Assessment of Pre- and Postnatal Exposure to Polychlorinated Biphenyls: Lessons from the Inuit Cohort Study

Pierre Ayotte,[1] Gina Muckle,[1] Joseph L. Jacobson,[2] Sandra W. Jacobson,[3] and Éric Dewailly[1]

[1]Department of Social and Preventive Medicine, Laval University and Public Health Research Unit, CHUQ-Laval University Medical Centre, Québec, Québec, Canada; [2]Department of Psychology, Wayne State University, Detroit, Michigan, USA; [3]Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, Michigan, USA

Polychlorinated biphenyls (PCBs) are food-chain contaminants that have been shown to induce adverse developmental effects in humans. In the course of an epidemiologic study established to investigate neurodevelopmental deficits induced by environmental PCB exposure in the Inuit population of northern Québec (Nunavik, Canada), we compared three biomarkers of prenatal exposure and models to predict PCB plasma concentration at 6 months postpartum. Concentrations of 14 PCB congeners were measured by high-resolution gas chromatography with electron capture detection in lipids extracted from maternal plasma, cord plasma, breast milk (collected at ~1 month postpartum), and 6-month-old infant plasma samples. Similar congener profiles were observed in all biologic samples, and PCB-153, the most abundant and persistent PCB congener, was strongly correlated with other frequently detected PCB congeners in all biologic media. When expressed on a lipid basis, maternal plasma, cord plasma, and milk concentrations of this congener were strongly intercorrelated, indicating that PCB concentration in any of these biologic media is a good indicator of prenatal exposure to PCBs. A multivariate model that included maternal PCB-153 plasma lipid concentration, breast-feeding duration, and the sum of two skin-fold thicknesses (an index of infant body fat mass) explained 72% of PCB-153 plasma concentration variance at 6 months postpartum ($p < 0.001$). By contrast, based on the product of breast-feeding duration times the concentration of PCBs in plasma lipids, which was used as an index of postnatal PCB exposure in several studies, only 36% of infant plasma concentration was explained. *Key words:* breast-feeding, Canada, infant, Inuit, lactational exposure, polychlorinated biphenyls, prenatal exposure. *Environ Health Perspect* 111:1253–1258 (2003). doi:10.1289/ehp.6054 available via *http://dx.doi.org/* [Online 2 April 2003]

Polychlorinated biphenyls (PCBs) and other organochlorines that are emitted into the environment at middle and lower latitudes reach the Arctic via long-range atmospheric and oceanic transport (Barrie et al. 1992; Macdonald et al. 2000). High lipophilicity and poor biodegradability lead to their bioconcentration in fatty tissues of organisms. Biomagnification also occurs through the Arctic aquatic food chain, resulting in relatively high levels of PCBs being found in sea mammal species (Muir et al. 1992; Norstrom and Muir 1994).

For cultural and economic reasons, the Inuit from Nunavik (Arctic Québec, Canada) rely heavily on marine foods for their subsistence (Dewailly et al. 1993). A population study conducted in 1989–1990 revealed that because of their heavy consumption of sea mammal fat (in particular, ringed seal and beluga), Inuit women display a mean total PCB concentration in breast milk exceeding that of southern Québec women by a factor of 7 (Dewailly et al. 1993).

Prospective longitudinal studies conducted in The Netherlands and in Michigan, North Carolina, and Oswego, New York (USA), have found adverse developmental effects from birth to childhood in relation to prenatal exposure to PCBs and other organochlorines from environmental sources. Associations between PCB exposure and decreased newborn behavioral function (e.g., reflexes, tonicity, and activity levels) were reported in three of the four studies (Huisman et al. 1995a; Rogan et al. 1986a; Stewart et al. 2000). Adverse neurologic effects lasting up to 18 months of age were found in the Dutch study (Huisman et al. 1995b). Both the Michigan and Dutch studies reported that prenatal PCB exposure was associated with lower birth weight and slower growth rate (Fein et al. 1984; Jacobson et al. 1990a; Patandin et al. 1998). In the Michigan and Oswego cohorts, prenatal PCB exposure was associated with poorer visual recognition memory during infancy (Darvill et al. 2000; Jacobson et al. 1985, 1990b, 1992). Deficits in psychomotor development lasting up to 24 months were noted in the most highly exposed children of the North Carolina cohort (Gladen et al. 1988; Rogan and Gladen 1991). Prenatal PCB exposure was linked to poorer intellectual function at 4 and 11 years in the children of the Michigan cohort (Jacobson et al. 1990b; Jacobson and Jacobson 1996) and at 42 months in the Dutch cohort (Patandin et al. 1999). Recently, results from a fifth cohort, from Düsseldorf, indicated that prenatal exposure to PCBs was negatively related to mental/motor development at 30 and 42 months. These effects were considered "PCB matrix" dependent because associations were noted with breast milk levels and not with cord blood concentrations. In addition, the authors reported a negative effect of postnatal PCB exposure on an intelligence test performed at 42 months (Walkowiak et al. 2001).

