Organochlorines in Swedish Women: Determinants of Serum Concentrations

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We studied associations between lifestyle/medical factors and lipid-adjusted serum concentrations of seven polychlorinated biphenyl (PCB) congeners and five chlorinated pesticides/metabolites among 205 Swedish women (54–75 years old). Serum concentrations were significantly associated with age, body mass index, body weight change, diabetes mellitus, consumption of fatty fish, and place of residence. The findings suggest that lifestyle/medical factors may confound results in epidemiologic studies when they are related to both serum concentrations and disease. Moreover, disease itself may influence serum concentrations of some organochlorines, as indicated by the negative associations between recent weight change and serum concentrations of some PCB congeners, *p,p′*-dichlorodiphenyldichloroethylene (DDE), and hexachlorobenzene (HCB) and the positive association between diabetes mellitus and HCB concentrations. Age was the only determinant that showed a consistent association with all compounds studied (positive); otherwise associations with single determinants varied among compounds even within the PCB group. This shows that the studied organochlorines should not be treated as a homogeneous group of compounds in epidemiologic studies. *Key words:* **age, BMI, chlordane, DDE, diabetes, fish, HCB, HCH, PCB, weight.** *Environ Health Perspect* **111:349–355 (2003). doi:10.1289/ehp.5456 available via *http://dx.doi.org/* [Online 28 October 2002]**

Persistent and lipid-soluble organochlorines, such as the industrial chemical polychlorinated biphenyl (PCB) and the pesticide dichlorodiphenyltrichloroethane (DDT), are ubiquitously present as a complex mixture in the environment. In Sweden, the use of DDT was banned in the 1970s, but in the 1960s more than 100 metric tons/year were applied mainly to arable land. The chlorinated pesticides hexachlorobenzene (HCB), hexachlorocyclohexane (HCH), and chlordane have been used less extensively in Sweden, but these compounds still contaminate the food chain mostly because of their persistence and long-range atmospheric transport of the compounds (Atuma et al. 1996; Bernes 1998). PCBs hold a special position among industrial chemicals because of their lipid solubility, persistence to degradation, and toxicity. More than 1.5 million metric tons of PCB have been produced in the world for a variety of uses—for example, as additives in heat transfer and hydraulic fluids, as solvent extenders, and as flame retardants. At least one-third of this production is believed to have found its way into the natural environment (Bernes 1998). Between 1957 and 1980, 8,000–10,000 metric tons of PCB were imported into Sweden (Hammar 1992).

In countries where use and production of organochlorines have been banned for decades, food of animal origin is currently the major source of human exposure (Ahlborg et al. 1995). Although the human exposure to PCB and persistent chlorinated pesticides has declined, there are indications that the presence of organochlorines in food may be a risk factor for neurologic, hormonal, and immunologic effects in infants and children (Brouwer et al. 1995; Jacobson and Jacobson 1997; Ribas-Fito et al. 2001; Weisglas-Kuperus et al. 2000). Moreover, there are indications of associations between organochlorines and altered thyroid function in women (Hagmar et al. 2001; Koopman-Esseboom et al. 1994). Worries about organochlorines as risk factors for cancer of the breast and endometrium of women have prompted a large number of epidemiologic studies on women from North America and Europe. However, the results do not suggest that PCB and DDT compounds are important risk factors for these types of cancer at current background levels in food (Ahlborg et al. 1995; Laden et al. 2001; Snedeker 2001). A few studies indicate, however, that there may be a slightly increased risk of breast cancer at high dichlorodiphenyldichloroethylene (DDE)/DDT exposure levels (Hoyer et al. 2000; Romieu et al. 2000).

In epidemiologic studies, serum concentrations of organochlorines are commonly used in exposure assessment, but little is known about the reasons behind the findings of large interindividual variation in concentrations. Serum/plasma concentrations of organochlorines among women are associated with personal attributes such as food habits, age, body mass index (BMI), breast-feeding, and place of residence (Laden et al. 1999; Rylander et al. 1997; Schildkraut et al. 1999; Schmid et al. 1997). The lifestyle/medical factors studied so far, however, can explain only a minor part of the interindividual variation in serum concentrations in epidemiologic studies. If these factors are related both to serum concentrations and to disease, they may confound results of epidemiologic studies.

Organochlorines are often treated as a homogeneous group of compounds in epidemiologic studies. In exposure assessment of PCB, for example, commonly used analytic methods only give information about total PCB concentrations, even though the PCB group consists of many congeners with different biologic activity. Information about associations between lifestyle/medical factors and serum concentration of different PCB congener is scarce, but urgently needed to improve handling of confounding factors in epidemiologic studies where congener-specific analysis of PCB is used.

