Environmental Exposure to Polychlorinated Biphenyls and Placental CYP1A1 Activity in Inuit Women from Northern Québec

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Some polychlorinated biphenyl (PCB) congeners are CYP1A1 inducers, and induction of this enzyme in the placenta has been linked to adverse effects on fetal development. The objective of this study was to determine if the body burden of PCBs is related to placental CYP1A1 activity in Inuit women from Nunavik (northern Québec), a population highly exposed to organochlorines. Placenta and cord blood samples were obtained from 35 Inuit women and 30 women from a southern Québec community exposed to background levels of organochlorines. We measured PCB concentrations in all cord plasma samples and in a subset of placenta samples from the Nunavik group and assessed CYP1A1 activity (ethoxyresorufin-*O*-deethylase; EROD) in placental microsomes from all participants. Concentrations of PCBs in cord plasma were strongly correlated to those in placenta (Pearson's $r = 0.77–0.97$, $p < 0.001$) and were on average 4-fold higher in Inuit women than in southern Québec women [for PCB 153, the geometric means (geometric SDs) were 83.3 (1.9) ng/g lipid vs. 16.9 (1.6) ng/g lipid, respectively]. Despite this difference in PCB body burden, both study groups had similar EROD activities when data were stratified according to tobacco smoking. Although simple correlation analysis first showed that placental EROD activity was correlated with PCB 153 plasma concentration in the Nunavik group, a multivariate analysis failed to demonstrate a significant contribution of PCBs to EROD activity when tobacco smoking was included in the analysis. We conclude that dietary exposure to PCBs in Inuit women from Nunavik does not significantly influence EROD activity in the placenta, implicating tobacco smoking as the major modulating factor. *Key words:* CYP1A1, Inuit, placenta, polychlorinated biphenyl, tobacco smoke. *Environ Health Perspect* 110:607–612 (2002). [Online 29 April 2002]

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Polychlorinated biphenyls (PCBs) are synthetic compounds containing a biphenyl moiety substituted with 1–10 chlorine atoms (209 possible congeners). PCBs were synthesized and sold as congener mixtures characterized by their chlorine content (*1*). Their chemical and thermal stability made them suitable for diverse industrial applications, but their resistance to metabolic degradation contributed to their persistence in the environment and their biomagnification in food chains all over the world. Despite the ban on production, sale, and import of PCBs into North America since 1978, animal and human populations are still being exposed to these compounds (*2,3*), even in areas far away from industrial sources, due to long-range atmospheric and oceanic transport (*4,5*).

Prenatal exposure to PCBs has been linked to adverse developmental effects in human populations exposed accidentally (*6–10*), occupationally (*11*), and environmentally (*12–19*) to these compounds. The underlying mechanisms of these toxic effects have not been fully elucidated, but several lines of evidence suggest that the mechanism may involve altered signaling in pathways modulated by the aryl hydrocarbon receptor (AhR) (*20,21*). AhR ligands include polycyclic aromatic hydrocarbons (PAHs), polychlorodibenzo-*p*-dioxins (PCDDs), polychlorodibenzofurans (PCDFs), coplanar PCBs [International Union of Pure and Applied Chemistry (IUPAC) numbers, 77, 81, 126, and 169], and mono-*ortho*-substituted PCBs (PCBs 105, 114, 118, 123, 156, 157, 189) (*22,23*). Binding of these compounds to the AhR activates the receptor, which in turns binds to DNA and regulates the expression of several genes (potentially mediating toxicity), including cytochrome P450 1A1 (CYP1A1) (*24,25*).

CYP1A1 induction was previously used as a biomarker of environmental exposure to AhR agonists (mostly PAHs) in animal (*26*) and human (*27,28*) populations. Placental CYP1A1 induction was also reported in women who smoked during pregnancy (*29–32*). In addition, CYP1A1 induction was suggested as a biomarker of adverse developmental effects. In a study by Pelkonen et al. (*33*), newborns from smokers with high placental aryl hydrocarbon hydroxylase (AHH) activity (CYP1A1-related) had lower birth weights than newborns from smokers with lower placental AHH activity. CYP1A1 activity (AHH) was also 100-fold higher in Taiwanese women with Yu-Cheng syndrome (which resulted from high-level exposure to PCBs and their degradation by-products, such as PCDFs) than in Taiwanese and American women exposed to background levels of these compounds (*6*). Placental CYP1A1 activity (AHH) in Taiwanese women with Yu-Cheng syndrome was also about 10-fold higher than in American women exposed to background levels of organochlorines who smoked during pregnancy (*6*). In addition, an inverse correlation of ethoxyresorufin-*O*-deethylase (EROD) and AHH enzyme activities to birth weight was subsequently reported in Yu-Cheng patients (*34*). These results indicated that accidental exposure to PCBs and PCDFs induced placental CYP1A1 activity and further suggested a relation between placental CYP1A1 activity and adverse developmental effects. However, the effects of an environmental exposure to PCBs and other AhR agonists on placental CYP1A1 activity has yet to be investigated in populations exposed through dietary intake.

