Influence of the Consumption of Fatty Baltic Sea Fish on Plasma Levels of Halogenated Environmental Contaminants in Latvian and Swedish Men

Andreas Sjödin,[1] Lars Hagmar,[2] Eva Klasson-Wehler,[1,] Jonas Björk,[2] and Åke Bergman[1]*

[1]Department of Environmental Chemistry, Stockholm University, Stockholm, Sweden; [2]Department of Occupational and Environmental Medicine, Lund University Hospital, Lund, Sweden

We examined the influence of widely varied consumption of fatty fish from the Baltic Sea and of age on plasma concentrations of polychlorinated biphenyls (PCBs), polychlorobiphenylols (OH-PCBs), 2,2-bis(4-chlorophenyl)-1,1,1-trichloroethane (4,4′-DDT), 2,2-bis(4-chlorophenyl)-1,1-dichloroethane (4,4′-DDE), 2,2′,4,4′-tetrabromodiphenyl ether (BDE-47), hexachlorobenzene (HCB), and pentachlorophenol (PCP) in Latvian and Swedish men. Both age and fish consumption were significantly correlated with the concentrations of ΣPCB, ΣOH-PCB, 4,4′-DDE, 4,4′-DDT, and HCB. In the case of BDE-47, no significant relationship with age was observed, and fish consumption had the largest relative effect on plasma concentrations of this contaminant. This relationship may be a result of exposure to BDE-47 having been more recent than that of PCBs and DDE, or because the half-life of BDE-47 may be shorter than that of PCB and DDE. Latvian men demonstrated higher plasma levels of DDE and DDT but lower levels of ΣPCB and PCP than did Swedish men. The corresponding levels of HCB and BDE-47 were similar in both countries. The Spearman's rank correlation coefficient obtained by comparing the level of the metabolite 4-hydroxy-2,3,3′,4′,5-pentachlorobiphenyl (4-OH-CB107) to the combined levels of its parent compounds, 2,3,3′,4,4′-pentachlorobiphenyl (CB-105) and 2,3′,4,4′,5-pentachlorobiphenyl (CB-118), was higher than the median correlation coefficient obtained upon comparing the level of this metabolite to all other possible combinations of two PCB levels. No other increased correlation between metabolite and parent PCB concentration was observed. *Key words*: endocrine disruptors, fish consumption, hexachlorobenzene, pentachlorophenol, polychlorobiphenylols, polybrominated diphenyl ethers, thyroid hormone. *Environ Health Perspect* 108:1035–1041 (2000). [Online 10 October 2000]

http://ehpnet1.niehs.nih.gov/docs/2000/108p1035-1041sjodin/abstract.html

The extensive production and use of organohalogen substances (OHS), including polychlorinated biphenyls (PCBs), 2,2-bis(4-chlorophenyl)-1,1,1-trichloroethane (4,4′-DDT), and pentachlorophenol (PCP), have resulted in their ubiquitous distribution in the environment. In particular, closed aquatic ecosystems, such as the Baltic Sea, have become heavily polluted by OHS (*1*). 2,2-Bis(4-chlorophenyl)-1,1-dichloroethene (4,4′-DDE) and PCBs have been and are still the major environmental contaminants in this geographic area. Correlated toxic effects have been observed among white-tailed sea eagles (*2,3*) and in seals living in the Baltic Sea area (*4,5*).

Metabolites of OHS, and in particular of PCB and DDT, may play a central role in producing such toxic effects. PCB methyl sulfones ($MeSO_2$-PCBs) and polychlorobiphenylols (OH-PCBs) are major metabolites of PCB and are found in humans and wildlife at comparatively high concentrations (*6*). Other pollutants of concern in the case of the Baltic Sea are the polybrominated diphenyl ethers (PBDEs) and hexachlorobenzene (HCB) (*7*). The levels of the OHS detected in Baltic wildlife at high trophic levels range from low to high parts per million per lipid weight, with the highest concentrations being demonstrated by 4,4′-DDE and certain persistent PCB congeners. For example, the levels of 4,4′-DDE, 2,2′,4,4′,5,5′-hexachlorobiphenyl (CB-153), 2,2′,4,4′-tetrabromodiphenyl ether (BDE-47), and HCB in salmon (*Salmo salar*) from the Baltic Sea, caught in a Swedish river in 1995, were 3,200, 1,100, 200, and 95 ng/g lipid weight, respectively (*7*). The Swedish program for monitoring changes in the concentrations of DDT, PCB, HCB, and hexachlorocyclohexane in Baltic wildlife species has revealed significant decreases since the 1970s (*8*).

This contamination of the Baltic Sea has resulted in higher levels of persistent OHS in humans who consume large quantities of local fatty fish (*9,10*). Asplund et al. (*9*) reported that plasma levels of 4,4′-DDE and CB-153 were 4,500 and 1,000 ng/g lipid weight, respectively, in Swedish men with an average fatty fish consumption of about 2,700 g/month (corresponding to approximately 12 fish meals/month). This 4,4′-DDE concentration was 6-fold greater than in men who did not eat any fish, whereas the corresponding difference for the persistent CB-153 was 2-fold.

Both age and period of lactation exerted a major influence on plasma PCB levels in a group of 50 fishermen's wives, whereas only a weak influence from consumption of fish was observed (*10*). Since the beginning of the 1970s, contamination in Swedish women in general has been monitored by analyzing the levels of a large number of OHS in mother's milk (*11–13*). With regard to the OHS studied here, decreases in the levels of 4,4′-DDE, CB-153, and HCB in mother's milk have been reported, with the mean levels of these substances in the early 1990s being 230, 96, and 31 ng/g lipid weight, respectively (*12*). In contrast, exponentially increasing levels of BDE-47 and other PBDE congeners have recently been reported (*13*). However, the concentration of BDE-47 in milk pooled from different mothers in 1997 was still low (2.3 ng/g lipid weight) compared to that of, for example, CB-153 (96 ng/g lipid weight) (*12,13*).

The phenolic OHS (e.g., PCP and OH-PCBs) examined in the present study are present in the blood of humans and wildlife, primarily bound to serum proteins. Phenolic OHS can compete for binding to the thyroxin (T_4) binding site in transthyretin (TTR), a T_4 transporting protein (*14*), and/or bind due to binding to other blood proteins (*15*). In a group of 120 women from six different municipalities in Sweden, the average PCP plasma concentration in the mid-1980s was 4,000 ng/g lipid weight (range 970–12,000 ng/g) (*16*). PCP is also detected in salmon blood at a level of 1,200 ng/g lipid weight (range 880–1,800 ng/g), although the corresponding level in muscle is much lower, (32 ng/g lipid weight; range 16–64 ng/g) (*7*). Retention of OH-PCBs in the blood of humans and wildlife was first reported in the mid-1990s (*17*). Five OH-PCB congeners predominate in human

Address correspondence to Å. Bergman, Department of Environmental Chemistry, Wallenberg Laboratory, Stockholm University, SE-106 91 Stockholm, Sweden. Telephone: +46-8-16 39 14. Fax: +46-8-15 25 61. E-Mail: anita.hjelm@mk.su.se

*E. Klasson-Wehler is currently at AstraZeneca R&D Södertälje, SE-151 85 Södertälje, Sweden.

