



PCB exposure *in utero* and via breast milk. A review

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A review of the literature was conducted to investigate the importance to offspring of *in utero* and breast milk polychlorinated biphenyl (PCB) exposure. All reports that we could identify ($n=25$) were included, representing 16 study populations. Tissue-specific PCB concentrations in human placenta, breast milk, maternal blood and cord blood were compared to determine accumulation ratios between tissue compartments. On a lipid basis, the highest concentration of PCB in placenta (5027 ng/g fat) was 2.8 times higher than the highest concentration of PCB in breast milk (1770 ng/g fat). While there are limitations with regard to quantitation methods and statistical methods utilized by the reviewed studies, our results suggest that PCBs may be capable of crossing the placenta to a greater extent than previously believed. Future studies of PCB body burden in the perinatal period should include placenta, breast milk, maternal and cord blood specimens. In order to compare PCB concentrations in various tissues and with other studies, concentrations should be determined on a lipid basis. *Journal of Exposure Analysis and Environmental Epidemiology* (2000) **10**, 285–293.

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Introduction

Polychlorinated biphenyls (PCBs) and other halogenated aromatic hydrocarbons are ubiquitous environmental contaminants that accumulate in lipid-rich body tissues. Produced in the United States until 1977 (Laden et al., 1999), PCBs are highly resistant to degradation, persist in animal and environmental reservoirs, and ascend the food chain, depositing in human tissues. Research suggests that PCB exposure *in utero* or during infancy is associated with lowered birth weight and gestational age (Fein et al., 1984; Taylor et al., 1984), intellectual impairment (Jacobson and Jacobson, 1996), and delayed development (Guo et al., 1994).

Human PCB exposure can occur through environmental accidents, dietary intake, and *in utero* to unborn children (Rappolt and Hale, 1968; Polishuk et al., 1977; Brown et al., 1994; Guo et al., 1994; Stewart et al., 1999). PCBs accumulate in adipose tissue, blood lipids, and breast milk, and evidence indicates that this class of xenobiotics travels with the lipid components of blood (VLDL, LDL, HDL, and chylomicron remnants) and likely gains access to the many tissue compartments of the human body by utilizing the lipoprotein lipase mechanism (Spindler-Vomachka et al., 1984; Gallenberg and Vodicknik, 1987; Soues et al., 1989; Borlakoglu et al., 1990a,b;

Laden et al., 1999). Differences in the lipid content of tissue compartments affect the distribution of PCBs. As the lipid content of breast milk is high, around 45 g/l (Diem, 1962), it is generally believed that the highest degree of newborn exposure to PCBs and other lipophilic xenobiotics is through the ingestion of contaminated breast milk. Eyster and Kimbrough (1983) showed that mothers exposed to polybrominated biphenyls (PBBs), which closely mimic the behavior of PCBs, had breast milk concentrations over 100 times the quantity found in maternal serum; however these values are uncorrected for lipid concentration. PCB studies have similarly reported higher concentrations of PCBs in breast milk than in maternal blood (Jacobson et al., 1984; Rogan et al., 1986; Koopman-Esseboom et al., 1996).

Our objective was to review the published literature and to compare the relative lipid-based ratios of PCB accumulation via multiple perinatal exposure routes, with particular attention to *in utero* and breast milk exposures.

Methods

A search of the MEDLINE and TOXLINE literature on perinatal PCB studies was conducted to assess the broad range of PCB concentrations in various human tissues. Twenty-five publications on 16 study populations were reviewed and their tissue-specific PCB concentrations were recorded. The reported concentrations from each study were grouped by tissue compartment. In nine instances, multiple

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publications analyzed members of the same data set. For our analysis, only one set of results from each study population was used. We selected the publication that reported values for the largest proportion of the study population (the largest sample size). When multiple publications utilized the same proportion of the study population, the publication that reported the highest tissue-specific PCB concentrations was selected.

