Human Prenatal and Postnatal Exposure to Polybrominated Diphenyl Ethers, Polychlorinated Biphenyls, Polychlorobiphenylols, and Pentachlorophenol

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The aim of this study was to determine human prenatal and postnatal exposures to polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), hydroxylated metabolites of PCBs (polychlorobiphenylols; OH-PCBs), and pentachlorophenol (PCP). The median PBDE fresh-weight concentrations in maternal and cord blood plasma and in breast milk were 24, 4.3, and 75 pg/g, respectively. The PCB concentrations were approximately 60 times higher in each compartment (1,560, 277, and 4,310 pg/g, respectively). Calculated on a lipid weight basis, the levels were comparable in maternal blood plasma and breast milk. In contrast to PCBs, differences were found between PBDE congener distribution in maternal and cord blood plasma. The OH-PCBs constituted up to 26% of the PCB levels in maternal blood plasma and 53% in cord blood plasma, with levels of 120 and 88 pg/g fresh weight, respectively, and in breast milk 3 pg/g. The corresponding concentrations for PCP were 2,830, 1,960, and 20 pg/g. The ratios of PCB to OH-PCB were 13, 3, and 1,400 in maternal, cord plasma, and breast milk, respectively. It is evident that prenatal exposures occur for all the analytes. Moreover, the exposure continues after birth via breast milk. However, levels of OH-PCBs and PCP in breast milk are low compared with levels in blood plasma. Exposures to both PCBs and PBDEs, and in particular to the endocrine-active halogenated phenolic compounds, are of concern and implicate a potential risk for developmental disturbances. *Key words:* **breast milk, cord blood, hydroxylated polychlorinated biphenyls, maternal blood, pentachlorophenol, polybrominated diphenyl ethers, polychlorinated biphenyls, postnatal, prenatal.** *Environ Health Perspect* **111:1235–1241 (2003). doi:10.1289/ehp.5946 available via** *http://dx.doi.org/* **[Online 21 January 2003]**

Polybrominated diphenyl ethers (PBDEs) are used as flame retardant additives in polymers with a wide variety of applications, for example, electronic equipment, construction materials, and textiles [World Health Organization (WHO) 1997]. In recent years it has become evident that certain PBDEs are generally found in humans, as are other well-known environmental pollutants such as polychlorinated biphenyls (PCBs) (WHO 1992) and pentachlorophenol (PCP) (WHO 1987). Although decabromodiphenyl ether is the dominating commercial PBDE product, the environmental occurrence is dominated by lower brominated PBDE congeners, substituted with fewer than seven bromine atoms (reviewed by Bergman et al. 2002; Darnerud et al. 2001; de Boer et al. 2000; de Wit 2002). Several studies have reported PBDE levels in human blood (Schröter-Kermani et al. 2000; Sjödin et al. 1999, 2001; Thomsen et al. 2001), adipose tissue (Haglund et al. 1997; Hardell et al. 1998; Meironyté Guvenius et al. 2001), liver (Meironyté Guvenius et al. 2001), and milk (Fürst 2001; Meironyté et al. 1999; Päpke et al. 2001; Ryan and Patry 2001; Strandman et al. 2000). Generally, 2,2′,4,4′-tetrabromodiphenyl ether (BDE-47) is the predominant congener both in environmental and human samples, followed by 2,2′,4,4′,5-pentabromodiphenyl ether (BDE-99) and 2,2′4,4′,5,5′-hexabromodiphenyl ether (BDE-153). These PBDE congeners are the major constituents of commercial pentabrominated diphenyl ethers (Sjödin et al. 1998a).

Toxicologic studies on PBDEs have shown that certain PBDEs affect the thyroid hormone system. Exposure to commercial penta- and octabromodiphenyl ethers decreases thyroxine (T_4) and vitamin A levels and induces microsomal enzyme activities in mice and rats (Fowles et al. 1994; Hallgren et al. 2001; Zhou et al. 2001, 2002). Furthermore, it has been shown that exposure of mice to BDE-47 and BDE-99 during the critical neonatal period causes neurotoxic effects in adult animals (Eriksson et al. 2001; Viberg et al. 2002). Similar effects have previously been reported for certain coplanar and *ortho*-substituted PCBs (Eriksson and Fredriksson 1996a, 1996b, 1998; Eriksson et al. 1991). In addition, effects of prenatal and postnatal exposure to PCBs, such as lower gestational age and birth weight (Fein et al. 1984; Rylander et al. 2000; Taylor et al. 1984), delayed development (Guo et al. 1994), and intellectual impairment (Jacobson and Jacobson 1996), have been reported in humans.

Because brain development depends on thyroid hormones, the neurodevelopmental toxicity of certain organohalogen compounds may be related to altered thyroid homeostasis. Hydroxylated metabolites of PBDEs (OH-PBDEs) are able to compete with T_4 for binding with the thyroid hormone transport protein transthyretin (Meerts et al. 2000). This property has previously been demonstrated for other hydroxylated organohalogen compounds, for example, PCP and hydroxylated metabolites of PCBs (polychlorobiphenylols; OH-PCBs) (Brouwer et al. 1998; Lans et al. 1993; van den Berg 1990). Several PBDE congeners, OH-PBDEs, and OH-PCBs have shown estrogenic and antiestrogenic activities in experimental studies (Connor et al. 1997; Fielden et al. 1997; Meerts et al. 2001). So far, only one study has reported the occurrence of one OH-PBDE congener (6-OH-BDE47) in human blood (Hovander et al. 2002), whereas several OH-PCBs have been identified in blood plasma (Bergman et al. 1994; Fängström et al. 2002; Hovander et al. 2002; Sandau et al. 2000; Sjödin et al. 2000), and in liver and adipose tissue samples (Meironyté Guvenius et al. 2002).

Experimental studies have shown that exposure to certain organohalogen pollutants during the specific period of rapid brain growth disturbs the brain function of adult animals. In humans, the rapid brain growth begins during the third trimester of pregnancy and continues throughout the first 2 years of life (Dobbing and Sands 1979). Exposure to organohalogen compounds during this sensitive period constitutes a potential risk for human health.

In the present study, we investigated exposures to PBDEs, PCBs, OH-PCBs, and PCP by comparing the levels of these compounds in human maternal blood plasma, cord blood plasma, and breast milk. Our overarching aim was to determine fetal and infant exposures for these compounds.