We thank I. Athanasiadis for mass spectrometry analyses and M. Kajanus, A. Nilsson, A. Schütz, and A.J. Schütz for recruiting volunteers and collecting blood samples.

Financial support was provided by the European Union Environment and Climate Program (ENV4-CT96-0170), the Swedish Medical Research Council, the Swedish Foundation for Strategic Environmental Research, and the Medical Faculty at Lund University.

Received 20 March 2000; accepted 29 June 2000.

blood, and the plasma levels of these hydroxylated derivatives are lower than those of the most persistent PCB congeners (*17*).

Risk for neurodevelopmental and reproductive toxicity and endocrine disruption in humans from dietary exposure to OHS has received increasing attention (*18*). Similarly, potential risk for immunosuppression and cancer caused by OHS are of concern (*19,20*). A prerequisite for conducting reliable epidemiologic studies designed to evaluate these risks is the availability of well-characterized OHS exposure markers.

The major objective of the present investigation was to relate OHS concentrations in the plasma of Latvian and Swedish men to fish consumption, age, and country of origin. In addition, this study was designed to determine the levels of the predominant OH-PCBs present in human blood and to compare these levels to those of the parent PCB congeners. Furthermore, the level of the more recent environmental contaminant BDE-47, the major PBDE congener present in environmental samples, was determined and compared to the levels of other major environmental pollutants known to be present in humans.

Materials and Methods

Chemicals. The reference compounds used for preparation of standard solutions, their abbreviations, and their sources of origin are listed in Table 1. The internal surrogate standards used were CB-189 for quantitation of PCBs, 4,4′-DDE, 4,4′-DDT, and HCB; 4-OH-CB193 for quantitation of OH-PCBs; and 2,3,4-trichlorophenol (2,3,4-triCP) for quantitation of PCP. A volumetric standard BDE-128 was added for quantitation of BDE-47.

Hexane (distol grade; Fisher Scientific, Leicestershire, UK); methyl *tert*-butyl ether (MTBE; HPLC grade; Rathborn, Walkerburn, Scotland); 2-propanol [analytical (p.a.) grade; Prolabo, Cedex, France]; silica gel 60 (0.063–0.200 mm), sulfuric acid, and hydrochloric acid (p.a. grade; Merck, Darmstadt, Germany); and potassium hydroxide (p.a. grade; Eka Nobel, Bohus, Sweden) were used. Diazomethane, used for derivatization of phenolic compounds, was prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Dielsald) (*24*) obtained from Sigma-Aldrich (Steinheim, Germany).

Instrumentation. Gas chromatography with electron capture detection (GC-ECD) was performed on a Varian 3400 gas chromatograph (Varian, Walnut Creek, CA, USA) using a DB-5 capillary column (30 m × 0.25 mm i.d., 0.25 µm phase thickness; J&W Scientific, Folsom, CA, USA). Hydrogen was used as the carrier gas and nitrogen as the make-up gas. Injections were performed in the splitless mode. The column oven temperature was programmed as follows: 80°C (2 min), 10°C/min up to 300°C (5 min). The injector and detector temperatures were 250°C and 360°C, respectively. Data were collected and processed using a PC-based ELDSPro v1.0 system (Chromatographic Data System AB, Stockholm, Sweden).

Gas chromatography/mass spectrometry (GC/MS) was performed using a Finnigan TSQ 700 (TermoQuest, Bremen, Germany) connected to a Varian 3400 gas chromatograph fitted with a DB-5HT capillary column (15 m × 0.25 mm i.d., 0.10 µm phase thickness; J&W Scientific) and with helium as the carrier gas. Splitless injections were performed at an injector temperature of 260°C. The column oven temperature was programmed as follows: 80°C (1 min), 15°C/min up to 300°C (10 min). The ion source temperature was 200°C and the pressure was 6.5 torr. The instrument was operated in the electron capture negative ionization (ECNI) mode with a primary electron energy of 70 eV. Selected ion monitoring (SIM) of the bromine isotopes, *m/z* 79 and 81, was carried out (*25*). Methane (AGA, Stockholm, Sweden) of ≥ 99.995% purity and containing ≤ 5 ppm O_2 was used as the electron thermalization buffer gas.

Study groups and sampling of plasma. We actively recruited the study groups to obtain a large interindividual contrast in consumption of fatty Baltic Sea fish, mainly salmon and herring. In 1991, 43 men (median age 42 years, range 23–69 years) from southeast Sweden donated blood samples. The majority of those with high fish consumption were professional fishermen. In 1993, blood samples were drawn from 67 Latvian men (median age 48 years, range 24–79 years). All of those with high fish consumption were coastal fishermen from fishing villages around the Gulf of Riga. The others had varying occupations and were recruited from the general population in Riga and four small villages in the Latvian inland. These samples were originally taken to investigate possible immunosuppression or endocrine disruption due to high consumption of fish contaminated with OHS (*26–28*). Venous blood sampling was performed in the morning before the subjects had done any major physical activity. Blood was collected in tubes containing heparin, and the plasma was stored frozen. Each subject was interviewed concerning his average consumption of different kinds of fish, using a food-frequency technique (*29*). For stratified analyses we categorized the subjects with respect to their consumption of fatty fish from the Baltic Sea as follows: "none or low,"

Table 1. Reference compounds used for analyses of organohalogen substances in human plasma samples.

