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The Role of African American Ethnicity and Metabolism in Sentinel Polychlorinated Biphenyl Congener Serum Levels

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Abstract

Polychlorinated biphenyls (PCBs) are environmental contaminants found in the serum of human populations across the globe. A small set of sentinel PCB congeners (IUPAC# 101, 118, 138, 153, and 180) commonly sought in human serum are often used as markers of exposure. The Chicago Great Lakes cohort of pregnant African American women was developed to study organochlorine exposure through Great Lakes resources in a pregnant African American population and their children. Comparison of PCB serum concentrations in women reporting mixed race/ethnicity within the cohort shows significant elevations of serum PCB 101 and 118 in women reporting exclusive African American ancestry.

Incubations were performed using pooled human liver microsomes followed by individual recombinant human CYP isoform microsomes to identify whether the other sentinel congeners are metabolized by human CYP 450. In human liver microsome metabolism experiments with the sentinel PCB congeners (IUPAC# 101, 118, 138, 153, and 180), only PCB 101 metabolism produced an identifiable metabolite. However, a significant loss of parent compound was observed for PCB 118 incubations with human liver microsomes. The loss of PCB 101 and PCB 118 in microsome experiments indicates they are likely metabolized in human liver. Therefore, CYP 450 mediated metabolic differences may contribute to differences in serum concentrations by race/ethnicity.

PCB metabolism has an important impact on toxicity. PCB metabolites have been shown to differ significantly in toxicity profiles relative to parent compounds. Biomonitoring studies of PCB serum levels have correlated with toxicity for the metabolizable congeners such as PCB 101 and PCB 118. However, measureable amounts of metabolizable parent congeners such as PCB 101 may not be detectable in the serum of study participants. Because PCB 118 is metabolized, but is also readily found in human serum, it may be a better marker of metabolism related PCB toxicity. Human specific PCB metabolism is difficult to characterize but has important pathophysiological ramifications and deserves further study.

Keywords

Race; metabolism; CYP 450; polychlorinated biphenyls; Great Lakes; Pregnant African American Women

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Introduction

Polychlorinated biphenyls (PCBs) are recognized as one of the most important toxic persistent environmental contaminants by environmental agencies across the globe including the EPA, ATSDR, WHO and IJC [1–4]. The term PCB reflects any number of 209 possible combinations of chlorine and hydrogen positioned around a biphenyl ring. Despite a ban on U.S. production since 1979, urban centers such as Chicago still provide a site for slow release of PCBs into the environment today [5,6]. Sentinel PCB congeners are often found in environmental matrices. The sentinel PCB congeners most often found in human serum include PCB 118, 138, 153, and 180. Despite the body of evidence supporting an intimate relationship between PCB metabolism and toxicity, minimal information describing human metabolism of sentinel PCBs exists [1,7].

Metabolism of many xenobiotics differs in African Americans versus those of European descent. Cytochrome P450 (CYP 450) oxidation is the rate limiting step in the metabolism of numerous xenobiotics including persistent organic pollutants such as polychlorinated biphenyls (PCBs). Significant differences in metabolism for a number of human CYP 450 mediated reactions have been observed between Caucasian and African Americans [8–11]. Expectedly, serum concentrations of many persistent organic pollutants also differ by race. Differences in exposure undoubtedly play a role in human serum pollutants, but the role of differing metabolism is less well defined. Distinguishing between exposure and metabolism is vital to understanding the pathophysiology of toxic exposure in humans.

The Chicago Great Lakes cohort of pregnant African American women was developed to study organochlorine exposure through Great Lakes resources in a pregnant African American population and their children [12,13]. Within the GLCPAAW, PCB 101 and 118 were found in higher concentrations in those who reported exclusive African American descent versus mixed race/ethnicity. Review of the literature shows elevated PCB 101 and PCB 118 concentrations and increased frequency of observations in those of African descent [14–16]. Significant research efforts have focused on the link between PCB exposure and risk of adverse developmental outcomes such as low birth weight [17]. However, research in this area has not emphasized the role of PCB metabolism [18]. Metabolism of PCB parent compounds might obscure associations with outcomes or metabolites might be the true causative factor. In researching the link between PCBs and low birth weight in the GLCPAAW we were forced to further characterize the role of race and metabolism as both of these covariates strongly impact risk modeling. This work takes on special significance since African Americans suffer from increased rates of low birth weight deliveries likely due to both genetics and environment [19,20].