The Inuit population of Nunavik (northern Québec, Canada) is exposed to unusually high doses of PCBs and other organochlorines due to their consumption of a traditional diet that includes large quantities of sea mammal fat (*35–40*). Concentrations of PCBs in breast milk were 5-fold greater in the Nunavik population than in populations from southern Québec (*41*). The difference between plasma concentrations of dioxin-like compounds in Inuit adults and southern Québec adults was even more pronounced [184 ng toxic equivalents (TEQ)/kg lipid vs. 26 ng TEQ/kg lipid], and TEQs were mostly accounted for by PCBs in the Inuit population (*35*). The present investigation was part of a cohort study addressing child development in Nunavik Inuit. The objective was to investigate the distribution of PCBs in the

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fetal–placental unit and the relationship between PCB exposure and CYP1A1 activity in placental tissue from Inuit women in Nunavik. Tobacco smoking during pregnancy was assessed because of its potential confounding effect on CYP1A1 induction.

Materials and Methods

Population description and sampling. Thirty-five Inuit women residing in Nunavik were recruited upon entering Kuujjuaq hospital to give birth. Thirty white women were also recruited in a southern Québec population (Sept-Iles) exposed to background levels of organochlorines (*42*). After thorough explanation of the project and after signing a consent form, women answered a questionnaire addressing smoking and dietary habits and gave their consent to placental and umbilical cord blood sampling. The southern Québec group comprised 15 smokers and 15 nonsmokers; the Nunavik group comprised 23 smokers and 12 nonsmokers (based on self-declared cigarette smoking during pregnancy). Maternal smoking status was ascertained using cotinine content in meconium (*32,43*) in order to adequately control for the potential confounding effect of tobacco smoke-related placental CYP1A1 induction (*29–33*).

Umbilical cord blood samples (30 mL) were collected in vacutainers containing EDTA as the anticoagulant and centrifuged, and the plasma was transferred to glass vials prewashed with hexane. Plasma samples were stored at –20°C until analysis. Placentas were collected within 1 hr after delivery. Connective tissue and blood vessels were removed, and then 10-g samples were cut and frozen at –80°C in polycarbonate vials until they were shipped to the laboratory on dry ice. Meconium was collected from the diaper, transferred into a 50-mL conical tube, and kept frozen at –20°C until analysis.

Cotinine determination in meconium. We extracted cotinine from meconium according to the procedure developed by Lewis (*44*). Meconium samples were homogenized in glacial acetic acid and acetone/diphenylamine solution (1:2). The solvents were evaporated and the residue dissolved in phosphate buffer (60 mM, pH 6.0). Cotinine was extracted by solid-phase extraction and measured by mass spectrometry. The detection limit for cotinine in meconium was 5 ng/g dry weight, and the coefficient of variation was 8.8% (based on seven analyses of the same sample). Average recoveries varied from 95% to 122% in spiked samples. We reassigned participants to the appropriate smoking category (nonsmokers, moderate, and heavy smokers) based on the cotinine content of meconium samples and on cut-off values determined previously (< 5 ng/g, 5 to < 86 ng/g, ≥ 86 ng/g) (*32*).

Analyses of PCBs in plasma and placenta samples. We measured PCBs in all umbilical cord plasma samples from both groups and in a subset of placental samples from the Nunavik group (n = 20). Extraction of plasma samples (2 mL) was carried out with ammonium sulfate:ethanol:hexane (1:1:3). Extracts were concentrated and purified by chromatography on Florisil columns. Lipids were extracted from placental tissue with acetone:hexane (2:1). An aliquot of the organic fraction was evaporated to constant weight for the gravimetric determination of the lipid content. The remaining organic fraction was washed with concentrated sulfuric acid, distilled water, and potassium hydroxide and concentrated under vacuum. The extracts were then purified by chromatography on acidified silica gel and Florisil columns. Fourteen PCB congeners (PCBs 28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 170, 180, 183, 187) were measured in the plasma and placenta extracts by high-resolution gas chromatography with electron capture detection. PCB analyses were carried out using an HP-5890 series II gas chromatograph equipped with dual-capillary columns (Ultra-1 and Ultra-2, Hewlett Packard, Palo Alto, CA, USA) and dual Ni-63 electron-capture detectors (Hewlett Packard). Using a computer program developed in-house, we identified peaks by their relative retention times obtained on the two columns.