Substance	Abbreviation	Reference
Polychlorinated biphenyls (PCBs)		
2,3,3′,4,4′-Pentachlorobiphenyl	CB-105	[a]
2,3′,4,4′,5-Pentachlorobiphenyl	CB-118	(*21*)[b]
2,2′,3,3′,4,5-Hexachlorobiphenyl	CB-129	[a]
2,2′,3,4,4′,5′-Hexachlorobiphenyl	CB-138	[a]
2,2′,3,4′,5,5′-Hexachlorobiphenyl	CB-146	[a]
2,2′,4,4′,5,5′-Hexachlorobiphenyl	CB-153	(*21*)[b]
2,3,3′,4,4′,5-Hexachlorobiphenyl	CB-156	(*21*)[b]
2,3,3′,4,4′5′-Hexachlorobiphenyl	CB-157	[a]
2,3′,4,4′,5,5′-Hexachlorobiphenyl	CB-167	[a]
2,2′,3,3′,4,4′,5-Heptachlorobiphenyl	CB-170	[a]
2,2′3,3′,4′,5,6-Heptachlorobiphenyl	CB-177	(*21*)[b]
2,2′,3,4,4′,5,5′-Heptachlorobiphenyl	CB-180	[a]
2,2′,3,4,4′,5′,6-Heptachlorobiphenyl	CB-183	(*21*)[b]
2,2′,3,4′,5,5′,6-Heptachlorobiphenyl	CB-187	[a]
2,3,3′,4,4′,5,5′-Heptachlorobiphenyl (IS)	CB-189	(*21*)[b]
Methoxy-PCBs		
4-Methoxy-2,3,3′,4′,5-Pentachlorobiphenyl	4-MeO-CB107	(*22*)[b]
3-Methoxy-2,2′,3′,4,4′,5-Hexachlorobiphenyl	3′-MeO-CB138	(*22*)[b]
4-Methoxy-2,2′,3,4′,5,5′-Hexachlorobiphenyl	4-MeO-CB146	(*22*)[b]
3-Methoxy-2,2′,4,4′,5,5′-Hexachlorobiphenyl	3-MeO-CB-153	(*22*)[b]
4-Methoxy-2,2′,3,4′,5,5′,6-Heptachlorobiphenyl	4-MeO-CB187	(*22*)[b]
4-Methoxy-2,3,3′,4′,5,5′,6-Heptachlorobiphenyl (I.S.)	4-MeO-CB193	(*22*)[b]
Miscellaneous compounds		
2,2′,4,4′-Tetrabromodiphenyl ether	BDE-47	(*23*)[b]
2,2′,3,3′,4,4′-Hexabromodiphenyl ether (I.S.)	BDE-128	(*23*)[b]
1,1-dichloro-2,2-bis(4-chlorophenyl)-ethene	4,4′-DDE	[c]
1,1,1-Trichloro-2,2-bis(4-chlorophenyl)-ethane	4,4′-DDT	[c]
Hexachlorobenzene	HCB	[d]
2,3,4-Trichlorophenol	2,3,4-triCP	[e]
Pentachlorophenol	PCP	[f]

IS, internal surrogate standard.
[a]ProChem GmbH, Wesel, Germany. [b]Synthesized as described. [c]Sigma-Aldrich Chemie GmBH, Steinheim, Germany. [d]Dr Ehrenstorfer GmbH, Augsburg, Germany. [e]Janssen Chimica, Beerse, Belgium. [f]Kebo, Stockholm, Sweden.

0–1 fish meals/month, "moderate," 2–11 fish meals/month, and "high," ≥ 12 fish meals/month (Table 2). This stratification provided reasonable numbers of subjects in each category. Informed consent was obtained from all participating subjects, and the study was approved by the Ethics Committee of Lund University.

Clean-up and analysis. The procedure for extraction of the OHS from plasma has been described fully elsewhere (*30*). The extracts were evaporated to dryness and their lipid content determined gravimetrically. In addition, plasma lipid content was also determined enzymatically as the sum of the cholesterol, triglyceride, and phospolipids present (*31*). The lipid content determined enzymatically was on the average 20% higher (SD 13, n = 110) than that determined gravimetrically. However, least square regression analysis revealed good agreement between the values obtained using these two different procedures (r^2 = 0.75). We used the enzymatically determined values for expressing OHS concentrations per lipid weight. Neutral compounds were separated from acidic substances by partitioning with 0.5 M potassium hydroxide in 50% ethanol. After subsequent acidification of the aqueous phase with 2 M HCl, acidic compounds were extracted into hexane/MTBE (1:1). The acidic fraction was subsequently derivatized, after which both the neutral and acidic fractions were treated with concentrated sulfuric acid to remove lipids. This treatment with sulfuric acid was repeated a second time for the acidic fraction. The neutral fraction was then subjected to cleanup using a silica gel/sulfuric acid column (2:1 w/w, 0.5 g), with hexane as the mobile phase, before analysis. BDE-47 was analyzed by GC/MS (ECNI) and the other substances by GC-ECD. Blank samples (n = 6) were run in parallel. Quantitation of BDE-47 was carried out only in those cases where the amount of this substance in the plasma sample was at least twice that in the blank. For BDE-47, the limit for quantitation (0.1 ng/g lipid weight) was thus directly related to the blank level. The levels of the remaining compounds analyzed by GC-ECD were well above the limits of quantification, and no interference was observed. Recovery of the internal surrogate standards CB-189, 4-OH-CB193, and 2,3,4-triCP was 86% (SD 7.5, n = 110), 84% (SD 13, n = 110) and 80% (SD 12, n = 110), respectively. After the completion of the present study, phenolics used as internal surrogate standards were observed to adsorb to glass during preparation of these standards. Reanalysis of selected samples, using a volumetric standard, showed that this discrepancy resulted in an overestimation of the OH-PCB concentration by a factor of less than 3.

Statistical evaluation. We used the Mann-Whitney U-test to test group differences. Spearman's rank correlation coefficients were calculated to compare the concentrations of each OHS and fish consumption and age. We performed multiple regression analyses using the logarithms of the OHS values, adjusting for fish consumption, age, and country of origin. All p-values < 0.05 were considered as significant.

Results

The plasma concentrations of 14 PCB congeners, 5 OH-PCBs, BDE-47, 4,4′-DDE, 4,4′-DDT, HCB, and PCP in Latvian and Swedish males, stratified on fish consumption habits, are presented in Table 3. With the exception of PCP, the plasma concentrations of all the OHS were significantly correlated to the estimated fish consumption (r_s = 0.55–0.70). In contrast, PCP levels were inversely correlated to fish consumption (r_s = –0.37). Bivariate analyses revealed that age was positively correlated with the levels of all OHS (r_s = 0.26–0.51), again with the exception of PCP.

Multiple regression analysis including all subjects confirmed a significant positive effect of fish consumption on the plasma levels of all OHS, except PCP (Table 4). The ΣPCB level increased by 7% [95% confidence interval (CI), 6–9] with each additional fish meal per month. The most pronounced relative impact of fish consumption was observed for BDE-47, which increased by 13% (CI, 9–16) with each additional fish meal per month. The relative effects of fish consumption and age on the levels of 4,4′-DDE, 4,4′-DDT, and HCB were all similar to that observed for ΣPCB. The association between age and plasma level of BDE-47 observed in the bivariate analysis was no longer seen when the multivariate model was applied, but the other age-related associations remained. The ΣPCB levels increased by 2% (CI, 1–3) for each additional year of age including all the subjects. Multiple regression analysis revealed that the plasma level of ΣPCB in Latvian men was on average 70% (CI, 57–86) of the corresponding Swedish level, whereas the ΣOH-PCB levels in the Latvian and Swedish samples did not differ. The levels of CB-105 and CB-118 were 66% (CI, 26–120) and 34% (CI, 5–72), respectively, higher in the Latvian than in the Swedish males. Similarly, the levels of 4-OH-CB107, a metabolite of CB-105 and CB-118 (*32*), was 94% (CI, 42–165) higher in Latvian than in Swedish males. The effects of country of residence on the levels of the other individual PCB and OH-PCB congeners studied were similar to those observed in the case of ΣPCB and ΣOH-PCB, respectively. Swedish men had higher plasma levels of PCP but lower levels of 4,4′-DDE and 4,4′-DDT, whereas the HCB and BDE-47 levels did not differ significantly between the two countries. The variance explained by the three independent variables (fish consumption, age, and country) varied for the different OHS between 29% and 62%, with 4,4′-DDT being the lowest and ΣPCB the highest.

