the exposure [49]

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Lastly, models were stratified separately by maternal smoking status and/or infant sex to examine potential heterogeneity in the association between OH-PCBs and pregnancy outcomes. We tested for significant interaction using an F-test where OH-PCBs were treated as categorical variables in regression models including exposure, modifier, and a cross-product term between OH-PCBs and the potential modifier. All statistical tests were 2-sided and were performed using SAS version 9.3 (SAS Institute, Inc., Cary, North Carolina).

3. Results

The 600 randomly selected participants did not differ from those who were not selected in most of the relevant variables, including birth weight, parity, maternal smoking status, infant

sex, and mother's education [11]. Among the 600 participants, the 442 participants with OH-PCB measurements for the current analysis did not significantly differ from the 158 participants without OH-PCB measurements on any covariates except for infant sex ($p<0.0001$) (Table 1). The percent of male infants is higher among participants with OH-PCB measurements than those without OH-PCB measurements, for reasons described above (Section 2.2). Among the 442 participants with OH-PCB measures, the mean birth weight was 3398 g and the gestational length was 282 days. The distributions of OH-PCBs, thyroid hormones, and pregnancy outcomes did not significantly differ between the participants with and without complete covariate information (Supplementary Table S1).

Table 2 shows the distribution of maternal OH-PCB concentrations. 4-OH-CB187 showed the highest concentration (0.41 ± 0.21 ng/mL), followed by 4-OH-CB107 (0.10 ± 0.11 ng/mL). These two congeners are among the major OH-PCBs detected in other populations [22, 37, 50, 51]. Figure 1 shows Spearman's rank correlation coefficients between OH-PCBs and their parent compounds.

Concentrations of OH-PCBs did not increase with age (Table 3), which is different from their parent compound PCBs [11]. Those who were employed full-time had slightly lower concentrations of 3'-OH-CB138 and 4-OH-CB146 than those who were not. Women who smoked during pregnancy had double the concentration of 4-OH-CB107 compared to former and nonsmokers.

Both maternal smoking and infant sex were strong predictors of birth weight and birth length in bivariate and multiple linear regression analyses (all $p<0.01$ for birth weight and $p<0.05$ for birth length). Infant sex predicted gestational length in bivariate analyses only ($p=0.049$) while maternal smoking was not associated with gestational length ($p>0.50$ in all models). Likewise, head circumference was predicted by infant sex ($p<0.01$) but not predicted by maternal smoking in our data ($p>0.30$). Thus, infant sex and maternal smoking were examined as potential modifiers of birth weight and birth length, while only infant sex was examined in gestational length and head circumference analyses.

In multiple linear regression analyses, we found evidence of a dose-response relationship between 4-OH-CB107 and decreased birth weight. In unadjusted analyses, newborns exposed to the highest quartile of 4-OH-CB107 were 147 g (95% CI: 283, 11) lighter compared with newborns exposed to the lowest quartile of exposure (Table 4, Model 1); the dose-response trend persisted after adjusting for all covariates (Table 4, Model 2). When analyses were stratified by maternal smoking status, we found that the association was restricted to newborns of mothers who smoked during pregnancy, and that among smokers there was a strong dose-response trend across all quartiles of exposure (Table 4, Model 2). Unlike smoking, infant sex did not modify the association between 4-OH-CB107 and birth weight.

The negative association between 4-OH-CB107 exposure and birth weight among smokers was magnified after adding PCB118, the primary parent compound of 4-OH-CB107, to the covariate adjusted regression model (Table 4, Model 3). Among smokers and after further adjusting for PCB118, there is a trend of birth weight decreasing with increasing 4-OH-