Materials and Methods

Samples. Samples of maternal blood plasma, cord blood plasma, and breast milk were

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collected during 2000–2001 from 15 mothers living in Stockholm, 13 of whom were native Swedish. The study population was randomly chosen from those who voluntarily agreed to participate in the investigation. All mothers delivered by cesarean surgery, according to their own wish. The mothers were healthy and delivered healthy babies. The participants were asked to answer a questionnaire about age, number of children, earlier place of residence, fish consumption, and other factors. The average maternal age was 32 years (range, 28–38); 53% of them gave birth to their first child, 33% their second, and 14% their third. One mother reported eating eight meals of fatty fish per month; the others reported zero to two. Their consumption of fatty fish from the Baltic was low; one mother reported two meals per month.

Blood samples were collected at the Karolinska Hospital into heparinized Venoject glass tubes (Terumo Europe N.V., Leuven, Belgium). Blood samples (30 mL) from the mothers were collected when they arrived at the hospital for delivery, and cord blood (15–20 mL) was collected at delivery. The plasma was separated by centrifugation at 3,500 rpm for 10 min, transferred to glass tubes, and stored at –20°C. Milk samples were collected at 2–77 days after delivery of the child.

Chemicals. Organic solvents and adsorbents used in the analysis were prepared as previously described (Meironyté et al. 1999; Meironyté Guvenius et al. 2002).

PBDE standards BDE-85, BDE-99, BDE-153, and [^{13}C]-BDE-77 were purchased from CIL (Andover, MA, USA). BDE-17, BDE-28, BDE-47, BDE-66, BDE-100, and BDE-154 were synthesized as described elsewhere (Marsh et al. 1999; Örn et al. 1996). PCB congeners were purchased from Ehrenstorf (Augsburg, Germany). The PBDE and PCB congeners are numbered as suggested by Ballschmiter et al. (1992) for single PCB congeners.

The OH-PCB congeners were purchased from Larodan Fine Chemicals AB (Gothenberg, Sweden) or synthesized as described elsewhere (Bergman et al. 1995). OH-PCB congeners in the present work are numbered according to the recommendations of Letcher et al. (2000).

Methoxy-PCBs used for identification and quantification of methylated OH-PCBs were synthesized (Bergman et al. 1995) or derivatized from OH-PCBs as described below. PCP was purchased from Riedel-de Haën AG (Seelze-Hannover, Germany).

Instruments. We used gas chromatography (GC) on a Chrompack CP 2009 instrument (Middelburg, The Netherlands) equipped with an on-column injector and electron capture detector to detect and measure PCBs. We used a mass spectrometer (model VG 70-250; Fisons Instruments, VG Analytical, Manchester, UK), equipped with a Hewlett-Packard gas chromatograph (model HP 5890A; Geneva, Switzerland), for determination of PBDEs, methylated OH-PCBs, and PCP. Further details are given elsewhere (Meironyté et al. 1999; Meironyté Guvenius et al. 2002).

Analysis of blood plasma. The previously described method for analysis of organochlorine compounds in blood plasma (Weistrand et al. 1995) was modified to incorporate determination of PBDEs, OH-PCBs, and PCP. The method was also adapted for a smaller sample volume. Blood plasma (10 mL) was weighed into a 100-mL flask with polytetrafluoroethylene-lined screw cap. In case of smaller plasma volumes, water was added to the total volume of 10 mL. A blank sample (10 mL water) was run with each set of samples. Internal standards for each group of analytes (50 µL of 10 pg [^{13}C]-BDE-77/µL hexane, 50 µL of 10 pg 4-OH-CB162/µL hexane, 100 µL of 90 pg CB-198/µL hexane) were added to all samples. After addition of formic acid (10 mL), the samples were left for 15 min. Then, 2-propanol (4 mL), water (4 mL), and Lipidex 5000 (3 g) were added, and the mixture was shaken in a water bath (35°C) for 3 hr.

After extraction, the mixture was transferred to a glass column, and the gel was eluted with solvents of decreasing polarity. Polar compounds were eluted with 30% methanol in water (10 mL) and 50% methanol in water (10 mL). Organohalogen compounds and some lipids were eluted with acetonitrile (50 mL), and the rest of the lipids, with a mixture of methanol/chloroform/hexane (1/1/1, vol/vol/vol, 20 mL). The last two fractions containing organohalogen compounds and lipids were evaporated to near dryness and dried in a desiccator to a constant weight. The sum of the weights of these two fractions constituted the lipid amount in the sample.

The residue of the acetonitrile fraction was further purified on aluminum oxide (Meironyté Guvenius et al. 2002) and silica gel columns (Meironyté et al. 1999). Four fractions were collected from the aluminum oxide column. PBDEs and PCBs were eluted in the first fraction with hexane (10 mL). The following two fractions (hexane, 5 mL, and dichloromethane/hexane, 10 mL) were not analyzed in the present study. The phenolic compounds were eluted in the subsequent fraction with acidified methanol (1/100 vol/vol sulfuric acid/methanol, 20 mL) and methanol (10 mL).

The fraction containing PCBs and PBDEs was concentrated and applied to a silica gel column (0.6 g). PCBs were eluted in the first fraction with dry hexane (4 mL); PBDEs were eluted in the second fraction with 25% dichloromethane in hexane (5 mL). The fraction containing PBDEs was dropped onto a Pasteur pipette column packed with silica gel (0.1 g) and sulfuric acid–prepared silica gel (0.3 g, 2:1 silica gel:90% sulfuric acid). The second column was eluted with an additional 25% dichloromethane in hexane (1.5 mL). The volume of the fraction was reduced by evaporation with a gentle stream of nitrogen to approximately 50 µL; injection standard (100 µL of 1.1 pg CB-209/µL hexane) was then added, and the sample was analyzed by high-resolution GC/mass spectrometry (GC/MS), using selected ion monitoring (Meironyté et al. 1999).

The fraction containing OH-PCBs was concentrated under reduced pressure to 2 mL and transferred to a glass tube. The flask was rinsed with methanol (2 × 0.5 mL), followed by hexane (3 × 1 mL). The mixture was shaken cautiously with water (3 mL) and centrifuged. The hexane phase was transferred to another tube, and the aqueous phase was shaken twice more with hexane (3 and 2 mL). The combined hexane phases were concentrated with a gentle stream of nitrogen to approximately 100 µL. Five drops of methanol were added, and the phenolic compounds were derivatized with diazomethane in diethyl ether (0.5 mL). The mixture was left to react overnight. The solvent was evaporated with

Table 1. PBDE concentrations (median and range, ng/g lipids) in maternal blood plasma, cord blood plasma, and breast milk from 15 individuals.