Microsomal incubations of sentinel PCB congeners were performed to identify if any of the sentinel PCB congeners (PCB 118, 138, 153, and 180) were metabolized by CYP 450. Neither the role of metabolism in human serum organochlorines, nor the role of African American race/ethnicity in human serum PCB concentrations, has been extensively studied. Race was identified as an important factor in serum PCB 101 and 118 concentrations in the Chicago Great lakes cohort of pregnant African American women. However, the role of metabolism in elevations of serum PCBs by race has not been studied. We investigated in-vitro human liver microsome and CYP isoform mediated PCB metabolism to identify whether metabolism may be a factor in the differences observed in sentinel serum PCB congeners by race.

Materials and Methods

1) Serum Analysis

Extraction Method—Serum samples were obtained at the time of delivery for PCB analysis. PCBs were analyzed as individual congeners. The analytical method used was described by Burse et al 1990. One ml of serum was added to a round bottom culture tube to which 0.5 mL methanol was added. Extraction was performed thrice by adding 5 ml of hexane:ethyl-ether (1:1) was added and the mixture was vortexed. Samples were capped and placed on a rotator for 15 minutes at 20 RPM, then centrifuged for 10 minutes at 1800 RPM. Supernatant was transferred to a conical tube (45 ml) with a full lined cap. Five drops of paraffin-hexane solution (keeper solution) was added to each extract in the capped conical tube and the sample was concentrated to 1.0 to 1.5 ml with a slow stream of nitrogen. The sample was added to a prewashed (5ml hexane) silica chromatography column (18 cm × 9 mm i.d., 50 ml reservoir, Teflon stopcock). Conical sample tubes were rinsed with 1ml hexane two times and rinses were added to the column. Five ml of hexane was run through the column. Five drops of keeper solution was added to the eluant. Sample eluant was concentrated to dryness under a steady stream of nitrogen and reconstituted by adding 1.0ml isooctane, spiked with internal standards. Internal standards dichloronaphthalene (DCN), heptachlor epoxide (HE), and octachloronaphthalene (OCN) were all at a final concentration of 25ng/ml.

GC methodology—Samples were run on an Agilent 5890 Gas Chromatogram using an auto injector system, 7673, and a dual column system with dual ECD's, fitted with 2 DB5 columns, 30 meters in length, .32 mm i.d., and a film of 0.25 microns, obtained from Alltech Associates of Deerfield, IL., 60015. One microliter was the injection volume, inlet: 250; Detector ~ 300. Oven program: Initial temp: 90°C, Initial time: 2.70, then raised by 15° C/min to 160° C for 2.7 min, then raised by 0.9° C/min to 200° C and held for 2.7 min, then raised by 1.5° C/min to 240 and held for 2.7 min. Data was obtained and analyzed using HP Chemstation. Individual congeners ordered from AccuStandard were used as external quantitation standards. Internal standards were DCN, HE, and OCN. The non-coplanar PCB congeners identified by external standards were IUPAC #: 28, 20, 52, 47, 101, 151, 118, 114, 122, 153, 105, 138, 167, 157, 180, and 170. A three point calibration curve of 10, 1.0, 0.10 ng/ml was constructed for each congener with correlation >0.90 and run to run standard recalibration.

The analyses reported was based on PCB congeners found in more than 80% of the maternal serums sampled above the limit of detection (LOD) (LOD = 0.05 ng/ml). The five congeners meeting the aforementioned criteria were: 101, 118, 153, 138, and 180.