CB107 quartiles, while increasing PCB118 was generally associated with increased birth weight (Figure 2). In this final model, the overall p-value for interaction across quartiles of 4-OH-CB107 exposure was not significant ($P > F = 0.27$); however, the individual Wald p-value of each cross-product term suggested differences by smoking were most pronounced in the highest quartile of exposure ($Q2 \times \text{smoking}$, $p=0.14$; $Q3 \times \text{smoking}$, $p=0.30$; $Q4 \times \text{smoking}$, $p=0.01$), which is consistent with the stratum specific estimates presented in Model 3 of Table 4. Among smokers, newborns of women with concentrations of 4-OH-CB107 in the highest quartile had birth weights 316 g (95% CI: 566, 65) lighter than those with concentrations in the lowest quartile (Table 4, Model 3). In contrast, concentrations of PCB118 in the highest quartile were associated with an increase in birth weight of 271 g (95% CI: 61, 481). The average of PCB118 concentrations was slightly yet significantly lower in smoking vs nonsmoking mothers (0.06 vs 0.07 $\mu\text{g/g}$), whereas smoking mothers had twice the mean concentration of 4-OH-CB107 as nonsmoking mothers (Figure 3). Results examining exposure to the ratio of 4-OH-CB107/PCB118 also showed significantly reduced birth weight for the highest compared to lowest quartile of exposure (beta: -321 g, 95% CI: -565, -76). Analyses using birth weight percentiles as the outcome were consistent with birth weight analyses (Supplementary Figure S1).

None of the other OH-PCBs were associated with birth weight (Supplementary Table S2) and there was no association between any OH-PCB and gestational length (Supplementary Table S3). In fully adjusted analyses among the total sample there was a suggestion of reduced head circumference (Supplementary Table S4) and birth length (Supplementary Table S5) in the highest quartile of 4-OH-CB107 exposure, though these associations did not reach statistical significance. Infant sex was not a modifier of any associations between OH-PCBs and birth outcomes (Supplementary Tables S2–S5). In general, within strata infant sex associations across quartiles of OH-PCBs for all outcomes were inconsistent (no trends), in the same direction for boys and girls, or, when not in the same direction, non-significant with overlapping confidence intervals across strata (data not shown). With the exception of 4-OH-CB107 this is true of modification by maternal smoking as well. Because of the suggested association in the highest quartile of 4-OH-CB107 exposure with head circumference we explored associations within strata of maternal smoking; however, given the lack of an independent association between maternal smoking and head circumference we interpret these findings cautiously. There appeared to be stronger effects of 4-OH-CB107 on both head circumference (Supplementary Figure S2) and birth length (Supplementary Figure S3) among smokers compared to non-smokers; however, the same dose-response relationship observed for birth weight was not apparent for these outcomes.

Finally, there was no evidence supporting that the effect of 4-OH-CB107 on birth weight was mediated by maternal thyroid hormone levels. Though 4-OH-CB107 was positively associated with FT4 (but not TSH) and FT4 was non-significantly associated with decreased birth weight, both of these associations are opposite of the suspected direction. Further, parameter estimates for the main exposure were not appreciably reduced with the inclusion of the mediator in the regression models (in the total sample and when restricted to just smokers).

4. Discussion

Our analysis finds associations between prenatal exposure to 4-OH-CB107 and birth weight among mothers who were smokers. The association was most prominent for the highest levels of 4-OH-CB107 exposure. 4-OH-CB107 is one of the major OH-PCB metabolites detected in human population studies [18, 20, 22, 45, 52–54]. In our study, we detected a mean serum 4-OH-CB107 concentration of 0.1 ng/mL (comparable to 0.1 ng/g wet weight), a level that is still of environmental relevance, despite the banning of PCBs. Recent studies have reported mean or median maternal serum levels of 4-OH-CB107 ranging from 0.01 ng/g fresh weight (collected from 2000–2001 in a low exposure Swedish population [20]) to as high as 0.47 ng/g wet weight among women living within close proximity to a chemical plant [6], and 0.49 ng/g fresh weight among pregnant women who consume contaminated marine food regularly [18] (summarized in Glynn et al. (2011), Table 4 [55]).