To investigate the age effect within each fish consumption group in more detail, separate multiple regression analyses for each group were performed with respect to the OHS studied, except PCP (data not shown). Using this approach, influence of age on plasma levels of these OHS was apparent only in men with a high dietary intake of fish. Weak age-related associations with OHS levels among subjects with a lower fish consumption cannot, however, be ruled out because of the relatively small number of subjects in each group. Age did not affect the plasma levels of BDE-47, irrespective of the levels of fish consumption. This lack of effect of age on BDE-47 concentration is illustrated in Figure 1 and contrasted to the influence of age on CB-153.

The correlation coefficient for the comparisons of 4-OH-CB107 with the sum level of its potential parent compounds (CB-105 and CB-118; r_s = 0.70) was higher than the median correlation of the 4-OH-CB107 level to all possible sums of two PCB congeners (r_s = 0.59, 90th percentile, 0.70). In contrast, other correlation coefficients between the level of an OH-PCB to its potential parent compound(s) (*6,32*) were all close to the median correlation coefficient for each OH-PCB to any other PCB or to all possible combinations of two PCB congeners [depending on whether these are one or two

Table 2. Age and consumption of fatty fish from the Baltic Sea for the Latvian and Swedish males involved in the present study.

Nationality and fish consumption groups	No.	Age (years)		Fatty fish (meals/month)	
		Median	Range	Median	Range
Latvian					
None or low	19	43	27–64	0	0–1
Moderate	22	45	31–64	4	2–11
High	26	55	24–79	19	13–32
Swedish					
None	20	37	23–62	0	0
Moderate	11	51	34–69	8	4–8
High	12	48	23–63	16	12–20

potential parent PCBs; data not shown; i.e., 3′-OH-CB138 and CB-138; 3-OH-CB153 and CB-153; 4-OH-CB146 and Σ(CB-138, CB-153); and 4-OH-CB187 and Σ(CB-183, CB-187)]. Furthermore, in addition to the variation in 4-OH-CB107 levels discussed above, individual differences in the relative distribution of OH-PCB congeners were observed. This can be illustrated by the fact that the ratio of 3-OH-CB153/4-OH-CB146 concentration ranged from 0.15 to 1.35 (mean 0.40) for the Swedish population and from 0.15 to 0.80 (mean 0.27) for the Latvian population. This difference between the two countries was significant ($p < 0.01$).

Discussion

The present study was performed using blood samples drawn from men with different levels of consumption of fatty fish from the Baltic Sea. These samples were originally taken to investigate possible immunosupression or endocrine disruption due to high consumption of fish contaminated with OHS (*26–28*), but no clearcut effects were observed. Even though these samples were obtained in the early 1990s, they are still suitable not only for determining OHS concentrations but also for examining the relative influence of fish consumption, age, and country of residence on these concentrations. Previous studies have shown that frequent consumption of fatty fish from the contaminated Baltic Sea results in higher plasma levels of OHS such as PCBs, 4,4′-DDE, and 4,4′-DDT (*9*).

The analytical procedure used was designed to quantitate both neutral and phenolic OHS. The cleanup was based on a procedure developed recently for the analysis of both of these classes of environmental contaminants in human blood (*30*). GC-ECD was used to quantitate all the compounds, with the exception of BDE-47, which, due to its low concentrations, had to be quantitated by GC/MS (ECNI) (*25*).

The range of BDE-47 levels in the plasma of all individuals analyzed here was < 0.1–11 ng/g lipid weight, which can be compared to 22–2,300 ng/g lipid weight for the major PCB congener, CB-153. A recent study found median plasma levels of BDE-47 in female hospital cleaners and clerks from the south of Sweden (sampled in 1997) to be 1.6 and 1.5 ng/g lipid weight, respectively (*33*). Swedish mother's milk from the same year has been reported to contain 2.3 ng BDE-47/g lipid weight (*13*), which is similar

Table 3. Concentrations (ng/g lipid weight) of neutral and phenolic organohalogen compounds in the plasma of Latvian and Swedish men with different dietary consumptions of fatty fish from the Baltic Sea.

	None/low fish consumption		Moderate fish consumption		High fish consumption	
Compound	Latvia Median (10–90%)[a]	Sweden Median (10–90%)[a]	Latvia Median (10–90%)[a]	Sweden Median (10–90%)[a]	Latvia Median (10–90%)[a]	Sweden Median (10–90%)[a]
Polychlorinated biphenyls						
CB-105	9 (4.4–16)	2.5 (1.7–10)	9.7 (3.0–37)	13 (3.3–25)	43 (16–60)	16 (7.2–36)
CB-118	43 (19–66)	16 (7.4–51)	39 (14–120)	56 (16–110)	200 (61–250)	67 (37–180)
CB-129	3.6 (2.2–8.1)	9.8 (4.9–18)	4.6 (3.0–20)	18 (13–39)	28 (9.6–50)	19 (12–40)
CB-138	120 (76–180)	160 (80–300)	110 (72–570)	360 (260–620)	730 (260–1,500)	360 (30–840)
CB-146	13 (7.2–22)	18 (8.7–43)	15 (8.4–64)	46 (27–97)	95 (32–180)	49 (29–110)
CB-153	160 (100–230)	220 (120–390)	130 (93–660)	410 (340–730)	920 (320–1,700)	450 (280–1,000)
CB-156	20 (12–29)	24 (12–49)	20 (13–73)	44 (40–96)	90 (32–150)	43 (20–98)
CB-157	5.9 (2.9–9.5)	3.1 (1.5–7)	5.5 (3.3–16)	6.4 (5.1–12)	23 (8.0–37)	6.9 (3.5–15)
CB-167	6.3 (3.8–11)	5.5 (3.3–16)	6.1 (3.4–24)	19 (8.3–38)	42 (15–59)	19 (13–41)
CB-170	31 (15–60)	74 (37–120)	36 (20–120)	120 (96–230)	160 (54–240)	110 (83–270)
CB-177	8.7 (5.3–12)	21 (8.6–35)	11 (5.9–41)	42 (25–90)	51 (16–89)	42 (29–81)
CB-180	74 (42–160)	160 (84–260)	87 (51–350)	280 (210–540)	420 (150–820)	260 (180–540)
CB-183	7.9 (5.7–13)	18 (10–31)	8.4 (6.2–38)	34 (28–57)	43 (19–76)	38 (26–67)
CB-187	34 (16–72)	37 (16–76)	58 (24–120)	78 (40–180)	120 (54–210)	90 (60–210)
ΣPCB	550 (340–890)	780 (390–1,400)	520 (380–2,100)	1,500 (1,200–2,800)	3,000 (1,000–5,300)	1,600 (1,000–3,600)
Polychlorobiphenylols						
4-OH-CB107	82 (31–150)	36 (15–110)	73 (30–490)	78 (31–150)	290 (87–770)	58 (27–290)
3′-OH-CB138	18 (9.1–33)	20 (7.5–45)	20 (9.6–72)	43 (17–66)	74 (29–230)	28 (14–68)
4-OH-CB146	31 (17–62)	39 (12–140)	44 (20–240)	100 (55–170)	160 (57–540)	66 (43–290)
3-OH-CB153	12 (7.3–28)	15 (5.1–31)	16 (7.2–68)	30 (14–44)	57 (16–280)	20 (11–51)
4-OH-CB187	34 (23–61)	74 (54–110)	55 (27–140)	120 (62–170)	120 (66–430)	68 (57–280)
ΣOH-PCB	200 (105–290)	180 (95–450)	230 (110–1,000)	350 (180–750)	750 (270–2,200)	240 (170–980)
Miscellaneous compounds						
BDE-47[b]	0.26 (< 0.1–0.72)	0.4 (< 0.1–2.5)	0.65 (< 0.1–6.3)	1.8 (0.19–4.5)	2.4 (1.4–5.5)	2.2 (0.96–5.7)
4,4′-DDE	660 (250–2,200)	290 (140–900)	680 (210–2,400)	960 (530–1,800)	2,200 (850–4,200)	1,100 (330–3,900)
4,4′-DDT	40 (6.8–240)	15 (5.1–48)	59 (17–230)	53 (20–110)	100 (33–200)	43 (24–110)
HCB	71 (29–160)	44 (25–81)	70 (27–150)	86 (64–130)	240 (110–410)	100 (60–150)
PCP	610 (240–3,400)	1,600 (600–5,000)	420 (170–820)	720 (460–1,400)	330 (140–1,500)	1,100 (760–1,800)