Total cholesterol, free cholesterol, and triglycerides were measured in plasma samples by standard enzymatic procedures, and phospholipids were determined according to the enzymatic method of Takayama et al. (*45*), using a commercial kit (Wako Pure Chemical Industries, Richmond, VA). We estimated the concentration of total plasma lipids according to the formula developed by Phillips et al. (*46*).

Table 2. PCB concentrations (ng/g plasma lipids) in umbilical cord plasma from southern Québec and Nunavik groups.

		Southern Québec (n = 30)		Nunavik (n = 35)	
Congener	Cl position	GM (GSD)[a]	Percent detected	GM (GSD)	Percent detected
PCB 28	2,4,4′	< LOD[b]	6.7	< LOD	0
PCB 52	2,2′5,5′	< LOD	30	< LOD	43
PCB 99	2,2′,4,4′,5	5.7 (1.5)	50	18.9 (1.8)	97
PCB 101	2,2′,4,5,5′	9.7 (2.1)	63	7.7 (1.8)	63
PCB 105	2,3,3′,4,4′	< LOD	3.3	< LOD	20
PCB 118	2,3′,4,4′,5	< LOD	40	16.7 (1.8)	97
PCB 128	2,2′,3,3′,4,4′	< LOD	—	< LOD	0
PCB 138	2,2′,3,4,4′,5′	12.7 (1.6)	93	58.4 (1.9)*	100
PCB 153	2,2′,4,4′,5,5′	16.9 (1.6)	97	83.3 (1.9)*	100
PCB 156	2,3,3′,4,4′,5	< LOD	—	< LOD	40
PCB 170	2,2′,3,3′,4,4′,5	< LOD	10	10.4 (2.3)	71
PCB 180	2,2′,3,4,4′,5,5′	7.2 (1.6)	67	31.8 (2.0)	100
PCB 183	2,2′,3,4,4′,5′,6	< LOD	13	6.5 (1.6)	51
PCB 187	2,2′,3,4′,5,5′,6	< LOD	17	18.4 (1.8)	97

[a]Calculated for congeners detected in > 50% of samples. [b]Mean value below the limit of detection (LOD; range, 5–8 ng/g plasma lipids). *p < 0.001; Student's t-tests conducted for congeners detected in > 70% of samples.

Table 1. Characteristics of participants.

	Southern Québec				Nunavik				
Characteristic	Percent	Mean[a]	SD	No.	Percent	Mean[a]	SD	No.	p-Value[b]
Maternal									
Age (year)	–	25.9	5.2	30	–	24.2	7.1	35	0.264
Weight before pregnancy (kg)	–	59.7	11.6	30	–	59.8	13.6	25	0.960
Smoked during pregnancy (%)	50.0	–	–	30	65.7	–	–	35	0.219
Cigarettes per day during pregnancy[c]	–	11.7	6.6	15	–	12.6	9.2	23	0.742
Parity (percent primiparous)	36.6	–	–	30	11.4	–	–	35	0.020
Newborn									
Male (%)	46.6	–	–	30	34.2	–	–	35	0.325
Weight (kg)	–	3.33	0.49	30	–	3.44	0.44	33	0.343
Length (cm)	–	50.9	2.1	30	–	50.1	2.4	33	0.737

[a]Arithmetic mean. [b]p-Value for Student's t-test (comparison of means) or Fisher's exact test (comparison of proportions). [c]Among smokers; one nonsmoker in each group reported smoking before pregnancy (five cigarettes/day).

