Polychlorinated Biphenyls in Blood Plasma among Swedish Female Fish Consumers in Relation to Low Birth Weight

Lars Rylander, Ulf Strömberg, Eva Dyremark, Conny Östman, Peter Nilsson-Ehle, and Lars Hagmar

The authors examined the hypothesized association between the body burden of polychlorinated biphenyls (PCB) in women and the risk of low birth weight for their infants. In Sweden, a main exposure route for PCBs and other persistent organochlorine compounds is through the consumption of fatty fish from the Baltic Sea (on the Swedish east coast). A previous comparison between a cohort of consumers of large quantities of fish from the Swedish east coast and a reference population, together with a following analysis based on questionnaire data from a case-control study within the east coast cohort, supported the hypothesized association. In 1995, blood samples were collected from the wives and ex-wives of fishermen from the Swedish east coast (n = 192) who had given birth during the period 1973–1991. Cases (n = 57), i.e., infants with low birth weight (1,500–2,750 g), were matched with controls (n = 135; birth weight, 3,250–4,500 g) on gender, parity, and calendar year of birth. The concentration of 2,2',4,4',5,5'-hexachlorobiphenyl (CB-153) in plasma was analyzed; it has been suggested that CB-153 is a relevant biomarker of exposure to PCBs. The concentration of CB-153 in the plasma of mothers during the year of childbirth was "estimated" using some alternative plausible kinetic models. For two alternative estimated exposure datasets, which were focused on separately, an increase in the risk of a low birth weight was observed at a CB-153 concentration of 300 and 400 ng/g lipid weight, respectively (adjusted odds ratios of 2.1 (95% confidence interval (CI) 1.0–4.7) and 2.3 (95% CI 0.9–5.9)). The present results strengthen the findings reported previously for this study population. Am J Epidemiol 1998;147:493–502.

Exposure to persistent organochlorine compounds, such as polychlorinated biphenyls (PCB), polychlorinated dibenzo-p-dioxins (PCDD), and polychlorinated dibenzofurans (PCDF) have, in experimental animal studies as well as in human studies, indicated reproductive disturbances (1–3). Among the reproductive effects reported are decreased birth weight, retarded growth, altered activity levels, impaired learning, and delay in psychomotor development.

In Sweden, the main exposure route for persistent organochlorine compounds is through consumption of fatty fish from the Baltic Sea, on the eastern coast of Sweden (4–6). The wives and ex-wives of fishermen from the Swedish east and west coasts have reported that they consume more than twice as much fish than women from the general population (7, 8). The fish from the western coast of Sweden are, however, much less contaminated with persistent organochlorine compounds (9). This, taken together with a reasonable socioeconomic comparability of the groups, suggest that these women constitute proper study populations.

In a previous cohort study we have shown that infants born to the wives of fishermen from the Swedish east coast during the period 1973–1991 had a higher frequency of low birth weight compared with infants born to wives of fishermen from the Swedish west coast (7). Furthermore, a first analysis of a nested case-control study, within the cohort of infants born to wives of fishermen from the Swedish east coast, indicated an increased risk of low birth weight among infants born to mothers who reported a relatively high intake of fish from the Baltic Sea, as well as among infants born to mothers who had grown up in a fishing village (10). Because the children studied were born in the period 1973–1991, retrospective exposure assessments were of interest. No clear association was
observed for the recalled estimated intake of fish for the time period during which the infant was born. The reliability of such long-term dietary recall is, however, not satisfactory (11). This stresses the importance of supplementing interview data with exposure estimates based on persistent biomarkers of fish consumption.

Evidence for the use of 2,2',4,4',5,5'-hexachlorobiphenyl (CB-153, International Union of Pure and Applied Chemistry (IUPAC) number) as a marker for "dioxin-like" congeners of PCBs, and, under certain restrictions, also for total toxic equivalents (including PCDDs and PCDFs) in biotic samples, has been provided (1, 4). In a study of 50 wives of fishermen from the Swedish east coast (a subset of the women in our present study), the correlation coefficient between CB-153 in plasma and the total PCB-toxic equivalent was 0.91 (12). Moreover, in the same study, the plasma concentration of CB-153 and the sum of all 14 analyzed chlorinated biphenyls (CBs) in plasma was highly correlated (r = 0.99).

