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Prenatal exposure to PCB-153, *p,p′*-DDE and birth outcomes in 9000 mother–child pairs: Exposure–response relationship and effect modifiers

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ABSTRACT

Low-level exposure to polychlorinated biphenyl-153 (PCB-153) and dichlorodiphenyldichloroethylene (*p-p′*-DDE) can impair fetal growth; however, the exposure–response relationship and effect modifiers of such association are not well established. This study is an extension of an earlier European meta-analysis. Our aim was to explore exposure–response relationship between PCB-153 and *p-p′*-DDE and birth outcomes; to evaluate whether any no exposure–effect level and susceptible subgroups exist; and to assess

Abbreviations: BM, breast milk; BMI, Body Mass Index; CI(s), Confidence Interval(s); CS, cord serum; CP, cord plasma; DAGs, Directed Acyclic Graphs; FAROES, Children's Health and the Environment in the Faroes; FLEHSI, Flemish Environment and Health Study-I; GAM, General Additive Models; GRD, Groningen, Rotterdam, Düsseldorf; GWG, Gestational Weight Gain; HCB, Hexachlorobenzene; HUMIS, Norwegian Human Milk Study; INMA, Childhood and Environment; INMA cord, Childhood and Environment — cord serum; INMA mat, Childhood and Environment — maternal serum; INUENDO, Biopersistent organochlorines in diet and human fertility; MS, maternal serum; MW, maternal whole blood; PCB cohort, Early Childhood Development and PCB exposures in Slovakia; OC(s), Organochlorine Compound(s); OR, Odds Ratio; *P*, *p*-Value; *p,p′*-DDE, Dichlorodiphenyldichloroethylene; *p,p′*-DDT, Dichlorodiphenyltrichloroethane; *o,p′*-DDT, 2,4′-Dichlorodiphenyltrichloroethane; p, Percentile; PCB(s), Polychlorinated Biphenyl(s); PCB-153, Polychlorinated Biphenyl-153; PÉLAGIE, Endocrine Disruptors: Longitudinal Study on Pregnancy Abnormalities, Infertility, And Childhood; RHEA, Mother Child Cohort in Crete; SD, Standard Deviation.

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the role of maternal gestational weight gain (GWG). We used a pooled dataset of 9377 mother–child pairs enrolled in 14 study populations from 11 European birth cohorts. General additive models were used to evaluate the shape of the relationships between organochlorine compounds and birth outcomes. We observed an inverse linear exposure–response relationship between prenatal exposure to PCB-153 and birth weight [decline of 194 g (95% CI −314, −74) per 1 μg/L increase in PCB-153]. We showed effects on birth weight over the entire exposure range, including at low levels. This reduction seems to be stronger among children of mothers who were non-Caucasian or had smoked during pregnancy. The most susceptible subgroup was girls whose mothers smoked during pregnancy. After adjusting for absolute GWG or estimated fat mass, a reduction in birth weight was still observed. This study suggests that the association between low-level exposure to PCB-153 and birth weight exists and follows an inverse linear exposure–response relationship with effects even at low levels, and that maternal smoking and ethnicity modify this association.

1. Introduction

Synthetic organochlorine compounds (OCs) have been extensively employed for electrical insulators and pesticides until their production and use were banned in the US in the late 1970s and in Europe in 2001. However, they persist in the environment for many years and due to their high lipophilicity and biomagnifying properties they are still being detected in human samples in most parts of the world (Consonni et al., 2012; Porta et al., 2008). Fetuses and neonates are exposed to these compounds via placental transfer and through breastfeeding, and due to their relatively immature organs and detoxification mechanisms they are considered to be especially vulnerable to their adverse health effects (Grandjean et al., 2008).

