A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP553.

Prenatal and Postnatal PCB-153 and *p,p′*-DDE Exposures and Behavior Scores at 5–9 Years of Age among Children in Greenland and Ukraine

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Background: Studies have reported some evidence of adverse effects of organochlorine exposures on child development, but the results have been inconsistent, and few studies have evaluated associations with child behavior.

Objective: We investigated the association between prenatal and early-life exposures to 2,2′,4,4′,5,5′-hexachlorobiphenyl (PCB-153) and 1,1-dichloro-2,2-bis(*p*-chlorophenyl)-ethylene (*p,p′*-DDE) and behaviors in children between 5 and 9 y of age.

Methods: In the Biopersistent organochlorines in diet and human fertility: Epidemiologic studies of time to pregnancy and semen quality in Inuit and European populations (INUENDO) cohort, consisting of mother–child pairs from Greenland and Ukraine ($n = 1{,}018$), maternal serum PCB-153 and *p,p′*-DDE concentrations were measured during pregnancy, and cumulative postnatal exposures during the first 12 months after delivery were estimated using a pharmacokinetic model. Parents completed the Strengths and Difficulties Questionnaire (SDQ), and children's behaviors were dichotomized as abnormal (high) versus normal/borderline for five SDQ subscales and the total difficulties score.

Results: The total difficulties score, an overall measure of abnormal behavior, was not clearly associated with pre- or postnatal exposures to PCB-153 or to *p,p′*-DDE. However, pooled adjusted odds ratios (ORs) for high conduct problem scores with a doubling of exposure were 1.19 (95% CI: 0.99, 1.42) and 1.16 (95% CI: 0.96, 1.41) for pre- and postnatal PCB-153, respectively, and 1.25 (95% CI: 1.04, 1.51) and 1.24 (95% CI: 1.01, 1.51) for pre- and postnatal *p,p′*-DDE, respectively. Corresponding ORs for high hyperactivity scores were 1.24 (95% CI: 0.94, 1.62) and 1.08 (95% CI: 0.81, 1.45) for pre- and postnatal PCB-153, respectively, and 1.43 (95% CI: 1.06, 1.92) and 1.27 (95% CI: 0.93, 1.73) for pre- and postnatal *p,p′*-DDE, respectively.

Conclusion: Prenatal and early postnatal exposures to *p,p′*-DDE and PCB-153 were associated with a higher prevalence of abnormal scores for conduct and hyperactivity at 5–9 y of age in our study population. These findings provide further support for the importance of minimizing organochlorine exposures to young children and to women of childbearing age. https://doi.org/10.1289/EHP553

Introduction

Polychlorinated biphenyls (PCBs) have been widely used in, for example, hydraulic equipment, dyes, plasticizers, capacitors, transformers and flame retardants. Dichlorodiphenyltrichloroethane (DDT) has been used primarily as a pesticide and for vector control. Even though PCBs and DDT were banned from use in most Western countries in the 1970s and 1980s, DDT continues to be used for disease vector control in some developing countries (van den Berg 2009), and both are persistent and ubiquitous substances found in the environment (Ibarluzea et al. 2011).

The main exposure routes of organochlorine compounds such as PCBs and DDT and its breakdown product dichlorodiphenyldichloroethylene (DDE) are through food consumption and breastfeeding, and given their lipophilic properties and long half-lives of 5 to 10 y, they bioaccumulate within human adipose tissue (Glynn et al. 2007; Malarvannan et al. 2013; Ribas-Fitó et al. 2005). These compounds may also cross the placental barrier, potentially resulting in fetal exposures decades after maternal exposure (Glynn et al. 2007; Vizcaino et al. 2014). Environmental pollutants such as pesticides, solvents, and organochlorines may act as developmental neurotoxins, inducing brain injury during early-life development at doses much lower than those required for adverse effects in adults, with potential long-term implications for the child (Grandjean and Landrigan 2006; Rosas and Eskenazi 2008).

Based on concentrations measured in cord serum, prenatal exposures to PCBs and DDE were found to be associated with attention deficit hyperactivity disorder (ADHD)-related behaviors in 573 U.S. children at 8 y of age (Sagiv et al. 2010). Verner et al. (2015) used a pharmacokinetic model to estimate postnatal exposures in the same cohort and reported positive associations between postnatal PCB exposures and ADHD-related behaviors that were weaker than associations with prenatal exposures. PCB concentrations in maternal blood samples were also negatively associated with attention deficit disorders in 117 German children at 8–9 y of age (Neugebauer et al. 2015). However, other studies have not found associations between behavior outcomes and PCB or DDE exposures (Grandjean et al. 2012; Ribas-Fitó et al. 2007b; Strøm et al. 2014).

In the present prospective cohort study, we investigated associations between prenatal and early-life exposures to organochlorine compounds, specifically 2,2′,4,4′,5,5′-hexachlorobiphenyl (PCB-153) and 1,1-dichloro-2,2-bis(*p*-chlorophenyl)-ethylene (*p,p′*-DDE), and abnormal behavior scores among children at 5–9 y of age.

Methods

Study Population

The study population consisted of mother–child pairs from the Biopersistent organochlorines in diet and human fertility:

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Supplemental Material is available online (https://doi.org/10.1289/EHP553).

The authors declare they have no actual or potential competing financial interests.

Received 24 May 2016; Revised 29 August 2017; Accepted 29 August 2017; Published 3 October 2017.