4-OH-CB107 is the major OH-PCB congener that has been associated with adverse health outcomes in the human population. Previous studies have explored its effect on neurodevelopment [22, 24, 45]. Park et al. (2009) found a significant association between maternal concentrations of 4-OH-CB107 and decreased scores on the Mental Development Index of the Bayley Scales of Infant Development in children aged 16 months in a Slovakian cohort [21]. In a Dutch cohort, prenatal exposure to higher 4-OH-CB107 levels was associated with reduced motor function [23] and sex-specific reductions in neurological functioning in three-month-old infants (less optimal functioning was seen in males) [24]. In both studies, the detected mean of 4-OH-CB107 concentration in maternal sera was lower than the levels detected in our study (0.037 ng/g wet weight [21] and 0.067 ng/g wet weight [23]).

The only previous study to examine prenatal OH-PCB exposure and infant anthropometrics was based on 79 mother-infant pairs in Japan and used stepwise regression methods to select the variables predictive of outcomes; only the model R^2 and not the point estimates for the exposures (regardless of statistical significance) were reported [25]. Thus, we are not able to discern whether the associations, albeit not statistically significant, were suggestive in this low-powered study. Further, only one of the 79 mothers reported smoking during pregnancy; our observed association between 4-OH-CB107 and birth weight was restricted to smokers.

Our findings suggest that the adverse effect of 4-OH-CB107 was modified by maternal smoking status. Smoking is a strong and independent predictor of birth weight [56, 57]. In our sample, smoking is associated with a 130 g (95% CI: 233, 27) decrease in adjusted mean birth weight, which is consistent with previous studies [58]. In our total sample, a 137 g reduction in birth weight was observed for mothers in the highest quartile of 4-OH-CB107 exposure compared to those in the lowest, while the same comparison, but only among smokers, resulted in a reduction in birth weight of 316 g. The added risk resulting from the combination of exposure to both of these risk factors resulted in deficits in birth weight for our sample that are quite large in magnitude relative to those resulting from other known risk factors (e.g., smoking, alcohol consumption, caffeine [58]). Similarly, we observed that the effect of smoking on birth weight was modified by 4-OH-CB107 (Supplemental Figure S4). Interestingly, we also found that among smokers, the effect of 4-OH-CB107 on birth weight

was opposite of the effect of its primary parent compound PCB118. The opposite effects of PCB118 and 4-OH-CB107 are similar to the effects of DDT, an organochlorine pesticide, where, when analyzed together, the parent compound, *p,p'*-DDT, is positively associated with birth weight but the metabolite, *p,p'*-DDE, is negatively associated [59]. The associations between PCB118, 4-OH-CB107, and birth weight, however, are distinct in the sense that they are restricted to smokers. In our sample, mothers who were smokers during pregnancy had a two-fold increased serum 4-OH-CB107 concentration and slightly lower PCB118 levels compared with mothers who were not. As a result, the 4-OH-CB107/PCB118 ratio is significantly higher in the smokers than former/non-smokers ($p < 0.001$). We found significantly reduced birth weight for the highest quartile of the 4-OH-CB107/PCB118 ratio compared to the lowest (beta: -321 g, 95%CI: -565, -76). Among non-smokers, exposure to 4-OH-CB107, PCB118, or their ratio did not affect birth weight in a consistent or meaningful way. Based on the evidence, it is reasonable to speculate that smoking modifies the adverse association between 4-OH-CB107 and birth weight, either by increasing the metabolism of PCB118 to 4-OH-CB107 and/or decreasing the clearance of 4-OH-CB107.

Though there are few epidemiologic studies of OH-PCB exposure and pregnancy outcomes, many studies have examined the associations between parent PCBs and birth weight, with inconsistent findings. While some studies found PCBs to be associated with decreased birth weight [39, 47], others did not [11, 60]. The inconsistency could be attributed to varied background exposure levels of PCBs and different methods used to group PCB congeners. Based on our findings showing an interaction between a PCB metabolite with smoking, differences in findings could also depend on the proportion of smokers in various studies. Indeed, a recent prospective cohort study found no association between PCB118 and birth weight in a sample of pregnant women [61]; although in this cohort PCB118 was detected at higher levels than most other congeners, the mothers in that study were nearly all non-smokers (98.8%) — in our sample, associations with 4-OH-CB107 (and PCB118) were only observed among smokers. In contrast, in a population in which 32% of the mothers were current smokers and PCB118 was the most prevalent congener, significant interactions between PCBs and maternal smoking were reported for birth weight [41]. Like our study, they observed that PCB concentrations were lower in smokers than non-smokers, however because they presented findings where PCBs (dioxin-and non-dioxin-like) were summed together, it is unclear the extent to which PCB118 contributes to this observation. Further, this study reported a decrease in birth weight with increasing quartiles of PCB exposure among smokers, which is opposite of what we observed. Still, our results are not directly comparable as their reported findings are not for PCB118 alone; further, neither of these studies adjusted for PCB metabolites.