Quality control was performed using the SRM-1588 standard (National Institute of Standards and Technology, Gaithersburg, MD, USA). In placental samples, percent recovery ranged between 74% and 106% for all PCB congeners (n = 3). The detection limit for PCB congeners ranged between 2.3 and 4.1 ng/g lipids. Coefficients of variation were between 9.1% and 29.9%, and biases ranged from –23.4% to +5.6%, based on 20 determinations. In plasma samples, percent recoveries were > 92%, and the detection limit was 0.02 µg/L for all congeners. Coefficients of variation ranged from 2.1% to 7.5%, and bias ranged from –10.9% to +3.0%. PCB analyses were carried out by the laboratory of the Institut National de Santé Publique du Québec, which is accredited by the Canadian Association for Environmental Analytical Laboratories.

Determination of CYP1A1 enzyme activity. Microsomal fractions were isolated from placental tissue by differential centrifugation and stored in Tris-sucrose buffer (50 mM Tris-0.25 M sucrose, pH 8.0) at –80°C until further processing. We assayed EROD activity in 96-well plates with simultaneous protein quantification using fluorescamine labeling, according to a modification of a method described previously (*47,48*). Each sample was analyzed in quadruplicate (2 × 25 µL and 2 × 10 µL microsomes) and assayed on different plates. We used microsomes from cells expressing CYP1A1 (Gentest Corp., Woburn, MA, USA) as positive controls, and analyzed six blank wells on each plate to determine the detection limit of resorufin and fluorescamine fluorescence. We always performed a dual standard curve of bovine serum albumin and resorufin on each plate. EROD activity was expressed in picomoles of resorufin formed per minute per milligram of microsomal proteins.

Statistical analyses. PCB plasma concentrations and EROD activity did not follow a normal distribution, and these variables were normalized through a logarithmic conversion ($\log_{10}$) before further processing. A value equal to one-half the detection limit was attributed to samples below the detection limit. We calculated geometric means (GMs) and standard deviations (GSDs) for congeners detected in > 50% of samples. Statistical testing was conducted for congeners detected in > 70% of samples. We compared means using Student's t-tests and compared proportions by Fisher's Exact tests. Correlations between concentrations of PCBs were tested using Pearson correlation coefficients, whereas Spearman correlation coefficients were used to test correlations involving cotinine concentration in meconium. Analyses of variance or covariance were carried out to test the effect of PCB exposure and smoking on EROD activity. For all analyses, the level of significance (α) was 0.05. All statistical tests were performed using the SPSS 8.0 for Windows statistical package (SPSS Inc., Chicago, IL, USA).

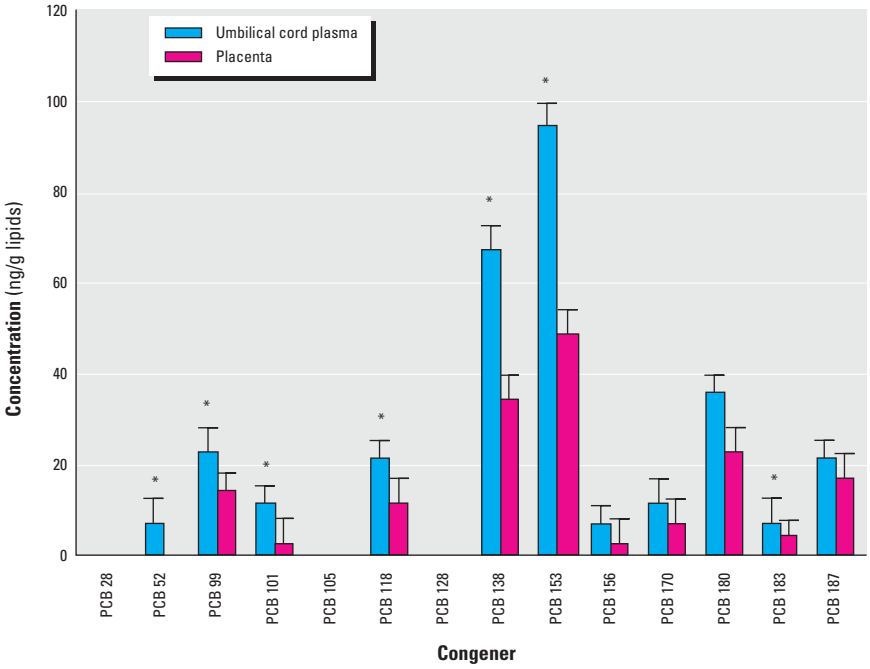

Figure 1. Concentrations of PCB congeners in umbilical cord plasma and placental samples in a subset of the Nunavik group (n = 20). Bars represent the GM and GSD.
*Statistically significant difference between placental and plasma concentrations.