Epidemiologic studies of time to pregnancy and semen quality in Inuit and European populations (INUENDO) birth cohort. The target population was pregnant women attending antenatal care visits between May 2002 and February 2004 at three hospitals and eight antenatal clinics in Kharkiv, Ukraine, and at 19 local hospitals in municipalities and settlements in Greenland. Ukraine was chosen because of recent agricultural organochlorine pesticide use, and Greenland was chosen owing to a diet with a high bioaccumulation of organochlorines. Furthermore, women from Warsaw, Poland, were included in the cohort as a reference population, but given the low participation rate at follow-up ($n = 92$), these women were not included in the main analyses of this study. Women were eligible for the study if they were pregnant (regardless of the week of gestation), ≥18 y of age, and born in the country where they were being recruited. Neither paternal participation nor a successful delivery was required to be eligible for the cohort. At baseline, 1,238 women were enrolled, with a participation rate (out of all potentially eligible women in each respective subcohort, including women who declined to provide a blood sample) of 90% in Greenland and 26% in Ukraine. After providing informed consent, enrolled women were interviewed and had a venous blood sample drawn. Further details on the baseline study population are available elsewhere (Toft et al. 2005).

A follow-up study was conducted between January 2010 and May 2012, when the children were 5–9 y of age (Høyer et al. 2015). Parents or guardians responded to retrospective questions concerning behavioral development and other characteristics in a face-to-face interview or by filling in a questionnaire themselves. Out of the women participating at baseline, the follow-up participation rate was 88% in Greenland and 77% in Ukraine. The decision to participate at both baseline and follow-up was made without personal knowledge of the exposure levels.

Mother–child pairs that completed follow-up were included in the present analysis if the child was a singleton birth and the blood sample collected at enrollment was sufficient to measure the exposures of interest ($n = 1{,}018$). The study population was evenly distributed between Greenland (52%) and Ukraine (48%).

Ethics

The study was approved by local ethics committees: the Ethical Committee for Human Research in Greenland (approval no. 2010-13), and the Commission on Ethics and Bioethics Kharkiv National Medical University in Ukraine (protocol no. 7, 7 October 2009). The storage and use of data are registered at the Danish Data Protection Agency. All participants signed an informed consent prior to study enrollment at baseline as well as at follow-up.

Prenatal Exposure

The median gestational week of baseline enrollment and blood sample collection (10th–90th percentile) was 25 (13–37) in Greenland and 23 (9–40) in Ukraine. Cubital vein blood samples were drawn into 10-mL vacuum tubes without additives (Becton Dickinson) for serum collection. Sera were stored at −20°C until shipment. After arrival at the Department of Occupational and Environmental Medicine in Lund, Sweden, sera were stored at −80°C until analysis within one year after sample collection.

Maternal serum concentrations of PCB-153 and *p,p′*-DDE were analyzed using gas chromatography–mass spectrometry following solid-phase extraction. PCB-153 was chosen as a proxy for PCB exposure because it is strongly correlated with other PCB congeners and has a long half-life in humans (DeVoto et al. 1997; Muckle et al. 2001; Ritter et al. 2011). The levels of PCB-153 and *p,p′*-DDE were adjusted for lipids based on serum concentrations of cholesterol and triglycerides determined using enzymatic methods (Rylander et al. 2006).

The limits of detection (LODs) were 0.05 ng/mL for PCB-153 and 0.1 ng/mL for *p,p′*-DDE. For PCB-153, 24 samples were below the LOD, and for *p,p′*-DDE, nine samples were below the LOD. When concentrations were below the LOD, they were set to half of the LOD based on fresh-weight concentrations and adjusted for lipids for all subsequent analyses. For each blood sample, analyses were performed twice on different days, and the mean concentration of the two was used. If the difference between the two samples was >30%, a third, and if necessary, a fourth, reanalysis was performed, and the concentration was calculated as a mean of two sample concentrations that met the criteria. However, at sample concentrations <0.2 ng/mL, a deviation of 0.1 ng/mL between the duplicate samples was accepted. The relative standard deviations were calculated from samples with concentration >LOD analyzed in duplicate on different days for all samples included in the original study (Jönsson et al. 2005). The total sample in the INUENDO cohort was divided into three groups ($n = 990$ in each group for PCB-153; $n = 1{,}058$ in each group for *p,p′*-DDE). For PCB-153 (2,970 total samples), the relative standard deviations for samples in the lowest, middle, and highest thirds of the overall distribution were 18% (mean = 0.1 ng/mL), 10% (mean = 0.5 ng/mL), and 10% (mean = 2 ng/mL), respectively. For *p,p′*-DDE (3,174 total samples), the corresponding relative standard deviations were 11% (mean = 1 ng/mL), 8% (mean = 3 ng/mL), and 7% (mean = 8 ng/mL), respectively. For external quality control, the laboratory participates in an international round-robin intercomparison program. Further details on the analysis of the serum samples can be found elsewhere (Jönsson et al. 2005).

Postnatal Exposure

We used a pharmacokinetic model developed by Verner et al. (2013) to estimate cumulative postnatal exposures to PCB-153 and *p,p′*-DDE over the first 12 months after delivery. A validation study of the pharmacokinetic model that compared predicted values to measured serum concentrations in samples collected at 6 months of age from children enrolled in Slovakian ($n = 216$) and Canadian Inuit ($n = 150$) birth cohorts reported R^2 values of 0.59 and 0.81, respectively, for PCB-153, and 0.49 and 0.83, respectively, for *p,p′*-DDE (Verner et al. 2013). The model inputs used in the present study were maternal age at delivery; maternal prepregnancy weight; duration of exclusive breastfeeding; duration of partial breastfeeding; gestational age at birth; child's sex, birth weight, weight and age at one or more postnatal measurements, weight at the follow-up, and age at the follow-up; maternal serum levels of PCB-153 and *p,p′*-DDE during pregnancy; gestational age at blood sampling; and half-life of the compounds (Verner et al. 2013). Because duration of exclusive breastfeeding had the largest influence on the model estimates, only mother–child pairs with available breastfeeding data and measured maternal levels of PCB-153 and *p,p′*-DDE ($n = 977$; 96%) were included in the postnatal modeling.