In animal studies, exposure to OCs in utero has been linked to various adverse effects on the developing fetus, including the nervous, endocrine, immunologic and reproductive systems (ATSDR, 2000, 2002). In particular, the impact of prenatal polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethylene (*p,p′*-DDE) exposures on birth weight and gestational age has been assessed in several epidemiological studies due to their steroid-hormone like properties (reviewed by El Majidi et al., 2012; Toft et al., 2004). Findings are consistent in populations accidentally exposed to high levels of these compounds but results are not as consistent in groups of the general population exposed to lower levels (Toft et al., 2004). Results from previous epidemiological studies examining the association between prenatal PCBs exposure and birth weight are difficult to compare due to differences in design, exposure measurement, and background populations. Further, the "biological concentration–response" relationship is not clearly established (El Majidi et al., 2012). There is some evidence that sex of the child and sociodemographic or lifestyle factors such as education, ethnicity, and smoking may modify the effect of PCBs on birth outcomes but the potential effect modifiers of these associations are not well established (Rylander et al., 1995, 1996; Sagiv et al., 2007; Sonneborn et al., 2008). Moreover, it has been suggested that maternal gestational weight gain (GWG) can act as confounder of such associations as weight gain may dilute PCB levels in blood and increase birth weight (Verner et al., 2013), although it can be argued that it may also act as mediator.

In a recent meta-analysis of 7990 mother–child pairs enrolled in 12 European birth cohorts we found an inverse association between low-level exposure to PCBs and birth weight while no such association was found for *p,p′*-DDE (Govarts et al., 2012). The meta-analysis results of the cohort specific summary statistics, however, did not allow for an adequate modeling of exposure–response relationship or for an appropriate analysis of effect modifiers due to the limited sample size of each individual cohort. Since the publication of that article, we have obtained more individual-pollutant level data from the RHEA cohort (Vafeiadi et al., 2014) and on GWG. Therefore, as an extension of the Govarts et al. (2012) study, we pooled the datasets to obtain a unique dataset of these European birth cohorts to: i) examine exposure–response relationship between PCB-153 and *p-p′*-DDE and selected birth outcomes; ii) to evaluate whether any no exposure–effect level and susceptible subgroups exist; and iii) to assess the potential confounding from GWG in such associations.

2. Materials and methods

2.1. Participating cohorts and data collection

The 12 European birth cohorts included in the previous analysis (Govarts et al., 2012) were invited to participate in this new study conducted within the CHICOS project (Developing a Child Cohort Research Strategy for Europe — www.chicosproject.eu). Eleven birth cohorts accepted to participate in the analysis. The population sample was restricted to live-born singleton births with known concentrations of PCB-153 and/or *p,p′*-DDE measured in maternal serum/whole blood, cord serum/plasma, or breast milk. A data transfer agreement document was signed by each cohort and datasets were transferred to CREAL (Centre for Research in Environmental Epidemiology) with personal identifiers removed using a Secure File Transfer Protocol. Informed consent was obtained from all study participants as part of the original studies and in accordance with each study's institutional review board. Each dataset was checked for inconsistencies and completeness.

In this new study, the ELFE pilot cohort did not participate and the RHEA cohort provided more samples than in the initial study (n = 1115 (Vafeiadi et al., 2014); n = 30 (Govarts et al., 2012)). Finally, a total of 14 study populations from 11 birth cohorts were included in the analyses resulting in 9377 mother–child pairs: 9011 of them with PCB-153 measurements and 8853 with *p-p′*-DDE measurements. A detailed description of the participating birth cohorts can be found in Table 1 of Govarts et al. (2012).

2.2. PCB-153 and p,p′-DDE exposure assessment

PCB-153 and *p,p′*-DDE compounds were selected for the analysis; PCB-153 because it is a good marker of overall exposure to PCBs (Hagmar et al., 2006), and *p,p′*-DDE because it is the most persistent of the DDT metabolites (ATSDR, 2002). Since cord serum is considered the best proxy of OC exposure during fetal life (Korrick et al., 2000), we estimated the equivalent concentrations in cord serum from the concentrations measured in maternal serum/whole blood or breast milk. While the Govarts et al. (2012) analyses used general conversion factors, obtained from literature [see Supplemental material of Govarts et al. (2012)], for this study we calculated cohort-specific conversion factors using paired cord and maternal measurements (serum or milk) of PCB-153 and *p,p′*-DDE in cohorts where these measurements were available (FAROES3, INMA, GRD, and PCB cohort) (Supplemental material, p. 1–5 and Table S1). For cohorts without available paired mother–child measurements we applied the cohort-specific conversion factor of the geographically nearest cohort. In the case of HUMIS, with no available paired mother–child samples, and Duisburg, with no available non-lipid adjusted concentrations, we applied the conversion factors from Govarts et al. (2012). Non-lipid adjusted concentrations of PCB-153 and *p,p′*-DDE were used in all the analyses.