Mean Testing by Race—The entire cohort consisted of African American women, however, some of the women reported mixed race ethnicity (at least one grandparent was a different race). Women were stratified into African American and mixed race/ethnicity groups. Geometric means of serum PCBs differed by race/ethnicity (separate variance t-tests and Mann Whitney U-test, $p < 0.05$).

Logistic regression models were created from data acquired through questionnaires filled out by the women in the GLCPAAW, medical records, and anthropomorphic measures taken before and after delivery. Variables were entered into SPSS as either categorical or continuous variables. Categorical data used in modeling included age, race, education, income, parity, and smoking status. Continuous anthropomorphic measures used in models included body weight and total serum lipids (obtained from serum samples collected at delivery). Race was used as the dependent variable in models with women reporting mixed race/ethnicity being coded as “1” and women reporting African American only ancestry being coded as “2”. PCB serum levels were coded into tertiles and the odds ratios for the higher tertiles compared to the lowest

tertile by race were calculated. Odds ratios greater than one indicate serum levels of the African American women were elevated relative to the women of mixed race/ethnicity.

2) a. Microsomal Incubations

Materials—2,2',4,5,5'-PCB IUPAC#101, 2,3',4,5,5'-PCB IUPAC#118, 2,2',3',4,5,5'-PCB IUPAC#138, 2,2',4,4',5,5'-PCB IUPAC#153, 2,2',3',4,4',5,5'-PCB IUPAC#180, and 4-hydroxy-2,2',4,5,5'-PCB IUPAC#101 neat standards were obtained from Accustandard Inc. New Haven, CT. Solvents used were pesticide grade when available. Microsomal preparations were obtained from BD Biosciences Gentest (Woburn, MA). Pooled human liver microsomes were obtained with characterization of enzyme activity by CYP 450 specific substrate probes. BD Biosciences Gentest Supersomes are recombinant human CYP isoforms with CYP 450 reductase created from baculovirus transfected insect cells. Specific human CYP isoforms were obtained with cytochrome b5 where available as cytochrome b5 has been shown to increase enzyme activity. The specific individual Gentest Supersomes used were CYP 1A2+b5, 2A6+b5, 2B6+b5, 2C8+b5, 2C9+b5, 2C19+b5, 3A4+b5 (1nmol P450 in 1ml) while the Supermix contained 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 (2nmol P450 in 1ml).

Incubations—An NADPH generating solution was created by mixing 20 µl of 20mg/ml G6P (1.32mM), 20mg/ml NADP (0.5mM), 13.3mg/ml MgCl₂*6H₂O (1.32mM) and 5µl of 40U/ml G6PDH in 5mM sodium citrate (tribasic) (0.2U/ml) in a 1.5ml microcentrifuge tube. Sufficient buffer (HEPES 0.1M or Potassium Phosphate 0.05M) was added to substrate solution (30mM) and the NADPH generating system to make 1ml of reaction volume (Final 0.3mM PCB). The incubation mixtures were pre-warmed to 37°C. PCB substrate standards were created by dissolving neat PCBs in DMSO. Final PCB concentration was 300µM in screening incubations using human liver microsomes and Supersomes, while DMSO was kept at 1% v/v for all incubations. Ten µl of Supersomes (0.075mg, 10pmoles) or Human liver microsomes (HLMs) (0.2mg, 76pmoles) were added to incubation mixtures to initiate incubation reactions. Five µl of CYP 2B6 Supersomes (0.0375mg, 5pmoles) were used in PCB 153 incubations.

All incubations were performed as duplicates. The reactions were stopped by adding 100µl of concentrated sulfuric acid and 0.5 ml of a 2:1 chloroform:methanol solution. The entire mixture was then added to a disposable glass culture tube and the microcentrifuge tube was rinsed with 1.5 ml of hexane. The glass culture tube was vortexed and the organic fraction was extracted thrice. The organic fraction was then evaporated under gentle nitrogen. Samples were reconstituted in 1ml hexane for GC analysis. Control incubations were conducted for each set of incubations and included Insect Control, BD Supersomes™ Enzymes Cat. No. 456201 (formerly P201), and identical reaction conditions as above except for the addition of concentrated sulfuric acid and chloroform:methanol solution at time 0. Controls consisting of the same reaction mixtures as above without NADPH regeneration solutions were also used. PCB substrate standard curves were also created within the ranges of substrate added to incubation and substrate lost in incubations. None of the controls differed significantly from one another.