Table 3. Correlations between concentrations of PCB congeners in umbilical cord plasma and placenta in a subsample of the Nunavik group (n = 20).

Congener	r^a	Plasma (% detected)	Placenta (% detected)
PCB 99	0.89	100	100
PCB 118	0.83	100	100
PCB 138	0.96	100	100
PCB 153	0.96	100	100
PCB 170	0.91	75	90
PCB 180	0.97	100	100
PCB 183	0.77	75	85
PCB 187	0.88	100	100

[a]Pearson's correlations for congeners detected in > 70% of plasma and placenta samples. All correlation coefficients were statistically significant (p < 0.001).

Results

Among all maternal and newborn characteristics listed in Table 1, only parity differed between groups. There were fewer primiparous women in the Inuit group than in the southern Québec group (p = 0.02). Birth weight was similar in both groups, but when data were stratified by smoking status, mean birth weight of newborns from smokers was lower than that from nonsmokers by an average of 359 g in the southern Québec group (p = 0.04) and 272 g in the Nunavik group (p = 0.16).

Most PCB congeners were detected more frequently in plasma samples from the Nunavik group than in those from the southern Québec group (Table 2). PCB 138 and PCB 153 were detected in > 90% of samples in both groups, and their plasma concentrations were on average 4-fold higher in the Nunavik group than in the southern Québec group. Other congeners detected in > 50% of samples in the Nunavik group were PCBs 99, 101, 118, 170, 180, 183, and 187.

PCB analyses in placental samples from the Nunavik group (n = 20) revealed lower concentrations in placenta than in umbilical

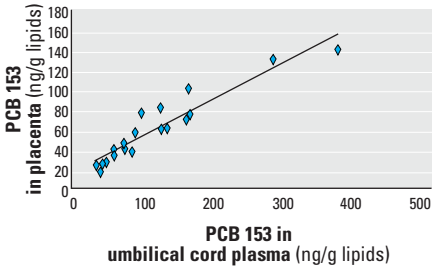

Figure 2. Correlation between PCB 153 concentrations in placenta and umbilical cord plasma in a subset of the Nunavik group (n = 20).

cord plasma. This observation was particularly striking for highly persistent congeners 138, 153, and 180, as well as for mono-*ortho*-substituted congener 118, which were all 1.5- to 2-fold lower in placenta than in umbilical cord plasma (Figure 1). PCB concentrations in placenta were highly correlated with those in umbilical cord plasma, and correlation coefficients ranged from 0.77 to 0.97 ($p < 0.001$) for all congeners detected in > 70% of samples (Table 3). Figure 2 illustrates the correlation for PCB 153. Correlations among PCBs congeners detected in > 70% of umbilical cord plasma samples from Nunavik are shown in Table 4. PCB concentrations were strongly intercorrelated (Pearson's $r > 0.75$, $p < 0.001$). In particular, the highly persistent congener PCB 153 was strongly correlated with other frequently detected PCB congeners in the Nunavik group, including PCB 118, a known AhR agonist. Hence PCB 153 is a good predictor of all major PCB congeners found in umbilical cord plasma samples from the Nunavik group. Furthermore, in view of the strong correlation noted above between PCB 153 concentrations in plasma and placenta (Figure 2), we selected PCB 153 concentration in umbilical cord plasma as the exposure variable in further statistical analyses involving placental biomarkers.

We assessed CYP1A1 activity (EROD) in placental microsomes. EROD activity levels [GM (GSD)] in the southern Québec and Nunavik groups were 6.1 (3.6) and 4.6 (3.6) pmol resorufin/min/mg protein, respectively. A statistically significant correlation of placental EROD activity to PCB 153 plasma concentration was observed in the Nunavik group (Pearson's $r = 0.38$, $p = 0.02$), but not in the southern Québec group ($p = 0.69$). Placental EROD activity was also significantly correlated with cotinine concentration in meconium in the Nunavik group (Spearman's $r = 0.80$, $p < 0.001$), as well as in the southern Québec group ($r = 0.78$, $p < 0.001$).

Table 5 shows the number of participants in each smoking category before and after reclassification based on the concentration of cotinine in meconium samples. Several women from both groups were reclassified in appropriate smoking categories based on cutoff values determined previously (*32*). Figure 3 presents EROD activities in both groups according to these smoking categories. The mean value in moderate smokers was approximately 2-fold greater than that of nonsmokers. EROD activities in heavy smokers were further increased by a factor of four compared to those of moderate smokers.