Strengths of our study include that data were collected prospectively, which allowed us to establish the temporality between the exposure, smoking status, and the outcome. Self-reporting of smoking was likely not subject to the same biases as it would be currently, since the pregnancy data were collected prior to increased publicity regarding the dangers of smoking during pregnancy. Selection bias was also minimized because the CHDS cohort had high participation rates and little attrition. The sample for our study was randomly selected among those who were followed up through adolescence and who had an adequate amount of maternal serum available. Those selected did not differ from those who were not selected

in major characteristics, including birth weight and the covariates. Among the 600 selected, 158 did not have OH-PCB measurements because OH-PCB analyses were only conducted in one of the original study laboratories (ECL). However, the 442 participants that had OH-PCB measurements did not differ from the 158 in any key characteristics except infant sex; the group of participants with OH-PCB measurements consisted of a higher percentage of male infants than those without, for reasons explained above. Male sex is associated with larger birth weight. In analyses stratified by sex, there was a larger reduction of birth weight associated with the highest quartile of 4-OH-CB107 exposure in female infants ($\beta = -189$, 95% CI: $-366, -11$) than in male infants ($\beta = -96$, 95% CI: $-276, 83$), though the difference was not significant. Our sample size is at least twice as large as sample sizes of previous studies on OH-PCBs in pregnant women [16–20, 22].

In addition, the associations are unlikely to be the result of unmeasured confounding, as this was a rich data set in which to control for potential confounders. The covariates we include in the models are established predictors of the outcomes and we found the expected relationships. Maternal BMI, parity, and gestational length were positively associated with birth weight, being a male infant and being white were associated with increased birth weight, and maternal smoking was associated with decreased birth weight. In sensitivity analyses we additionally adjusted our models for maternal alcohol consumption and results were unchanged.

Our results explore potential mechanisms by which OH-PCBs may impact pregnancy outcomes, such as modification by smoking and mediation by thyroid hormone status. PCBs are metabolized by cytochrome P450 (CYP) enzymes; structural variations in PCB congeners result in metabolism by different CYP enzymes [29]. Evidence suggests that PCB118 and cigarette smoke may operate via the same CYP pathway: PCB118 is a group 2 congener (dioxin-like, [62]); these compounds are primarily metabolized via CYP1A enzymes [29, 63] and cigarette smoke has been shown to be a potent inducer of CYP1A2 [63, 64]. The potential for PCB118 and cigarette smoking to interact via a shared detoxification pathway is supported by the fact that PCB118 — and not non-dioxin-like PCBs from alternative groupings such as PCBs 153, 170, 180, or 187 — has been shown in studies to be lower in smokers than non-smokers or ex-smokers [65–69]. The possible increased rate of PCB118 metabolism as a result of CYP1A2 induction by cigarette smoke could explain the higher body burden in smokers of its hydroxylated metabolite, 4-OH-CB107, which has been suggested to be more toxic than its parent congener [9, 10]. In a meta-analysis that examined effect modification by smoking, no significant interactions were reported with PCB153 exposure and birth weight [47]. Since PCB153 is a non-dioxin-like congener whereas PCB118 is dioxin-like, if synergistic effects are only observed between smoking and dioxin-like congeners, then the findings in this meta-analysis are unsurprising.