GC Analysis of Incubation Products—Analyses were performed using an HP 5890 Series II gas chromatograph with ECD detection. Grade 6 (ultrapure) Helium was the carrier gas (flow rate 2ml/min) with Methane/Argon makeup. The column was a J&W Scientific DB5 column (30m × 2.5µm). The temperature program was as follows; Inlet 260, Detector 300, Initial temp: 150°C time 4min, 8°C/min to 280°C for 5min

GC-MS Analysis—GC methods used were as described in McGraw and Waller [13]. However, only PCB 101 provided a detectable product through screening runs with GC/ECD. PCB 101 metabolism has been previously described [13].

2) b. Time courses of PCB metabolism

Materials—Materials are described above.

Incubations—The PCB 101 and PCB 118 time incubations performed in duplicate included 5 μ l (final concentration 152.5 μ M) PCB 101 or 10 μ l (final concentration 300 μ M) PCB 118, 20 μ l G6P, 5 μ l G6PDH, 900 μ l buffer, and 5 μ l CYP 2A6. The timed incubations were performed for 5, 15, 30, and 60 minutes. However, PCB 101 metabolism did not change after 15 minutes so a second time run was performed for PCB 101 to identify short term metabolism rate. The incubation times were 10, 40, 60, 360, 420, 600, and 900 seconds. Both parent loss and product formation are reported for PCB 101. Since the product of PCB 118 could not be quantified only change in parent concentration is reported for PCB 118. Controls consisted of deactivated enzymes incubated for 900 seconds (15minutes) for PCB 101 and 60 minutes for PCB 118.

Results

1) Serum Analysis

Tables 1 and 2 show the cohort characteristics stratified by race/ethnicity. No significant differences were found between categorical variables (chi square $p < 0.05$) or continuous variables (t-test $p < 0.05$) used in the logistic regression models. The percentages by category for each categorical variable show the distribution of individuals by race/ethnicity are quite similar. There was a notable high prevalence of cigarette smoking during pregnancy in both groups of women in the cohort.

Table 3 shows the sentinel PCB congeners in the serum of the Great Lakes cohort of pregnant African American women (GLCPAAW) followed by the Odds Ratios of elevated serum levels in the African American women versus the women of mixed race/ethnicity. The tertile ranges in ng/ml (ppb) of each congener are also presented in Figure 2. The highest mean serum PCB concentrations were found for PCB 138 followed by PCB 153, 101, 118, and 180. The presence of detectable PCB 101 levels in most individuals of the cohort is an uncommon finding in cohorts previously studied. In most U.S. studies of serum PCB body burden, the primary non-coplanar PCB congeners found to be present and in high concentrations are similar and invariably include 118, 138, 153, and 180 [21]. Figure 2 shows women of exclusive African American race/ethnicity bear significantly lower serum levels of both PCB 101 and PCB 118 compared to those of mixed race/ethnicity. PCB 153 and 180 appeared to follow the same trend but to a lesser extent and they were not significantly different.

2) a. Microsomal Incubations

Human Liver Microsomes (HLM's) were evaluated for their ability to produce metabolites of PCBs 101, 118, 138, 153, and 180. The GC chromatograms of the human liver microsome incubations compared to the parent PCB mixtures showed significant amounts of metabolite for PCB 101. However, both PCB 101 and 118 showed significant decreases in parent peak areas in HLM incubations while PCB 180 incubations revealed a modest decrease in parent area. Percent decreases in peak area for PCB 101 and 118 are shown in Figure 1.