To determine the PCB accumulation ratio between various tissue compartments, a lipid-based ratio was calculated for the concentration of PCB (in units of nanogram PCB per gram fat) between compartments. Accumulation ratios were calculated within study populations. For example, to calculate the placenta-to-maternal blood ratio, a ratio for population A was calculated using data from population A only; a separate ratio was calculated for population B.

PCB quantitation methods vary greatly. Methods utilized by the reviewed studies include packed column gas chromatography (PCGC) (Kodama and Ota, 1980; Jacobson et al., 1984; Rogan et al., 1986; Krauthacker, 1992, Czaja et al., 1998) and congener-specific or capillary column gas chromatography (CCGC) (Polishuk et al., 1977; Janousek et al., 1994; Schlebusch et al., 1994; Bosse et al., 1996; Dewailly et al., 1996; Koopman-Esseboom et al., 1996; Kostyniak et al., 1999; Kivirianta et al., 1998; Lanting et al., 1998a,b; Laden et al., 1999). Additionally, some report contaminant concentrations on a volume basis (e.g. nanogram PCB per milliliter tissue), a mass basis (e.g. nanogram PCB per gram tissue), or on a lipid basis (e.g. nanogram PCB per gram fat). To account for the variety of concentration units reported and to enable comparison between tissue compartments, we converted all reported values, as far as the data permitted, to a lipid basis of nanogram PCB per gram fat (nanogram per gram fat). The conversion factors used and an example of the method to convert PCB tissue concentrations are presented in Table 1. We numerically equated specific

gravity with density since the maximum density of water, the reference substance, is 1 g/ml (Diem, 1962).

The publications reviewed in this analysis reported either median or mean values. We cannot adjust for these differences in parameters of central tendencies that result from skewed distributions.

Results

The concentrations of PCBs by tissue compartment are reported in Table 2. The middle column shows the concentration of PCB in the tissue converted to a lipid basis (nanogram PCB per gram lipid). The range of tissue concentrations of PCBs reflects differences in the populations sampled and the different quantitation and statistical methods employed in analysis. Some concentrations represent populations where there was no known exposure event—"unexposed"—(Bosse et al., 1996) while others represent "exposed" populations, for example those living near a highly polluted industrial site (Schlebusch et al., 1994). Figure 1 shows the range of median and mean lipid-based PCB concentrations across studies that reported total PCBs in various tissues. Nine studies determined PCB concentrations in breast milk, six in maternal blood components, five in cord blood components, four in placental tissue, and one each for amniotic fluid, uterine muscle, maternal adipose tissue, fetal and stillborn adipose tissue, non-pregnant adult and "Yusho" adipose tissue. On a lipid basis, the highest concentration of PCB in placenta (5027 ng/g fat) was 2.8 times higher than the highest concentration of PCB in breast milk (1770 ng/g fat).

Lipid-based ratios of accumulation between tissue compartments are presented in Table 3. PCB concentrations in placental tissue range from 0.13 to 1.80 times the concentration in maternal blood (three studies). The ratios calculated for the study population of Rogan et al. (1986)

Table 1. Conversion factors used.

Specific gravity ^a	blood=1.05	plasma=1.027	serum=1.026
Total lipids in blood ^a (g/l serum or plasma)	cord blood=3.47	blood of non-pregnant female=6.17	blood of pregnant female=9.0
Total lipids in breast milk ^a	45.4 g/l (4.5%)		
Total lipids in placenta ^b	1–1.5% by weight (wet)		
Fat content in fetus ^a	12% by weight		
Composition of blood ^c	45% cells, 55% serum		
Example calculation: Given: 1.0 ng PCB/g cord blood			
$1.0 \text{ ng PCB/g cord blood} \times 1.026 \text{ g blood/ml blood} \times 100 \text{ ml blood/55 ml serum} \times 100 \text{ ml serum/347 mg fat} \times 1000 \text{ mg/g} = 537.6 \text{ ng PCB/g fat}$			

^aDiem, 1962.