That we did not observe significant evidence of mediation by FT4 or TSH suggests that 4-OH-CB107 impacts birth weight through a mechanism other than perturbation of maternal thyroid hormone levels. PCBs are able to cross the placenta [20, 22] so it is possible that the direct impact of the placental transfer of 4-OH-CB107 to the developing fetus may be more harmful to birth weight than any effect mediated by thyroid hormone levels in the mother

during pregnancy. There are also some limitations of this study. First, for practical reasons, the concentrations of OH-PCBs were measured at one time in post-partum blood samples. Intra-individual variability may have affected the accuracy of the measures. Although blood levels of PCBs are highly correlated across different stages of pregnancy [70], it has also been shown that estimated concentrations of PCBs decrease over the course of pregnancy [71]; OH-PCB concentrations may fluctuate throughout pregnancy as they are generally more soluble than PCBs. Glynn et al. (2011) found that among pregnant women, the concentrations of 4-OH-CB107 were significantly lower in blood samples taken during the 2nd and 3rd trimester than in samples taken during the 1st trimester, and the correlation between OH-PCB levels detected in late pregnancy and the levels detected in the first trimester were small [55]. However, the sample size of that study was very small as it consisted of only 10 women. In our study, the post-partum blood samples used were all collected within 3 days of delivery and we can only generalize to exposure during late pregnancy.

Second, we only examined smoking as a dichotomous variable in our analyses. A reasonable alternative hypothesis is that because metabolism of PCB118 to 4-OH-CB107 may be increased by maternal smoking, mothers who smoked more might have higher levels of 4-OH-CB107. Thus, the dose-response relationship we observed between quartiles of 4-OH-CB107 exposure and decreased birth weight within smokers could simply be driven by detrimental effect on birth weight of higher levels of maternal smoking (quartiles of 4-OH-CB107 serving as a marker for the extent of maternal smoking). We were unable to examine our results within categories quantity of maternal smoking. However, in the total sample the apparent dose-response association between quartiles of 4-OH-CB107 and birth weight persists when adjustment is made for maternal smoking, albeit the magnitude of the association is attenuated, suggesting that the associations between 4-OH-CB107 on birth weight are likely independent of maternal smoking.

Lastly, 4-OH-CB107 is a metabolite of both PCB118 and PCB105 [37, 50]. For our analysis, only data on PCB118 concentrations were available because levels of PCB105 were not measured. As a result, we were not able to explore any possible effect of PCB105 may have on the association between 4-OH-CB107 and birth weight.

Conclusions

In a population sample drawn from a California pregnancy cohort of infants born between 1960 and 1963, we found that among smokers, prenatal exposure to 4-OH-CB107 was negatively associated with birth weight, whereas its parent compound PCB118 was positively associated with birth weight. Our findings, along with findings from previous studies on OH-PCBs, suggest 4-OH-CB107 may be of particular concern for adverse effects on developmental outcomes in the human population. The evidence that smoking may modify the association between 4-OH-CB107 and birth weight should be considered as it can inform studies of other chlorinated compounds that pose similar health hazards. Further study exploring the relations between smoking and the metabolism of chlorinated compounds would provide a better understanding of how these compounds and their

metabolites affect health outcomes and whether co-exposure to PCBs contributes to the health hazards associated with smoking.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Among pregnant women who smoked, high levels of 4-OH-CB107, a metabolite of PCB118, was associated with a reduction in birth weight of 316 (95% confidence interval 566, 65) grams. The association was not present for nonsmoking mothers.
- Among pregnant women who smoked PCB118 was associated with increases in birth weight.
- These associations were not mediated by maternal thyroid status.
- These results may provide insight into the mechanisms underlying associations between halogenated endocrine disruptors and pregnancy outcomes.

Fig. 1.
Spearman correlation coefficients among OH-PCBs and Parent PCBs.
Pairing done according to Hovander et al. [44].

Fig. 2.

Among smokers, covariate adjusted mean birth weight within quartiles of both 4-OH-CB107 and PCB118 exposure, in a model mutually adjusted for the metabolite and its parent PCB congener.