When the current CB-153 concentration is used to estimate past CB-153 concentration, it is important to account for certain factors. Bühler et al. (13) estimated the half-life of CB-153 to be about 11 months when a single dose of a PCB mixture was orally ingested by a volunteer. However, the biologic half-life of CB-153 under prolonged exposure in humans is unknown. Based on experimental animal studies (14, 15) and analyses among long-term exposed participants in Operation Ranch Hand in Vietnam (16), there is circumstantial evidence for a longer half-life for CB-153 in humans under prolonged exposure.

It is important to address the decreasing concentration of PCBs in fatty fish from the Baltic Sea over the last decades when interpreting the present CB-153 concentrations in plasma. According to data presented by Bignon et al. (17), a yearly decrease between 3 and 5 percent seems a reasonable assumption.

Another aspect that has to be considered when assessing PCB exposure in women is that lactation probably substantially decreases the body burden. Only limited quantitative information is available; according to data from Skaare and Polder (18) a reduction of the body burden by a third for each lactation period seems to be a reasonable approximation. The most marked decline in PCB concentration was seen during the first weeks of lactation.

The aim of the present analysis in the nested case-control study was to assess the association between body burden of PCBs in women and the risk of low birth weights for their infants, using CB-153 in plasma as a relevant biomarker.

**MATERIALS AND METHODS**

**Study base**

A cohort of women who are, or were, married to fishermen from the Swedish east coast was established by linkage to the national Swedish population register and to registers at local parish offices (7). These women were linked to the Swedish Medical Birth Register (19). During the period 1973–1991, 757 women in the cohort had given birth to 1,501 infants.

**Cases**

In the cohort, 89 “case mothers” had, during the period 1973–1991, given birth to an infant who fulfilled the following criteria: singleton, birth weight within the interval 1,500–2,750 g, and without any major malformation (10). If a mother had given birth to more than one infant with low birth weight, only the infant born first was eligible as a case. Of the 72 case mothers who were involved in our previous analysis (10), 57 (79 percent) took part in the present study (table 1).

**Controls**

The potential control mothers had given birth to an infant who fulfilled the following criteria: singleton, birth weight within the interval 3,250–4,500 g, and without any malformation (10). Originally, two controls (referring to infants) were matched to each case according to gender, parity (1, 2, or ≥3), and calendar year of birth (± 5 years). Among the 162 control mothers who were involved in the previous analysis, 135 (83 percent) took part in the present study (table 1). Due to nonparticipant case mothers, controls were reallocated according to the matching criteria. This procedure resulted in five matched sets with one control, 32 sets with two controls, 14 sets with three controls, and six sets with four controls. For two of the included controls, however, it was impossible to fulfill the matching criteria; their and the corresponding cases’ calendar years of birth differed by 7 and 8 years, respectively.

**Blood sampling**

From the 192 women studied, venous blood was drawn in 1995 from a cubital vein and collected in metal-free evacuated tubes (Venoject (Terumo Europe n.v., Leuven, Belgium)) with heparin as the anticoagulant. The plasma was stored at 4–8°C for a maximum of 72 hours before it was deep-frozen in ethanol-washed glass bottles and stored at −70°C until the analyses were performed. All samples were sent coded to the analytic laboratory.

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### TABLE 1. Background characteristics of cases, controls, and their respective mothers married to fishermen from the Swedish east coast