Here we report determinants of serum concentrations of seven PCB congeners and five chlorinated pesticides and metabolites among elderly women in Sweden. Our aim was to study associations between lifestyle/medical characteristics of Swedish women and serum concentrations of organochlorines. We selected personal characteristics that in previous studies have been associated to serum concentrations of organochlorines (age, BMI, fish consumption, smoking, and breast-feeding), as well as less studied factors (place of residence, body weight change, diabetes mellitus). Age, fish consumption, and place of residence may be related to serum/plasma concentrations because of higher cumulative exposures among older women, higher exposures among women with high consumption of organochlorine-contaminanted fish, and higher exposures among women living in contaminated areas (Laden et al. 1999; Rylander et al., 1997). BMI also is a predictor of serum *p,p′*-DDE concentrations, suggesting that BMI may affect circulating levels of contaminants (Schildkraut et al. 1999). Furthermore, diabetes mellitus was chosen as a potential determinant because chronic metabolic diseases could alter the toxicokinetics of lipid-soluble

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organochlorines by disease-related changes in metabolizing capacity and alterations in lipid distribution in the body. Positive associations between serum concentrations of PCB and diabetes (type 1) have been found among pregnant women (Longnecker et al. 2001). We also studied recent weight change because a few experimental studies suggest that rapid weight loss is associated with increased serum/plasma concentrations of PCB, probably caused by mobilization of lipid-soluble PCB from body fat (Chevrier et al. 2000; Imbeault et al. 2001; Walford et al. 1999). This could be a problem in studies where disease-induced weight change has occurred. Breast-feeding also mobilizes organochlorines from body stores, and the body burden of organochlorines usually decreases during breast-feeding (Kodama and Ota 1980). Finally, we explored whether smoking is associated with concentrations of PCB and chlorinated pesticides/metabolites, because a few studies have indicated that smoking may be positively related to organochlorine concentrations in plasma (Deutch and Hansen 2000; Lackmann et al. 2000).

Materials and Methods

Study population and serum sampling. Our sample consisted of 205 women 50–74 years old, participating as controls in a population-based case–control study of organochlorines and endometrial cancer risk (Table 1) (Weiderpass et al. 2000). Both cases and controls were born in Sweden and resided between February 1996 and November 1997 in 12 Swedish counties on the coasts of the Gulf of Bothnia, the Baltic Sea, and the largest Swedish lakes. In these areas, organochlorine-contaminated fish are highly available on the food market, and sport fishing is popular. We therefore anticipated that these women would have organochlorine levels above Swedish background (Atuma et al. 1996, 1998; Weiderpass et al. 2000).

Control women were selected from a continuously updated population register and were frequency matched to the case series by 5-year age groups. Among the 742 matched control women, 559 (75.3%) responded to the study questionnaire. Among the respondents, 492 (66.3%) agreed to donate blood samples. Because of the design of the case–control study, we excluded 46 women with prior hysterectomy and 241 women who had experienced hormone replacement therapy. Thus, 205 control women were included in the present study (Table 1). Excluded subjects did not differ meaningfully from those who were included in the study in terms of age and BMI.

The local ethics committee approved the design of this study, and informed consent was obtained from the study participants.

Questionnaire. Data were obtained from a mailed questionnaire, which contained posed questions about lifestyle/medical factors, such as age, weight, height, weight change during the preceding 3 months, reproductive and medical history, diet and physical activity. The dietary questions were designed to collect information about consumption of fruits, vegetables, legumes, high fiber grains, dairy products, fish, chicken, and meat, which were food groups hypothesized to alter the risk of endometrial cancer (Weiderpass et al. 2000). Participants were asked how often, on average, they had consumed the different types of foods during the preceding 1-year period.

We concentrated the statistical analysis to fish consumption because fish is the food group that contributes the most to organochlorine exposure in Sweden (Asplund et al. 1994; Glynn et al. 1996). Questions were asked about consumption of fatty fish (herring, mackerel, and salmon species) that are commonly consumed by women in the age group studied, as well as total fish consumption. Fish in general contain considerably higher concentrations of organochlorines than do other food products on the Swedish market. Among fish, fat-rich fish such as herring and wild and farmed salmonids usually contain higher concentrations of organochlorines than lean fish, even if the lean fish originate from more contaminated waters than do the fat-rich fish (Atuma et al. 1996, 1998). Especially high concentrations, however, are found in herring from the Gulf of Bothnia and the Baltic Sea and wild salmon species from these areas and the large Swedish lakes (Atuma et al. 1996, 1998). The questionnaire was not designed to study food habits in detail, and it was therefore not possible to determine the origin of the consumed herring and salmon species.