Models were adjusted for maternal BMI, race, infant sex, parity, gestational length centered at its mean and lipid-standardized quartiles of PCB118. The lowest quartile of exposure was used as the reference in regression models. Quartile cut-points were 0.04, 0.08, and 0.14 ng/mL for 4-OH-CB107 and 0.044, 0.057 and 0.076 µg/g for PCB118. Quartile medians were 0.01, 0.05, 0.10, and 0.19 for 4-OH-CB107 and 0.038, 0.050, 0.065, and 0.099 µg/g for PCB118. The p-value for the association across quartiles was obtained from regression models that treated quartiles of exposures as grouped-linear variables. *p<0.05

Fig. 3.

Distribution of 4-OH-CB107 (ng/mL) and PCB118 (µg/g lipid standardized) by maternal smoking status in our analytic sample (N=414).

Mean $\pm$ SD values of 4-OH-CB107 were 0.16 ± 0.14 ng/mL for current smokers and 0.08 ± 0.08 ng/mL for never/former smokers ($p < 0.01$). Mean $\pm$ SD values of lipid-standardized PCB118 were 0.06 ± 0.03 µg/g for current smokers and 0.07 ± 0.05 µg/g for never/former smokers ($p = 0.01$). For comparison (not shown in figure), mean $\pm$ SD values of lipid-unadjusted PCB118 were 0.41 ± 0.20 ng/mL for current smokers and 0.46 ± 0.29 ng/mL for never/former smokers ($p = 0.039$).

Table 1

Comparison of characteristics of CHDS participants with (N=442) and without (N=158) OH-PCBs measurements.

Characteristics	With OH-PCB Measurement (N=442)			Without OH-PCB Measurements (N=158)			P-value
	N	Mean	SD	N	Mean	SD	
Birth weight (g)	442	3398	495	158	3354	487	0.33
Gestational length (days)	442	282	12.3	158	283	13.6	0.36
Maternal age	441	28.8	5.97	158	29.3	6.57	0.40
Maternal BMI	431	23.3	3.76	152	23.0	3.80	0.51
Parity	442	1.65	1.65	158	1.88	1.81	0.15
	N	%		N	%		
Maternal smoking	438			158			0.78
Former	76	17.3		25	15.8		
Current	129	29.5		51	32.3		
Never	233	53.2		82	51.9		
Missing	4			0			
Maternal education	441			158			0.91
<High school	53	12.0		21	13.3		
High school graduate	152	34.5		50	31.7		
Some college/trade school	147	33.3		53	33.5		
College graduate or higher	89	20.2		34	21.5		
Missing	1			0			
Maternal race/ethnicity	442			158			0.38
White	308	69.7		116	73.4		
Non-white	134	30.3		42	26.6		
Maternal occupation	436			157			0.19
Housewife/part-time	262	60.1		85	54.1		
Full-time employed	174	39.9		72	45.9		
Missing	6			1			
Sex of infant	442			158			<0.01
Male	258	58.4		42	26.6		

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Characteristics	With OH-PCB Measurement (N=442)			Without OH-PCB Measurements (N=158)		
	N	Mean	SD	N	Mean	SD
Female	184	41.6	11.6	73.4		

N: Number of participants

SD: Standard deviation

Table 2

Distribution of maternal OH-PCBs (ng/mL wet weight) and thyroid hormone concentrations measured in maternal sera.

Exposure	N	Mean $\pm$ SD	Min	Quantile [#]			Max	LOD	%<LOD
				25%	50%	75%			
4-OH-CB107	442	0.10 $\pm$ 0.11	<LOD	0.04	0.08	0.14	1.01	0.010	12%
3'-OH-CB138	442	0.05 $\pm$ 0.06	<LOD	<LOD	0.03	0.07	0.47	0.027	47%
4-OH-CB146	442	0.05 $\pm$ 0.06	<LOD	<LOD	0.03	0.07	0.62	0.010	26%
3-OH-CB153	442	0.05 $\pm$ 0.07	<LOD	<LOD	0.03	0.07	0.86	0.033	54%
4-OH-CB187	442	0.41 $\pm$ 0.21	<LOD	0.29	0.38	0.5	2.08	0.023	<1%
FT4(ng/dL)	442	1.26 $\pm$ 0.21	0.76	1.13	1.23	1.39	2.46	0.023	–
TSH (μ U/mL)	442	1.49 $\pm$ 1.09	LOD	0.84	1.26	1.90	11.3	0.005	–