^bRogan et al., 1986.

^cEnglish, 1995.

indicate that cord blood PCB concentrations in their study population were twice as high as placental values when examined on a lipid basis. The cord-to-maternal blood-based ratios of four studies demonstrate that placental transfer of PCBs occurs and suggest that cord blood component concentrations can be at least as high as 60% of maternal levels (range: 0.59–1.1). The ratios of cord blood component concentrations to breast milk concentrations range from 0.35 to 1.36 (four studies), whereas the ratios of maternal blood component concentrations to breast milk concentrations in four studies range from 0.60 to 1.79 (Table 3).

Discussion

The purpose of this review was to examine the published literature and compare accumulation gradients of multiple perinatal exposure routes. Our analysis suggests that, when assessed on a lipid basis, placental transfer of PCBs seems to be underestimated as a source of fetal exposure.

PCBs are stored in tissues that are high in lipids. As the percentage of lipid varies from tissue to tissue, PCB content follows patterns of fat content. Determination of tissue PCB concentrations, therefore, should be performed on a lipid basis. This permits comparison of the contaminant concentrations in different organs and tissues within the body and allows for comparison with exposure levels of different populations reported by other studies. It is for this reason that we converted tissue-specific PCB concentrations to a lipid basis. For these conversions, we assumed that blood is typically 0.5% fat, placenta 1–1.5%, and milk 1–6% (Rogan et al., 1986).

We were surprised by the accumulation ratios of PCB in placenta to maternal blood (Table 3). The minimum value of 0.13 would lend support to the common assumption that placental storage of PCBs is relatively low. On the other hand, the ratios calculated for Polishuk et al. (1977) and Rogan et al. (1986) suggest that PCBs accumulate in the placental tissue.

Table 2 and Figure 1 illustrate the wide range of reported placental concentrations of PCBs. The “unexposed population” studied by Bosse et al. (1996) yielded higher concentrations than the population studied by Schlebusch et al. (1994), which resided in a highly polluted industrial area in the former German Democratic Republic. Polishuk et al. (1977), Rogan et al. (1986), and Bosse et al. (1996) report placental concentrations (range: 800–5027 ng/g fat) that are 1.24 times higher than 8 of the 10 breast milk concentrations when compared on a lipid basis. Assuming a placental weight of 550 g (Diamant et al., 1982), a fat content of 1.25% (Table 1), and an average PCB concentration in placental fat of 1000 ng/g fat, a placenta would contain about 6.9 μ g PCB.

The ratio of PCB in newborn fat to placental fat is also suggestive of a high degree of placental transfer (73.5% of the concentration in placental fat, Table 3). The accumulation ratios of placenta to fetal blood and placenta to cord blood are between 51% and 71%. If one were to assume a newborn weight of 3300 g, a fat content of 12% in newborns (Diem, 1962), and a PCB fat concentration of 700 ng/g fat, a newborn would have a burden of 277 μ g PCB. Thus, as the fetus increases in mass during the pregnancy period, it can catch up to and surpass the placental burden of PCB (6.9 μ g PCB). Therefore, trans-placental exposure to PCBs may play a larger role than expected.