We estimated the cumulative exposure of PCB-153 and *p,p′*-DDE during the first 12 months based on the area under the curve for the estimates at each individual month. The model has previously been used by Høyer et al. (2014) in the same birth cohort. The pharmacokinetic modeling was performed using acslX software (Aegis Technologies Group, Inc.).

Outcome Assessment

We assessed behavioral development using country-specific versions of the Strengths and Difficulties Questionnaire (SDQ)

administered in the local language. The SDQ is a standardized screening tool comprising 25 questions, including both strengths and difficulties, on five different scales (emotional symptoms, conduct problems, hyperactivity, peer relationship problems, and prosocial behavior) (Goodman 1997). The SDQ can be applied internationally and has been thoroughly validated in the British population (Goodman et al. 2000; Goodman 2001). The questionnaire is used to assess the mental health of 2- to 17-y-old children. Three response options are available for each question ("not true," "somewhat true," or "certainly true," assigned values of 0, 1, or 2, respectively), and responses to the five questions for each subscale are summed to derive subscale scores from 0 through 10. A high score on the prosocial scale reflects strengths, whereas high scores on the other four scales indicate difficulties. In addition to individual subscales, scores for the emotional, conduct, hyperactivity, and peer problems scales may be summed to derive a "total difficulties" score ranging from 0 through 40 points. In a community sample of 9,998 British children 5–15 y of age, Cronbach's α for the parent-reported total difficulties SDQ score was 0.82, indicating high consistency (internal validity) among the individual SDQ questions (Goodman 2001).

In the present study, parents completed the SDQ at follow-up when the children were between 5 and 9 y of age, reflecting their child's behavior during the preceding 6 months. We used the total difficulties score and the SDQ subscale according to guidelines published by the developer of the SDQ as outcomes (Goodman 1997, 2001). The SDQ scores were categorized into normal, borderline, and abnormal scores based on cut-off points (total difficulties score: normal 0–13, borderline 14–16, abnormal 17–40; emotional symptoms score: normal 0–3, borderline 4, abnormal 5–10; conduct problems score: normal 0–2, borderline 3, abnormal 4–10; hyperactivity score: normal 0–5, borderline 6, abnormal 7–10; peer problems score: normal 0–2, borderline 3, abnormal 4–10; prosocial behavior score: normal 6–10, borderline 5, abnormal 0–4) (Goodman 1997). We dichotomized the individual subscale and total difficulties scores as abnormal versus normal or borderline using the following cut-off points from published guidelines to define abnormal scores: total difficulties score $\geq$17, emotional symptoms score $\geq$5, conduct problems score $\geq$4, hyperactivity score $\geq$7, peer problems score $\geq$4, and prosocial behavior score $\leq$4 (Goodman 1997).

Statistical Analyses

We derived Spearman's correlation coefficients to assess correlations between prenatal and estimated postnatal PCB-153 and *p,p′*-DDE concentrations. We used separate logistic regression models to estimate associations between abnormal SDQ scores (for individual subscales and for the total difficulties score, dichotomized as indicated above) and each exposure (prenatal PCB-153, postnatal PCB-153, prenatal *p,p′*-DDE, and postnatal *p,p′*-DDE), and we performed additional sensitivity analyses using separate sets of mutually adjusted logistic regression models that included both prenatal PCB-153 and prenatal *p,p′*-DDE, or postnatal PCB-153 and postnatal *p,p′*-DDE. All exposures were modeled after $\log_2$ transformation such that odds ratios (ORs) represent the relative difference in the odds of an abnormal SDQ score associated with a doubling of exposure. The SDQ scores of the children were dichotomized into normal and borderline versus abnormal according to the approach described by Goodman et al. (Goodman 1997; Goodman et al. 2000). All analyses were performed separately for each subcohort and as pooled analyses for both countries combined. In addition, we report estimates from crude models (with pooled analyses adjusted for country) and from adjusted models. We performed complete-case analyses, such that observations with missing covariate data were excluded.

We identified potential confounders *a priori* based on previous evidence of associations with behavioral outcomes in children, associations with early-life organochlorine exposures, or associations with both (Ellis et al. 2012; Fergusson and Woodward 1999; Pauly and Slotkin 2008; Zahn-Waxler et al. 2008). Because we performed complete-case analyses, we also considered the potential impact of missing data on our sample size and power when selecting covariates. Based on these considerations, we adjusted our primary models for maternal age at birth (continuous, years), maternal smoking during the index pregnancy (yes or no, based on serum cotinine >10 ng/mL or ≤ 10 ng/mL measured at enrollment in the INUENDO cohort), child's sex, child's age at follow-up (continuous, years), and, for pooled analyses, country. Our primary models of associations with postnatal PCB and *p,p′*-DDE exposures were additionally adjusted for breastfeeding duration (categorized as none, <6 months, 6–12 months, or >12 months) because breastfeeding duration has been associated with better child behavior and with higher postnatal exposures (Mimouni-Bloch et al. 2013; Ribas-Fitó et al. 2007a). We also performed secondary models of prenatal exposures after additional adjustment for breastfeeding duration because breastfeeding might act as a causal intermediate between maternal blood levels during pregnancy and subsequent child behaviors by influencing postnatal exposure levels.