PBDE congeners	Maternal blood plasma		Cord blood plasma		Breast milk	
	Median	Range	Median	Range	Median	Range
BDE-17	< 0.01	< 0.01–0.03	< 0.01	< 0.01–0.1	< 0.01	< 0.01
BDE-28	0.07	< 0.01–0.2	0.07	< 0.01–0.31	0.06	0.02–0.18
BDE-47	0.83	0.3–5.1	0.98	0.33–3.28	1.15	0.26–4.01
BDE-66	0.02	< 0.01–0.14	0.01	< 0.01–0.11	0.02	< 0.01–0.07
BDE-100	0.17	< 0.01–0.52	0.07	< 0.01–0.27	0.14	< 0.01–0.69
BDE-99	0.19	< 0.01–1.43	0.07	< 0.01–0.85	0.21	0.07–2.20
BDE-85	< 0.01	< 0.01–0.07	< 0.01	< 0.01–0.09	0.04	< 0.01–0.17
BDE-154	0.04	< 0.01–0.16	< 0.01	< 0.01–0.17	0.02	< 0.01–0.14
BDE-153	0.56	0.27–1.03	0.17	< 0.01–0.32	0.32	0.03–1.16
BDE-183	0.06	0.01–0.44	0.01	< 0.01–0.1	0.01	< 0.01–0.14
Sum	2.07	0.71–8.39	1.69	0.46–4.28	2.14	0.56–7.72
	(23.6)	(6.53–57.9)	(4.29)	(1.12–9.42)	(75.1)	(18.3–347)

Values in parentheses are on fresh-weight basis (pg/g fresh weight).

nitrogen gas, and the residue was dissolved in hexane. The methylated phenolic compounds were purified on a Pasteur pipette column packed with silica gel (0.1 g) and sulfuric acid–prepared silica gel (0.5 g, 2:1 silica gel:90% sulfuric acid). The analytes were eluted with 70% dichloromethane in hexane (6 mL). The fraction was concentrated with nitrogen to approximately 50 µL; then, injection standard (100 µL of 1.1 pg CB-209/µL hexane) was added before analysis by high-resolution GC/MS (Meironyté Guvenius et al. 2002).

Analysis of human milk. Breast milk was analyzed as described elsewhere (Meironyté et al. 1999; Norén and Sjövall 1987), with minor modifications. PBDEs were separated from PCBs using silica gel and purified on a sulfuric acid–prepared silica gel column as described above. Some changes were introduced in order to include analysis of phenolic compounds. OH-PCBs and PCP were eluted from the aluminum oxide column with acidified methanol (1/100 vol/vol sulfuric acid/methanol, 30 mL) and methanol (10 mL) and derivatized as described for the blood plasma samples. The residue obtained after derivatization was dissolved in hexane (2 mL) and shaken with sulfuric acid (90%, 1 mL), and the phases were separated by centrifugation. The sulfuric acid fraction was shaken with hexane (1 mL). The combined hexane phases were concentrated and purified on silica gel and sulfuric acid–prepared silica gel as described above.

Results

The modified analytical methods were evaluated by recovery studies. Samples were fortified with the PBDE congeners listed in Table 1 (50 pg/g plasma), with PCP (400 pg/g plasma and milk), and with the OH-PCB congeners 4-OH-CB107, 4′-OH-CB121, 4′-OH-CB130, 4-OH-CB146, 4-OH-CB162, 4′-OH-CB172, 4-OH-CB187, and 4-OH-CB193 (50 pg/g plasma and milk) before extraction. The mean recoveries of PBDEs and phenolic compounds were 67–88% (SD, 4–11; $n = 4$) and 69–97% (SD, 6–24; $n = 5$), respectively. The average recoveries of the internal standards added before extraction to all samples of maternal blood plasma, cord blood plasma, and breast milk were, respectively, 75, 77, and 84% of [^{13}C]-BDE-77; 77, 80, and 87% of 4-OH-CB162; and 70, 75, and 76% of CB-198.

Samples of maternal blood plasma, cord blood plasma, and breast milk from 15 mothers were analyzed for PBDEs, PCBs, OH-PCBs, and PCP. The median concentrations and ranges of 10 PBDE congeners are given in Table 1, and those of 15 PCB congeners are shown in Table 2. The PCB congeners CB-123 and CB-189 were not detected in any of the samples (detection limit, 0.5 ng/g lipids). The median sums of PBDEs were 2.07, 1.69, and 2.14 ng/g lipids in maternal blood plasma, cord blood plasma, and breast milk, respectively. The PCB levels were two orders of magnitude higher than those of PBDEs, with median values of 176, 104, and 190 ng/g lipids in maternal blood plasma, cord blood plasma, and breast milk, respectively. The median lipid content was 0.7% (range, 0.5–1.4%) in maternal blood plasma, 0.2% (0.2–0.3%) in cord blood plasma, and 1.9% (0.8–4.9%) in breast milk. Because phenolic compounds are retained in blood mainly due to their affinity to plasma proteins and not due to their lipophilic properties (Letcher et al. 2000), the concentrations of OH-PCBs and PCP are given on a fresh-weight basis (Table 3). The median sums of 12 OH-PCB congeners in maternal and cord blood plasma were 124 and 88 pg/g plasma, respectively. 4′-OH-CB121 and 3′-OH-CB188 were not found in the samples (detection limit, 0.1 pg/g sample). The OH-PCB levels in breast milk were very low; the median sum was 3 pg/g milk. Calculated on a fresh-weight basis, the ratios of PCBs to OH-PCBs were 13, 3, and 1,400 in maternal blood plasma, cord blood plasma, and breast milk, respectively. PCP was the predominant phenolic compound in all sample matrices (Table 3). The median levels in maternal blood plasma, cord blood plasma, and breast milk were 2.83, 1.96, and 0.02 ng/g fresh weight, respectively. Figure 1 shows the 10th through 90th percentiles of PBDEs, PCBs, OH-PCBs, and PCP in the blood and breast milk samples. The individual concentrations are shown in Figures 2 and 3. No influence of maternal age, number of nursed children, or time of milk collection was ascertained.

Table 2. PCB concentrations (median and range, ng/g lipids) in maternal blood plasma, cord blood plasma, and breast milk from 15 individuals.