Due to the higher lipid content of breast milk, it is often assumed that the greatest source of PCB exposure to the infant in the perinatal period is via the ingestion of contaminated milk. Studies have shown breast-feeding to increase levels of PCBs in infants of exposed mothers. Lanting et al. (1998a) reported that each additional week of full breast-feeding increased the plasma concentration of PCBs in 42-month-old children by 0.3%. Assuming first that milk consumption in infancy varies (weeks 1–2: 507 ml/day, weeks 3–6: 630 ml/day, weeks 7–10: 744 ml/day, Feer et al., 1980), second, that human milk is 4.54% fat (Table 1), and third, that the concentration of PCB is 550 ng/g fat in human milk, we would estimate a PCB intake of 1528 μ g in 13 weeks of nursing. As the percentage of fat in breast milk varies from 2.9% (Jacobson et al., 1984) to 4.54% (Diem, 1962), our value may be an overestimate. If we considered the PCB burden in a 3-month-old breast-fed infant with a weight of 5.9 kg, a 12% fat content (by weight), a PCB concentration in whole blood of 3.6 ng/g blood (Kodama and Ota, 1980), a steady state of blood fat and body fat, and the conversion factors in Table 1, we calculate an infant body burden of 823 μ g PCB. From delivery to 3 months, the infant increases its mass by a factor of 1.8 and has almost a threefold increase in total PCB body burden. As the difference of the estimated PCB burden at birth and at 13 weeks (546 μ g) is much lower than the estimated intake in that period (1528 μ g), it appears that only a portion of the PCB content of breast milk is retained by the infant. The cord blood component to maternal blood component ratios additionally suggest that infant PCB levels may reach high levels as a result of *in utero* exposure alone; three out of the four accumulation ratios suggest that about 60% of PCB concentration in maternal blood can be detected in the fetal circulation.

The cord plasma to breast milk accumulation ratio of 0.35 calculated for the data of Koopman-Esseboom et al. (1996) is at least half that of the other three cord-to-milk ratios (range: 0.71–1.36) (Table 3). Their maternal blood component to milk ratios show a similarly low value. This is likely explained by differences in study populations, sampling procedures, and analytical methods.

Table 2. PCB concentrations in maternal and infant tissue compartments.

Compartment	Subject	Concentration	Lipid basis (ng/g fat)	<i>n</i>	Comment	Study (detection method)
Placenta	women and offspring	5.0267 ppm (fat basis)	5027	19	mean	Polishuk et al., 1977 (CCGC ^a with ECD ^b)
Placenta	not random sample	<12.00 ppb	800–1200	790	median, 97% below quantitation limit; converted assuming 1–1.5% fat in placenta	Rogan et al., 1986 (PCGC ^c with ECD) ^e
Placenta	“exposed” European women	3.73 ppb	248–373	46	median; assumes original not on fat basis, converted to fat basis using 1–1.5% fat in placenta	Schlebusch et al., 1994 (CCGC with ECD)
Placenta	fetus, deceased children of “unexposed” women	0.95 mg/kg fat tissue	950	25	median	Bosse et al., 1996 (CCGC with ECD) ^f
Amniotic fluid	pregnant women	124.7529 ppm (fat basis)	124,753	4	mean	Polishuk et al., 1977 (CCGC with ECD)
Uterine muscle	pregnant women	14.0968 ppm (fat basis)	14097	7	mean	Polishuk et al., 1977 (CCGC with ECD)
Adipose tissue	maternal	1.2049 ppm (fat basis)	1205	8	mean	Polishuk et al., 1977 (CCGC with ECD)
Fetal fat	fetus, deceased children	0.7 mg/kg fat tissue	700	39	median	Bosse et al., 1996 (CCGC with ECD) ^f
Adipose tissue	stillborn	235 ng/g fat	235	9	“not representative”; median	Lanting et al., 1998b (CCGC with ECD)
Body fat	“unexposed” women	4.6 mg/kg fat	4600	8	mean total PCB	Janousek et al., 1994 (CCGC with ECD)
Skin surface lipids	“Yusho” patients	580 ng/g fat	580	32	mean	Ohgami et al., 1993 (method unknown)
Plasma	“unexposed” females, ages 30–56, nested in Nurses’ Health Study	5.01 ng/ml plasma	812	236	mean, pooled from four areas of US	Laden et al., 1999 (CCGC with ECD)
Maternal serum	“exposed” European women	13.3 ppb	1516	46	median; converted assuming original not on fat basis	Schlebusch et al., 1994 (CCGC with ECD)
Maternal blood	women during labor	2.799 ppm (fat basis)	2799	24	mean	Polishuk et al., 1977 (CCGC with ECD)