In the questionnaire, fish consumption was categorized into no consumption, consumption of less than 1 meal per month, 1–3 meals per month, 1 meal per week, 2 meals per week, 3–4 meals per week, 5–6 meals per week, 1 meal per day, 2 meals per day, and consumption of 3 meals or more per day. In the statistical analysis, fish consumption was categorized into three categories: no consumption, < 1 meal per week, and ≥ 1 meal per week. The validity of the food frequency questions was tested on a similar population of Swedish women, and the Pearson correlation between estimates of specific food consumption and 4 × 7-day diet records ranged between 0.3 and 0.6 (Wolk A. Personal communication). This indicates an imperfect, but reasonable, ranking of individuals according to the studied foods (Willett 1998).

Blood sampling. Blood samples from control subjects were drawn at a primary health care unit or at home; 15 control subjects failed to fast overnight before the blood sampling. Serum was separated within 2 hr of collection and frozen at –20°C until shipment to the Swedish National Food Administration laboratory for analysis.

Analysis of organochlorine compounds in human serum. We analyzed the lipid portion of serum samples for the chlorinated pesticides/metabolites *p,p′*-DDE, HCB, β-HCH, *trans*-nonachlor, and oxychlordane (Table 2) chosen *a priori* because of their likelihood of being present in the food chain in Sweden. Among the 209 theoretically possible PCB congeners, we analyzed International Union of Pure and Applied Chemistry (IUPAC) numbers 105, 118, 138, 153, 156, 167, and 180. These congeners have previously been shown to be present in quantifiable concentrations in serum from Swedish men (Glynn et al. 2000a). Congeners CB 105, CB 118, CB 156, and CB 167 were chosen to represent mono-*ortho* PCBs with dioxin-like activity (Van den Berg et al. 1998). Of these, CB 167 gives a low contribution to the concentrations of dioxin toxic equivalents (TEQs), but a previous study indicated that this congener may be used as a marker of TEQ body burden in Swedish women (Glynn et al. 2001). Among the congeners with no reported dioxin-like activity *in vivo*, the di-*ortho* congeners CB 138, CB 153, and CB 180 were chosen because they are present at high concentrations in Swedish food (Atuma et al. 1996; Glynn et al., 2000b) and are included in the PCB regulation in several European countries. The PCB congeners CB 28, CB 52, and CB 101 were also analyzed, but more than 50% of the women had concentrations below the quantification limit.

Table 1. Personal characteristics of the participating women.

Characteristics	No.	Mean (SD)	Percent
Age (years)	205	62.8 (7.4)	
Breast-feeding (months)	179	10.5 (10.3)	
BMI (kg/m^2)	205	26.0 (4.2)	
Fish consumption (meals/month)			
Total	205	5.2 (3.1)	
Fatty fish (herring, salmon, mackerel)	204	3.1 (1.1)	
Alcohol consumption (g/day)	185	1.9 (3.3)	
Ever smoked	205		33.2
Diabetes mellitus	205		3.4

These three congeners were therefore not included in this study.

The analytic method used is described in detail in Atuma and Aune (1999). After extraction and clean up of samples, they were analyzed on a gas chromatograph with dual capillary columns and electron capture detectors (^{63}Ni). The columns were of different polarity to ease identification of analytes, which was based on retention times relative to internal standards. Quantification was performed using multilevel calibration curves obtained by injection of standard solutions of at least three different concentrations.

The limit of quantification was 10 pg/g serum for the PCB congeners, β-HCH, oxychlordane, and *trans*-nonachlor; 50 pg/g serum for HCB; and 200 pg/g serum for *p,p′*-DDE. Reproducibility of the method was demonstrated by 21 replicate determinations using an in-house control serum sample, included among the analytic batches during the course of the study. The coefficients of variations were less than 13% for most of the compounds, except the PCB congener CB 105 (20%). The coefficient of variation for fat content was 4%, which was determined gravimetrically. Average recoveries of the different PCB congeners in spiked serum samples were 98 ± 12% (mean ± standard deviation) and 94 ± 8% for 0.1 and 0.8 ppb levels, respectively. The recoveries for the chlorinated pesticides varied from 78% to 118%. This shows that the loss of compounds during the analytic process was negligible. The results reported were not corrected for recovery. When concentrations were below the quantification limit, they were set to 50% of that limit in all statistical analysis.

Statistical analysis. Lipid-adjusted serum organochlorine concentrations were used in the analysis. Nonadjusted concentrations are influenced by temporal changes in serum lipid content. The distribution of organochlorines between serum lipids and lipids in body tissues is a dynamic equilibrium. A change in the lipid content of the blood alters this equilibrium (Phillips et al. 1989). Thus, if nonadjusted serum concentrations are used, two women with similar body burdens of organochlorines but with different serum lipid contents may be incorrectly classified in different exposure categories. Therefore, lipid adjustment of serum concentrations gives a better estimate of the body burden than does nonadjusted serum concentrations. Lipid adjustment also adjusts for any age-related differences in serum lipid content, which may confound organochlorine body burdens estimated from nonadjusted serum concentrations.