<table>
<thead>
<tr>
<th>Participants</th>
<th>Case (n = 57)</th>
<th>Control (n = 135)</th>
<th>No.</th>
<th>%</th>
<th>Median</th>
<th>Range</th>
<th>No.</th>
<th>%</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of lactation periods</td>
<td>24</td>
<td>42</td>
<td>57</td>
<td>42</td>
<td>5</td>
<td>33</td>
<td>8</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of lactation (months)*</td>
<td>14</td>
<td>25</td>
<td>34</td>
<td>25</td>
<td>4</td>
<td>27</td>
<td>9</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years since last lactation*</td>
<td>19</td>
<td>33</td>
<td>44</td>
<td>33</td>
<td>6</td>
<td>40</td>
<td>10</td>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>28</td>
<td>49</td>
<td>60</td>
<td>44</td>
<td>6</td>
<td>40</td>
<td>12</td>
</tr>
<tr>
<td>Maternal education</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>18</td>
<td>29</td>
<td>33</td>
<td>24</td>
<td>2</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Maternal age in 1995</td>
<td>5</td>
<td>7</td>
<td>13</td>
<td>27</td>
<td>47</td>
<td>58</td>
<td>43</td>
<td>7</td>
<td>47</td>
<td>16</td>
</tr>
<tr>
<td>Smoking habits during year of childbirth (cigarettes/day)</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>19</td>
<td>33</td>
<td>27</td>
<td>20</td>
<td>5</td>
<td>33</td>
<td>11</td>
</tr>
<tr>
<td>No.</td>
<td>%</td>
<td>Median</td>
<td>Range</td>
<td>No.</td>
<td>%</td>
<td>Median</td>
<td>Range</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>%</td>
<td>Median</td>
<td>Range</td>
<td>No.</td>
<td>%</td>
<td>Median</td>
<td>Range</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal education</td>
<td>21</td>
<td>37</td>
<td>46</td>
<td>34</td>
<td>5</td>
<td>33</td>
<td>14</td>
<td>52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td>21</td>
<td>37</td>
<td>83</td>
<td>47</td>
<td>10</td>
<td>67</td>
<td>9</td>
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<tr>
<td>Maternal education</td>
<td>15</td>
<td>29</td>
<td>25</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Includes the case mothers (n = 56) and control mothers (n = 132) with at least one lactation period.
In Sweden, blood sera have been collected at antenatal clinics in a rubella-screening program. In certain geographic regions these samples have systematically been stored for years. For 20 (two case and 18 control) mothers in the present study it was possible to obtain deep-frozen blood sera from a pregnancy during the time period 1975-1991 (median 1987; for 11 of the 20 women, blood sera were obtained from a pregnancy not included in the present study). The median age of the women in the rubella screening was 28 (range 17–38) years.

Determination of CB-153

Analyses were performed using 0.5–3 g of plasma or serum. Internal standards, 2,3,3’,5’-tetrachlorobiphenyl (CB-58) and 2,2’,3,3’,4,5,5’,6-octachlorobiphenyl (CB-198), respectively, were added prior to clean-up.

The samples were extracted two times with 3 ml of hexane:methyl-tert-butyl ether, 1:1, and subsequently with 3 ml of hexane. Formic acid, 1.5 ml, was added at the first extraction as a denaturing agent.

The combined organic phase was concentrated and subsequently purified on two open columns, each packed with 1.5 g of silica gel 60 (Merck, Darmstadt, Germany) and eluted with 10 ml of hexane. The silica gel was cleaned by Söhxlet extraction in dichloromethane (Merck, distilled in house) and activated at 350°C, followed by deactivation with 10 percent of water (w/w) prior to use.

The final analysis was performed by gas chromatography-electron capture detection on a Varian 3400 instrument (Varian, Walnut Creek, California) using a Rtx-5 column (60 m × 0.25 mm, degrees of freedom = 0.25 μm) (Restek, Bellefonte, California). Hydrogen was used as carrier gas and nitrogen as make-up gas. The injector, operated in splitless mode, and the detector were set to 280°C and 310°C, respectively. Formic acid, 1.5 ml, was added prior to clean-up.

The samples were extracted two times with 3 ml of hexane:methyl-tert-butyl ether, 1:1, and subsequently with 3 ml of hexane. Formic acid, 1.5 ml, was added at the first extraction as a denaturing agent.

Determination of lipids by enzymatic methods

For the 192 blood samples collected in 1995, plasma concentrations of triglycerides, cholesterol, and phospholipids were determined by enzymatic methods using reagents from Boeringer-Mannheim (Mannheim, Germany) (triglycerides and cholesterol) and Waco Chemicals GmbH (Neuss, Germany) (phospholipids). The total lipid concentration in plasma was calculated by summation of the amounts of triglycerides, cholesterol, and phospholipids. In these calculations, the average molecular weights of triglycerides and phospholipids were assumed to be 807 and 714, respectively. For cholesterol, an average molecular weight of 571 was used, postulating that the proportion of free and esterified cholesterol in plasma was 1:2.

Additional data collection

When the blood samples were taken, information on the mothers’ lactation history and smoking habits during the calendar year of childbirth were obtained by means of an interview (table 1).