PCB congeners	Maternal blood plasma		Cord blood plasma		Breast milk	
	Median	Range	Median	Range	Median	Range
CB-28	2	< 0.5–8	1	< 0.5–8	2	< 0.5–6
CB-47	< 0.5	< 0.5–7	< 0.5	< 0.5–8	1	< 0.5–8
CB-52	< 0.5	< 0.5–11	< 0.5	< 0.5–7	< 0.5	< 0.5–7
CB-101	4	1–20	< 0.5	< 0.5–4	2	< 0.5–9
CB-105	2	< 0.5–9	< 0.5	< 0.5–6	2	< 0.5–10
CB-114	4	2–13	1	< 0.5–8	4	1–16
CB-118	8	3–25	4	< 0.5–17	7	2–27
CB-122	1	< 0.5–5	< 0.5	< 0.5–3	2	< 0.5–4
CB-138	39	22–149	34	18–92	39	18–150
CB-153	56	27–203	44	20–107	61	24–193
CB-156	5	< 0.5–18	1	< 0.5–12	3	< 0.5–25
CB-157	1	< 0.5–10	< 0.5	< 0.5–4	2	< 0.5–5
CB-167	< 0.5	< 0.5–8	< 0.5	< 0.5–4	2	< 0.5–8
CB-170[a]	15	6–50	12	2–23	14	4–28
CB-180	29	12–94	17	5–51	27	9–66
Sum	176	104–598	104	67–330	190	77–547
	(1,560)	(602–3,128)	(277)	(102–641)	4,310	(1,081–9,653)

Values in parentheses are on fresh-weight basis (pg/g fresh weight).
[a]Includes both CB-170 and CB-190.

Table 3. OH-PCB and PCP concentrations (median and range, pg/g fresh weight) in maternal blood plasma, cord blood plasma, and breast milk from 15 individuals.

OH-PCB congeners	Maternal blood plasma		Cord blood plasma		Breast milk	
	Median	Range	Median	Range	Median	Range
4-OH-CB107[a]	10	4–29	5	< 0.1–11	1	< 0.1–4
4′-OH-CB120	2	< 0.1–47	2	< 0.1–12	< 0.1	< 0.1
4′-OH-CB130	4	0.3–21	3	0.2–48	< 0.1	< 0.1–1
3′-OH-CB138	9	2–54	9	2–56	< 0.1	< 0.1–1
4-OH-CB146	29	12–121	21	8–53	0.2	< 0.1–1
3-OH-CB153	7	1–36	5	1–32	< 0.1	< 0.1–1
4′-OH-CB172	5	2–12	4	2–11	< 0.1	< 0.1
4′-OH-CB178	1	1–6	1	0.5–8	< 0.1	< 0.1
3′-OH-CB180	2	0.5–11	1	0.3–6	< 0.1	< 0.1
3′-OH-CB187	3	1–9	2	1–8	< 0.1	< 0.1
4-OH-CB187	49	24–97	24	13–43	0.4	< 0.1–1
4-OH-CB193	2	< 0.1–29	2	< 0.1–5	< 0.1	< 0.1–2
Sum	124	82–328	88	35–271	3	< 0.1–5
PCP	2,830	1,360–13,200	1,960	820–7,580	20	10–570

[a]Includes both 4-OH-CB107 and 4′-OH-CB108.

Discussion

PBDEs and PCBs. Although there were large differences in the concentrations of PBDEs and PCBs, the distribution of these classes of compounds was similar between the sample matrices. The levels (nanograms per gram

lipids) were comparable in maternal blood and breast milk, whereas the levels in the cord blood were generally lower (Figure 1). The sums of PBDEs and PCBs in cord blood plasma constituted, on average, 72 and 70% of the sums in maternal blood plasma, respectively, calculated on lipid weight. The differences were more obvious (21 and 19%) when the comparison was made on a fresh-weight basis. Consequently, the lower lipid content of the fetal blood "protects" the fetus, at least to some extent, from these contaminants from the mother. Further, we found no correlation between PBDE and PCB levels. The highest PCB levels were found in the samples from the mother who consumed fatty fish most frequently (eight meals per month). This is in accordance with previously reported findings that fish is an important source of human exposure (Asplund et al. 1994; WHO 1992). The lowest PCB levels were in samples from two immigrant mothers (Figure 2). No such relations were found for PBDEs. We assume that exposures to PCBs and PBDEs differ, even though the major proportion of PBDEs may also be ingested via the diet, as are PCBs. Further, PCBs have been regulated and not produced for decades, whereas PBDEs are still produced and are present in many goods around us. It therefore cannot be ruled out that inhalation may play a more important role for PBDEs than for PCBs. The individuals participating in the present study were from the general population with no known specific exposure to PBDEs. Therefore, the concentrations in breast milk and blood plasma may be considered as background levels and are in the range of recently reported levels in human milk from Sweden (Meironyté et al. 1999), Finland (Strandman et al. 2000), and Germany (Fürst 2001) and blood from Sweden (Sjödin et al. 1999), Norway (Thomsen et al. 2001), and Germany (Schröter-Kermani et al. 2000).

BDE-47 was the predominant PBDE congener in all sample matrices, followed by BDE-153, BDE-99, and BDE-100 (Table 1). BDE-47 constituted 46–70% of the PBDEs determined in breast milk, 31–61% in blood plasma, and 45–94% in cord blood plasma. The levels of BDE-47 were equal in maternal blood plasma and cord blood plasma (r = 0.94, p < 0.01), whereas the levels of the higher brominated congeners, BDE-99, BDE-100, and BDE-153, did not correlate. In cord blood plasma, BDE-153 constituted, on average, 27% of the levels in maternal blood plasma. The higher levels of these congeners in maternal blood than in cord blood (Table 1) indicate that the higher brominated PBDEs do not pass through the placenta to the same extent as do the lower brominated congeners. This may, at least in part, be explained by the high mass of hexabrominated diphenyl ether, BDE-153.

In contrast to PBDEs, no difference in congener distribution between maternal and cord blood plasma was found for PCBs. CB-153, CB-138, and CB-180 were the predominant PCB congeners and constituted together, on average, 72–79% of the total sum of PCBs in all samples. The individual levels of these PCB congeners correlated well in maternal and cord blood plasma (r = 0.73, 0.81, and 0.78, p < 0.01). Several studies have shown the occurrence of PCBs in the cord blood, suggesting that PCBs pass the placental barrier (e.g., Bjerregaard and Hansen 2000; Korrick et al. 2000; Sala et al. 2001). The present study confirms the transfer of PCBs to the fetus.

Hydroxylated PCB metabolites and PCP. The distribution of OH-PCBs and PCP in the samples differed from those of PBDEs and PCBs. The highest levels of phenolic compounds were found in maternal blood plasma, and the lowest in breast milk (Figure 1). This is not surprising because the distribution in the blood is entirely different, the former being bound to proteins and the latter localized to the blood lipids.