Although a metabolite of PCB 118 was not isolated, significant loss of parent was seen in incubations with human liver microsomes (Figure 1). A suspect peak was identified in GC ECD but it was below the limits of quantitation for GC ECD and not verifiable through GCMS. Several recombinant liver microsomes, and a recombinant mixture of microsomes known as "Supermix" (Figure 2) also showed significant losses of PCB 118. The recombinant mixture of microsomes "Supermix" contained only the primary CYP isoforms found in human liver (CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, and CYP 3A4). Expectedly, the recombinant

mixture metabolized more PCB 118 per pmol protein than the HLMs as the proportions of the individual isoforms which metabolize PCB 118 is higher than in harvested human liver microsomes.

2) b. Time courses of PCB metabolism

We previously identified the metabolism of PCB 101 by human microsomes, therefore isoform specific incubations were not repeated. However, a mass balance of PCB 101 metabolism by CYP 2A6 over time is presented in Figure 3. The figure shows PCB 101 parent compound metabolism loss rate and the 4-hydroxy PCB 101 product formation rate over time. The figure indicates PCB 101 is rapidly metabolized for the first minute of the reaction with minimal to no metabolism after 5 minutes. Although the parent loss and product formation follow similar curves parent loss exceeds product formation by several orders of magnitude. This indicates tremendous inefficiency of product formation. In fact, parent and product both seem to slowly decline after 5 minutes. When incubations were deactivated but allowed to sit idle without extraction there was also a significant loss of product (data not shown). This may be due to loss of product through binding to microsomal protein. Although the mechanism of PCB metabolism has not been illustrated, these results show PCB 101 is rapidly metabolized and, like other studies have shown, may exhibit significant covalent binding to CYP 450 protein. Hsu et al. showed metabolites of the closely related congener PCB 52 (2,5,2'5') were likely formed from an arene oxide intermediate [22] and PCB arene oxide intermediates have been known to bind CYP 450 protein and heme [23,24]. Using another radiolabeled non-coplanar PCB congener with open vicinal carbons Schnellmann et. al. showed significant covalent binding of PCB metabolites to microsomal protein [23].

Metabolism of PCB 118 by human liver microsomes (HLMs) over time is shown in Figure 4. A product of PCB 118 was not isolated but parent loss over time follows a pattern consistent with enzyme mediated metabolism providing further evidence that metabolism is taking place. Unlike PCB 101, PCB 118 is not rapidly metabolized nor does it appear to be metabolized by one single CYP isoform. We previously showed PCB 101 shares a specific relationship between CYP 2A6 metabolism in HLMs and recombinant CYP isoforms [13]. Figures 3 and 4 show the reaction rates of PCB 101 and PCB 118 metabolism also differ. If PCB 118 is metabolized to reactive intermediates the hope of capturing them may be limited by the slower enzymatic turnover relative to PCB 101.

No product was observed for PCBs 138, 153, or 180 incubations with HLMs.

Discussion

Serum PCBs

Elevations of serum PCB 101 and PCB 118 in women of African heritage have been observed in several studies [2,14–16,25]. James et al. 2002 showed significantly elevated serum levels of several PCB congeners in African American women [26]. Demers et. al reported elevated PCB 118 levels in breast cancer cases versus controls and higher levels of PCB 118 in African American women [27].

PCB metabolism by CYP 450 in several mammalian species has shown that increased chlorination results in increased resistance to metabolism [28]. PCB 101 and PCB 118 are the least chlorinated (pentachlorinated) of the reported sentinel congeners. The two vicinal hydrogens on the 3,4 position of one of PCB 101's rings form a known oxidation site for CYP 450 [29,30]. Therefore, it is not surprising that PCB 101 parent concentrations are usually low or undetectable while metabolites are often found in human serum [31–33]. Figure 3 shows PCB 101 metabolism versus time. The results of the experiment show metabolism of PCB 101

by CYP 2A6 is extremely rapid. Metabolism of PCB 101 illustrates that although a product is formed readily, a large disconnect exists between parent loss and product formation. Indeed, this may explain the very small amounts of PCB metabolism products found in human serum relative to parent for other PCB congeners which are much less readily metabolized [32,34–38].