Statistics

Among the 20 mothers from whom sera at the rubella screening was obtained, the agreement between the fresh-weight concentration of CB-153 in plasma drawn in 1995, and at the rubella screening was calculated by the weighted kappa statistic (20), using three categories (700, 701-1,200, and >1,200 pg/g plasma). We also analyzed data, without applying any categorization, by statistics based on pairwise differences between individual CB-153 concentrations. Moreover, based on the concentration of CB-153 in 1995, we estimated the concentration level of CB-153 for each woman in the year of rubella screening from models that accounted for the impact of elimination rates during lactation and nonlactation periods, and the decrease of CB-153 concentration in fatty fish from the Baltic Sea over calendar time. Due to the limited knowledge about the impact of these factors on the kinetics of CB-153, we performed calculations based on different assumptions: 25, 33, 50, and 67 percent reduction of body burden of CB-153 in plasma at each period of lactation; 1, 5, 10, 15, and 20 years biologic half-lives of CB-153 during nonlactation time periods; 1, 3, 5, 8, and 10 percent yearly reduction of CB-153 in the fish. The model can partly be expressed as:

\[
CB-153(y) = A(y) \times (1 - \exp(-B \times y)),
\]

where \(CB-153(y)\) denotes the concentration (fresh-weight: pg/g; lipid-adjusted: ng/g) in calendar year \(y\), \(A(y)\) denotes the steady state concentration (which depends on \(y\), since the PCB contamination of fish decreases over the calendar years), and \(B = \ln(2)/t_{1/2}\) where \(t_{1/2}\) denotes the assumed half-life of CB-153 during nonlactating periods. In addition, the model...
accounts for "momentary" reductions of CB-153 due to lactations. Figure 1 illustrates the model for back-calculation of CB-153. The agreement between the estimated and measured CB-153 in the year of rubella screening was also assessed.

The odds ratio, adjusted for (in addition to the matching factors) maternal age and smoking habits during year of childbirth, was used for measuring the effect of exposure to CB-153 on low birth weight. The measured concentration of CB-153 in 1995, and the estimated concentration in the year of childbirth obtained under some alternative models (as described above), were considered as exposure variables. These were analyzed as continuous as well as categorized variables. The effect estimation was performed by means of conditional logistic regression (21).

RESULTS

Agreement between estimated and measured CB-153 concentrations

The agreement between the CB-153 concentrations in the 1995 samples and in the rubella screening samples was fair ($\kappa = 0.30$) (figure 2). The estimated concentrations at the year of rubella screening, based on several different model assumptions, gave higher $\kappa$ values with respect to measured concentrations in the rubella screening samples (table 2). Figure 2 demonstrates an improved agreement by estimating the concentrations using a plausible kinetic model. Even though the $\kappa$ values, as well as the statistics based on individual differences, differed somewhat for the different model assumptions, the agreement improved significantly when using the plausible kinetic model.
TABLE 2. Agreement between the concentrations of CB-153* in the rubella screening samples and the estimated concentrations of CB-153 in plasma during year of rubella screening (n = 20), based on 1995 data of women married to fishermen from the Swedish east coast

<table>
<thead>
<tr>
<th>Biological half-life of CB-153 (years)</th>
<th>Reduction in body burden of CB-153 at each period of lactation (%)</th>
<th>Yearly reduction of CB-153 in the fish (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>x† Mean† SD*†</td>
<td>x† Mean† SD†</td>
</tr>
<tr>
<td>1</td>
<td>25</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>0.47</td>
</tr>
<tr>
<td>1</td>
<td>33</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>0.53</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0.60</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>0.66</td>
</tr>
</tbody>
</table>

* CB-153, 2,2',4,4',5,5'-hexachlorobiphenyl; SD, standard deviation.
† Weighted kappa statistic based on the categories: ≤700, 701-1,200, and >1,200 pg/g.
‡ Statistics based on individual differences on continuous data.

ferent models applied, a fairly wide range of assumptions implied similar agreements (table 2). However, a yearly reduction of CB-153 in fish of more than 5 percent led to worse agreement (data not shown). Moreover, biologic half-lives of CB-153 longer than 15 years, and higher than 50 percent reductions of body burden at each lactation period, did not improve the agreement.

In the following we focus on two alternative sets of assumptions: a 3 or 5 percent yearly reduction of CB-153 in fish, a 33 percent reduction of body burden of CB-153 at each period of lactation, and a 5-year half-life of CB-153 during nonlactating periods. We also briefly report on how robust the results are to variation in these model assumptions.

Measured CB-153 concentrations

The median concentration in 1995 of fresh-weight CB-153 in plasma was, for the whole study group (n = 192), 940 (range 80-4,300) pg/g. The case mothers had a higher median concentration than the control mothers (median concentrations were 1,000 (range 290-3,960) pg/g and 920 (range 80-4,300) pg/g). Also, for the lipid-adjusted concentrations of CB-153, a higher median concentration was seen among the case mothers (190 versus 160 ng/g lipid) (table 3). The lipid-adjusted concentrations were strongly correlated with the fresh-weight concentrations (r = 0.92).