[a]Percentile range. [b]Values corrected for interference present in blank samples.

Table 4. The relative effects of age, fish consumption, and country of origin on the levels of organohalogen compounds in the plasma of Latvian and Swedish men as determined by multiple regression analysis.

	Fish consumption			Age			Country[a]			Adjusted
Compound	exp(B)	95% CI	*p*	exp(B)	95% CI	*p*	exp(B)	95% CI	*p*	R^2
ΣPCB	1.07	1.06–1.09	< 0.001	1.02	1.01–1.03	< 0.001	0.70	0.57–0.86	< 0.001	0.62
ΣOH-PCB	1.06	1.04–1.08	< 0.001	1.02	1.00–1.03	0.01	1.09	0.85–1.41	0.49	0.45
BDE-47	1.13	1.09–1.16	< 0.001	1.00	0.98–1.02	0.75	0.69	0.45–1.07	0.1	0.43
4,4′-DDE	1.06	1.04–1.08	< 0.001	1.02	1.01–1.04	< 0.001	1.37	1.01–1.86	0.05	0.45
4,4′-DDT	1.04	1.02–1.07	< 0.001	1.02	1.01–1.04	0.01	1.69	1.15–2.49	0.01	0.29
HCB	1.05	1.04–1.07	< 0.001	1.01	1.00–1.03	0.02	1.25	0.97–1.60	0.08	0.44
PCP	0.98	0.96–0.99	0.01	1.00	0.99–1.02	0.68	0.38	0.29–0.51	< 0.001	0.34

[a]Distinct variable, the value 1 was used for Latvia and 0 for Sweden.

to the levels obtained for the Latvian and Swedish men with no or low intake of fatty fish and lower than the levels of all other OHS. The largest relative effect of fatty fish consumption was observed for BDE-47, indicating that consumption of such fish is a major route of exposure for high consumers.

Meironyté et al. (*13*) found increasing levels of BDE-47 in human milk during the period 1972–1997, but the plasma levels of BDE-47 in the present study were not related to age, in contrast to PCBs and DDT (Figure 1, Table 4). The absence of an age-dependent increase in the plasma levels of BDE-47 (Figure 1) may be a reflection of the later introduction of PBDEs in the ecosystems. This is supported by increasing levels of BDE-47 in guillemot eggs from Stora Karlsö in the Baltic Sea until the early 1990s, after which the concentrations leveled off but showed large between-year variations (*34*). It is thus reasonable that the subjects in the present study were mainly exposed to BDE-47 during the years preceding the blood sampling, which diminishes the possibility of detecting an accumulation in body burden with age. Another possible explanation for the absence of any obvious age effect would be that BDE-47 has a much shorter half-life than that of CB-153, for example. Thus, a more rapid turnover of BDE-47 would lead to a steady-state situation that would be reached rather quickly, and no increase should be expected thereafter. However, BDE-47 seems to be a highly persistent PBDE congener because this is the major compound detected in all humans and wildlife analyzed, whereas other PBDE congeners are not (*35*). BDE-47 and 2,2′,4,4′,5-tetrabromodiphenyl ether (BDE-99) are both present in similar concentrations in commercial PBDE products (*36*), but the latter is a minor constituent in biota (*35*).

The OHS found at highest levels in human plasma here was 4,4′-DDE, the highly persistent major metabolite of 4,4′-DDT. The plasma levels of 4,4′-DDT and 4,4′-DDE were strongly correlated with both fish consumption and age (Table 4). These two contaminants were also present in larger amounts in Latvian than in Swedish men. This finding is consistent with reports on 4,4′-DDE levels in perch from Latvian waters, which indicate local sources of this compound in the Riga area (*37,38*). The concentration of 4,4′-DDE in Swedish men with a low fish consumption observed here is comparable to the mean 4,4′-DDE level of 260 ng/g lipid weight in mother's milk from the Stockholm region in 1991 (*12*). Considerably higher levels have been reported from areas where DDT is still in use, especially in developing countries (*39*). The population half-life of ΣDDT, calculated on the basis of published levels in human milk in countries where the use of DDT is either banned or restricted, is 4.2–5.6 years (*39*).

In the multiple regression analysis performed on each fish consumption group separately (data not shown), a significant effect of age on the levels of ΣPCB, 4,4′-DDE, 4,4′-DDT, and HCB remains for those with a high dietary intake of fatty fish from the Baltic Sea (compare the age-dependent increase in CB-153 level in the group with high fish consumption in Figure 1). No such effect was apparent among men with moderate or low consumption of fatty fish from the Baltic Sea. These observations indicate that the age effect is dependent on fish consumption (aging in combination with fish consumption results in increasing plasma levels of OHS). Furthermore, the rates of uptake and elimination seem to be similar in men with a moderate or low fish consumption, leading to a steady-state situation with respect to the levels of ΣPCB, 4,4′-DDE, 4,4′-DDT, and HCB. At the same time, it may be noted that the concentrations of these OHS in the fish consumed have decreased since the 1970s (*8*). This may have exaggerated the observed age effect because the older men have consumed fish with higher OHS concentrations than the younger men.