The distributions of the organochlorine analytic results closely followed a log-normal distribution; therefore, all statistical analysis was performed on logarithmically transformed data. The variation in the different organochlorine concentrations was analyzed with an analysis of covariance model including both continuous and categorical explanatory variables. As a consequence of the logarithmic transformation, the means presented for categorical variables were geometric means (corresponding to the median of the log-normal distribution), and influences of continuous variables are presented as percentage change of the median per measurement unit. The primary explanatory variables considered in this study were age, BMI, body weight change during the preceding 3 months, and place of residence (geographic region). The first four variables were used as continuous variables in the analyses, but approximate linearity was confirmed by categorizing the variables. We also studied the associations between organochlorine concentrations in serum lipids and smoking (never/former/current), diabetes mellitus (yes/no), duration of breast-feeding (months), and intake of fatty fish and total intake of fish (never, < 1 portion per week, ≥ 1 portion per week).

For the statistical analysis of regional differences in organochlorine concentrations, we divided the country into four regions, with one medical center in each region (Malmö, Linköping, Uppsala, and Umeå). The division into four regions ensured that each region contained a reasonable number of study participants (39–61 women per region). Moreover, we also wanted to study whether there is a geographic gradient in average serum concentrations between the southern, more inhabited and industrialized, part of Sweden and the northern, less populated part of the country. Malmö was the southernmost region studied, including Blekinge and Skåne Counties (latitude 55°–56°). Progressively northward came the Linköping region (Kalmar, Jönköping, and Östergötland Counties; latitude 56°–59°) and the Uppsala region (Södermanland, Värmland, Uppsala, and Gävleborg counties; latitude 58°–62°). Umeå (Västernorrland, Västerbotten, and Norrbotten Counties) was the most northern region studied (latitude 62°–69°).

Results

Median concentrations higher than 100 ng/g lipid were found for PCB congeners CB 138, CB 153, and CB 180, and for the DDT metabolite *p,p′*-DDE (Table 2). CB 105 and CB 167 had median concentrations below 10 ng/g lipid. Correlation analysis showed that the concentrations of PCB congeners were positively correlated to each other (r = 0.39–0.95) (Table 3). High correlations ($r \geq 0.70$) were found between the di-*ortho* PCB congeners CB 138, CB 153, and CB 180, and between the mono-*ortho* congeners CB 105, CB 118, and CB 167. Among the mono-*ortho* PCBs, CB 156 and CB 167 were strongly correlated to the di-*ortho* congeners CB 138, CB 153, and CB 180 ($r \geq 0.70$). Correlation coefficients for correlations between chlorinated pesticides and metabolites were, with a few exceptions (HCB and β-HCH; *trans*-nonachlor and oxychlordane), lower than 0.65. Coefficients for correlations between PCB congeners and pesticides/metabolites ranged from 0.35 to 0.78, with the highest correlations between *p,p′*-DDE and CB 138 (r = 0.78), HCB and CB 167 (r = 0.76), HCB and CB 153 (r = 0.71), and *trans*-nonachlor and CB 167 (r = 0.71) (Table 3).

Age was a significant determinant of serum concentrations of all studied organochlorines (Table 4). The regression analysis indicated that the concentrations of PCB and chlorinated pesticides increased on average 1.8–4.3% per year of age, after adjustment for BMI, weight change, and region. The concentrations of some PCB congeners, *p,p′*-DDE, HCB, and β-HCH were positively associated with BMI (Table 4), whereas CB 156 and CB 180 were negatively associated with BMI. Most of the PCB congeners studied were negatively associated with body weight change during the preceding 3 months. This was also the case for *p,p′*-DDE and HCB, whereas concentrations of β-HCH, *trans*-nonachlor and oxychlordane showed no significant association with weight change.

Only seven women were reported as having diabetes mellitus. Nevertheless, the adjusted mean concentration of HCB in serum was significantly higher among women with diabetes mellitus after adjustment for age, BMI, weight change, and region (Table 5). For the other organochlorines, differences in serum concentrations between

Table 2. Serum concentrations of PCB congeners and chlorinated pesticides/metabolites (n = 205).

PCB	Median (min–max) (ng/g lipid)	Pesticide/metabolite	Median (min–max) (ng/g lipid)
PCB 105	6 (< 2–21)	*p,p′*-DDE	497 (32–2,542)
PCB 118	43 (5–178)	HCB	65 (15–351)
PCB 138	101 (18–264)	β-HCH	51 (7–744)
PCB 153	223 (60–607)	Oxychlordane	13 (3–48)
PCB 156	18 (6–58)	*trans*-Nonachlor	23 (6–70)
PCB 167	9 (< 2–28)		
PCB 180	152 (56–397)		

Abbreviations: max, maximum; min, minimum.

women with and without diabetes were not statistically significant.