PCP was the dominating phenolic compound in all samples, with notably high concentrations in the blood plasma samples (Table 3). The levels of PCP in cord blood plasma correlated well with those in maternal blood plasma (r = 0.73, p < 0.01) and constituted 67% of the levels in maternal blood plasma. The PCP levels in maternal and cord blood plasma were, on average, 30 and 36 times higher than the sum of OH-PCBs. The OH-PCB levels in cord blood plasma correlated well to those in maternal blood plasma (r = 0.60, p < 0.05) and constituted 62% of the levels in maternal blood plasma. The concentrations of OH-PCB congeners in cord blood plasma were lower than the previously reported levels in cord blood plasma from coastal populations in Quebec, whereas the PCP levels were similar (Sandau et al. 2002). It is evident from the present study that exposure to PCP and OH-PCBs is only slightly higher in the mother than in the fetus. This behavior of OH-PCBs stands in contrast to that of parent PCBs. The results imply that the potential health impact of halogenated phenolic compounds may have hitherto been underestimated compared with the impact of neutral persistent chemicals.

The predominant OH-PCB congeners in blood samples were 4-OH-CB187 and 4-OH-CB146, followed by 4-OH-CB107 and 3′-OH-CB138 (Table 3). The similar congener pattern was previously reported in other studies from Sweden (Bergman et al. 1994; Sjödin et al. 2000), Faroe Islands (Fängström

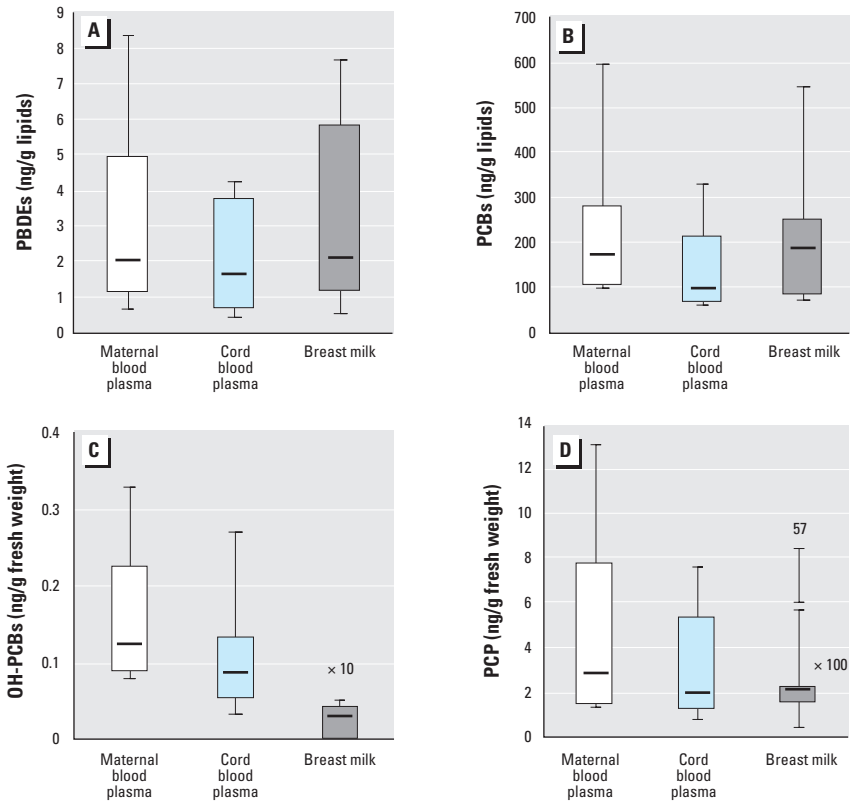

Figure 1. The 10th–90th percentiles (boxes), median (solid line), and range (whiskers) of the sums of (*A*) PBDEs, (*B*) PCBs, (*C*) OH-PCBs, and (*D*) PCP in maternal blood plasma, cord blood plasma, and breast milk. OH-PCB and PCP levels in breast milk have been multiplied by 10 and 100, respectively. In (*D*), the cut whisker shows the highest level of PCP (0.57 ng/g milk).

et al. 2002), and Canada (Sandau et al. 2000, 2002). A somewhat different pattern of OH-PCB congeners was reported in blood from Latvian men (Sjödin et al. 2000), where 4-OH-CB107 occurred at the highest levels.

Hydroxylated metabolites of PCBs are formed from PCBs by cytochrome P450–mediated direct hydroxylation or via formation of an arene oxide (reviewed by Letcher et al. 2000). Several OH-PCBs may be formed from certain PCB congeners; for example, 4-OH-CB146 can be formed from CB-138 and CB-153, 4-OH-CB107 from CB-118 and CB-105, and 4-OH-CB187 from CB-187 (Sjödin et al. 1998b). Possibly, 4-OH-CB187 may also be formed from CB-183. However, it is not yet possible to predict the relative contribution of different PCB congeners to each one of the specific OH-PCB metabolites. All the identified OH-PCB congeners have an OH group in *para*- or *meta*-position, with two chlorine atoms on the neighboring carbon atoms. These OH-PCBs have structural similarities to T_4 and have high competitive binding potency to transthyretin (Lans et al. 1993). Even though thyroid-binding globulin is the major T_4 transporting protein in humans, transthyretin also plays a role, particularly during fetal development (Brouwer et al. 1998). The interaction between transthyretin and OH-PCBs and other halogenated phenolic compounds suggests a plausible mode of endocrine-mediated actions of these compounds that could make them important for in-depth studies.

The levels of OH-PCBs and PCBs correlated well in cord blood plasma samples (r = 0.78, p < 0.01). OH-PCBs constituted 5–26% and 14–53% of the sum of PCBs in maternal and cord blood plasma samples, respectively, calculated on a fresh-weight basis. The high percentage of OH-PCBs in cord blood suggests that OH-PCBs may pass the placenta to a higher extent than do PCBs or possibly that they may be formed to some extent on the fetal side. An efficient transfer of the halogenated phenolic compounds is supported by the similar high concentrations of PCP in the maternal and cord blood plasma. In this case, the major contribution is from PCP, even though a slight contribution of PCP may originate from metabolized hexachlorobenzene (Renner 1988).

The levels of OH-PCBs and PCP in breast milk were approximately 35 and 100 times lower than in maternal and cord blood plasma (Figure 1), confirming poor transfer of halogenated phenolics via lipids. The dominating OH-PCB congeners were 4-OH-CB107 and 4-OH-CB193 (Table 3). The congener 4-OH-CB187 has been previously reported in Canadian breast milk samples (Newsome and Davies 1996).