A two-way analysis of variance ($R^2 = 0.56$, $p < 0.001$) showed that EROD activity was related to smoking status during pregnancy ($p < 0.001$), but not to the study group to which women belonged ($p = 0.42$), suggesting that smoking was the main determinant of EROD activity variation. An analysis of covariance carried out in the Nunavik group only ($R^2 = 0.52$, $p < 0.001$) revealed that the relation initially found between placental EROD activity and PCB 153 in simple correlation analysis was no longer statistically significant when tobacco smoke exposure was accounted for, and that the latter explained most of the variability in EROD activity ($p < 0.001$). Further analyses showed that the mean PCB 153 plasma concentration in smokers was greater than that in nonsmokers of the Nunavik group (mean difference = 1.28 ng/g lipids, $p = 0.01$). Furthermore, cotinine concentration in meconium was correlated with PCB 153 plasma concentration (Spearman's $r = 0.42$, $p = 0.011$) in this group. Smoking was not related to PCB 153 plasma concentration in the southern Québec group.

Discussion

The objective of the present study was to determine if placental CYP1A1 activity, a potential marker of adverse developmental effects, was related to dietary PCB exposure in the Inuit population of Nunavik. The potential confounding effect of tobacco smoking was accounted for in the analysis because it is known to modulate placental CYP1A1 activity. Our results demonstrate that PCB body burden does not significantly influence placental CYP1A1 activity, implicating smoking during pregnancy as the major modulating factor.

Placental CYP1A1 induction has been previously reported in women who smoked during pregnancy (*30,31,49*) and further related to lower birth weight (*33*). In the present study, the Nunavik and the reference groups were similar with regard to several maternal and newborn characteristics. Smoking is more prevalent in the Nunavik population than elsewhere in Québec (*50*), a situation that made rigorous matching for smoking status nearly impossible. However, oversampling of smokers in the southern Québec group and of nonsmokers in the Nunavik group was performed to reach a balanced study design, thereby allowing us to test the effect of PCBs on CYP1A1 activity while controlling for the effect of tobacco smoking. Smoking status was further ascertained by the use of cotinine concentration in meconium, a biomarker previously validated (*32*), which led to the reclassification of several participants in the appropriate smoking category. This emphasizes the potential misclassification bias that may be induced by relying only on self-declared cigarette consumption to determine smoking status during pregnancy.

Body burden of PCBs observed in the Nunavik study group, as assessed by umbilical cord plasma concentrations expressed on a lipid basis, was consistent with that documented in earlier reports (*35,41*), with concentrations of major PCB congeners being approximately 4-fold higher in the Nunavik group than in the southern Québec group. Strong CYP1A1 inducers such as coplanar PCBs (PCBs 77, 126, and 169) and PCDDs/PCDFs could not be measured in the present study due to the high volume of umbilical cord plasma needed to conduct these analyses

Table 4. Pearson's correlation coefficients between concentrations of various PCB congeners in umbilical cord plasma from Nunavik neonates.

	PCB 99	PCB 118	PCB 138	PCB 153	PCB 170	PCB 180	PCB 183
PCB 118	0.92	—	—	—	—	—	—
PCB 138	0.92	0.88	—	—	—	—	—
PCB 153	0.90	0.85	0.99	—	—	—	—
PCB 170	0.79	0.74	0.93	0.94	—	—	—
PCB 180	0.82	0.78	0.95	0.97	0.97	—	—
PCB 183	0.77	0.76	0.81	0.79	0.77	0.80	—
PCB 187	0.83	0.82	0.94	0.95	0.93	0.96	0.81

[a]Pearson's *r* were calculated for congeners detected in > 70% of plasma and placental samples. All correlation coefficients were statistically significant ($p < 0.001$).

Table 5. Classification of participants in smoking categories based on self-declared cigarette smoking and after reclassification based on cotinine concentration in meconium.

	Southern Québec (*n*)	Nunavik (*n*)
Self-declared smoking (cigarettes/day)		
Nonsmokers (0)	15	12
Moderate smokers (1–10)	6	11
Heavy smokers (> 10)	9	12
Total	30	35
After reclassification (cotinine, ng/g)		
Nonsmokers (ND)	15	8
Moderate smokers (< 86)	6	10
Heavy smokers (≥ 86)	9	17
Total	30	35

ND, not detected.