We performed sensitivity analyses of the impact of adjusting for additional potential confounders that were not included in the primary model because of missing data. We used separate models to evaluate one additional potential confounder at a time, including parity (first vs. second or above), maternal educational level (left school at or before 15 y of age , left school at 16–17 y of age, left school at 18 y of age or older), gestational age at blood draw (continuous, weeks), and gestational age at birth (continuous, weeks) because the models could not accommodate all confounders at once without significant loss of power. In a sensitivity analysis, we used the top 10th percentile of the SDQ scores as the abnormal groups instead of the cut-off points given by Goodman (1997) because the questionnaires were validated in the British population and not in the Greenlandic or Ukrainian populations; this analysis was performed within each country specifically as well as in the pooled data. Furthermore, to assess the excluded participants from Poland, we performed a sensitivity analysis including Poland in the pooled analysis.

All statistical analyses were performed using Stata software (version 14.1; StataCorp LLC). A p-value <0.05 was considered statistically significant.

Results

Baseline characteristics of the 1,018 mother–child pairs included in the study are shown in Table 1. The median total difficulties score was 7 in Greenland and 8 in Ukraine, and 30 Greenlandic children (6%) and 27 Ukrainian children (5%) were classified as having abnormal total difficulties scores ($\geq$17). In Greenland, 56% of the women were classified as having smoked during pregnancy (based on serum cotinine >10 ng/mL at the time of enrollment in the study cohort), and 11% reported that they consumed more than seven alcoholic drinks per week when they were trying to conceive; whereas in Ukraine, only 15% were classified as having smoked during pregnancy, and none reported consuming more than seven drinks per week. The women from Greenland were more often multiparous and were slightly older than the women from Ukraine. Further, the women from Greenland completed fewer years of school on average, and 45% breastfed their children for >12 months, compared with 22% in Ukraine. Among

Table 1. Characteristics of mothers and their children.

Characteristic	Greenland ($n = 525$)	Ukraine ($n = 493$)	Pooled ($n = 1,018$)
Exposure [median (10th–90th percentile)]			
Pregnancy serum PCB-153 (ng/g lipids)	107 (30–369)	27 (11–54)	45 (15–253)
Estimated postnatal PCB-153 (ng/g lipids)	2647 (558–9,618)	516 (104–1,419)	1001 (173–6,368)
Pregnancy serum *p,p′*-DDE (ng/g lipids)	299 (75–954)	639 (329–1,303)	465 (124–1,158)
Estimated postnatal *p,p′*-DDE (ng/g lipids)	7075 (1,282–23,133)	12,459 (2,914–34,724)	9642 (1,836–28,807)
Outcome [median score (number of children with abnormal scores[a])]			
Total difficulties (score 0 to 40)	7 (30)	8 (27)	7 (57)
Emotional problems (score 0 to 10)	1 (44)	1 (26)	1 (70)
Conduct problems (score 0 to 10)	1 (58)	1 (40)	1 (98)
Hyperactivity (score 0 to 10)	2 (23)	3 (24)	3 (47)
Peer problems (score 0 to 10)	2 (113)	2 (69)	2 (182)
Prosocial behavior (score 0 to 10)	6 (65)	6 (51)	6 (116)
Maternal characteristics			
Maternal age at delivery (y), median (10th–90th percentile)	26 (20–36)	24 (19–32)	25 (20–35)
Parity, *n* (%)			
1st	166 (33)	402 (82)	568 (57)
2nd or above	335 (67)	91 (18)	426 (43)
Smoking during pregnancy,[b] *n* (%)			
Yes (serum cotinine >10 ng/mL)	295 (56)	75 (15)	370 (37)
No (serum cotinine ≤10 ng/mL)	230 (44)	413 (84)	643 (63)
Alcohol consumption when trying to conceive, *n* (%)			
≤7 drinks per week	465 (89)	493 (100)	958 (94)
>7 drinks per week	60 (11)	0 (0)	60 (6)
Educational level, left school at age (y), *n* (%)			
≤15	44 (10)	25 (6)	69 (8)
16–17	169 (36)	116 (27)	285 (32)
≥18	251 (54)	293 (67)	544 (60)
Child characteristics			
Sex, *n* (%)			
Male	284 (54)	261 (53)	545 (54)
Female	239 (46)	229 (47)	468 (46)
Age at follow-up (y), median (10th–90th percentile)	8 (7–9)	7 (7–8)	7 (7–9)
Total breastfeeding duration (months), *n* (%)			
0	18 (4)	42 (9)	60 (6)
<6	120 (25)	165 (34)	285 (30)
6–12	124 (26)	175 (36)	299 (31)
>12	213 (45)	108 (22)	321 (33)
Gestational age at blood sample (weeks), median (10th–90th percentile)	25 (13–37)	23 (9–40)	24 (10–39)
Gestational age at birth (weeks), *n* (%)			
≥37 weeks	498 (95)	481 (98)	979 (97)
<37 weeks	25 (5)	9 (2)	34 (3)

Note: PCB-153, 2,2′,4,4′,5,5′-hexachlorobiphenyl; *p,p′*-DDE, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)-ethylene.
[a]Total difficulties score: abnormal ≥17; Emotional Symptoms Score: abnormal ≥5; Conduct Problems Score: abnormal ≥4; Hyperactivity Score: abnormal ≥7; Peer Problems Score: abnormal ≥4; Prosocial Behavior Score: abnormal ≤4.
[b]Yes or no, based on serum cotinine >10 ng/mL or ≤10 ng/mL measured at enrollment.