Nicotine is a xenobiotic differentially metabolized in African Americans. In-vitro studies show it is specifically metabolized by CYP 2A6 and to a lesser extent by CYP 2B6 [39]. Decreased nicotine clearance in African Americans has been attributed to decreased enzyme activity of CYP 2A6 [40–42]. Conversely, pregnancy may increase CYP 2A6 mediated metabolism. Dempsey et al. showed a 23% decrease in urine nicotine output during pregnancy indicating increased metabolism of nicotine during pregnancy [43]. We have previously shown that PCB 101 is also specifically metabolized by CYP 2A6 [13]. PCB 101's elevation in the GLCPAAW despite the fact that the cohort is pregnant is remarkable. The elevated PCB 101 in the GLCPAAW and its association with African American race/ethnicity indicates race may be a more important factor in CYP 2A6 activity than pregnancy. Findings of elevated PCB 101 serum concentrations in African Americans are explained by lower CYP 2A6 activity as previously demonstrated for cotinine and nicotine [41,44,45].

PCB 118's structure does not include open 3,4 vicinal hydrogens which accounts for its resistance to metabolism relative to PCB 101. An additional "rule" of PCB metabolism is that congeners with no ortho chlorines (also known as coplanar or "dioxin-like" congeners) are usually metabolized by CYP 1A family enzymes [46]. PCB 118 carries one ortho chlorine and is thought to be a substrate and inducer of CYP 1A enzymes [47]. Human CYP 1A metabolism of PCB 118 has not been characterized. In a recent National Toxicology Program study, PCB 118 did not follow kinetic patterns which would suggest CYP 1A mediated metabolism in rats [48]. PCB 118 incubations with recombinant human CYP 1A2 in the present study did not show product formation or loss of parent.

Significant loss of parent PCB 118 was observed in human liver microsome incubations. Figure 4 shows PCB 118 incubation reaction rate, as monitored through parent loss, over time is much slower than PCB 101. The reaction rate versus time profile resembles an enzyme mediated reaction as well. The lack of identifiable product is likely due to a large disconnect between parent loss and product formation. Similar to PCB 101 metabolism shown in figure 3, PCB 118 extractable product formation is likely much lower than parent loss. Indeed, significant differences between product recovery and parent loss may be explained by a CYP 450 generated reactive epoxide intermediate mechanism which has been noted for PCB 118 and many other PCB congeners [49–52]. In-vivo metabolism of PCB 118 by human liver is also consistent with findings of the hydroxy product of PCB 118 in human serum [31,32,37].

Figure 2 shows PCB 118 parent loss was also observed in incubations with recombinant CYP 2C8, 2C9, 2C19 and 3A4. CYP 3A and 2C isoforms account for the majority of human liver CYP 450 expression with CYP 3A4 usually predominating. The loss of parent PCB 118 in CYP 3A4 incubations is not surprising since CYP 3A4 has a large active site and is known to accommodate the largest and most diverse set of xenobiotics in comparison to other isoforms [53]. Pharmacogenomic studies often identify CYP 450 isoform phenotype of an individual or group using xenobiotics which are specifically metabolized by a certain isoform. Xenobiotic clearance is then used as a surrogate for CYP 450 mediated metabolic activity. The xenobiotic being studied is often referred as a substrate probe. Mirghani et al. and Diczfalusy et al. showed CYP 3A4 activity was significantly lower in a group of Tanzanians compared to Swedes using quinine and 4b-Hydroxycholesterol as substrate probes of activity [54,55]. These findings have added significance since they were conducted in-vivo. Indeed, lower CYP 3A4 activity in

African Americans offers a plausible explanation for elevated PCB 118 serum levels in African Americans.