The PCP levels in breast milk were an order of magnitude lower than previously reported in Swedish breast milk collected in 1980 (Norén 1988). The levels of PCP in blood plasma reported in this study were similarly lower than PCP concentrations determined in blood from Stockholm women sampled around 1980 (Jensen S. Personal communication). However, one individual diverged by having a PCP concentration in breast milk almost 30 times higher (0.57 ng/g

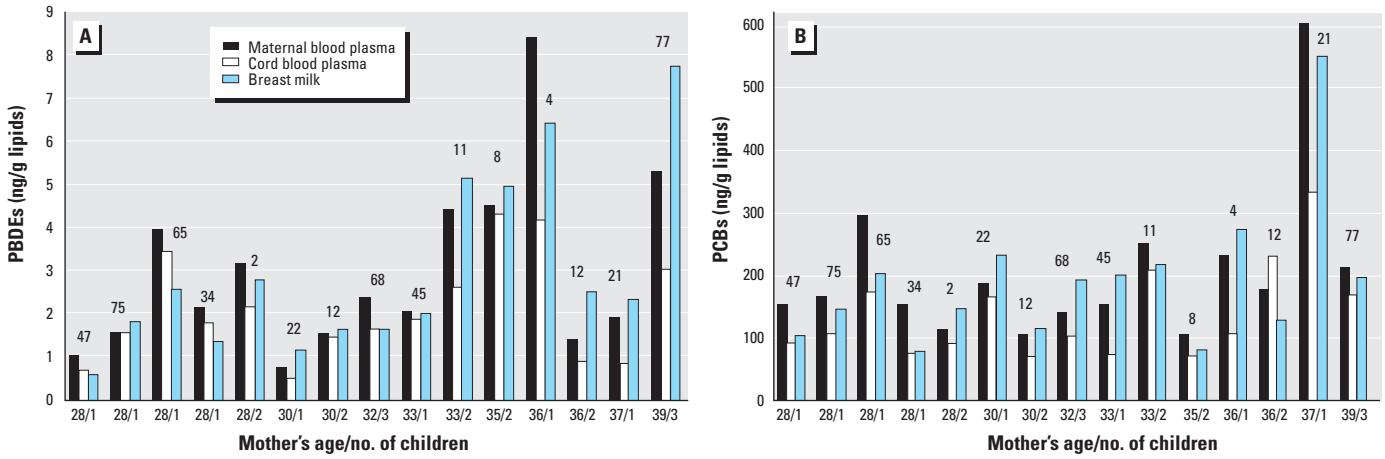

Figure 2. Sums of 10 PBDE congeners (*A*) and 15 PCB congeners (*B*) (ng/g lipids) in maternal blood plasma, cord blood plasma, and breast milk. Numbers above the bars indicate the number of days postpartum that milk was collected.

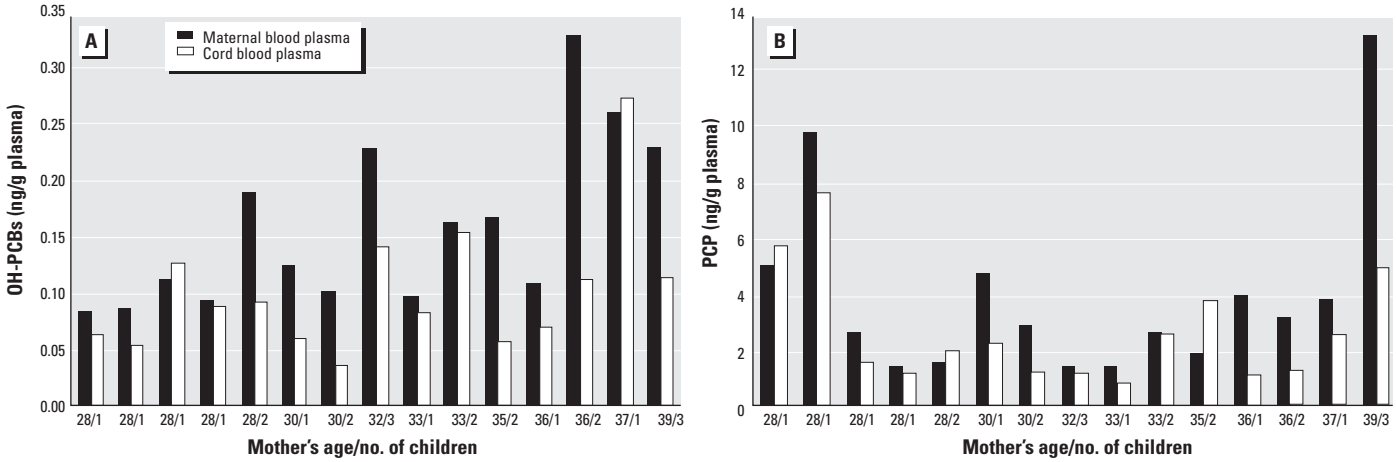

Figure 3. Concentrations (ng/g plasma) of OH-PCBs (sum of 12 congeners) (*A*) and PCP (*B*) in maternal and cord blood plasma.

fresh weight) than any of the other subjects (Figure 3).

The low levels of halogenated phenolic compounds in breast milk compared with their levels in blood are most likely explained by their low accumulation in lipids [e.g., in human adipose tissue, OH-PCBs constituted only 0.03–0.4% of the PCB levels (Meironyté Guvenius et al. 2002)] and their specific binding properties to transthyretin (Lans et al. 1993).

Even though fetal exposures of PBDEs, PCBs, OH-PCBs, and PCP may be predicted from their levels in maternal blood, there are differences in congener distribution of, for example, PBDEs and OH-PCBs that must be considered. This has yet to be done through congener-specific analysis. Our results show that the fetus is probably continuously exposed to PBDEs, PCBs, OH-PCBs, and PCP during development. However, more work needs to be done to describe the exposure situation for the fetus during the entire developmental period. Exposure to PBDEs and PCBs as well as to other persistent organohalogen pollutants continues by breastfeeding and possibly at a higher level than during fetal development, whereas the exposure to halogenated phenols is strongly reduced via this route.

References

Asplund L, Svensson B-G, Nilsson A, Eriksson U, Jansson B, Jensen S, et al. 1994. Polychlorinated biphenyls, 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (*p,p´*-DDT) and 1,1-dichloro-2,2-bis(*p*-chlorophenyl)-ethylene (*p,p´*-DDE) in human plasma related to fish consumption. Arch Environ Health 49:477–486.

Ballschmiter K, Bacher R, Mennel A, Fischer R, Riehle U, Swerev M. 1992. The determination of chlorinated biphenyls, chlorinated dibenzodioxins and chlorinated dibenzofurans by GC-MS. J High Resol Chromatogr 15:260–270.

Bergman Å, Hagmar L, Höglund P, Sjödin A. 2002. Polybrominated diphenyl ethers: route, dose, and kinetics of exposure to humans. In: Biomarkers of Environmentally Associated Disease: Technologies, Concepts, and Perspectives (Wilson SH, Suk WA, eds). Boca Raton, FL:CRC Press, 471–481.

Bergman A, Klasson-Wehler E, Kuroki H. 1994. Selective retention of hydroxylated PCB metabolites in blood. Environ Health Perspect 102:464–469.