Women from the southernmost region of Sweden tended to have higher adjusted mean serum concentrations of CB 153, CB 156, CB 167, CB 180, HCB, and β-HCH than did women from the other three regions after adjustment for age, BMI, and weight change (Table 6). On the contrary, the concentrations of oxychlordane were highest in the northernmost region. No significant regional differences were found for the other three PCB congeners, *p,p′*-DDE, and *trans*-nonachlor.

We found a positive association between concentrations of PCB congeners and intake of fatty fish, which remained significant after adjustment for age, BMI, weight change in the preceding 3 months, and region (Table 7). CB 138 and CB 180 were the only PCB congeners that did not show statistically significant associations with fatty fish consumption, whereas none of the chlorinated pesticides/metabolites showed significant associations with fatty fish consumption. Furthermore, no meaningful significant associations were found between serum concentrations of PCB/pesticides/metabolites and total fish consumption (results not shown). This was also the case for associations between PCB/pesticide concentrations and duration of breast-feeding and smoking (results not shown).

Discussion

Our results show that, among elderly Swedish women, lipid-adjusted serum concentrations of PCB and chlorinated pesticides/metabolites are significantly associated with age, BMI, body weight change, diabetes mellitus, consumption of fatty fish, and region of residence.

We included results of seven PCB congeners in this study (CB 105, CB 118, CB 138, CB 153, CB 156, CB 167, and CB 180) that are commonly used in PCB monitoring programs. Three other PCB congeners (CB 28, CB 52, and CB 101) were analyzed, but the concentrations were too low to make statistical analysis meaningful. One could argue that inclusion of a larger number of congeners would be relevant in an investigation of nonhomogeneity within the PCB group. However, the congeners chosen represented two of the toxicologically interesting groups of PCB compounds, mono-*ortho* PCBs with dioxin-like activity (CB 105, CB 118, CB 156, and CB 167) and di-*ortho* PCBs with no reported dioxin-like activity (CB 138, CB 153, and CB 180) (Van den Berg et al. 1998). The third important group of PCBs, dioxin-like non-*ortho* PCBs, could not be analyzed in this study because of technical and economic reasons. Results from more than seven congeners might lead to more conclusive results, but even with a limited number of congeners we found that some determining factors showed inconsistent associations within the two studied subgroups of PCBs.

Concentrations of PCBs and pesticides/metabolites were positively correlated with each other in all cases. Strong correlations between serum/plasma concentrations of certain organochlorines are common findings in earlier studies (DeVoto et al. 1997; Gladen et al. 1999; Grimvall et al. 1997; Glynn et al. 2000a), and this may make it difficult to draw correct conclusions about possible casual relationships between the body burden of individual compounds and disease in epidemiologic studies. Despite the strong correlations between a large number of the studied organochlorines, we found inconsistent associations between some of the compounds and single determining factors. This indicates that the complex organochlorine mixture should not be treated as a homogeneous group of compounds in exposure assessment.

Fish, especially fatty fish from the Baltic Sea and the large Swedish lakes, contain high concentrations of PCB and chlorinated pesticides compared with other foods in Sweden (Atuma et al. 1996, 1998; Glynn et al. 2000b). An earlier Swedish study showed that commercial fishermen with a high consumption of contaminated fish (several times per week or day), such as Baltic herring and salmon, have higher plasma concentrations of PCBs and DDT/DDE than do individuals reporting low or normal fish consumption (Asplund et al. 1994). Similarly, among the Swedish women, consumption of fatty fish was positively associated with serum concentrations of several PCB congeners. The adjusted mean concentrations of mono- and di-*ortho* PCBs were 1.2–1.6-fold higher in women eating fatty fish once or more per week than in women reporting no consumption at all.

Our questionnaire contained questions about commonly consumed fatty fish (salmon species, mackerel, and herring). However, the questionnaire was not designed to study fish consumption patterns in detail, and it was not possible to identify the origin of the fish consumed. Our data were also limited by the

Table 4. Percentage change in concentrations of PCB congeners and chlorinated pesticides/metabolites per unit change in age, BMI, and weight.[a]