The latter results raise two controversial issues that researchers in this field have argued over for years. First, because associations with adverse developmental effects have been observed with PCB levels in some biologic media but not others, uncertainty has emerged regarding the most appropriate index of prenatal exposure to PCBs (Ribas-Fitó et al. 2001). Hence, there is a need to investigate the validity of various biologic measures of prenatal exposure to PCBs. Second, developmental deficits have been most consistently linked to prenatal, not postnatal, exposure (Jacobson and Jacobson 2001). However, assessing postnatal exposure to PCBs in infants is problematic because of the difficulty in obtaining a sufficient volume of plasma to perform PCB analysis. To circumvent this problem, some researchers have estimated postnatal exposure to PCBs by multiplying the concentration of PCBs in breast milk by the breast-feeding duration (Koopman-Esseboom et al. 1996; Walkowiak et al. 2001). More elaborate models have been proposed to predict PCB body burden in 42-month-old children (Lanting et al. 1998; Patandin et al. 1997), but these may not be applicable to infants during the first year of life.

In 1995, we initiated The Inuit Cohort Study to investigate adverse neurodevelopmental effects induced by developmental PCB exposure in Inuit infants from Nunavik.

Address correspondence to P. Ayotte, Public Health Research Unit, CHUQ-CHUL, 945 Ave Wolfe, Québec, Québec, Canada G1V 5B3. Telephone: (418) 650-5115 ext 4654. Fax: (418) 654-2148. E-mail: pierre.ayotte@inspq.qc.ca

We gratefully acknowledge the support of the Nunavik Nutrition and Health Committee, Municipal Councils, the Pauktuutit Inuit Women's Association, and the Nunalituqait Ikaluqatigiitut Association. Many thanks to E. Lachance, C. Bouffard, K. Poitras, C. Vézina, J. Gagnon, L. Chiodo, and B. Tuttle for their committed involvement in this research. Thanks to M-F. Gagnon for producing the Nunavik map.

This study was funded by National Institute of Environmental Health Sciences/National Institutes of Health (R01-ES07902), Indian and Northern Affairs Canada (Northern Contaminants Program), Health Canada, and Hydro-Québec (Environmental Child Health Initiative).

The authors declare they have no conflict of interest.

Received 11 October 2002; accepted 2 April 2003.

This article is the third in a series reporting results from this epidemiologic study. The first article described determinants of PCBs and methylmercury exposure in Inuit women participating in the study (Muckle et al. 2001a). Fish and seal meat consumption was associated with increased hair Hg concentrations. Traditional food intake during pregnancy was unrelated to PCB body burden, which is more a function of lifetime consumption. The second article presented data on the magnitude of prenatal exposure of Inuit mothers and their newborns to these contaminants and to selected nutrients (Muckle et al. 2001b). To assess prenatal exposure in this study, we measured concentrations of 14 PCB congeners and 11 chlorinated pesticides in maternal plasma, umbilical cord plasma, and breast milk samples. Postnatal exposure was evaluated by quantifying PCBs in plasma samples from 6-month-old infants. Here we report on PCB profiles in the various biologic samples and the correlations between PCB levels among biologic media. Factors associated with PCB plasma lipid concentrations in 6-month-old infants are also presented. Finally, we compare the predictive value of various models to estimate PCB plasma concentrations in Inuit infants during the first year of life.

Materials and Methods

Population. Nunavik is a region of Québec located north of the 55 parallel, where 7,660 Inuit reside in 14 villages scattered along 2,000 km of the Hudson Bay and Ungava Bay shorelines (Figure 1). Starting in November 1995, all pregnant women from three communities (Puvirnituq, Inukjuaq, Kuujjuaraapik) were invited to participate in a longitudinal study of determinants of health and development during infancy. A research assistant explained the purpose of the study, and women were enrolled after signing an informed consent form. The study protocol was reviewed and approved by the Nunavik Nutrition and Health Committee and by ethic committees of Université Laval and Wayne State University. As of November 1998, 141 mothers had completed the prenatal and postnatal interviews (84% participation rate), and PCB plasma concentrations were available from 128 of them. Data on PCB plasma concentration were available for 90 infants who had reached the age of 6 months.

Sociodemographic and physical characteristics of the mother were obtained during one prenatal and two postnatal interviews (1 month and 12 months postpartum). Infant body weight, height, and skin-fold thickness (triceps and subscapular) were measured during an additional visit at the local clinic when infants were approximately 6 months old (median = 210 days postpartum).

PCB analyses in biologic samples. Maternal blood samples (12.5 mL) were collected for the most part at delivery (median = 2 days postpartum). Cord blood samples (30 mL) were collected after the umbilical cord was severed. Infant blood samples (5 mL) were drawn when infants were approximately 6 months old (median = 206 days postpartum). Blood samples were collected in vials containing ethylenediamine tetraacetate and centrifuged (10 min, 5,000 rpm), and the plasma was transferred in glass vials prewashed with hexane. Plasma samples were stored frozen at –80°C until time of analysis. A 2-mL aliquot of plasma was first extracted with a mixture of ammonium sulfate/ethanol/hexane (1:1:3), and the lipid extract was concentrated and cleaned up on Florisil columns. Fourteen PCB congeners (International Union for Pure and Applied Chemistry no. 28, 52, 99, 101, 105, 118, 128, 138, 153, 156, 170, 180, 183, 187) (Ballschmitter and Zell 1980) were quantified in the eluate using a HP-5890 series II gas chromatograph (Hewlett-Packard, Palo Alto, CA, USA) equipped with dual-capillary columns (HP Ultra I and Ultra II; Hewlett-Packard) and dual Ni-63 electron-capture detectors (Hewlett-Packard). Peaks were identified by their relative retention times obtained on the two columns, using a computer program developed in-house. Quantification was mainly performed on the Ultra-1 column. Quality control procedures for PCB analyses were described previously (Rhainds et al. 1999). The limit of detection of the method [mean of blank + (3× standard deviation of blank)] was about 0.02 µg/L for each PCB congener (0.02–0.1 µg/L in the case of infant blood samples). Percent recoveries varied from 92 to 98% for individual congeners. Coefficients of variation (n = 20, different days) ranged from 2.1 to 7.5% and biases from –10.9 to 3.8%. The laboratory of the Institut National de Santé Publique du Québec is accredited by the Canadian Association for Environmental Analytical Laboratories.