Bergman Å, Klasson Wehler E, Kuroki H, Nilsson A. 1995. Synthesis and mass spectrometry of some methoxylated PCB. Chemosphere 30:1921–1938.

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.

Brouwer A, Morse DC, Lans MC, Schuur AG, Murk AJ, Klasson-Wehler E, et al. 1998. Interactions of persistent environmental organohalogens with the thyroid hormone system: mechanisms and possible consequences for animal and human health. Toxicol Ind Health 14:59–84.

Connor K, Ramamoorthy K, Moore M, Mustain M, Chen I, Safe S, et al. 1997. Hydroxylated polychlorinated biphenyls (PCBs) as estrogens and antiestrogens: structure-activity relationships. Toxicol Appl Pharmacol 145:111–123.

Darnerud PO, Eriksen GS, Johannesson T, Larsen PB, Viluksela M. 2001. Polybrominated diphenyl ethers: occurrence, dietary exposure, and toxicology. Environ Health Perspect 109:49–68.

de Boer J, de Boer K, Boon JP. 2000. Polybrominated biphenyls and diphenylethers. In: Handbook of Environmental Chemistry. New Types of Persistent Halogenated Compounds, Vol 3, Part K (Paasivirta J, ed). Berlin:Springer Verlag, 61–95.

de Wit C. 2002. An overview of brominated flame retardants in the environment. Chemosphere 46:583–624.

Dobbing J, Sands J. 1979. Comparative aspects of the brain growth spurt. Early Hum Dev 3:79–83.

Eriksson P, Fredriksson A. 1996a. Neonatal exposure to 2,2´,5,5´-tetrachlorobiphenyl causes increased susceptibility in the cholinergic transmitter system at adult age. Environ Toxicol Pharmacol 1: 217–220.

———. 1996b. Developmental neurotoxicity of four *ortho*-substituted polychlorinated biphenyls in the neonatal mouse. Environ Toxicol Pharmacol 1:155–165.

———. 1998. Neurotoxic effects in adult mice neonatally exposed to 3,3´,4,4´,5-pentachlorobiphenyl or 2,3,3´,4,4´-pentachlorobiphenyl. Changes in brain nicotinic receptors and behaviour. Environ Toxicol Pharmacol 5:17–27.

Eriksson P, Jakobsson E, Fredriksson A. 2001. Brominated flame retardants: a novel class of developmental neurotoxicants in our environment? Environ Health Perspect 109:903–908.

Eriksson P, Lundkvist U, Fredriksson A. 1991. Neonatal exposure to 3,3´,4,4´-tetrachlorobiphenyl: changes in spontaneous behaviour and cholinergic muscarinic receptors in the adult mouse. Toxicology 69:27–34.

Fängström B, Athanasiadou M, Grandjean P, Weihe P, Bergman Å. 2002. Hydroxylated PCB metabolites and PCBs in serum from pregnant Faroese women. Environ Health Perspect 110:895–899.

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.

Fielden MR, Chen I, Chittim B, Safe SH, Zacharewski TR. 1997. Examination of the estrogenicity of 2,4,6,2´,6´-pentachlorobiphenyl (PCB 104), its hydroxylated metabolite 2,4,6,2´,6´-pentachloro-4-biphenylol (HO-PCB 104), and a further chlorinated derivative, 2,4,6,2´,4´,6´-hexachlorobiphenyl (PCB 155). Environ Health Perspect 105:1238–1248.

Fowles JR, Fairbrother A, Baecher-Steppan L, Kerkvliet NI. 1994. Immunologic and endocrine effects of the flame retardant pentabromodiphenyl ether (DE-71) in C7BL/6J mice. Toxicology 86:49–61.

Fürst P. 2001. Organochlorine pesticides, dioxins, PCBs and polybrominated biphenylethers in human milk from Germany in the course of time. Organohalogen Compounds 52:185–188.

Guo YL, Chen YC, Yu ML, Hsu CC. 1994. Early development of Yu-Cheng children born seven to twelve years after the Taiwan PCB outbreak. Chemosphere 29:2394–2404.

Haglund PS, Zook DR, Buser H-R, Hu J. 1997. Identification and quantification of polybrominated diphenyl ethers and methoxy-polybrominated diphenyl ethers in Baltic biota. Environ Sci Technol 31:3281–3287.

Hallgren S, Sinjari T, Hakansson H, Darnerud PO. 2001. Effects of polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) on thyroid hormone and vitamin A levels in rats and mice. Arch Toxicol 75:200–208.

Hardell L, Lindström G, van Bavel B, Wingfors H, Sundelin E, Liljegren G. 1998. Concentrations of the flame retardant 2,2´,4,4´-tetrabrominated diphenyl ether in human adipose tissue in Swedish persons and the risk for non-Hodgkin's lymphoma. Oncol Res 10:429–432.

Hovander L, Malmberg T, Athanasiadou M, Athanassiadis I, Rahm S, Bergman A, et al. 2002. Identification of hydroxylated PCB metabolites and other phenolic halogenated pollutants in human blood plasma. Arch Environ Contam Toxicol 42:105–117.

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

Korrick SA, Altshul LM, Tolbert PE, Burse VW, Needham LL, Monson RR. 2000. Measurement of PCBs, DDE, and hexachlorobenzene in cord blood from infants born in towns adjacent to a PCB-contaminated waste site. J Expo Anal Environ Epidemiol 10:743–754.

Lans MC, Klasson-Wehler E, Willemsen M, Meussen E, Safe S, Brouwer A. 1993. Structure-dependent, competitive interaction of hydroxy-polychlorobiphenyls, -dibenzo-*p*-dioxins and -dibenzofurans with human transthyretin. Chem Biol Interact 88:7–21.

Letcher RJ, Klasson-Wehler E, Bergman Å. 2000. Methyl sulfone and hydroxylated metabolites of polychlorinated biphenyls. In: Handbook of Environmental Chemistry. New Types of Persistent Halogenated Compounds, Vol 3, Part K (Paasivirta J, ed). Berlin:Springer-Verlag.

Marsh G, Hu J, Jakobsson E, Rahm S, Bergman Å. 1999. Synthesis and characterization of thirty-two polybrominated diphenyl ethers (PBDEs). Environ Sci Technol 33:3033–3037.

Meerts IATM, Letcher RJ, Hoving S, Marsh G, Bergman Å, Lemmen JG, et al. 2001. *In vitro* estrogenicity of polybrominated diphenyl ethers, hydroxylated PBDEs, and polybrominated bisphenol A compounds. Environ Health Perspect 109:399–407.