Whereas neutral lipophilic contaminants such as 4,4′-DDE are present in blood primarily as a consequence of equilibrium with lipid-rich tissues (*40*), PCP is mainly retained in the blood due to binding to albumin and TTR (*41*). The PCP level in plasma was inversely related to fish consumption and not affected by age, but was strongly correlated with the country in which the subjects lived, with the PCP levels being much lower in Latvia than in Sweden. Obviously, consumption of fish is not a major source of exposure to PCP. This conclusion is supported by the low concentration of this compound in fish muscle, in contrast to the higher concentrations seen in fish blood (*7*). Further, the group with low fish consumption demonstrated levels of PCP that were approximately 50% of the corresponding levels in Swedish

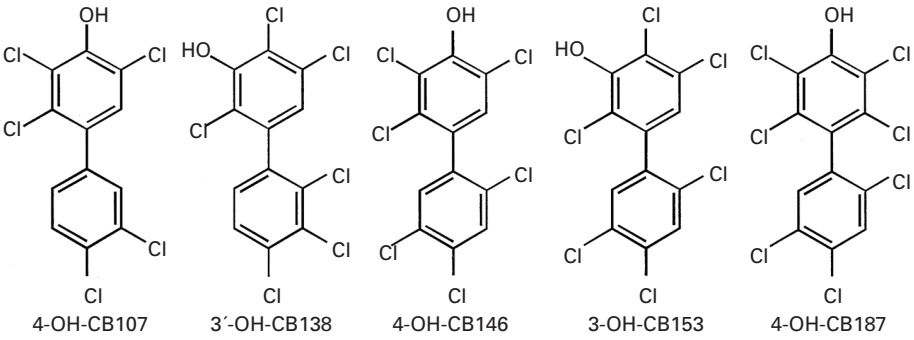

Figure 2. Structures of the predominant polychlorobiphenylols present in human blood.

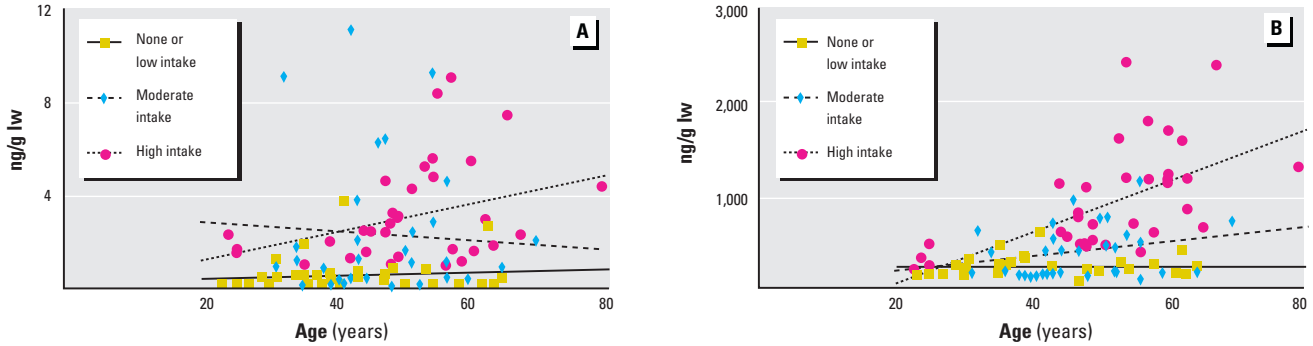

Figure 1. Plasma levels of (*A*) BDE-47 and (*B*) CB-153 in relationship to age for the three groups of men with different fish consumption: none or low (0–1 fish meals/month), moderate (2–11 fish meals/month), or high (> 12 fish meals/month). lw, lipid weight. Spearman's rank correlation coefficients and levels of significance are $R_s = -0.03$, $p > 0.5$; $R_s = 0.00$, $p > 0.5$; and $R_s = 0.28$, $p = 0.10$ for BDE-47; and $R_s = 0.00$, $p > 0.5$; $R_s = 0.22$, $p > 0.20$; and $R_s = 0.71$, $p > 0.001$ for CB-153 for low, moderate, and high consumption, respectively.

women in the early 1980s (*16*). HCB is metabolized to PCP to some extent, but this does not explain the high levels of PCP present in blood because the level of HCB was inversely correlated to that of PCP (r_s = –0.29, $p < 0.05$). Clearly, there must be other sources of PCP in the environment which remain to be identified. It can be speculated that exposure to PCP, due to its use as a wood preservative, occurs via indoor air (*42*). The use of PCP was banned in Sweden in 1975.

The present study has partly focused on determining the patterns and levels of OH-PCBs in the plasma of humans with different levels of fish consumption and, accordingly, different body burdens of PCB. Similar to PCP, OH-PCBs are retained in the blood plasma as a result of protein binding, primarily to TTR (*15*). The OH-PCB congeners are retained at relatively high concentrations compared to ΣPCB in the blood (Table 3), even though the mechanism of accumulation is different. The PCB congeners are accumulated in the fat, whereas the OH-PCBs are bound to plasma proteins. The retention of a cluster of OH-PCBs in human plasma was first reported in 1994 (*17*). Additional information has since been presented (*6*), and recently an additional number of OH-PCB congeners present in human blood have been identified (*43*). A total of 30 OH-PCB congeners have been observed in human blood plasma (*6*), of which the five OH-PCB congeners (Figure 2) quantified here represent the major metabolites in human plasma.

The higher plasma levels of 4-OH-CB107 determined in Latvian men is most probably due to their higher plasma levels of the corresponding parent compounds CB-105 and CB-118, as indicated by the high correlation coefficient for the parent PCBs and OH-PCB metabolite. The other OH-PCB congeners quantified are formed from the more persistent PCB congeners, CB-138, CB-153, and CB-187, as shown by *in vivo* experiments (*6,32*). These latter PCB congeners were not observed to have better correlation coefficients than the median correlation coefficient for each OH-PCB to any other PCB or to all possible combinations of two PCB congeners (depending on whether these are one or two potential parent PCBs). This is most likely due to the strong intercorrelation of these stable and persistent PCBs, which may be contrasted to the large differences observed between Latvian and Swedish men for the levels of CB-105 and CB-118.

The relative abundance of the major OH-PCBs in the plasma varies between individuals, as exemplified by the ratio of 3-OH-CB153 to 4-OH-CB146. The reasons for such individual variations are not yet known. The high affinity of these OH-PCBs for the plasma transport protein TTR, with competing potencies of 4–14 times relative to thyroxin, can hardly explain these differences because TTR is constitutively expressed (*15*). With a slow rate of formation, evidenced by the persistence of the parent PCBs and relatively high plasma levels, the OH-PCBs seem to have long half-lives. The formation of OH-PCBs is catalyzed by cytochrome P450s (*44*) and variations in individual expression of enzymes, and thereby metabolic capacity may, in part, explain the variations. The pharmacokinetic behavior of OH-PCBs is almost completely unknown, and further studies are necessary to explain the observed variations in individual OH-PCB patterns.