Compound	Age (% per year of age)	BMI (% per kg/m^2)	Weight (% per kg)
PCB 105	3.7 (2.5–4.9)	2.7 (0.6–4.9)	–7.2 (–12.3–$^{-}$1.8)
PCB 118	3.4 (2.5–4.3)	1.7 (0.1–3.4)	–5.7 (–9.7–$^{-}$1.4)
PCB 138	2.3 (1.4–3.1)	NS	–5.5 (–9.7–$^{-}$1.5)
PCB 153	1.8 (1.1–2.5)	NS	–4.5 (–7.7–$^{-}$1.2)
PCB 156	1.9 (1.2–2.5)	–2.4 (–3.5–$^{-}$1.3)	NS
PCB 167	3.1 (2.2–4.1)	NS	NS
PCB 180	1.4 (0.8–2.0)	–2.3 (–3.4–$^{-}$1.2)	–3.4 (–6.3–$^{-}$0.5)
p,p′-DDE	2.3 (0.9–3.8)	3.9 (1.3–6.6)	–7.2 (–13.8–$^{-}$0.1)
HCB	2.6 (2.0–3.3)	1.1 (0.5–2.3)	–3.2 (–6.2–$^{-}$1.7)
β-HCH	4.3 (3.3–5.2)	3.8 (2.1–5.6)	NS
trans-Nonachlor	2.7 (1.9–3.5)	NS	NS
Oxychlordane	3.3 (2.5–4.2)	NS	NS

NS, not significant. $p > 0.05$, $n = 205$.
[a]Change of geometric means (95% confidence interval) was mutually adjusted for each other and region.

Table 3. Correlation coefficients for correlations among lipid-adjusted serum concentrations of PCB congeners, chlorinated pesticides, and metabolites.[a]

PCB IUPAC no.	118	138	153	156	167	180	DDE	HCB	β-HCH	TN	OC
CB 105	0.84[b]	0.70[b]	0.60	0.45	0.73[b]	0.39	0.59	0.58	0.48	0.62	0.59
CB 118		0.76[b]	0.72[b]	0.56	0.83[b]	0.52	0.60	0.68	0.55	0.67	0.62
CB 138			0.92[b]	0.70[b]	0.79[b]	0.73[b]	0.78[b]	0.67	0.52	0.60	0.68
CB 153				0.83[b]	0.81[b]	0.88[b]	0.65	0.71[b]	0.50	0.60	0.68
CB 156					0.77[b]	0.95[b]	0.35	0.60	0.48	0.64	0.55
CB 167						0.74[b]	0.53	0.76[b]	0.61	0.71[b]	0.62
CB 180							0.40	0.61	0.43	0.60	0.51
DDE								0.48	0.52	0.59	0.54
HCB									0.70[b]	0.64	0.62
β-HCH										0.61	0.63
TN											0.89

Abbreviations: OC, oxychlordane; TN, *trans*-nonachlor.
[a]Correlations were made on log-transformed values and correlation coefficients higher than 0.14 were statistically significant ($p < 0.05$, $n = 205$). [b]Correlation coefficients ≥ 0.70.

possibility of nondifferential measurement error with respect to fish consumption. Errors could be caused by inaccurate recall of past diet or because of changes in diet over time. Factors not included in the study could also be possible sources of variation in our results. Nevertheless, the results are in line with the hypothesis that fatty fish may be an important source of PCB exposure in Sweden.

Surprisingly, fatty fish consumption was not associated with serum concentrations of chlorinated pesticides/metabolites, among them *p,p′*-DDE, even though these compounds are present in high concentrations in fatty fish (Atuma et al. 1996, 1998). In corroboration with our results, a recent study from the United States indicated contaminated fish to be a source of PCB exposure in the general population living in regions with a high environmental load of organochlorines but found no association between DDE and fish consumption (Laden et al. 1999). Similarly, no significant associations between fish consumption and DDE/DDT concentrations in adipose tissue or plasma/serum were found in other studies from Europe and North America (DeVoto et al. 1998; Inmaculada Sanz-Gallardo et al. 1999; Laden et al. 1999). These results suggest that consumption of PCB/DDE-contaminated fish has a larger impact on the PCB body burden than on the body burden of *p,p′*-DDE.

Contrary to our findings, no association was found between fish consumption and PCB concentration in plasma from fishermen's wives living in the same areas as the women in our study (Rylander et al. 1997). Comparisons between studies, however, are complicated by differences in methods of quantification of food consumption. Furthermore, questionnaires can only give rough estimates of the real food habits because it is difficult to provide accurate answers to the questions posed (Rylander et al. 1998).

The adjusted means of CB 153, CB 156, CB 167, CB 180, HCB, and β-HCH concentrations tended to be highest in southern Sweden. It is not possible to draw firm conclusions from our results about the observed regional differences in serum concentrations. The regional distribution of organochlorines may be a result of both point-source pollution and long-range atmospheric transport. A factor that could contribute to clarification of our findings is the higher population density in the southern part of Sweden; not only is it highly industrialized, but it also has a more intensive agricultural industry than do the northern parts of the country. This could lead to a higher environmental load of organochlorines in the south. A few studies have indicated a south–north gradient of decreasing concentrations of PCB in meat products, dairy products, and freshwater fish in Sweden (Bernes 1998; Glynn et al. 2000b; Linder et al. 1982). Moreover, along the eastern coast of Sweden, PCB contamination of fatty fish, such as herring, is higher in the southern Baltic proper than in the northern Gulf of Bothnia (Bernes 1998). Other possible explanations for the observed regional variations are differences in the distribution of compounds in food and differences in food consumption patterns between the studied regions.