Greenlandic women, the median (10th–90th percentile) pregnancy serum concentration was 107 (30 – 369) ng/g lipids for PCB-153 and 229 (75 – 954) ng/g lipids for *p,p′*-DDE. Among Ukrainian women, the median (10th–90th percentile) pregnancy serum concentration was 27 (11 – 54) ng/g lipids for PCB-153 and 639 (329 – 1,303) ng/g lipids for *p,p′*-DDE. The same pattern of considerably higher levels of PCB-153 in Greenlandic women and *p,p′*-DDE in Ukrainian women was observed in the estimated postnatal exposures.

The Spearman's correlation coefficient between PCB-153 and *p,p′*-DDE was 0.92 in Greenland and 0.46 in Ukraine for the prenatal exposures and 0.93 in Greenland and 0.76 in Ukraine for the postnatal exposures. In Greenland, the correlation between the prenatal and postnatal exposures was 0.81 for PCB-153 and 0.82 for *p,p′*-DDE. In Ukraine, the correlation between the prenatal and postnatal exposures was 0.56 for PCB-153 and 0.49 for *p,p′*-DDE.

Crude odds ratios for associations between the exposures and outcomes are presented (see Table S1), and adjusted estimates (from the primary model) are presented in Table 2. In general, crude ORs were consistent with adjusted estimates with regard to the direction and patterns of associations.

Prenatal PCB-153 exposures were positively associated with abnormal conduct problem scores in both cohorts {adjusted OR for a doubling of exposure = 1.18 [95% confidence interval (CI): 0.96, 1.46] based on 54 children with abnormal scores, hereafter referred to as "cases" for convenience, in Greenland; OR = 1.32 (95% CI: 0.89, 1.96) based on 37 cases in Ukraine; pooled OR = 1.19 (95% CI: 0.99, 1.42)} (Table 2). Associations differed between cohorts for total difficulties scores, with a null association in the Greenland cohort [OR = 1.02 (95% CI: 0.77, 1.36); 26 cases] and nonsignificant positive associations in the Ukraine cohort [OR = 1.24 (95% CI 0.77, 1.99); 25 cases] and in the pooled population [OR = 1.09 (95% CI 0.86, 1.38)]. ORs also varied between the cohorts for prenatal PCB-153 exposure and abnormal hyperactivity scores, with a nonsignificant positive association in the Greenland cohort (19 cases), a null association in the Ukraine cohort (22 cases), and a nonsignificant positive association overall [OR = 1.24 (95% CI: 0.94, 1.62)]. Associations between prenatal PCB-153 exposure and other outcomes were essentially null.

Patterns of results for estimated postnatal PCB-153 exposure were similar to those for prenatal PCB-153 exposure for conduct scores [nonsignificant positive associations for both subcohorts, pooled OR for a doubling of exposure = 1.16 (95% CI: 0.96, 1.41)] and abnormal total difficulties scores (nonsignificant associations

Table 2. Adjusted odds ratios (95% confidence intervals) for abnormal[a] behavior scores associated with a doubling of prenatal and postnatal PCB-153 and *p,p′*-DDE.

	Greenland			Ukraine			Pooled[b]		
Outcome	*n* cases	*n* total	Adjusted OR (95% CI)[c]	*n* cases	*n* total	Adjusted OR (95% CI)[c]	*n* cases	*n* total	Adjusted OR (95% CI)[c]
Prenatal PCB-153									
Total difficulties	26	452	1.02 (0.77, 1.36)	25	456	1.24 (0.77, 1.99)	51	908	1.09 (0.86, 1.38)
Emotional	37	454	0.88 (0.70, 1.11)	23	456	1.16 (0.71, 1.90)	60	910	0.94 (0.76, 1.15)
Conduct	54	454	1.18 (0.96, 1.46)	37	456	1.32 (0.89, 1.96)	91	910	1.19 (0.99, 1.42)
Hyperactivity	19	452	1.35 (0.96, 1.89)	22	456	0.96 (0.60, 1.53)	41	908	1.24 (0.94, 1.62)
Peer	92	453	1.04 (0.88, 1.22)	66	456	1.19 (0.88, 1.61)	158	909	1.05 (0.92, 1.21)
Prosocial	51	453	1.17 (0.94, 1.45)	47	456	0.83 (0.59, 1.16)	98	909	1.06 (0.89, 1.26)
Postnatal PCB-153									
Total difficulties	19	412	0.90 (0.65, 1.25)	24	449	1.30 (0.81, 2.10)	43	861	1.06 (0.82, 1.38)
Emotional	31	414	0.87 (0.67, 1.12)	22	449	1.16 (0.70, 1.91)	53	863	0.94 (0.75, 1.17)
Conduct	46	414	1.14 (0.91, 1.42)	36	449	1.24 (0.84, 1.83)	82	863	1.16 (0.96, 1.41)
Hyperactivity	15	412	1.05 (0.72, 1.53)	21	449	1.03 (0.64, 1.66)	36	816	1.08 (0.81, 1.45)
Peer	81	413	1.03 (0.86, 1.22)	64	449	1.51 (1.11, 2.04)	145	862	1.12 (0.97, 1.30)
Prosocial	43	413	1.16 (0.92, 1.45)	46	449	0.88 (0.64, 1.22)	89	862	1.06 (0.89, 1.28)
Prenatal *p,p′*-DDE									
Total difficulties	26	452	1.09 (0.82, 1.45)	25	456	1.46 (0.87, 2.44)	51	908	1.15 (0.90, 1.48)
Emotional	37	454	0.94 (0.76, 1.17)	23	456	1.24 (0.71, 2.15)	60	910	0.97 (0.79, 1.19)
Conduct	54	454	1.24 (1.00, 1.54)	37	456	1.58 (1.02, 2.44)	91	910	1.25 (1.04, 1.51)
Hyperactivity	19	452	1.36 (0.95, 1.94)	22	456	1.42 (0.84, 2.40)	41	908	1.43 (1.06, 1.92)
Peer	92	453	1.11 (0.94, 1.30)	66	456	1.36 (0.96, 1.91)	158	909	1.12 (0.97, 1.29)
Prosocial	51	453	1.24 (1.00, 1.54)	47	456	0.99 (0.66, 1.47)	98	909	1.16 (0.97, 1.39)
Postnatal *p,p′*-DDE									
Total difficulties	19	412	1.02 (0.74, 1.41)	24	449	1.51 (0.93, 2.45)	43	861	1.16 (0.88, 1.52)
Emotional	31	414	0.97 (0.76, 1.23)	22	449	1.23 (0.73, 2.08)	53	863	1.00 (0.80, 1.25)
Conduct	46	414	1.21 (0.96, 1.52)	36	449	1.42 (0.93, 2.18)	82	863	1.24 (1.01, 1.51)
Hyperactivity	15	412	1.11 (0.76, 1.60)	21	449	1.50 (0.90, 2.52)	36	861	1.27 (0.93, 1.73)
Peer	81	413	1.10 (0.93, 1.31)	64	449	1.79 (1.28, 2.50)	145	862	1.20 (1.03, 1.40)
Prosocial	43	413	1.28 (1.01, 1.61)	46	449	1.03 (0.70, 1.49)	89	862	1.20 (0.99, 1.45)