It remains unclear whether high concentrations of OH-PCBs exert toxic effects on humans and/or wildlife. It is, however, known that OH-PCBs can competitively inhibit binding of T_4 to TTR, as well as inhibit type I deiodinase activity (*45,46*). OH-PCBs have also been shown to act as inhibitors of T_2 sulfotransferase activity *in vitro* (*47*). A weak negative correlation between the levels of CB-153 in plasma and total T_3 in serum in fishermen's wives from the Swedish Baltic Sea area was recently reported (*48*). It is notable that the levels of OH-PCBs are in the same range as the PCBs concentrations. Further work is in progress to determine the impact these PCB metabolites may have in humans and wildlife. The PBDE concentrations are much lower than those of PCBs and OH-PCBs, but because the levels seem to increase in humans (*13*), it is of concern that this is a serious contamination of the environment. Recently PBDEs and hydroxylated PBDEs have been indicated to have effects on the endocrine systems (*49–51*). More detailed knowledge is necessary to better assess the toxicological impact that this class of environmental contaminants may have.

In conclusion, consumption of fatty fish from the Baltic Sea has a significant influence on the plasma levels of neutral OHS and OH-PCBs, but not of PCP. The low plasma levels of BDE-47 observed were strongly related to fish consumption, which indicates a need for further information concerning dietary exposure of the population in the Baltic Sea region to PBDEs. An impact of fish consumption on plasma OH-PCB levels was also seen, and studies are now required to determine whether this represents a potential risk to human health.

References and Notes

1. de March BGE, de Wit CA, Muir DCG. Persistent organic pollutants. In: AMAP, Assessment Report: Arctic Pollution Issues. Oslo, Norway:Arctic Monitoring and Assessment Programme 1998;183–371.
2. Helander B, Olsson M, Reutergårdh L. Residue levels of organochlorine and mercury compounds in unhatched eggs and the relationships to breeding success in white-tailed sea eagles *Haliaeetus albicilla* in Sweden. Holarct Ecol 5:349–366 (1982).
3. Olsson A. Applications of Various Analytical Chemical Methods for Exposure Studies of Halogenated Environmental Contaminants in the Baltic Environment [PhD Thesis]. Stockholm, Sweden:Stockholm University, 1999.
4. Bergman A, Olsson M. Pathology of Baltic grey seal and ringed seal females with special reference to adrenocortical hyperplasia: is environmental pollution the cause of a widely distributed disease syndrome? Finn Game Res 44:47–62 (1985).
5. Bergman A, Olsson M, Reiland S. Skull-bone lesions in the Baltic grey seal (*Halichoerus grypus*). Ambio 21:517–519 (1992).
6. Letcher RJ, Klasson-Wehler E, Bergman Å. Methyl sulfone and hydroxylated metabolites of polychlorinated biphenyls. In: The Handbook of Environmental Chemistry: New Types of Persistent Halogenated Compounds, Vol 3 (Paasivirta J, ed). Berlin, Heidelberg:Springer-Verlag, 2000;315–359.
7. Asplund L, Athanasiadou M, Sjödin A, Bergman Å, Börjeson H. Organohalogen substances in muscle, egg and blood from healthy Baltic salmon (*Salmo salar*) and Baltic salmon that produced offspring with the M74 syndrome. Ambio 28:67–76 (1999).
8. Bignert A, Olsson M, Persson W, Jensen S, Zakrisson S, Litzén K, Eriksson U, Häggberg L, Alsberg T. Temporal trends of organochlorines in Northern Europe, 1967–1995. Relation to global fractionation, leakage from sediments and international measures. Environ Pollut 99:177–198 (1998).
9. Asplund L, Svensson B-G, Nilsson A, Eriksson U, Jansson B, Jensen S, Wideqvist U, Skerfving S. 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 (1994).
10. Grimvall E, Rylander L, Nilsson-Ehle P, Nilsson U, Strömberg U, Hagmar L, Östman C. Monitoring of polychlorinated biphenyls in human blood plasma: Methodological developments and influence of age, lactation, and fish consumption. Arch Environ Contam Toxicol 32:329–336 (1997).
11. Norén K, Lundén Å. Trend studies of polychlorinated biphenyls, dibenzo-*p*-dioxins and dibenzofurans in human milk. Chemosphere 23:1895–1901 (1991).
12. Lundén Å, Norén K. Polychlorinated naphthalenes and other organochlorine contaminants in Swedish human milk, 1972–1992. Arch Environ Contam Toxicol 34:414–423 (1998).
13. Meironyté D, Norén K, Bergman Å. Analysis of polybrominated diphenyl ethers in Swedish human milk. A time-related trend study, 1972–1997. J Toxicol Environ Health 58:329–341 (1999).
14. Lans MC. Thyroid Hormone Binding Proteins as Novel Targets for Hydroxylated Polyhalogenated Aromatic Hydrocarbons (PHAHs): Possible Implications for Toxicity [PhD Thesis]. Wageningen, Netherlands: Agricultural University Wageningen, 1995.
15. Brouwer A, Morse DC, Lans MC, Schuur G, Murk AJ, Klasson-Wehler E, Bergman Å, Visser TJ. 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 (1998).
16. Jensen S. Personal communication.
17. Bergman Å, Klasson-Wehler E, Kuroki H. Selective retention of hydroxylated PCB metabolites in blood. Environ Health Perspect 102:464–469 (1994).
18. Brouwer A, Longnecker MP, Birnbaum LS, Cogliano J, Kostyniak P, Moore J, Schantz S, Winneke G. Characterization of potential endocrine-related health effects at low-dose levels of exposure to PCBs. Environ Health Perspect 107(suppl 4):639–649 (1999).
19. Schuurman HJ, Van Loveren H, Rozing J, Vos JG. Chemicals trophic for the thymus: risk for immunodeficiency and autoimmunity. Int J Immunopharmacol 14:369–375 (1992).
20. Ahlborg UG, Lipworth L, Titus-Ernstoff L, Hsieh CC, Hanberg A, Baron J, Trichopoulos D, Adami HO. Organochlorine compounds in relation to breast cancer,