Contrary to the higher serum concentrations of some organochlorine compounds in southern Sweden, the adjusted mean concentration of the chlordane metabolite oxychlordane showed an increasing south–north gradient in serum concentrations. Furthermore, several of the PCB congeners and *p,p′*-DDE did not demonstrate significant regional patterns in serum concentrations. These diverging findings indicate differences in geographic dispersion of individual organochlorines in Sweden.

The serum concentrations of all studied compounds increased with age, which is a

Table 5. Organochlorine concentrations in women with or without diabetes.[a]

Compound	Diabetes ($n = 7$) (ng/g lipid)	No diabetes ($n = 198$) (ng/g lipid)	*p*-Value[b]
PCB 105	8 (5–12)	5 (5–6)	0.07
PCB 118	58 (40–84)	40 (38–43)	0.06
PCB 138	115 (82–160)	98 (92–104)	0.35
PCB 153	251 (190–330)	219 (208–230)	0.33
PCB 156	20 (16–26)	18 (17–19)	0.32
PCB 167	11 (8–16)	8 (8–9)	0.10
PCB 180	171 (135–215)	153 (146–160)	0.35
p,p′-DDE	602 (331–1,095)	464 (415–519)	0.39
HCB	85 (66–109)	60 (58–63)	0.008
β-HCH	64 (44–94)	49 (45–52)	0.16
trans-Nonachlor	29 (21–40)	23 (21–24)	0.12
Oxychlordane	17 (12–23)	13 (12–14)	0.12

[a]Adjusted geometric mean (95% confidence interval); results adjusted for region, age, BMI, and weight change; diabetes type not specified. [b]Significance levels represent the overall test of differences in geometrical means.

Table 6. Regional differences in serum organochlorine concentrations among elderly Swedish women.[a]

Compound	Malmö ($n = 57$) (ng/g lipid)	Linköping ($n = 47$) (ng/g lipid)	Uppsala ($n = 62$) (ng/g lipid)	Umeå ($n = 39$) (ng/g lipid)	*p*-Value[b]
PCB 105	5 (4–6)	4 (4–5)	5 (4–6)	6 (5–7)	0.26
PCB 118	44 (39–50)	39 (34–45)	37 (32–41)	44 (38–51)	0.13
PCB 138	110 (98–123)	93 (82–105)	91 (82–102)	102 (89–118)	0.08
PCB 153	247 (225–272)	214 (193–238)	197 (180–216)	223 (199–251)	0.008
PCB 156	22 (20–23)	18 (16–20)	16 (15–18)	17 (16–19)	< 0.001
PCB 167	10 (9–11)	9 (8–10)	8 (7–8)	8 (7–10)	< 0.001
PCB 180	178 (164–192)	151 (138–165)	140 (130–151)	147 (134–162)	0.01
p,p′-DDE	529 (430–649)	406 (324–510)	436 (358–531)	511 (399–656)	0.27
HCB	71 (65–78)	58 (53–64)	55 (51–60)	60 (54–67)	< 0.001
β-HCH	74 (65–84)	47 (41–55)	42 (37–48)	39 (33–46)	< 0.001
trans-Nonachlor	23 (20–25)	21 (19–24)	22 (20–24)	26 (22–29)	0.17
Oxychlordane	12 (11–14)	11 (10–13)	12 (11–14)	16 (14–18)	0.005

[a]Geometric mean (95% confidence interval) adjusted for age, BMI, and weight change. [b]Significance levels represent the overall test of differences in adjusted geometric means between the regions.

Table 7. Serum organochlorine concentrations in women reporting no consumption of fatty fish and in women consuming less than one portion per week or one portion or more per week.[a]

Compound	No consumption ($n = 15$) (ng/g lipid)	< 1/week ($n = 109$) (ng/g lipid)	≥ 1/week ($n = 80$) (ng/g lipid)	*p*-Value[b]
PCB 105	3.6 (2.6–4.9)	5.0 (4.5–5.7)	5.7 (5.0–6.5)	0.03
PCB 118	30 (23–38)	40 (36–44)	45 (40–50)	0.01
PCB 138	84 (66–106)	96 (88–104)	106 (96–118)	0.12
PCB 153	182 (150–220)	212 (198–227)	238 (220–258)	0.01
PCB 156	15 (12–17)	18 (17–19)	19 (18–21)	0.01
PCB 167	6.1 (4.8–7.7)	8.5 (7.8–9.2)	9.1 (8.2–10.0)	0.01
PCB 180	133 (113–157)	150 (142–159)	162 (151–173)	0.06
p,p′-DDE	435 (284–665)	462 (397–536)	479 (401–572)	0.90
HCB	58 (49–70)	59 (56–63)	64 (60–69)	0.23
β-HCH	58 (44–77)	49 (45–54)	47 (42–53)	0.34
trans-Nonachlor	19 (15–24)	22 (21–24)	24 (22–27)	0.12
Oxychlordane	12 (9–15)	13 (12–14)	13 (12–15)	0.62