Maternal blood	women at delivery	4.5 ppb	932	76	mean	Kodama and Ota, 1980 (PCGC)
Maternal serum	women, post-partum	4.7 ng/ml serum	761	196	mean; post-delivery; converted using non-pregnant lipid content	Jacobson et al., 1984 (PCGC)
Maternal serum	women at birth	9.06 ppb	1033	872	median; 13% below quantitation limit	Rogan et al., 1986 (PCGC with ECD) ^c
Maternal plasma	women, last month of pregnancy	2.2 ng/g plasma	251	207	mean; general community, congeners 118, 138, 153, 180	Koopman-Esseboom et al., 1996 (CCGC with ECD)
Breast milk	women, 3 months post-partum	564 ppb (fat basis)	564	46	mean	Kodama and Ota, 1980 (PCGC)
Breast milk	women, general population	0.52 mg/kg lipids	520	536	sum of PCB (Aroclor 1260); mean	Dewailly et al., 1996 (CCGC with ECD)
Breast milk	lactating members and partners of male members of NY Angler Cohort	271 ng/g fat	271	100	total PCBs; mean	Kostyniak et al., 1999 (CCGC with ECD)
Breast milk	women 1–16 weeks post-partum	19.3 ng/ml milk; 732.6 ng/g fat basis	425	138	mean	Jacobson et al., 1984 (PCGC)
Breast milk	voluntary infant–mother pairs, 2 weeks post-partum	419 ng/g fat	419	100	mean, general population, congeners 118, 138, 153, 180	Koopman-Esseboom et al., 1996 (CCGC with ECD)
Breast milk	women at or near term; not random sample	1.77 ppm (fat basis)	1770	733	median; 13% below quantitation limit	Rogan et al., 1986 (PCGC with ECD) ^c
Breast milk	lactating women	540 mg/kg fat	540	78	median, range 150–1640 mg/kg	Krauthacker, 1992 (PCGC)
Breast milk	random primiparus women	496 ng/g fat	496	47	mean; urban area 1987	Kiviranta et al., 1998 (CCGC)
Breast milk	4 days post-partum	0.0076 mg/l milk	167	462	mean, Poland	Czaja et al., 1998 (PCGC with ECD) ^d
Breast milk	mature milk	0.0544 mg/l milk	1198	462	mean, Poland	Czaja et al., 1998 (PCGC with ECD) ^d
Cord blood	women and offspring during labor	7.1097 ppm (fat basis)	7110	23	mean	Polishuk et al., 1977 (CCGC with ECD)
Cord blood	infants at delivery	1.1 ppb	591	74	mean	Kodama and Ota, 1980 (PCGC)
Cord serum	infants at delivery	2.0 ng/ml serum	576	198	mean	Jacobson et al., 1984 (PCGC)
Cord plasma	human; voluntary mother–infant pairs	0.5 ng/g plasma	147	207	mean; general community sample, congeners 118, 138, 153, 180	Koopman-Esseboom et al., 1996 (CCGC with ECD)
Cord serum	infants at delivery; not random sample	<4.27 ppb	<1264	744	median, 88% below quantitation limit	Rogan et al., 1986 (PCGC with ECD) ^c

^aCCGC=capillary column gas chromatography, or congener-specific.

^bECD=electron capture detection.

^cPCGC=packed column gas chromatography.

^dDetection methods: Czaja et al., 1997.

^eDetection methods: McKinney et al., 1984.

^fDetection methods: Teufel et al., 1990.