Note: CI, confidence interval; DDE, dichlorodiphenyldichloroethylene; OR, odds ratio; PCB-153, 2,2′,4,4′,5,5′-hexachlorobiphenyl; *p,p′*-DDE, 1,1-dichloro-2,2-bis(*p*-chlorophenyl)-ethylene.

[a]Total difficulties score: abnormal ≥17; Emotional Symptoms Score: abnormal ≥5; Conduct Problems Score: abnormal ≥4; Hyperactivity Score: abnormal ≥7; Peer Problems Score: abnormal ≥4; Prosocial Behavior Score: abnormal ≤4.

[b]OR for the pooled cohort is adjusted for country.

[c]Adjusted for maternal age (continuous, years), maternal smoking during pregnancy (categorical, yes/no, based on serum cotinine >10 ng/mL or ≤10 ng/mL), child's sex (categorical, boy/girl), and child's age at follow-up (continuous, years). Estimated postnatal PCB-153 and *p,p′*-DDE are additionally adjusted for breastfeeding duration (categorical, >6 months, 6–12 months, or >12 months).

that were negative for Greenland, positive for Ukraine, and close to the null overall) (Table 2). In addition, postnatal PCB-153 exposures were positively associated with abnormal peer relationship scores in Ukraine [OR = 1.51 (95% CI: 1.11, 2.04); 64 cases] but were null for Greenland (81 cases), resulting in a pooled OR of 1.12 (95% CI: 0.97, 1.30).

Prenatal *p,p′*-DDE exposure was positively associated with abnormal scores in both cohorts for conduct [pooled OR for a doubling of exposure = 1.25 (95% CI: 1.04, 1.51); 54 Greenland cases and 37 Ukraine cases], hyperactivity [pooled OR = 1.43 (95% CI: 1.06, 1.92), 19 Greenland cases and 22 Ukraine cases], and, to a lesser extent, peer relationship problems [pooled OR = 1.12 (95% CI: 0.97, 1.29); 92 Greenland cases and 66 Ukraine cases] (Table 2). Associations with prenatal *p,p′*-DDE exposure differed between the subcohorts for abnormal total difficulties and emotional scores (nonsignificant positive associations in Ukraine and null or negative associations in Greenland) and abnormal prosocial scores (positive for Greenland, null for Ukraine).

Associations with estimated postnatal *p,p′*-DDE exposure were generally consistent with those for prenatal *p,p′*-DDE exposure, with regard to both patterns of associations by subcohort and the estimated ORs, with positive subcohort and pooled ORs for abnormal conduct, hyperactivity, and peer relation scores (Table 2). As was the case for associations with prenatal *p,p′*-DDE exposure, ORs for estimated postnatal *p,p′*-DDE exposure and abnormal total difficulties and emotional scores were also positive for Ukraine and null for Greenland, whereas ORs for abnormal prosocial scores were positive for Greenland and null for Ukraine.

When including both PCB-153 and *p,p′*-DDE in the models, the confidence intervals were wider and the overall associations with PCB-153 were attenuated, whereas the *p,p′*-DDE associations were enhanced in some cases, thus making it difficult to determine whether differences were simply the result of reduced precision, confounding by coexposure to each pollutant, or both (see Table S2).

We performed secondary analyses that adjusted for parity, maternal educational level, breastfeeding duration, gestational age at blood draw, and gestational age at birth. Including these covariates only changed the estimates marginally, and none of these covariates changed the significance level of the studied associations (data not shown).

Primary models of associations between prenatal exposures and behavioral outcomes were not adjusted for breastfeeding duration, which might act as an intermediate between prenatal exposures (maternal serum levels) and the outcomes by influencing postnatal exposures. Estimates from models of prenatal exposures that were additionally adjusted for breastfeeding duration (0, <6 months, 6–12 months, >12 months) were similar to those from the main analysis for the Ukraine cohort, whereas in the Greenland cohort, ORs were slightly attenuated toward the null (see Table S3). This result might reflect cohort-specific mediation by breastfeeding, but it might also be related to missing data for breastfeeding duration, which eliminated 40 observations for Greenland, but only 3 observations for Ukraine, from the adjusted complete-case analysis models. In the sensitivity analysis using the top 10th percentile of the SDQ scores as the abnormal group,

the overall pattern of the results did not change (see Table S4). In addition, including the excluded participants from Poland in the pooled analysis did not change the results (see Table S5).