The metabolism of PCB 118 by CYP 2C family enzymes may be also be significant. PCB 118 metabolism activity has correlated with CYP 2C19 activity in another study [56]. However, since CYP 2C enzymes are co-expressed, it is possible the correlation with CYP 2C19 activity was due to a relationship with the other CYP isoforms such as CYP 2C8 and/or CYP 2C9 [57]. CYP 2C inhibition by PCB 118 has been observed in dog and human liver microsomes while no metabolites were recovered [58]. Herrlin et al. showed lower CYP 2C19 activity in Tanzanians compared to Caucasians measured through chloroguanide, omeprazole, and mephenytoin as substrate probes [59,60].

Although PCB 118 is resistant to metabolism, in-vitro metabolism through human CYP 3A and CYP 2C isoforms has been demonstrated. A commonly found hydroxy PCB metabolite in human serum has been attributed to CYP mediated PCB118 metabolism in-vivo. Taken together, these results indicate PCB 118 is slowly metabolized by human CYP 450 in-vivo forming a reactive intermediate which reduces soluble product formation. Unlike PCB 101, PCB 118 is not metabolized primarily by one human CYP isoform nor is it metabolized to the same extent as PCB 101. The slower rate and selectivity of PCB 118 metabolism by human CYP 450 is the likely reason for its higher prevalence in human serum relative to PCB 101 in population studies. Future pharmacogenomic studies linking phenotypic activity of CYP isoforms and PCB congener serum levels would provide more definitive evidence.

CYP 2B family enzymes have been shown to metabolize PCBs in several species [61,62]. The human member of the 2B family, CYP2B6, was suspected of having the most activity towards human PCB metabolism. Other CYP 2B6 substrates found in higher levels in African Americans in biomonitoring studies include environmental contaminants such as DDT and chlorpyrifos [15,63,64]. However, CYP 2B6 was only implicated in the metabolism of the hexachlorinated congener PCB 153. PCB 153 human liver microsome incubations did not show significant loss of parent, however, CYP 2B6 supersome incubations showed a 20% loss of parent (results not displayed as a figure). Minimal metabolism has been shown through CYP 2B6 in another study using CYP 2B6 enzyme as well [65]. A proposed reason for elevated PCB 153 in most humans is that CYP 153 is not constitutively expressed in human liver and only comprises a small percentage of liver CYP 450 when it is found [66]. Serum levels of PCB 153 show a similar trend as PCB 101 and PCB 118 by race/ethnicity but were not statistically significant.

We provide convincing evidence that a contributing factor to elevated sentinel serum organochlorines in African Americans (such as PCB 101, PCB 118, and possibly PCB 153) is decreased clearance of these congeners through specific CYP 450 isoforms. Examples of isoforms with lower activity in African Americans (CYP 2A6, CYP 2B6, CYP 2C19, and CYP 3A4) correspond to isoforms which also metabolized the sentinel PCBs [40,41,54,55,59,60, 67]. The vast majority of research on human PCB research has focused on differing exposure to PCBs while few studies investigate endogenous human metabolism and kinetics of PCBs [1]. Additionally, animal models used as surrogates of human metabolism are inaccurate [68]. Metabolizable PCBs, such as PCB 101 and 118, have also been implicated in several adverse human health outcomes studies [27,69,70]. The role of human CYP 450 mediated metabolism/kinetics in PCB toxicity deserves further inspection, especially concerning different racial/ethnic groups.

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Fig. 1. Percent loss of parent PCBs in human liver microsome incubations. ** $p < 0.01$, * $p = 0.05$ t-test comparison of means after incubation versus standard controls

Isoform Metabolism of PCB 118

Fig. 2. Loss of PCB 118 in incubations with recombinant human CYP 450s, HLM, and recombinant isoform mixture (Supermix). Brackets indicate $\pm$ S.D.

Fig. 3.
PCB 101 parent lost and product formed versus time. Brackets indicate $\pm$ S.D.

Fig. 4.
Incubations of PCB 118 in HLMs over time. Brackets indicate $\pm$ S.D.