(at least 60 mL). However, strong correlations (Pearson's $r = 0.98$, $p < 0.001$) were previously reported between total TEQs and either total PCBs or PCB 153, using data from the analysis of pooled plasma samples collected from Inuit adults in the Nunavik population (*35,51*). In this data set, PCB 153 was also highly correlated with PCDD/PCDFs TEQs ($r = 0.85$, $p < 0.001$) and to non-*ortho* PCBs TEQs ($r = 0.90$, $p < 0.001$) (*51*). Furthermore, strong intercorrelations were observed among various PCB congeners in plasma, including a strong correlation between PCB 153 and PCB 118 (a known AhR agonist), in the present study (Table 4), as well as in our ongoing infant cohort study in Nunavik (*40*). Taken together, these lines of evidence support the use of PCB 153 as a surrogate marker of exposure to all organochlorines present in the Arctic food chain, including dioxin-like compounds.

There was a nearly 2-fold difference in PCB concentrations between cord plasma and placental samples from the Nunavik group. The higher concentrations of PCBs in cord plasma could be explained by differences in lipid composition between plasma and placenta that may influence the distribution of these lipophilic compounds. Nonetheless, concentrations of PCBs in umbilical cord plasma were highly correlated with placental concentrations, further supporting the use of PCB 153 cord plasma concentrations to estimate PCB concentrations in the fetal–placental unit. Therefore, PCB 153 cord plasma concentration was used as the exposure variable to be related to CYP1A1 activity in the placenta.

EROD activities measured in placental samples of Inuit women were not significantly higher than those measured in the southern Québec group, suggesting that the level of exposure to dioxin-like compounds was not high enough to induce placental CYP1A1 activity in this population. Nonetheless, simple correlation analysis showed a statistically significant correlation of placental EROD activity to PCB 153 plasma concentration in the Nunavik group, an observation consistent with the results of a previous study (*48*).

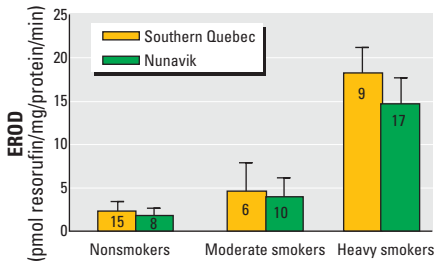

Figure 3. Placental EROD activity in Nunavik and southern Québec groups by smoking categories. Bars represent the GM and GSD; values shown inside bars = *n*.

However, further analyses proved these initial observations to be misleading. When tobacco smoking during pregnancy was accounted for in multivariate models, the influence of PCBs on placental CYP1A1 activity in the Nunavik group was no longer significant. In fact, CYP1A1 activity was modulated by tobacco smoke exposure, despite the relatively high exposure to PCBs and dioxin-like compounds in the Nunavik population. Hence, the apparent correlation of CYP1A1 activity to PCB 153 noted earlier was likely due to a confounding effect of smoking. This interpretation is supported by the statistically significant correlation noted between PCB 153 plasma concentration and cotinine concentration in meconium. Moreover, an association between consumption of sea mammal fat and tobacco smoking was reported among pregnant Inuit women in a recent study conducted in the Nunavik population (*50*).

Increased placental CYP1A1 activity was reported in women accidentally exposed to high levels of PCBs and PCDFs (*6,34*). However, the mean placental PCB 153 concentration in these women (Yu-Cheng patients) was about 12-fold greater than that reported here for the Nunavik group (8 ppb vs. 0.64 ± 0.02 ppb when converted to wet weight) (*34*). Furthermore, because Yu-Cheng patients were exposed to heat-degraded PCBs containing PCDFs, exposure to dioxin-like compounds is likely to be much lower in the Nunavik population, which is exposed to an environmental mixture of PCBs with less AhR agonistic activity.

Decreased birth weights have been associated with high placental CYP1A1 activities in women who smoked during pregnancy (*33*). A similar association was noted in Yu-Cheng women, suggesting an AhR-mediated mechanism underlying the adverse developmental effects of PCBs and PCDFs (*34*). In our study, small sample sizes precluded an investigation of the possible relationship between placental CYP1A1 activity and development (birth weight). Whether placental CYP1A1 induction is related to developmental deficits in Inuit children will be investigated in an ongoing study in Nunavik. However, based on results from the present study, it appears unlikely that PCBs found in the Arctic food chain would be involved in such potential adverse developmental effects through an AhR-signaling pathway and placental CYP1A1 induction.

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