Discussion

We found a consistent association between a doubling of prenatal exposure to *p,p′*-DDE and increased odds of conduct problems in Greenland and Ukraine as well as in the pooled analysis. In addition, postnatal *p,p′*-DDE exposure was associated with conduct problems in the pooled analysis. Prenatal and postnatal *p,p′*-DDE exposures were positively associated with abnormal hyperactivity scores in both cohorts (significant for the pooled prenatal exposure OR), as well as with abnormal peer relationship scores (significant for the pooled postnatal exposure OR). In addition, we estimated nonsignificant positive associations with abnormal conduct scores in both cohorts for prenatal and postnatal PCB-153 exposures. The associations with total difficulties scores were not significant.

Our findings suggest that prenatal and postnatal exposures to *p,p′*-DDE and potentially prenatal expsure to PCB-153 may increase the risk or prevalence of conduct problems and abnormal hyperactivity in children 5 to 9 y of age. These findings add to the growing body of evidence of adverse developmental effects of *in utero* exposure to neurotoxins such as PCBs and DDE (Grandjean and Landrigan 2014). In a cohort of 573 mother–child pairs from Massachusetts, Sagiv et al. (2010) reported an association between umbilical cord serum levels of four PCB congeners [median (5th–95th percentile): 0.19 (0.01, 4.41) ng/g] and DDE [median (5th–95th percentile): 0.31 (0.00, 14.93) ng/g]; they also reported ADHD-like symptoms in children at 8 y of age measured with the Conners' Rating Scale for Teachers (CRS-T). Those results are generally consistent with our findings for prenatal *p,p′*-DDE exposures, although abnormal hyperactivity scores were associated with prenatal PCB-153 exposures in only one of the two cohorts included in our analysis. In the same cohort, Verner et al. (2015) found associations between ADHD-related behavior (assessed by the CRS-T) and estimated postnatal PCB exposure for the first 12 months after delivery calculated using a pharmacokinetic model. In our study, we used the same pharmacokinetic model (Verner et al. 2013) to calculate postnatal exposure to PCB-153 and *p,p′*-DDE, and we observed that exposure–outcome associations similarly tended to be attenuated when comparing postnatal exposures with prenatal exposures. Another study found that maternal whole blood levels of three PCB congeners [arithmetic mean (SD): 0.19 (0.18) μg/g lipid] were associated with lowered attention function in a German birth cohort, but the number of participants was small ($n = 117$) (Neugebauer et al. 2015).

However, studies have also reported null findings for associations between PCBs, DDE, and behavior in children. Grandjean et al. (2012) studied a cohort of 917 seven-year-old children from the Faroe Islands and reported that attention [based on a Continuous Performance Test (CPT)] was positively associated with cord blood levels of DDE but was not clearly associated with the sum of four PCB congeners (geometric mean = 1.86 μg/L; interquartile range: 2 μg/L). This finding is in contrast to those of our study, which showed a positive association between prenatal and postnatal *p,p′*-DDE exposures and abnormal hyperactivity scores. Nevertheless, it is difficult to compare the studies given the different outcome ascertainment methods and behavioral aspects (i.e., attention vs. behavior) and the different exposure assessments (i.e., measured in maternal serum vs. cord blood). In a Danish cohort of 872 pregnant women, the sum of six PCB congeners [median (interquartile range): 9.2 (5.3) pmol/mL] and DDE [median (interquartile range): 2.5 (2.2) ng/mL] was measured in serum between 1988 and 1989, and the children were followed up through national registers until 2011 for diagnosis or prescription of medication for ADHD (Strøm et al. 2014). The study showed no association between prenatal exposure to PCB or DDE and ADHD (Strøm et al. 2014). These results, in which the outcome was ADHD medication and ADHD diagnosis of children followed up beyond childhood, are difficult to compare with those of our study, where behavioral symptoms, including hyperactivity and conduct problem dimensions, were reported by parents for children between 5 and 9 y of age. A follow-up of two Spanish birth cohorts ($n = 391$) showed an association between hexachlorobenzene and adverse social competences and ADHD-like behavior, but the investigators found no association for cord blood levels of PCB (concentration not given) and DDE (concentration not given) (Ribas-Fitó et al. 2007b). On the basis of the existing literature, it is difficult to draw a clear conclusion about the effects of the compounds on child behavior given the limited number of studies and because not all studies are directly comparable. Differences may be due to different rating scales; ages of the children at assessment; ages of the mothers; exposure levels; measured congeners; measurement error; whether the compounds were tested in cord blood, serum, or placental tissue; potential influence of uncontrolled confounding; and differences in susceptibility among populations.

The possible biological mechanisms behind behavioral disturbances and early-life exposure to PCBs and DDE are still unknown. However, studies have shown an association between the compounds and altered thyroid function. Herbstman et al. (2008) found an association between cord blood levels of six PCB congeners and lowered total thyroxin levels in infants born by spontaneous vaginal delivery. Similarly, Julvez et al. (2011) found an association for cord blood levels of four PCB congeners and *p,p′*-DDE with lowered resin triiodothyronine uptake ratio (a proxy of the binding capacity of thyroxine-binding globulin responsible for carrying thyroid hormones in the bloodstream). Altered thyroid function may affect development of the fetal brain (Morreale de Escobar et al. 2004). Furthermore, it has also been suggested that PCBs might affect neurodevelopment through diverse mechanisms related to endocrine disruption (Bell 2014). In addition, animal studies have shown that PCBs can alter the dopaminergic levels in the brain, which may lead to cognitive and behavioral impairment of the fetus during pregnancy (Arnsten 1997; Caudle et al. 2006; Seegal et al. 1997, 2002).