Meerts IATM, van Zanden JJ, Luijks EAC, van Leeuwen-Bol I, Marsh G, Jakobsson E, et al. 2000. Potent competitive interactions of some brominated flame retardants and related compounds with human transthyretin in vitro. Toxicol Sci 56:95–104.

Meironyté D, Norén K, Bergman Å. 1999. Analysis of polybrominated diphenyl ethers in Swedish human milk. A time-related trend study, 1972–1997. J Toxicol Environ Health 58:329–341.

Meironyté Guvenius D, Bergman Å, Norén K. 2001. Polybrominated diphenyl ethers in Swedish human liver and adipose tissue. Arch Environ Contam Toxicol 40:564–570.

Meironyté Guvenius D, Hassanzadeh P, Bergman Å, Norén K. 2002. Metabolites of polychlorinated biphenyls in human liver and adipose tissue. Environ Toxicol Chem 21:2264–2269.

Newsome WH, Davies D. 1996. Determination of PCB metabolites in Canadian human milk. Chemosphere 33:559–565.

Norén K. 1988. Changes in the levels of organochlorine pesticides, polychlorinated biphenyls, dibenzo-*p*-dioxins and dibenzofurans in human milk from Stockholm, 1972–1985. Chemosphere 17:39–49.

Norén K, Sjövall J. 1987. Analysis of organochlorine pesticides, polychlorinated biphenyls, dibenzo-*p*-dioxins and dibenzofurans in human milk by extraction with lipophilic gel Lipidex 5000. J Chromatogr 422:103–115.

Örn U, Eriksson L, Jakobsson E, Bergman Å. 1996. Synthesis and characterization of polybrominated diphenyl ethers—unlabelled and radiolabelled tetra-, penta- and hexa-bromodiphenyl ethers. Acta Chem Scand 50:802–807.

Päpke O, Bathe L, Bergman Å, Fürst P, Meironyté Guvenius D, Herrmann T, et al. 2001. Determination of PBDEs in human milk from the United States. Comparison of results from tree laboratories. Orgaohalogen Compounds 52:197–200.

Renner G. 1988. Hexachlorobenzene and its metabolism. Toxicol Environ Chem 18:51–78.

Ryan JJ, Patry B. 2001. Body burdens and food exposure in Canada for polybrominated diphenyl ethers (BDEs). Organohalogen Compounds 51:226–229.

Rylander L, Stromberg U, Hagmar L. 2000. Lowered birth weight among infants born to women with a high intake of fish contaminated with persistent organochlorine compounds. Chemosphere 40:1255–1262.

Sala M, Ribas-Fito N, Cardo E, de Muga ME, Marco E, Mazon C, et al. 2001. Levels of hexachlorobenzene and other organochlorine compounds in cord blood: exposure across placenta. Chemosphere 43:895–901.

Sandau CD, Ayotte P, Dewailly E, Duffe J, Norstrom RJ. 2000. Analysis of hydroxylated metabolites of PCBs (OH-PCBs) and other chlorinated phenolic compounds in whole blood from Canadian Inuit. Environ Health Perspect 108:611–616.

———. 2002. Pentachlorophenol and hydroxylated polychlorinated biphenyl metabolites in umbilical cord plasma of neonates from coastal populations in Quebec. Environ Health Perspect 110:411–417.

Schröter-Kermani C, Helm D, Herrmann T, Päpke O. 2000. The German environmental specimen bank—application in trend monitoring of polybrominated diphenyl ethers in human blood. Organohalogen Compounds 47:49–52.

Sjödin A, Hagmar L, Klasson-Wehler E, Björk J, Bergman Å. 2000. Influence of the consumption of fatty Baltic Sea fish on plasma levels of halogenated environmental contaminants in Latvian and Swedish men. Environ Health Perspect 108:1035–1041.

Sjödin A, Hagmar L, Klasson-Wehler E, Kronholm-Diab K, Jakobsson E, Bergman Å. 1999. Flame retardant exposure: polybrominated diphenyl ethers in blood from Swedish workers. Environ Health Perspect 107:643–648.

Sjödin A, Jakobsson E, Kierkegaard A, Marsh G, Sellström U. 1998a. Gas chromatographic identification and quantification on polybrominated diphenyl ethers in commercial product, Bromkal 70-5DE. J Chromatogr A 822:83–89.

Sjödin A, Patterson DGJ, Bergman A. 2001. Brominated flame retardants in serum from U.S. blood donors. Environ Sci Technol 35:3830–3833.

Sjödin A, Tullsten AK, Klasson-Wehler E. 1998b. Identification of the parent compounds to selectively retained hydroxylated PCB metabolites in rat plasma. Organohalogen Compounds 37:365–368.

Strandman T, Koistinen J, Vartiainen T. 2000. Polybrominated diphenyl ethers (PBDEs) in placenta and human milk. Organohalogen Compounds 47:61–64.

Taylor PR, Lawrence CE, Hwang HL, Paulson AS. 1984. Polychlorinated biphenyls: influence on birthweight and gestation. Am J Public Health 74:1153–1154.

Thomsen C, Lundanes E, Becher G. 2001. Brominated flame retardants in plasma samples from three different occupational groups in Norway. J Environ Monit 3:366–370.

van den Berg KJ. 1990. Interaction of chlorinated phenols with thyroxine binding sites of human transthyretin, albumin and thyroid binding globulin. Chem Biol Interact 76:63–75.

Viberg H, Fredriksson A, Eriksson P. 2002. Neonatal exposure to the brominated flame retardant 2,2´,4,4´,5-pentabromodiphenyl ether causes altered susceptibility in the cholinergic transmitter system in the adult mouse. Toxicol Sci 67:104–107.

Weistrand C, Jakobsson E, Norén K. 1995. Liquid-gel partitioning using Lipidex in the determination of polychlorinated biphenyls, naphthalenes, dibenzo-*p*-dioxins and dibenzofurans in blood plasma. J Chromatogr B Biomed Appl 669:207–217.

WHO. 1987. Pentachlorophenol. Environ Health Criteria 71. Geneva:World Health Organization.

———. 1992. Polychlorinated Biphenyls and Terphenyls, 2nd ed. Environ Health Criteria 140. Geneva:World Health Organization.

———. 1997. Flame Retardants: A General Introduction. Environ Health Criteria 192. Geneva:World Health Organization.

Zhou T, Ross DG, De Vito MJ, Crofton KM. 2001. Effects of short-term in vivo exposure to polybrominated diphenyl ethers on thyroid hormones and hepatic enzyme activities in weanling rats. Toxicol Sci 61:76–82.

Zhou T, Taylor MM, DeVito MJ, Crofton KM. 2002. Developmental exposure to brominated diphenyl ethers results in thyroid hormone disruption. Toxicol Sci 66:105–116.