Figure 1. Location of Nunavik communities (Arctic Québec, Canada).

Breast milk samples (25 mL) were collected by manual expression in polycarbonate vials approximately 1 month after delivery (median = 35 days postpartum). Milk samples were stored frozen at –20°C until time of analysis. PCB congeners were extracted from milk using a mixture of acetone/hexane, followed by hexane alone. Combined organic phases were washed with deionized water, concentrated, and purified on activated Florisil columns. A mixture of dichloromethane/hexane was used to elute the compounds, which were separated and quantified by high-resolution gas chromatography as described above. Detection limits vary from 0.08 to 0.16 µg/L for the various PCBs. Two certified milk reference materials (CRM 188 and 450; Community Bureau of Reference, Brussels, Belgium) were used to assess precision and accuracy of the results. Coefficients of variation varied from 10 to 20%, and relative biases 5 to 15%, depending on the specific congener.

Lipid analyses. Because PCBs distribute mainly in body fat, concentrations in plasma or milk samples were reported in micrograms per kilogram of lipids. Total cholesterol, free cholesterol, and triglycerides were measured in plasma samples by standard enzymatic procedures, whereas phospholipids were determined according to the enzymatic method of Takayama et al. (1977) using a commercial kit (Wako Pure Chemical Industries, Richmond, VA, USA). The concentration of total plasma lipids was estimated according to the formula developed by Phillips et al. (1989). An aliquot of the milk fat extract was weighed in order to determine the concentration of lipids in milk samples.

Statistical analysis. PCB concentrations in biologic samples followed a log-normal distribution. Hence, geometric means and confidence intervals are presented in descriptive statistics, and statistical analyses were performed using log-transformed values ($\log_e$). Whenever chemical analysis yielded a "not detected" result, a value equal to half the limit of detection of the analytical method was entered in the database. Pearson correlation coefficients were used to test *a*) intercorrelations among concentrations of various PCB congeners within each biologic medium and *b*) intercorrelations among PCB-153 concentrations in the four biologic media. An analysis of variance followed by the Bonferroni post hoc test was used to assess the impact of exclusive breast-feeding duration (never, ≤ 3 months, > 3 months) on infant plasma lipid PCB concentrations. Maternal and infant characteristics associated with infant plasma PCB concentrations were identified using stepwise multiple regression analyses. The following variables were included in the model: maternal plasma PCB concentration (log micrograms per kilogram lipids), maternal weight before pregnancy (kilograms), maternal height (centimeters), maternal age at birth (years), parity, the average number of cigarettes smoked per day during pregnancy, gestational age (weeks), exclusive breast-feeding duration (days), mixed breast- and bottle-feeding duration (days), infant's weight (kilograms), infant's height (centimeters), infant's body mass index (kilograms per square meter), and the sum of skin-fold thicknesses (millimeters). We included in the final model only the independent variables identified as statistically significant predictors by the stepwise procedure. All statistical analyses were performed using the SPSS for Windows statistical package (version 8.0; SPSS Inc., Chicago, IL, USA).

Results

Characteristics of Inuit women enrolled in the present study and their offspring are presented in Table 1. Fourteen percent of participants were younger than 18 years, and 4.7% were older than 35 years. Twenty-two percent of women were primiparous, and 33% already had three or more children. All but nine women (5.5%) smoked during pregnancy. Few women did not breast-feed their infants (13%); 32% of infants were exclusively breast-fed for 3 months or less, whereas 55% were exclusively breast-fed for more than 3 months. Two newborns (2%) weighed less than 2,500 g at birth.

PCB congeners 99, 118, 138, 153, 180, and 187 were detected in more than 70% of maternal and infant biologic samples. Congener profiles were remarkably similar among the different biologic samples (Figure 2). The most abundant PCB congener in all biologic samples was PCB-153, representing close to 40% of total PCB concentration defined as the sum of the 6 PCB congeners mentioned above. Congeners 138, 180, 99, 187, and 118 followed in decreasing order, averaging, respectively, 23, 15, 8, 8, and 6% of the total PCB concentration in each of the biologic media. Furthermore, PCB-153 concentration was strongly correlated to those of other frequently detected PCB congeners whether in plasma (maternal, neonate, infant) or breast milk (all Pearson's $r > 0.84$; $p < 0.001$). Further statistical analyses were limited to PCB-153 because its concentration is a good indicator of all persistent PCBs measured in the present study.

Table 2 presents concentrations of PCB-153 in all four biologic media. The highest concentrations were found in breast milk, followed by maternal plasma, cord plasma, and infant plasma. Mean cord plasma to breast milk concentration ratio was 0.63 (range, 0.22–1.71; $n = 55$), mean cord plasma to maternal plasma was 0.81 (range, 0.30–2.54; $n = 79$), and mean maternal plasma to breast milk was 0.77 (range, 0.29–1.37; $n = 84$). We noted very strong correlations among concentrations of PCB-153 in maternal and cord plasma and maternal milk samples, as indicated in Table 3 (all Pearson's $r > 0.92$; $p < 0.001$). In contrast, PCB-153 plasma concentrations in 6-month-old infants

Table 1. Characteristics of participants.