Among the 20 women from whom blood samples at the time of rubella screening were available, the median fresh-weight concentration of CB-153 in serum

<table>
<thead>
<tr>
<th>Lipid-adjusted CB-153 (ng • g⁻¹)</th>
<th>Case mothers (n = 57)</th>
<th>Control mothers (n = 135)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration in 1995</td>
<td>Median Range</td>
<td>Median Range</td>
</tr>
</tbody>
</table>
| Estimated concentration during year of childbirth
  33% reduction of body burden at each period of lactation and a 5-year biologic half-life during nonlactating periods
  3% yearly reduction in the fish
  5% yearly reduction in the fish
| 300 60-1,250 240 30-1,020      | 250 70-1,870 310 30-1,500 |

* CB-153, 2,2',4,4',5,5'-hexachlorobiphenyl.
was 1,050 (range 260–3,000) pg/g. For these women, in 1995, the median concentration of CB-153 in plasma was 700 (range 210–1,900) pg/g. However, for seven of the 20 women the concentration was higher in the 1995 sample.

### Estimated concentrations of CB-153 in plasma during the year of childbirth

The estimated median concentration of lipid-adjusted CB-153 in plasma during the year of childbirth was higher in the case mothers compared with the control mothers under the alternative models of interest (table 3).

Naturally, the magnitude of the estimated concentrations of CB-153 during the year of childbirth became higher under models assuming a relatively low reduction of body burden at each period of lactation, a relatively high yearly reduction of CB-153 in the fish, or a relatively long biologic half-life of CB-153 during nonlactating time periods.

### Lipid-adjusted concentration of CB-153 in plasma and low birth weight

After adjustment for maternal age and smoking habits during the year of childbirth, the concentration of plasma CB-153 in the 1995 samples, considered as a linear continuous variable, implied an odds ratio of 1.18 per 100 ng/g increase (95 percent confidence interval (CI) 0.86–1.63). When the exposure variable was dichotomized, a concentration of at least 200 ng/g lipid gave an odds ratio of 1.8 (95 percent CI 0.8–4.0) (table 4). Thus, the data indicated a threshold effect rather than a linear relation between the log-odds and the CB-153 concentration.

Similarly, when the CB-153 concentration during year of childbirth was estimated under the models of interest, the continuous exposure variables did not imply a positively linear relation. We also categorized the exposure variables. The cutoffs of the estimated CB-153 concentration that indicated an increased risk were 300 or 400 ng/g lipid (odds ratios of 2.1 (95 percent CI 1.0–4.7) or 2.3 (95 percent CI 0.9–5.9)) (table 4). Indeed, the exposure dichotomizations of the cases and controls based on measured and estimated CB-153 concentrations, respectively, were fairly similar, although the relevant cutoffs differed.

Other assumptions of the biologic half-life of CB-153 during nonlactating periods, implied similar risks of a low birth weight at CB-153 concentrations around 300–400 ng/g lipid (odds ratios between 1.8 and 2.3, 95 percent CIs 0.8–4.0 and 0.8–5.9).
with lower 95 percent confidence limits between 0.8 and 1.0). Moreover, other assumptions of yearly reduction of CB-153 concentration in fish and reduction of maternal body burden of CB-153 at each period of lactation implied fairly similar effect estimates.

Additional product terms between estimated CB-153 concentration (provided from the models focused on), on the one hand, and parity, gender of the infant, calendar year of childbirth, maternal age, or smoking during the year of childbirth, respectively, on the other, did not significantly improve the fits of the logistic models ($p > 0.10$, likelihood ratio test). Hence, there was no clear evidence of effect modification.

When the datasets were analyzed using an unmatched design, the results were not noticeably affected.

**DISCUSSION**

The main finding of the present study was that a relatively high prenatal exposure to CB-153 was associated with an increased risk for low birth weight. Incorporation of a dichotomous exposure variable into the logistic model generally revealed an increased risk, in contrast to continuous (not transformed) exposure variables. Thus, the results may suggest a threshold effect, both when the measured CB-153 concentrations in plasma in the 1995 samples and when the estimated concentrations during the year of childbirth were considered as the exposure variable. The results indicated an increased risk of a low birth weight at 300–400 ng/g lipid with respect to estimated concentrations of CB-153 in plasma during the year of childbirth, obtained under some biologically plausible assumptions.