This study has some limitations. Participation rates at baseline were 90% in Greenland and 26% in Ukraine, and although a nonresponse analysis at baseline showed almost no difference in age or parity among participants and nonparticipants in either cohort (Toft et al. 2005), we cannot rule out selection bias. A commonly stated reason for nonparticipation among women from Ukraine was a concern that collection of the blood sample might be harmful to the fetus. The decision to participate at both baseline and follow-up was made without knowledge of the prenatal or postnatal exposure levels.

Blood samples were collected throughout pregnancy, mainly in the second and third trimesters. Because PCBs and DDE tend to decrease throughout pregnancy, exposure misclassification might occur (Adetona et al. 2013; Glynn et al. 2011). We addressed this possibility in a sensitivity analysis adjusting for gestational age at blood sampling, which did not change the results (data not shown). For that reason, differences in gestational age at blood sampling do not seem to be of major concern.

In addition, we had no measurements of the postnatal exposure to PCB-153 and *p,p′*-DDE and used a pharmacokinetic model to estimate the cumulative exposure in the first 12 months after delivery. The model has been validated in a similar setting (Verner et al. 2013) and has previously been used in the same

birth cohort (Høyer et al. 2014). Nevertheless, exact measures of the postnatal exposures would have been preferable.

As the outcome measure, we used the SDQ, which can be applied internationally and has been thoroughly validated in the British population (Goodman et al. 2000; Goodman 2001). The SDQ is not a diagnostic tool, but it can be used as a screening tool to assess the mental health of children as both a total score and on five different subscales.

Because SDQ cut-off points were not validated in the Greenlandic and Ukrainian populations, we used the general cut-off points given by Goodman (1997) for the British population, which could lead to misclassification of the outcome estimate. We addressed this possibility in a sensitivity analysis using the top 10th percentile as the cut-off, which did not alter the results considerably. Furthermore, studies have provided evidence of useful psychometric properties of the SDQ across different Nordic countries including Sweden, Finland, Norway, Denmark, and Iceland (Obel et al. 2004), and to some extent in countries beyond Europe, including Brazil, Yemen, and Australia (Woerner et al. 2004).

Analyses were repeated using two-pollutant models that were mutually adjusted for PCB-153 and *p,p′*-DDE during the same time period. As expected, estimates were less precise when the highly correlated exposures were included in the same model. However, associations with *p,p′*-DDE were generally consistent with the primary model estimates after adjustment for PCB-153, whereas associations with PCB-153 were somewhat more likely to be attenuated when adjusted for coexposure to *p,p′*-DDE.

The proportions of participants classified as having abnormal total difficulties scores (6% in Greenland and 5% in Ukraine) were consistent with expectations (Elberling et al. 2010; Goodman et al. 2000), but the absolute numbers of children classified were small (30 in Greenland and 27 in Ukraine with abnormal total difficulties scores among children included in the study). In addition to limiting the precision of our estimates, this also limited our ability to adjust for potential confounders, particularly those with missing data for some study participants. To ensure sufficient power in relation to the number of missing values, we chose to adjust our main analysis only for maternal age at birth, maternal smoking during pregnancy, child's sex, and child's age at follow-up. Other covariates such as parity, maternal educational level, gestational age at blood sampling, and gestational age at birth were addressed in secondary analyses and did not change the estimate substantially (data not shown).

The strengths of our study include the prospective follow-up design. The follow-up period of 5 to 9 y enabled us to estimate associations of early-life exposures with behavioral outcomes in school-age children. In addition, the study population of mother–child pairs from Greenland and Ukraine enabled us to evaluate the consistency of exposure–outcome associations across different regions and exposure contrasts. Despite differences between Greenland and Ukraine regarding baseline characteristics (maternal age at delivery, parity, maternal educational level, alcohol consumption at the time of conception, smoking during pregnancy, and breastfeeding duration) and differences in exposure levels, remarkably similar associations between organochlorine exposures and behavior outcomes, measured as total difficulties as well as conduct and hyperactivity problems, were observed in results stratified by country.

Conclusion

We found no clear association between total difficulties scores and either prenatal or postnatal exposure to PCB-153 or *p,p′*-DDE. However, for the subscale scores, the results of this study indicated that prenatal and postnatal exposure to *p,p′*-DDE may increase the risk of conduct problems and, to some extent, the risk of hyperactivity in children at 5 to 9 y of age. Associations were less consistent for prenatal and postnatal PCB-153 exposures; nevertheless, we found a nonsignificant positive association for abnormal conduct scores in both cohorts. Our findings provide evidence that *in utero* exposure to organochlorines such as PCBs and DDE may contribute to adverse behavioral development and emaphasize the importance of minimizing organochlorine exposures to children and to women of childbearing age.

Acknowledgments

We acknowledge all families participating in the study as well as the hospitals and antenatal clinics.

The Climate change, environmental contaminants and reproductive health (CLEAR) and Biopersistent organochlorines in diet and human fertility: Epidemiologic studies of time to pregnancy and semen quality in Inuit and European populations (INUENDO) studies were funded by the European Commission's 7th and 5th Framework Programmes, respectively (grant nos. FP7-ENV-2008-1-226217 and QLK4-CT-2001-00202, respectively). A.H.R. received grants from The Danish Council for Independent Research - Medical Sciences (5053-00064A), the A.P. Møller Foundation (15-338), the Oticon Foundation (15-3689), and the Spar Nord Foundation. The funding agencies had no role in study design, collection, analysis, or interpretation of the data.

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