Characteristics	No.	Mean ± SD	Range
Maternal			
Age (years)	128	24.4 ± 5.7	14.1–40.7
Education (years)	128	8.7 ± 1.6	6–13
Language of interview (% Inuktitut)	128	20.0	—
Weight before pregnancy (kg)	89	59.8 ± 11.3	40.7–94.5
Parity	128	2.0 ± 1.8	0–9
Smoker (%)	128	94.5	—
Cigarettes/day[a]	121	10.5 ± 5.6	1–25
Breast-feeding (%)	94	87.2	—
Exclusive breast-feeding duration (days)	94	103.2 ± 82.5	0–292
Mixed breast- and bottle-feeding duration (days)	92	38.1 ± 64.7	0–239
Neonate			
Weight (kg)	108	3.5 ± 0.5	1.9–4.8
Gestational age (weeks)	108	38.8 ± 1.9	32–42
Infant (6 months old)			
Weight (kg)	80	9.6 ± 1.2	7.3–12.9
Height (cm)	83	67.6 ± 3.0	56.4–74.5
Body mass index (kg/m^2)	80	20.1 ± 2.3	16.1–26.8
Subscapular skin-fold thickness (mm)	83	12.4 ± 3.3	6.0–22.0
Triceps skin-fold thickness (mm)	84	13.5 ± 3.3	5.5–22.0
Sum of skin-fold thicknesses (mm)	83	25.9 ± 6.0	11.5–44.0

[a]Among smokers.

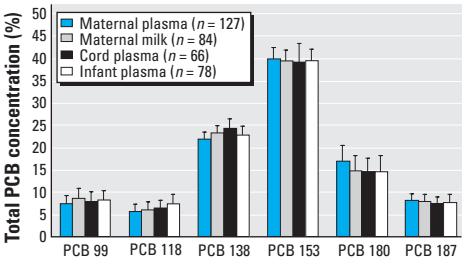

Figure 2. Percentage of total PCB concentration for six congeners detected in more than 70% of maternal and infant plasma samples. Each bar represents the mean ± SD. Only samples containing detectable concentrations of all six congeners were included in calculations.

were weakly correlated to maternal plasma, cord plasma, or breast milk concentrations (r = 0.29 – 0.42; $p < 0.01$).

We explored the relation between breast-feeding duration and plasma PCB levels in 6-month-old infants by stratifying in three categories: never breast-fed, exclusive breast-feeding for 3 months or less, and exclusive breast-feeding for more than 3 months (Table 4). Mean PCB plasma lipid concentration in infants who were breast-fed for more than 3 months was 4.3-fold greater and 6.6-fold greater, respectively ($p < 0.001$), than those of infants who were breast-fed for 3 months or less and never breast-fed infants.

Initially, we performed a stepwise regression analysis to identify, among several maternal and infant characteristics (see "Materials and Methods," Statistical analysis), those associated with plasma PCB concentration at 6 months of age. Maternal plasma lipid PCB-153 concentration, the duration of exclusive breast-feeding, the duration of mixed (breast + bottle) feeding, and the sum of skin-fold thicknesses were the only statistically significant predictors of infant plasma PCB-153 levels. In the final model shown in Table 5 (R^2 = 0.72; $p < 0.001$; n = 75), the duration of exclusive breast-feeding, the duration of mixed feeding, and maternal PCB-153 plasma lipid concentration were all positively associated with infant's PCB-153 plasma lipid concentration ($p < 0.001$), whereas the sum of two skin-fold thicknesses, a surrogate for infant body fat mass, was negatively associated with the dependent variable ($p < 0.01$). Substituting body weight for the sum of skin-fold thicknesses yielded a similar but slightly weaker model (R^2 = 0.69). Maternal plasma lipid PCB-153 concentration was used in regression analyses to index maternal body burden because it was very highly correlated with milk PCB-153 concentration and available for more infants.

Various regression models to predict PCB plasma lipid concentration in Inuit infants are presented in Table 6. Almost identical models were obtained using total PCBs concentrations instead of PCB-153 concentrations (data not shown). As expected, the concentration of PCB-153 in maternal plasma lipids and the breast-feeding duration considered individually (R^2 = 0.08 and 0.53, respectively) did not predict infant PCB concentration as well as when both factors were included in the model (R^2 = 0.66). Adding the sum of skin-fold thicknesses to the later model did not improve its predictive value (data not shown). A model that incorporates the product of total breast-feeding (exclusive and mixed) duration multiplied by PCB-153 concentration in maternal plasma lipids had only a weak predictive value (36% of the variance explained). Clearly, the multivariate model composed of the independent variables presented in Table 5 provides the strongest prediction; it explained 72% of the variance in infant PCB plasma concentration.

Discussion

Our study aimed to compare different biomarkers of prenatal PCB exposure and models to predict PCB plasma lipid concentration in 6-month-old infants, using data from the Inuit Cohort Study, a large epidemiologic study taking place in Nunavik that investigates the role of pre- and postnatal exposure to PCBs and heavy metals on various developmental end points during the first year of life (Muckle et al. 2001a, 2001b). When expressed on a lipid basis, concentrations of PCB-153 in umbilical cord plasma, maternal plasma, and breast milk were all highly intercorrelated, indicating that any of these biologic media can be used to assess prenatal PCB exposure. We also found that infant PCB plasma concentration was predicted best by a model that contained measures of maternal PCB concentration in body lipids, breast-feeding duration, and infant fat mass.