LOD: limits of detection

[#]Though the table shows quartile cut-points of all PCB metabolites, we were only able to analyze some OH-PCBs in quartiles. Where possible (i.e. 4-OH-CB107 and 4-OH-CB187) we categorized exposure into quartiles with the lowest quartile as the reference category; otherwise, we used <LOD as the reference category and grouped the remaining observations into approximate tertiles.

Table 3
Mean $\pm$ standard deviation concentrations of OH-PCBs by study sample characteristics (N=442).

Sample characteristics	4-OH-CB107	3'-OH-CB138	4-OH-CB146	3-OH-CB153	4-OH-CB187
Maternal age					
15–24	0.11 $\pm$ 0.09	0.04 $\pm$ 0.05	0.04 $\pm$ 0.06	0.05 $\pm$ 0.10	0.38 $\pm$ 0.18
25–19	0.10 $\pm$ 0.13	0.05 $\pm$ 0.07	0.05 $\pm$ 0.05	0.04 $\pm$ 0.05	0.41 $\pm$ 0.19
30–34	0.10 $\pm$ 0.10	0.05 $\pm$ 0.05	0.05 $\pm$ 0.07	0.06 $\pm$ 0.07	0.45 $\pm$ 0.27
35	0.10 $\pm$ 0.10	0.05 $\pm$ 0.07	0.04 $\pm$ 0.05	0.05 $\pm$ 0.05	0.43 $\pm$ 0.19
Maternal BMI					
Underweight	0.11 $\pm$ 0.08	0.04 $\pm$ 0.05	0.05 $\pm$ 0.04	0.04 $\pm$ 0.04	0.38 $\pm$ 0.13
Normal	0.10 $\pm$ 0.10	0.05 $\pm$ 0.06	0.05 $\pm$ 0.05	0.05 $\pm$ 0.07	0.42 $\pm$ 0.21
Overweight	0.11 $\pm$ 0.14	0.04 $\pm$ 0.06	0.05 $\pm$ 0.09	0.04 $\pm$ 0.07	0.39 $\pm$ 0.18
Obese	0.08 $\pm$ 0.08	0.06 $\pm$ 0.08	0.04 $\pm$ 0.05	0.07 $\pm$ 0.10	0.44 $\pm$ 0.33
Parity					
0	0.10 $\pm$ 0.08	0.04 $\pm$ 0.05	0.04 $\pm$ 0.05	0.05 $\pm$ 0.05	0.40 $\pm$ 0.19
1	0.10 $\pm$ 0.11	0.05 $\pm$ 0.07	0.05 $\pm$ 0.06	0.05 $\pm$ 0.10	0.44 $\pm$ 0.25
2	0.11 $\pm$ 0.11	0.05 $\pm$ 0.08	0.05 $\pm$ 0.05	0.05 $\pm$ 0.07	0.43 $\pm$ 0.24
3	0.11 $\pm$ 0.12	0.05 $\pm$ 0.06	0.05 $\pm$ 0.07	0.05 $\pm$ 0.05	0.39 $\pm$ 0.16
Smoking status					
Current	0.16 $\pm$ 0.14 ^{**}	0.04 $\pm$ 0.05	0.04 $\pm$ 0.04	0.04 $\pm$ 0.06	0.39 $\pm$ 0.17
Former	0.09 $\pm$ 0.12	0.06 $\pm$ 0.06	0.05 $\pm$ 0.07	0.05 $\pm$ 0.07	0.43 $\pm$ 0.24
Never	0.08 $\pm$ 0.07	0.05 $\pm$ 0.07	0.05 $\pm$ 0.06	0.05 $\pm$ 0.08	0.42 $\pm$ 0.22
Maternal education					
<High school	0.12 $\pm$ 0.16	0.04 $\pm$ 0.05	0.04 $\pm$ 0.05	0.03 $\pm$ 0.04	0.36 $\pm$ 0.15
High school graduate	0.09 $\pm$ 0.09	0.04 $\pm$ 0.05	0.04 $\pm$ 0.07	0.05 $\pm$ 0.07	0.40 $\pm$ 0.22
Some college/trade school	0.10 $\pm$ 0.09	0.06 $\pm$ 0.08	0.05 $\pm$ 0.05	0.06 $\pm$ 0.09	0.43 $\pm$ 0.21
College graduate or higher	0.12 $\pm$ 0.12	0.06 $\pm$ 0.05	0.05 $\pm$ 0.05	0.05 $\pm$ 0.05	0.43 $\pm$ 0.20
Maternal race					
Non-white	0.11 $\pm$ 0.12	0.05 $\pm$ 0.06	0.05 $\pm$ 0.08	0.05 $\pm$ 0.06	0.40 $\pm$ 0.21
White	0.10 $\pm$ 0.10	0.05 $\pm$ 0.07	0.05 $\pm$ 0.05	0.05 $\pm$ 0.08	0.42 $\pm$ 0.21
Occupation					