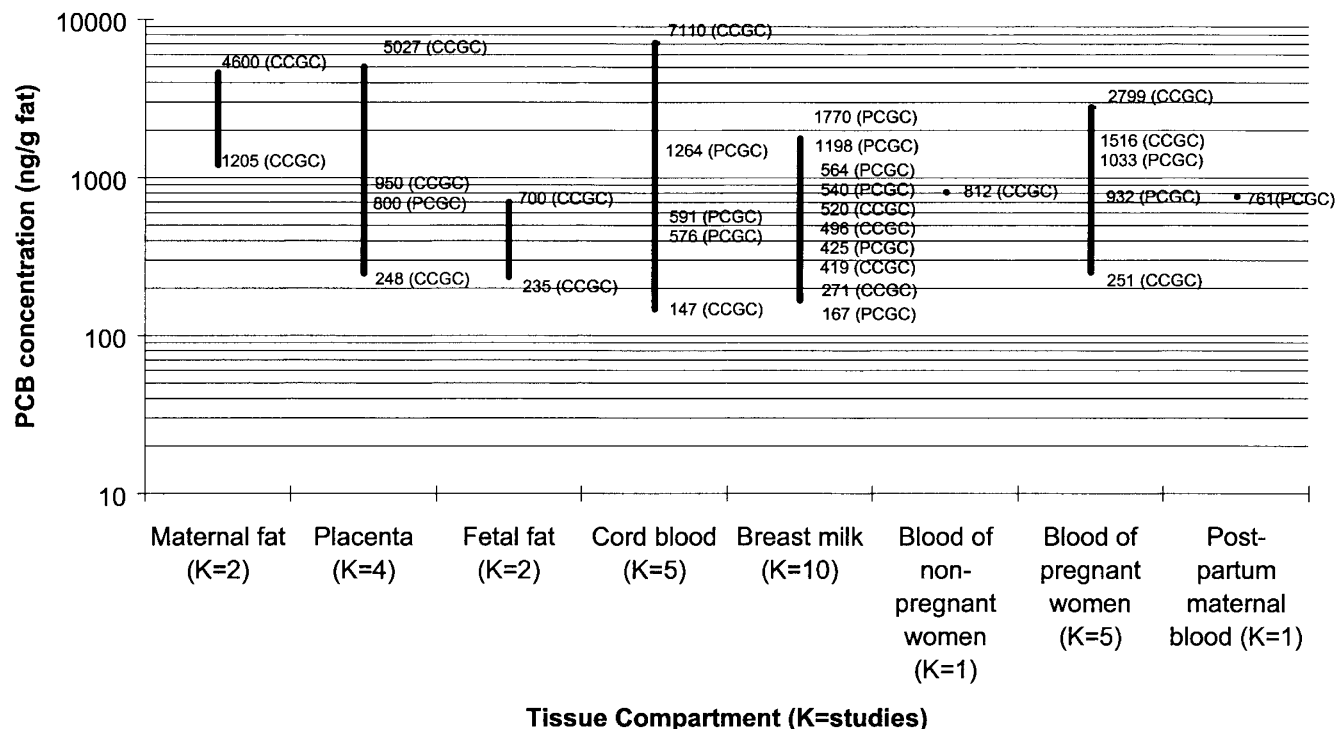


Figure 1. Range of tissue PCB concentrations on fat basis (ng/g fat).

The Dutch study (Koopman-Esseboom et al., 1996) sampled maternal blood during the last month of pregnancy (36th to 40th week) and milk samples were collected the second week after delivery. In the Michigan study (Jacobson et al., 1984), maternal blood specimens were collected following delivery, whereas milk samples were collected 1–16 weeks post-partum. Changes in plasma lipoprotein profiles during pregnancy could explain this apparent inconsistency. Gallenberg and Vodienik (1987) studied the change in PCB distribution with advancing pregnancy in rats. Blood levels of 2,4,5,2',4',5'-hexachlorobiphenyl (6-CB) decreased with advancing pregnancy until birth, when levels in the blood seem to peak. While this increase was not statistically significant, it could explain the discrepancy between the Dutch and Michigan studies. Collecting the blood sample before birth may result in lower PCB levels in the blood, yielding a smaller maternal plasma-to-milk ratio. Regardless, the accumulation ratios confirm that breast milk is a major source of PCB exposure to newborn children.