Previous studies have reported maternal concentrations of PCBs in milk or plasma (serum) samples and concentrations in umbilical cord plasma (serum) samples in various populations (Jacobson et al. 1984; Koopman-Esseboom 1994; Rogan et al. 1986b; Skaare et al. 1988). However, failure in most of these studies to report concentrations of these lipophilic compounds on a lipid basis made it difficult to assess properly the relationships between PCB concentrations in these biologic samples. For example, Skaare et al. (1988) reported a mean PCB concentration of 10 μg/kg wet weight in 20 maternal serum samples, whereas the mean concentration in corresponding cord plasma samples was only 3 μg/kg (12 of 20 cord plasma samples had detectable levels); the authors concluded that their results were consistent with the notion that the placenta may function as a partial barrier protecting the fetus from transplacental exposure. Dekoning and Karmaus (2000) recently reviewed the literature on this subject and calculated cord-to-maternal blood ratios ranging from 0.59 to 1.1 when data from four studies were expressed on a lipid basis. In our study, cord plasma PCB concentrations expressed on a lipid basis were on average 81% of those in maternal plasma. A similar ratio (0.87) was obtained recently among Inuit women and their neonates from Greenland when total PCB levels in plasma were expressed on a lipid basis (Bjerregaard and Hansen 2000). Furthermore, in our study very high correlation coefficients were noted between maternal plasma, breast milk, and cord plasma levels (Table 3), and similar congener profiles were noted in maternal and neonates samples (Figure 2). Taken together, these results indicate that the placenta does not constitute a barrier to the transfer of major PCB congeners from the mother to the fetus and that these compounds are transported by passive diffusion to all body lipids. It follows that concentrations of PCBs in maternal plasma, milk, and umbilical cord plasma can all be used as surrogates of prenatal exposure to PCBs. Therefore, associations reported previously between neurodevelopmental outcomes and prenatal PCB exposure that appeared dependent on the "PCB matrix" (i.e., associations observed with PCB concentrations in one biologic sample but not in others) are likely due to analytical problems, as suggested by Walkowiak et al. (2001). These problems may arise from the lower concentration of lipids in

Table 2. PCB-153 concentration (μg/kg lipids) in biologic samples from Inuit mothers and their offspring at birth and 6 months of age.

Biologic sample	No.	Percent detected	Geometric mean	95% CI	Range
Maternal plasma	128	100.0	105.1	92.5–119.5	18.9–709.0
Maternal milk	84	100.0	129.9	112.9–149.5	40.5–727.9
Cord plasma	79	100.0	82.5	69.1–98.5	13.4–550.9
Infant plasma	90	96.7	75.1	58.1–97.1	3.6–888.9

95% CI, 95% confidence interval.

Table 3. Correlations among PCB-153 concentrations in biologic samples (log-transformed values).

	Maternal plasma	Milk	Cord plasma	6-Month-old infant plasma
Maternal plasma	1.00 (128)[a]	0.95** (84)	0.94** (79)	0.29* (90)
Milk		1.00 (84)	0.92** (55)	0.42** (66)
Cord plasma			1.00 (79)	0.33* (57)
6-Month-old infant plasma				1.00 (90)

[a]Values are Pearson's r (n). *$p \le 0.01$; **$p \le 0.001$.

Table 4. Concentration of PCB-153 in plasma lipids of 6-month-old Inuit infants according to duration of exclusive breast-feeding.

Breast-feeding	No.	GM	95% CI	F-value[a]
Never	14	23.1	12.0–44.7	
≤ 3 Months	26	36.0	24.0–54.1	
> 3 Months	50	153.0[b]*	121.4–192.9	34.2*

Abbreviations: 95% CI, 95% confidence interval; GM, geometric mean.
[a]F-value for a one-way analysis of variance on log-transformed values. [b]Mean value significantly different from those of the other groups (Bonferroni post hoc test). *$p < 0.001$.

umbilical cord plasma than in maternal plasma (2.8 g/L vs. 7.9 g/L in the present study), which makes it more difficult to measure PCBs and other lipophilic compounds reliably in the former biologic medium.

To our knowledge, our study is the first to investigate factors influencing plasma PCB concentrations in infants during the first year of life. The major importance of breast-feeding as a determinant of postnatal PCB exposure in infants was demonstrated by stratifying according to the breast-feeding duration. We observed that infants who were breast-fed for more than 3 months displayed a mean plasma PCB concentration 6.6-fold higher than that of bottle-fed infants (Table 4). Breast-feeding during 3 months or less increased the mean PCB concentration by only 56% compared with the group never breast-fed. Lanting et al. (1998) reported a mean PCB concentration 4.5 times higher in 42-month-old Dutch children breast-fed for at least 6 weeks compared with those never breast-fed. In Dutch children of similar age, Patandin et al. (1997) reported a mean PCB plasma concentration 3-fold higher in the breast-fed group than in the bottle-fed group. In school-age children (7–10 years old) from Germany, exclusive breast-feeding during more than 3 months was associated with a doubling of PCB plasma concentrations (Karmaus et al. 2001). Hence, exposure to these lipophilic compounds through breast-feeding has a major and long-lasting influence on the offspring body burden. Using a toxicokinetic model that takes into account exposure, the diluting effect of body growth, and elimination processes, we have predicted that the influence of breast-feeding on the body burden of persistent organochlorines would last until adulthood in the Inuit population (Ayotte et al. 1996).