In the previous case-control study, the response rate was somewhat lower for case mothers than for control mothers (10); the fractions of mothers who also participated in the present investigation (i.e., who donated blood samples) were similar among the case and control mothers (about 80 percent), respectively. The educational levels were lower among both nonparticipating case and control mothers (table 1). On the other hand, based on data from the previous analysis (10), the fractions of nonsmokers among participating and nonparticipating mothers were almost the same (data not shown). In addition, the age distributions were similar among participants and nonparticipants.

We have, in a previous analysis of this case-control study using "estimated fish consumption" as well as "grown up in a fishing village" as the exposure measure, observed no distinct differences in the odds ratio estimates for low birth weight as compared with small for gestational age (10). The lack of precision in the Swedish Medical Birth Register for gestational length made such a discrimination difficult (19). It should be noticed, on the other hand, that the register quality of birth weight, which is used in the analysis, is good. Thus, misclassification of the employed outcome variable was not a problem.

In our previous cohort study, low birth weight was considered to be <2,500 g, as well as <3,000 g (7). We chose 1,500–2,750 g as the case definition in our following case-control study, which gave a sufficient number of cases. The birth weight interval of the controls was set to 3,250–4,500 g, rather than 2,750–4,500 g, in order to avoid adjacent outcome categories and, presumably, design a more efficient study (by assuming that the true odds ratio was thereby increased).

The precision of the concentrations of CB-153 in plasma in the 1995 samples was good. We also estimated the concentrations of CB-153 in plasma during the year of childbirth from models that accounted for the impact of influential factors. Due to the limited knowledge about the magnitude of such factors, there may have been a negative impact on precision, as well as accuracy, of estimated CB-153 concentrations. For validation of the estimated concentrations obtained from these models, the agreement between estimated and measured CB-153 concentrations in the year of rubella screening was assessed, based on a subset ($n = 20$) of study participants. This validation, however, had some shortcomings. 1) The concentrations of CB-153 in the samples obtained in the year of rubella screening were all determined from small amounts of sera, which might have decreased the precision of the laboratory analysis. 2) Even though lipid adjustment improves the comparability, it was only feasible to perform the comparisons between concentrations of fresh-weight CB-153. The fresh-weight and lipid-adjusted concentrations of CB-153 in the 1995 plasma samples, however, were highly correlated ($r = 0.90$; $n = 20$). 3) The obtained sera samples from the rubella screenings were mainly from the latter part of the study period, which made validation of the estimated concentrations during the earlier part of the study period impossible. 4) We disregarded data on individual fish consumptions when developing the kinetic models because these data were not sufficiently reliable (11) and, therefore, the exposure assessments based on CB-153 concentrations were aimed to be independent of reported fish consumption. An assumption on constant fish consumption over calendar time underlies the kinetic models considered. Such a restriction may be important in contributing to the lack of agreement. Despite these shortcomings, a better agreement was obtained for the comparison between
PCBs can have an even more long-term impact on intellectual functions (28); at 11 years of age, the most highly prenatally PCB-exposed children were about three times as likely to have a low average intelligence quotient score and about twice as likely to be at least 2 years behind in reading comprehension. In the Lake Michigan studies, the mean concentration of total PCBs in maternal serum samples was 5.5 ng/ml (standard deviation = 3.7) (25). The concentrations of total PCBs were not assessed in the present study. However, for 50 of the mothers in the present study, concentrations of 14 specific PCB congeners in plasma were assessed (12). The range of the sum of these CBs (1.0–10.7 ng/g) was very similar as compared with those for the Lake Michigan mothers. Due to differences in the analytic methods, the comparison, however, should be interpreted with some caution.

The median concentration of CB-153 in plasma among the wives of fishermen from the Swedish east coast was similar to the mean of the blood plasma concentration of CB-153 in samples collected from a group of women in the Netherlands during their last month of pregnancy (29). In the Netherlands study, subtle signs of neurologic dysfunctioning and a small delay in psychomotor development, together with a lower birth weight, were associated with prenatal exposure to persistent organochlorine compounds (30, 31). On the other hand, in a study on the general population in North Carolina, prenatal persistent organochlorine compound exposure was not associated with birth weight but with subtle neurologic developmental effects in infants up to 2 years of age (32, 33).

Our study is retrospective in design, and, therefore, does not allow a direct assessment of subtle neurologic developmental outcomes. Such an evaluation requires a prospective study with neuropsychologic tests at certain points in time. The observation made in most of the previous studies that prenatal persistent organochlorine compound exposure implied both subtle neurologic developmental deficits and low birth weight, is, however, noteworthy.

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