The accumulation of PCBs in maternal blood ranges from 60% to 1.79% of the concentrations detected in breast milk samples. Kodama and Ota (1980), Jacobson et al. (1984), and Koopman-Esseboom et al. (1996) obtained maternal blood samples at delivery but obtained breast milk samples up to 4 months post-partum (Tables 2 and 3). These ratios suggest that, while breast milk is a major

vehicle for infant exposure to PCBs while nursing, levels in maternal blood at birth can exceed those in milk.

The relatively small number of studies, the diverse populations they represent, and the dissimilar sampling procedures and analytical methods compared in this review prohibit us from drawing definite conclusions about the distribution of PCBs in the perinatal period. Additionally, quantitation limits and methods of statistical analysis (mean vs. median) vary from study to study. The results do suggest, however, that PCB transfer across the placenta may play a substantial role in fetal exposure to halogenated aromatic hydrocarbons. Rappolt and Hale (1968) determined the concentrations of other chlorinated hydrocarbon residues (p,p' -DDE and p,p' -DDT) in human tissues. Though their sample size was small, they found placental p,p' -DDE concentrations close to cord blood concentrations, suggesting a high degree of placental transfer.

The publication dates of studies included in this review span 22 years. During this time, there have been significant advances and refinements in analytical laboratory methods. Earlier studies utilized PCGC in quantifying PCB tissue concentrations (e.g. Jacobson et al., 1984; Krauthacker, 1992), while more recent studies use congener-specific CCGC (e.g. Janousek et al., 1994; Dewailly et al., 1996; Lanting et al., 1998b; Kostyniak et al., 1999). While these differences in quantitation techniques may influence the

Table 3. Gradient of PCB distribution between tissue compartments—lipid basis.

	Bosse et al., 1996 (<i>n</i> =25+ ^a)	Jacobson et al., 1984 (<i>n</i> =138+)	Koopman-Esseboom et al., 1996 (<i>n</i> =100+)	Kodama and Ota, 1980 (<i>n</i> =46+)	Polishuk et al., 1977 (<i>n</i> =19+)	Rogan et al., 1986 (<i>n</i> =744+)	Schlebusch et al., 1994 (<i>n</i> =46)
placenta/maternal blood					1.8	0.62	0.13
placenta/cord blood					0.71	0.51	
placenta/breast milk						0.45–0.68 ^b	
newborn fat/placental fat	0.74						
cord blood/maternal blood				0.63			
cord serum/maternal serum		1.1				0.66	
cord plasma/maternal plasma			0.59				
cord blood/milk				1.07			
cord serum/milk		1.36				0.71	
cord plasma/milk			0.35				
maternal blood/milk				1.69			
maternal serum/milk		1.79				0.58	
maternal plasma/milk			0.60				

^a“+” indicates that the sample size for the numerator and denominator is at least as large as “*n*”.

^bAssumes placenta 1–1.5% fat (Rogan et al., 1986).

comparability of the studies, 10 of these 16 studies utilized CCGC (Table 2) and the accumulation ratios calculated in our analysis were calculated using tissue concentrations within the same study. Figure 1 indicates that, with the exception of breast milk and post-partum maternal blood, CCGC, the preferred method, was used in PCB quantitation at both the high and low end of the concentration ranges; PCGC tended to fall in the middle of the ranges. The ratios still suggest that placental transfer of PCBs occurs to an appreciable extent.

Very few published studies determine placental concentrations of PCBs. It is common to measure only maternal blood, cord blood, and/or breast milk concentrations. The small number of placental studies that we were able to identify testifies to this; more research remains to be conducted. We recommend that future studies of the body burden of halogenated aromatic hydrocarbons in the perinatal period include analysis of placental tissue, breast milk, and maternal and cord blood. We also suggest that future research endeavors report both the median and geometric means of contaminant concentrations, measures which (versus arithmetic means) are not affected by outliers. Finally, we recommend that tissue concentrations be determined on a lipid basis, as accumulation is highly dependent on the lipid content of the tissue. These recommendations will enable comparison of concentrations between various tissue compartments and with results from other studies.

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