A multiple linear regression model that included as statistically significant predictors the exclusive breast-feeding duration, PCB concentration in maternal plasma, mixed (breast and bottle) feeding duration, and the sum of two skin-fold thicknesses explained 72% of plasma lipid PCB concentration in 6-month-old Inuit infants (Table 5). Although no other model was elaborated specifically for infants, others have looked at determinants of PCB plasma levels in children. Jacobson et al. (1989) studied determinants to PCB plasma concentration in 4-year-old Michigan children and found that maternal PCB milk level and breast-feeding duration jointly explained 60% of the variance. Lanting et al. (1998) presented a nonlinear model that explained 75% of the variance in children's levels and included as predictors breast-feeding duration (exclusive), feeding mode (breast or formula), and concentrations of PCBs in cord plasma and in breast milk. Patandin et al. (1997) presented separate models for breast-fed and bottle-fed infants. The formula-fed group model explained 36% of the variance and included as predictors maternal plasma levels, maternal age, the weight of the child, and its dietary PCB exposure. The breast-fed group model explained 63% of the variance and contained the following predictors: the duration of breast-feeding, breast milk PCB concentration, maternal plasma PCB concentration, maternal age, the weight of the child, and dietary intake of PCBs. However, only the duration of breast-feeding, breast milk PCB concentration, and the child's weight showed statistically significant associations with the child's plasma lipid concentration, similar to the model presented here for 6-month-old infants.

Throughout this study, we made the implicit assumption that the concentration of PCBs in infant body lipids is the most appropriate exposure metric to use in studying the relation of postnatal PCB exposure to developmental outcomes. Because PCBs are lipophilic and stored mainly in body fat, the higher the body fat mass, the greater the volume of distribution and the lower the plasma lipid PCB concentrations. In our model, the sum of two skin-fold thicknesses measured on the infants (triceps and subscapular), a marker of body fat mass, showed a negative association with PCB concentration in plasma lipids. Associations of both maternal plasma lipid PCB concentration and breast-feeding duration to infant plasma lipid PCB concentration become stronger when infant body fat mass is included in the model. A statistically significant negative but slightly weaker association was also noted when the infant body weight was entered in the model instead of the sum of skin-fold thicknesses. Skin-fold thicknesses are likely a better indicator of infant body fat mass than is body weight.

In view of the particular source of exposure to PCBs in the Inuit population (sea mammal fat consumption), one might question the degree to which our results are applicable to other populations environmentally exposed to these compounds. Longnecker et al. (2003) reviewed PCB exposure levels from 10 studies of PCB and neurodevelopment, including ours; the authors noted that besides PCB-153, which was the major congener present in maternal biologic samples from nearly all studies, congeners 118, 138, and 180 were also major congeners. Although similarities do exist among studies, the ratio of median PCB-118 concentration to median PCB-153 concentration was the lowest in the Inuit population (0.14), compared with values ranging from 0.18 to 0.87 in the other populations. These results suggest that some differences in PCB congener profiles exist across populations. Notwithstanding these differences, it seems reasonable to rely on a major congener such as PCB-153, which is quantified in biologic samples with relative ease, possesses a long biologic half-life, and is strongly correlated to other congeners, to assess PCB exposure within a given population.

The model developed here to predict postnatal PCB exposure (plasma lipid concentrations at 6 months of age) should be applicable to other populations environmentally exposed to PCBs. Indeed, there is no reason to believe that the factors associated with PCB plasma

Table 5. Multiple linear regression analysis of plasma lipid PCB-153 concentration in 6-month-old Inuit infants ($n = 75$).

	Pearson's r	Standardized β	Model R^2
Maternal plasma PCB-153 (log µg/kg)	0.29*	0.36**	
Exclusive breast-feeding duration (days)	0.68**	0.79**	
Mixed breast- and bottle-feeding duration (days)	0.17	0.37**	
Sum of skin-fold thicknesses (mm)	–0.07	–0.20*	0.72**

*$p < 0.01$; **$p < 0.001$.

Table 6. Models predicting PCB-153 concentrations (log value µg/kg lipids) in 6-month-old infant plasma samples.

Predictors	Equation	R^2
Maternal PCB-153 in plasma ($n = 90$)	$2.126 + 0.467 \times \ln\text{PCB-153}_{\text{maternal plasma}}$	0.08*
Exclusive breast-feeding duration ($n = 87$)	3.262 + 1.015E-02 × exclusive breast-feeding duration (days)	0.47**
Total breast-feeding duration ($n = 85$)	2.926 + 9.645E-03 × total breast-feeding duration (days)	0.53**
Total breast-feeding duration × maternal PCB plasma concentration ($n = 85$)	$3.745 + 2.873\text{E-}05 \times [\text{PCB-153}_{\text{maternal plasma}} \times \text{total breast-feeding duration}]$ (µg/kg lipids × days)	0.36**
Total breast-feeding duration and maternal PCB plasma concentration ($n = 85$)	$6.017\text{E-}02 + 9.961\text{E-}03 \times \text{total breast-feeding duration (days)} + 0.603 \times \ln\text{PCB-153}_{\text{maternal plasma}}$	0.66**
Multivariate model ($n = 75$)	$1.137 + 0.576 \times \ln\text{PCB-153}_{\text{maternal plasma}} + 1.171\text{E-}02 \times$ exclusive breast-feeding duration (days) $+ 6.901\text{E-}03 \times$ mixed breast-feeding duration (days) $- 6.73\text{E-}02 \times$ sum of skin-fold thicknesses (mm)	0.72**