[a]Geometric mean (95% confidence interval) adjusted for region, age, BMI, and weight change. [b]Significance levels represent the overall test of differences in adjusted geometric means between consumption categories.

common finding in earlier studies (Hunter et al. 1997; Laden et al. 1999; Romieu et al. 2000; Rylander et al. 1997; Wolff et al. 2000b). This increase could be caused by both an age-dependent bioaccumulation of the persistent and lipophilic compounds and a birth cohort effect (Laden et al. 1999); that is, the older women in our study have historically experienced higher exposures than the younger women have.

Our results indicate that there may be compound-specific differences in the modulating effects of BMI on serum organochlorine concentrations. On one hand, the circulating concentrations of CB 105, CB 118, *p,p′*-DDE, HCB, and β-HCH were positively associated with BMI. Serum concentrations of CB 156 and CB 180, on the other hand, were negatively associated with BMI. Associations between organochlorines and BMI may reflect BMI-related alterations in the toxicokinetics of the compounds. Alternatively, a positive association between prolonged high consumption of organochlorine-rich fatty foods and BMI could also be a reason behind the higher serum concentrations of some compounds in women with high BMI.

In several earlier studies of associations between BMI and serum organochlorine concentrations, congener-specific PCB results were not presented, making comparisons with our study difficult. Two studies on women from the United States found a negative association between BMI and serum concentrations of higher chlorinated or total PCB (Wolff et al. 2000a, 2000b), whereas no association was found between total PCB concentration and BMI in two other studies (Hunter et al. 1997; Laden et al. 1999). In one study, where congener-specific analysis was performed, concentrations of total PCB and PCB 138 were inversely related to BMI (Dorgan et al. 1999). The positive association between *p,p′*-DDE concentrations and BMI found in our study is consistent with the results in some of the U.S. studies (Hunter et al. 1997; Schildkraut et al. 1999; Wolff et al. 2000a), whereas other studies found no associations (Dorgan et al. 1999; Laden et al. 1999; Wolff et al. 2000b).

The negative associations between recent weight change (preceding 3 months) and serum concentrations of several PCB congeners and chlorinated pesticides among the Swedish women indicate that disease- or treatment-induced weight change may affect the serum concentrations of organochlorines. An earlier study failed to find associations between weight change the past year and serum concentrations of *p,p′*-DDE among women from the United States (Schildkraut et al. 1999). However, Danish women who lost weight between two blood samplings experienced a slower decline in serum concentrations of β-HCH, PCB, and *p,p′*-DDE than expected, whereas weight gain resulted in a faster decline (Hoyer et al. 2000). In accordance with our results, a few experimental studies have shown that rapid weight loss may cause increased serum concentrations of PCB (Chevrier et al. 2000; Imbeault et al. 2001; Walford et al. 1999). Taken together, the results indicate a mobilization of the compounds into the circulation during weight loss and a "dilution" of serum concentrations during weight gain.

More than 20% of the variation of HCB concentrations in serum could be explained by diabetes, after adjustment for the other determining factors. Our finding could be due to chance because only seven women had diabetes. The positive associations between the other studied organochlorines and diabetes were not statistically significant. A recent study, however, found a positive association between serum concentrations of PCBs and type 1 diabetes among pregnant women in the United States (Longnecker et al. 2001), supporting the possibility that diabetes may affect serum organochlorine concentrations. This hypothesis should be addressed in epidemiologic studies of organochlorines as risk factors for diabetes (Cranmer et al. 2000; Steenland et al. 2001).

Conclusion

Some of the lifestyle/medical factors studied may confound associations between serum concentrations of organochlorines and disease in epidemiologic studies, in cases when these factors are also related to the specific disease studied. For instance, age and BMI, which were significantly associated with serum organochlorine concentrations, are risk factors for several diseases. The results also highlight the possibility that disease itself may alter the toxicokinetics and/or distribution of certain organochlorines. We found negative associations between weight change, which could be induced by disease or medical treatment, and concentrations of several PCB and pesticide/metabolite compounds. Furthermore, higher HCB concentrations were indicated in women with diabetes mellitus. Concentrations of PCBs and pesticides/metabolites were positively correlated with each other in all cases. Nevertheless, some of studied organochlorines showed inconsistent associations with single determining factors, indicating that the complex organochlorine mixture should not be treated as a homogeneous group of compounds in epidemiologic studies.

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