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Sample characteristics	4-OH-CB107	3'-OH-CB138	4-OH-CB146	3-OH-CB 153	4-OH-CB 187
Employed	0.09 ± 0.10	0.04 ± 0.05 *	0.04 ± 0.04 *	0.05 ± 0.05	0.39 ± 0.17
Housewife/part Time	0.11 ± 0.11	0.05 ± 0.07	0.05 ± 0.07	0.05 ± 0.08	0.43 ± 0.23
Infant sex					
Female	0.10 ± 0.09	0.05 ± 0.06	0.05 ± 0.06	0.05 ± 0.06	0.40 ± 0.18
Male	0.10 ± 0.12	0.05 ± 0.07	0.05 ± 0.06	0.05 ± 0.08	0.43 ± 0.23

* p<0.05;

** p<0.001

Table 4

Coefficient estimates in multiple linear regression models relating prenatal 4-OH-CB107 exposure to birth weight, in the total sample and stratified by maternal smoking status.

	Birth weight (95%CI) (g)			
	Q2	Q3	Q4	p-int ^a
Modell: unadjusted				
Total sample (414)	54 (−86, 195)	−106 (−240, 28)	−147 [*] (−283, −11)	0.55
Former/nonsmoker (289)	94 (−64, 253)	−54 (−213, 106)	−32 (−215, 152)	
Smoker (N=125)	−147 (−477, 183)	−249 ⁺ (−540, 41)	−284 [*] (−561, −7)	
Model 2: covariate adjusted				
Total sample (414)	111 ⁺ (−16, 238)	−44 (−165, 78)	−95 (−218, 29)	0.17
Former/nonsmoker (N=289)	152 [*] (8, 295)	5 (−140, 149)	64 (−104, 232)	
Smoker (N=125)	−116 (−410, 178)	−188 (−450, 74)	−285 [*] (−534, −36)	
Model 3: covariate and parent PCB adjusted				
Total sample (414)	97 (−29, 224)	−62 (−184, 61)	−137 [*] (−264, −11)	0.27
Former/nonsmoker (N=289)	145 ⁺ (−0.32, 290)	−8 (−156, 140)	28 (−155, 211)	
Smoker (N=125)	−122 (−412, 168)	−190 (−453, 72)	−316 [*] (−566, −65)	

Model 1: Unadjusted model.

Model 2: Model adjusted for maternal BMI, race, parity, infant sex, and a term for gestational length centered at its mean.

Model 3: Model adjusted for maternal BMI, race, parity, infant sex, term for gestational length centered at its mean, and lipid-standardized quartiles of PCB118.

⁺ 0.05 < p < 0.10;

^{*} p < 0.05

^a p-int: p-value from F-test obtained from regression model that treated quartiles of 4-OH-CB107 as a categorical variable and additionally adjusted for maternal smoking and a cross-product term for maternal smoking × 4-OH-CB107.