*$p < 0.01$; **$p < 0.001$.

levels in Inuit infants at 6 months of age—breast-feeding duration, maternal PCB plasma levels, and infant body fat mass (as represented by skin-fold thickness measurements)—would not apply to infants from other populations. The ingestion of solid foods such as beluga whale skin and fat that are highly contaminated by PCBs could theoretically contribute to postnatal PCB exposure in Inuit infants. However, these traditional food items are rarely introduced in the diet at such an early age in this population (2% of mothers mentioned giving sea mammal fat or skin to their infant in our study).

Our model requires the knowledge of breast-feeding duration and an index of the body fat mass, in addition to a measure of maternal PCB body burden. However, it provides much more reliable predictions of the infant PCB plasma lipid concentration than does the simple product of PCB concentration in maternal lipids times the breast-feeding duration, which has been used by some researchers in previous developmental studies (Koopman-Esseboom et al. 1996; Walkowiak et al. 2001). Clearly, the possible involvement of postnatal PCB exposure on child development must be assessed using more appropriate models, such as the one presented in this article.

References

Ayotte P, Carrier G, Dewailly É. 1996. Health risk assessment for Inuit newborns exposed to dioxin-like compounds through breast feeding. Chemosphere 32:531–542.

Ballschmitter K, Zell M. 1980. Analysis of polychlorinated biphenyls (PCB) by glass capillary gas chromatography. Composition of technical Aroclor- and Clophen-PCB mixtures. Fresenius Z Anal Chem 302:20–31.

Barrie LA, Gregor D, Hargrave B, Lake R, Muir D, Shearer R, et al. 1992. Arctic contaminants: sources, occurrence and pathways. Sci Total Environ 122:1–74.

Bjerregaard P, Hansen JC. 2000. Organochlorines and heavy metals in pregnant women from the Disko Bay area in Greenland. Sci Total Environ 245:195–202.

Darvill T, Lonky E, Reihman J, Stewart P, Pagano J. 2000. Prenatal exposure to PCBs and infant performance on the Fagan Test of Infant Intelligence. Neurotoxicology 21:1029–1038.

DeKoning EP, Karmaus W. 2000. PCB exposure *in utero* and via breast milk. A review. J Expo Anal Environ Epidemiol 10:285–293.

Dewailly É, Ayotte P, Bruneau S, Laliberte C, Muir DC, Norstrom RJ. 1993. Inuit exposure to organochlorines through the aquatic food chain in Arctic Québec. Environ Health Perspect 101:618–620.

Fein GG, Jacobson JL, Jacobson SW, Schwartz PM, Dowler JK. 1984. Prenatal exposure to polychlorinated biphenyls: effects on birth size and gestational age. J Pediatr 105:315–320.

Gladen BC, Rogan WJ, Hardy P, Thullen J, Tingelstad J, Tully M. 1988. Development after exposure to polychlorinated biphenyls and dichlorodiphenyl dichloroethene transplacentally and through human milk. J Pediatr 113:991–995.

Huisman M, Koopman-Esseboom C, Fidler V, Hadders-Algra M, Van der Paauw CG, Tuinstra LGMT, et al. 1995a. Perinatal exposure to polychlorinated biphenyls and dioxins and its effect on neonatal neurological development. Early Hum Dev 41:111–127.

Huisman M, Koopman-Esseboom C, Lanting CI, Van der Paauw CG, Tuinstra LGMT, Fidler V, et al. 1995b. Neurological condition in 18-month-old children perinatally exposed to exposure to polychlorinated biphenyls and dioxins. Early Hum Dev 43:165–176.

Jacobson JL, Fein GG, Jacobson SW, Schwartz PM, Dowler JK. 1984. The transfer of polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs) across the human placenta and into maternal milk. Am J Public Health 74:378–379.

Jacobson JL, Humphrey HE, Jacobson SW, Schantz SL, Mullin MD, Welch R. 1989. Determinants of polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), and dichlorodiphenyl trichloroethane (DDT) levels in the sera of young children. Am J Public Health 79:1401–1404.

Jacobson JL, Jacobson SW. 1996. Intellectual impairment in children exposed to polychlorinated biphenyls *in utero*. N Engl J Med 335:783–789.

———. 2001. Postnatal exposure to PCBs and childhood development. Lancet 358:1568–1569.

Jacobson JL, Jacobson SW, Humphrey HEB. 1990a. Effects of exposure to PCBs and related compounds on growth and activity in children. Neurotoxicol Teratol 12:319–326.

———. 1990b. Effects of *in utero* exposure to polychlorinated biphenyls and related contaminants on cognitive functioning in young children. J Pediatr 116:38–45.

Jacobson JL, Jacobson SW, Padgett RJ, Brumitt GA, Billings RL. 1992. Effects of prenatal PCB exposure on cognitive processing efficiency and sustained attention. Dev Psychol 28:297–306.