Table 1

Categorical characteristics of the Great Lakes Cohort of Pregnant African American Women stratified by race/ethnicity

		Mixed Race/Ethnicity (N=13)	African American (N=241)	Total (N=254)
		Count (%)	Count (%)	Count (%)
Age Group in years	<20	2 (15.4)	68 (28.2)	70 (27.6)
	20–30	8 (61.5)	136 (56.4)	144 (56.7)
	>30	3 (23.1)	37 (15.4)	40 (15.7)
Highest level of Education	Grade School	6 (46.2)	77 (32.0)	83 (32.7)
	HS Grad	5 (38.5)	91 (37.8)	96 (37.8)
	Post Secondary College/Trade	2 (15.4)	73 (30.3)	75 (29.5)
Income	< \$15,500	8 (61.5)	181 (75.1)	189 (74.4)
	15,600–30,500	3 (23.1)	38 (15.8)	41 (16.1)
	>30,500	2 (15.4)	22 (9.1)	24 (9.4)
Parity	First Child	2 (15.4)	71 (29.5)	73 (28.7)
	Second Child	5 (38.5)	67 (27.8)	72 (28.3)
	Third Child	3 (23.1)	52 (21.6)	55 (21.7)
	Fourth or Greater Child	3 (23.1)	51 (21.2)	54 (21.3)
Current Smoking Status	Smoker	3 (23.1)	56 (23.2)	59 (23.2)
	Non-smoker	10 (76.9)	185 (76.8)	195 (76.8)

Table 2
Continuous variable characteristics of the Great Lakes Cohort of Pregnant African American Women stratified by race/ethnicity

	Mixed Race/Ethnicity (N=13)			African American (N=241)			Total (N=254)		
	Mean	Standard Deviation	Range	Mean	Standard Deviation	Range	Mean	Standard Deviation	Range
Total Lipids (mg/dl)	571.8	77.7	400–733	618.2	134.7	266–1775	615.8	132.7	266–1775
Body Weight (lbs)	184.8	19.1	156–228	196.1	44.5	119–371	195.5	43.6	119–371

Table 3

Odds ratios of serum PCB tertiles showing odds of African American women carrying elevated serum PCBs versus women of mixed race/ethnicity

	Mixed R/E (N)	African American (N)	Raw Odds Ratio	Corrected Odds Ratio*	95% C.I.
PCB 101 (ng/ml)					
≤0.180	8	77			
0.181≤0.346	5	80	1.5	1.7	0.5–6.1
≥0.347	0	84	7.6	12.4*	1.4–112.5

	Mixed R/E (N)	African American (N)	Raw Odds Ratio	Corrected Odds Ratio *	95% C.I.
PCB 118 (ng/ml)					
≤0.148	9	78			
0.149≤0.270	3	80	3.1	2.8	0.7–11.0
≥0.271	1	83	9.6*	9.1*	1.1–77.6

	Mixed R/E (N)	African American (N)	Raw Odds Ratio	Corrected Odds Ratio *	95% C.I.
PCB 138 (ng/ml)					
≤0.441	2	83			
0.442≤0.851	7	79	0.1	0.3	0.1–1.6
≥0.852	4	79	0.4	0.5	0.1–3.2

	Mixed R/E (N)	African American (N)	Raw Odds Ratio	Corrected Odds Ratio *	95% C.I.
PCB 153 (ng/ml)					
≤0.400	6	81			
0.401≤0.701	6	77	1.0	1.3	0.4–4.5
≥0.702	1	83	6.2	7.4	0.8–66.2

	Mixed R/E (N)	African American (N)	Raw Odds Ratio	Corrected Odds Ratio *	95% C.I.
PCB 180 (ng/ml)					
≤0.150	5	81			
0.151≤0.277	5	79	1.7	1.3	0.3–5.1
≥0.278	3	81	16.2	2.2	0.4–11.2

* Controlling for: age, education, income, parity, smoking status, body weight, and serum lipid