endometrial cancer, and endometriosis: an assessment of the biological and epidemiological evidence. Crit Rev Toxicol 25:463–531 (1995).
21. Sundström G. Polychlorinated biphenyls II. Synthesis of some tetra- and pentachlorobiphenyls. Acta Chem Scand 27:600–604 (1973).
22. Bergman Å, Klasson Wehler E, Kuroki H, Nilsson A. Synthesis and mass spectrometry of some methoxylated PCB. Chemosphere 30:1921–1938 (1995).
23. Örn U, Eriksson L, Jakobsson E, Bergman Å. Synthesis and characterization of polybrominated diphenyl ethers - unlabelled and radiolabelled tetra-, penta- and hexa-bromodiphenyl ethers. Acta Chem Scand 50:802–807 (1996).
24. Furniss BS, Hannaford AJ, Smith PWG, Tatchell AR. Vogel's Textbook of Practical Organic Chemistry. 5th ed. London:Longman Scientific & Technical, 1989.
25. Blum A, Gold MD, Ames BN, Kenyon C, Jones FR, Hett EA, Dougherty RC, Horning EC, Dzidic I, Carroll DI, et al. Children adsorb tris-BP flame retardant from sleepwear: urine contains the mutagenic metabolite, 2,3-dibromopropanol. Science 201:1020–1023 (1978).
26. Svensson B-G, Hallberg T, Nilsson A, Schütz A, Hagmar L. Parameters of immunological competence in subjects with high consumption of fish contaminated with persistent organochlorine compounds. Int Arch Occup Environ Health 65:351–358 (1994).
27. Hagmar L, Hallberg T, Leja M, Nilsson A, Schütz A. High consumption of fatty fish from the Baltic Sea is associated with changes in human lymphocyte subsets. Toxicol Lett 77:335–342 (1995).
28. Hagmar L, Björk J, Sjödin A, Bergman Å, Erfurth EM. Dietary exposure to persistent organohalogens and hormone levels in male adults Arch Environ Health (in press).
29. Hagmar L, Lindén K, Nilsson A, Norrving B, Åkesson B, Schütz A, Möller T. Cancer incidence and mortality among Swedish Baltic Sea fishermen. Scand J Work Environ Health 18:217–224 (1992).
30. Hovander L, Athanasiadou M, Asplund L, Jensen S, Klasson-Wehler E. Extraction and cleanup methods for analysis of phenolic and neutral organohalogens in plasma. J Anal Toxicol (in press).
31. Rylander L, Strömberg U, Dyremark E, Östman C, Nilsson-Ehle P, Hagmar L. Polychlorinated biphenyls in blood plasma among Swedish female fish consumers in relation to low birth weight. Am J Epidemiol 147:493–502 (1998).
32. Sjödin A, Tullsten A-K, Klasson-Wehler E. Identification of the parent compounds to selectively retained hydroxylated PCB metabolites in rat blood plasma. Organohalogen Comp 37:365–368 (1998).
33. Sjödin A, Hagmar L, Klasson-Wehler E, Kronholm-Diab K, Jakobsson E, Bergman Å. Flame retardant exposure: polybrominated diphenyl ethers in blood from Swedish workers. Environ Health Perspect 107:643–648 (1999).
34. Sellström U. Determination of Some Polybrominated Flame Retardants in Biota, Sediment and Sewage Sludge [PhD Thesis]. Stockholm, Sweden:Stockholm University, 1999.
35. de Boer J, de Boer K, Boon JP. Polybrominated biphenyls and diphenylethers. In: The Handbook of Environmental Chemistry: New Types of Persistent Halogenated Compounds, Vol 3 (Paasivirta J, ed). Berlin, Heidelberg:Springer-Verlag, 2000;61–95.
36. Sjödin A. Occupational and Dietary Exposure to Organohalogen Substances, with Special Emphasis on Polybrominated Diphenyl Ethers [PhD Thesis]. Stockholm, Sweden:Stockholm University, 2000.
37. Valters K, Olsson A, Vitinsh M, Bergman Å. Contamination sources in Latvia: levels of organochlorines in perch (*Perca fluviatilis*) from rivers Daugava and Lielupe. Ambio 28:335–340 (1999).
38. Olsson A, Vitinsh M, Plikshs M, Bergman Å. Halogenated environmental contaminants in perch (*Perca fluviatilis*) from Latvian coastal areas. Sci Total Environ 239:19–30 (1999).
39. Smith D. Worldwide trends in DDT levels in human breast milk. Int J Epidemiol 28:179–188 (1999).
40. Gómez-Catalán J, To-Figueras J, Rodamilans M, Corbella J. Transport of organochlorine resiudes in the rat and human blood. Arch Environ Contam Toxicol 20:61–66 (1991).
41. van den Berg KJ. Interaction of chlorinated phenols with thyroxine binding sites of human transthyretin, albumin and thyroid binding globulin. Chem Biol Interact 76:63–75 (1990).
42. WHO. Pentachlorophenol. Environmental Health Criteria 71. Geneva: World Health Organization, 1987.
43. Sandau CD, Ayotte P, Dewailly E, Duffe J, Norstrom RJ. 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 (2000).
44. Schenkman JB, Greim H. Handbook of Experimental Pharmacology, Cytochrome P450. Berlin,Heidelberg: Springer-Verlag, 1993.
45. Adams C, Lans MC, Klasson-Wehler E, van Engelen JGM, Visser TJ, Brouwer A. Hepatic thyroid hormone 5'-deiodinase, another target-protein for monohydroxy metabolites of 3,3',4,4'-TCB. In: Dioxin '90, Organohalogen Compounds, Vol 1 (Hutzinger O, Fielder H, eds). Bayreuth, Germany:Ecoinforma Press, 1990; 51–54
46. Lans MC, Spiertz C, Brouwer A, Koeman JH. Different competition of thyroxine binding to transthyretin and thyroxine-binding globulin by hydroxy-PCBs, PCDDs and PCDFs. Eur J Pharmacol 270:129–136 (1994).
47. Schuur AG, Legger FF, van Meeteren ME, Moonen MJH, van Leeuwen-Bol I, Bergman Å, Visser TJ, Brouwer A. *In vitro* inhibition of thyroid hormone sulfation by hydroxylated metabolites of halogenated aromatic hydrocarbons. Chem Res Toxicol 11:1075–1081 (1998).
48. Hagmar L, Rylander L, Dyremark E, Klasson-Wehler E, Erfurth EM. Plasma levels of persistent organochlorines in relation to TSH and thyroid hormone levels in adult women. Int Arch Occup Environ Health (in press).
49. Meerts IATM, Marsh G, van Leeuwen-Bol I, Luijks EAC, Jakobsson E, Bergman Å, Brouwer A. Interaction of polybrominated diphenyl ether metabolites (PBDE-OH) with human transthyretin *in vivo*. Organohalogen Compounds 37:309–312 (1998).
50. Zhou T, Ross DG, DeVito MJ, Crofton KM. Effect of short-term in-vivo exposures to polybrominated diphenyl ethers on thyroid hormones and hepatic enzyme activities in weanling rats. Toxicologist 48:267 (1999).
51. Meerts IATM, Letcher RJ, Hoving S, Marsh G, Bergman Å, Lemmen JG, van der Burg B, Brouwer A. Unpublished data.