Jacobson SW, Fein GG, Jacobson JL, Schwartz PM, Dowler JK. 1985. The effects of intrauterine PCB exposure in visual recognition memory. Child Dev 56:853–860.

Karmaus W, DeKoning EP, Kruse H, Witten J, Osius N. 2001. Early childhood determinants of organochlorine concentrations in school-aged children. Pediatr Res 50:331–336.

Koopman-Esseboom C, Huisman M, Weisglas-Kuperus N, van der Paauw CG, Tuinstra LG, Boersma ER, et al. 1994. PCB and dioxin levels in plasma and human milk of 418 Dutch women and their infants. Predictive value of PCB congener levels in maternal plasma for fetal and infant's exposure to PCBs and dioxins. Chemosphere 28:1721–1732.

Koopman-Esseboom C, Weisglas-Kuperus N, de Ridder MA, Van der Paauw CG, Tuinstra LG, Sauer PJ. 1996. Effects of polychlorinated biphenyl/dioxin exposure and feeding type on infants' mental and psychomotor development. Pediatrics 97:700–706.

Lanting CI, Fidler V, Huisman M, Boersma ER. 1998. Determinants of polychlorinated biphenyl levels in plasma from 42-month-old children. Arch Environ Contam Toxicol 35:135–139.

Longnecker MP, Wolff MS, Gladen BC, Brock JW, Grandjean P, Jacobson JL, et al. 2003. Comparison of polychlorinated biphenyl levels across studies of human neurodevelopment. Environ Health Perspect 111:65–70.

Macdonald RW, Barrie LA, Bidleman TF, Diamond ML, Gregor DJ, Semkin RG, et al. 2000. Contaminants in the Canadian Arctic: 5 years of progress in understanding sources, occurrence and pathways. Sci Total Environ 254:93–234.

Muckle G, Ayotte P, Dewailly É, Jacobson SW, Jacobson JL. 2001a. Determinants of polychlorinated biphenyls and methylmercury exposure in Inuit women of childbearing age. Environ Health Perspect 109:957–963.

———. 2001b. Prenatal exposure of the northern Québec Inuit infants to environmental contaminants. Environ Health Perspect 109:1291–1299.

Muir DC, Wagemann R, Hargrave BT, Thomas DJ, Peakall DB, Norstrom RJ. 1992. Arctic marine ecosystem contamination. Sci Total Environ 122:75–134.

Norstrom RJ, Muir DC. 1994. Chlorinated hydrocarbon contaminants in arctic marine mammals. Sci Total Environ 154:107–128.

Patandin S, Koopman-Esseboom C, De Ridder MAJ, Weisglas-Kuperus N, Sauer PJJ. 1998. Effects of environmental exposure to polychlorinated biphenyls and dioxins on birth size and growth in Dutch children. Pediatr Res 44:538–545.

Patandin S, Lanting CI, Mulder PG, Boersma ER, Sauer PJ, Weisglas-Kuperus N. 1999. Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. J Pediatr 134:33–41.

Patandin S, Weisglas-Kuperus N, de Ridder MA, Koopman-Esseboom C, van Staveren WA, van der Paauw CG, et al. 1997. Plasma polychlorinated biphenyl levels in Dutch preschool children either breast-fed or formula-fed during infancy. Am J Public Health 87:1711–1714.

Phillips DL, Pirkle JL, Burse VW, Bernert JT Jr, Henderson LO, Needham LL. 1989. Chlorinated hydrocarbon levels in human serum: effects of fasting and feeding. Arch Environ Contam Toxicol 18:495–500.

Rhainds M, Levallois P, Dewailly É, Ayotte P. 1999. Lead, mercury, and organochlorine compound levels in cord blood in Québec, Canada. Arch Environ Health 54:40–47.

Ribas-Fitó N, Sala M, Kogevinas M, Sunyer J. 2001. Polychlorinated biphenyls (PCBs) and neurological development in children: a systematic review. J Epidemiol Community Health 55:537–546.

Rogan WJ, Gladen BC. 1991. PCBs, DDE, and child development at 18 and 24 months. Ann Epidemiol 1:409–413.

Rogan WJ, Gladen BC, McKinney JD, Carreras N, Hardy P, Thullen J, et al. 1986a. Neonatal effects of transplacental exposure to PCBs and DDE. J Pediatr 109:335–341.

———. 1986b. Polychlorinated biphenyls (PCBs) and dichlorodiphenyl dichloroethene (DDE) in human milk: effects of maternal factors and previous lactation. Am J Public Health 76:172–177.

Skaare JU, Tuveng JM, Sande HA. 1988. Organochlorine pesticides and polychlorinated biphenyls in maternal adipose tissue, blood, milk, and cord blood from mothers and their infants living in Norway. Arch Environ Contam Toxicol 17:55–63.

Stewart P, Reihman J, Lonky E, Darvill T, Pagano J. 2000. Prenatal PCB exposure and neonatal behavioral assessment scale (NBAS) performance. Neurotoxicol Teratol 22:21–29.

Takayama M, Itoh S, Nagasaki T, Tanimizu I. 1977. A new enzymatic method for determination of serum choline-containing phospholipids. Clin Chim Acta 79:93–98.

Walkowiak J, Wiener JA, Fastabend A, Heinzow B, Kramer U, Schmidt E, et al. 2001. Environmental exposure to polychlorinated biphenyls and quality of the home environment: effects on psychodevelopment in early childhood. Lancet 358:1602–1607.