2.3. Birth outcomes and other covariates

We assessed gestational age (weeks) and birth weight (grams) obtained from clinical records. Gestational age calculation was based on the last menstrual period or ultrasound measurements. In some cohorts, when both estimations differed by more than 7–14 days, the last menstrual period measurement was replaced by ultrasound determination (Supplemental material, Table S2). We considered in analysis the same covariates as in previous analysis by Govarts et al. (2012) including maternal age, education, ethnicity, and smoking and alcohol consumption habits during pregnancy, and with the same categorization (Supplemental material, Table S2). Preterm birth was defined as birth before 37 completed weeks of gestation. Maternal GWG (kg) was extracted from prenatal records or based on mother's recall (Supplemental material, Table S3). Absolute GWG was determined by subtracting pre-pregnancy weight from the weight in late pregnancy and fat mass was estimated as a function of GWG (Butte et al., 2003) (Supplemental material, Table S3). For maternal education and ethnicity, cohort-specific categories were standardized to create common variables: low/medium/high education (Supplemental material, Table S4), and Caucasian/non-Caucasian (non-Caucasian included: Roma, Inuit, Latin American, Asian, Eastern European, and African).

2.4. Statistical analysis

PCB-153 and *p,p′*-DDE concentrations below the limit of detection (LOD) or quantification (LOQ) were replaced by the LOD or LOQ (specific for each cohort) divided by the square root of two (Hornung and Reed, 1990). Multiple imputation of missing values for the covariates was performed using chained equations where 10 completed datasets were generated, and analyzed using the standard combination rules for multiple imputations (Spratt et al., 2010). A different imputed dataset was generated for each of the exposure–outcome relationships (Supplemental material, Table S5).

Directed acyclic graphs (DAGs) (Shrier and Platt, 2008) were used to visualize the complex relationships between covariates that may influence the association between OC and birth weight and to select the covariates retained in the final regression models (PCB-153 and birth weight DAG, Supplemental Fig. S1). The minimal sufficient adjustment set estimated by the DAGs included cohort, maternal age, maternal education, maternal ethnicity, maternal pre-pregnancy BMI, maternal smoking in pregnancy, parity, and GWG. Because maternal ethnicity was not available in FLEHSI but in cohorts where available it did not modify the association (data not shown), this variable was not included into the model. Only seven cohorts had data available on GWG and we tested its influence in the final model only in a sensitivity analysis. We have further included in the final models the time of sample collection covariate as a predictor of the OC exposure and the covariates of gestational age, child's sex, and maternal height as predictors of birth weight with the aim to increase the precision of the linear regression effect estimates (Supplemental Fig. S1).

General additive models (GAMs) were used to evaluate the shape of the relationships between our exposure–outcome relationships. Linear mixed models were used to estimate the association between cord serum OC concentrations and birth weight or gestational age (pooled analysis). First, unadjusted models were fitted and then models including all the selected confounders from the DAGs were fitted. In the case of PCB-153, 99% of the population had concentrations below 1180 ng/L; therefore, the aforementioned analyses were repeated excluding those subjects with extreme values ($n = 90 \geq 1180$ ng/L) (Supplemental material, Fig. S2). The multivariate linear mixed models were also performed comparing quintiles of OC concentrations and calculating the linear test for trend across them. We used random-effects models including cohort and PCB-153 or *p,p′*-DDE as random effects and all other covariates as fixed effects. Finally, the overall summary effect of the individual cohorts was estimated using meta-analysis to check the consistency with Govarts et al. (2012).

Effect modification by child's sex, maternal pre-pregnancy BMI, GWG categories, maternal education, maternal ethnicity (FLEHSI not included), maternal smoking during pregnancy, maternal alcoholic beverages during pregnancy, time of sample collection, and geographical region (Northern–Western cohorts vs Southern–Eastern cohorts) was assessed through inclusion of the interaction terms in the models (statistically significant effect modification if p-value < 0.05) and stratified analyses.

Various sensitivity analyses were performed to assess the robustness of our results. First, we repeated the analysis leaving one population out at the time. Second, for cohorts with no available paired cord and maternal measurements (Greenland, Warsaw, Kharkiv and RHEA) we repeated the analyses taking another cohort-specific conversion factor (Supplemental material, p. 1–5 and Table S1). Third, we performed the analysis applying the non-cohort specific conversion factors used by Govarts et al. (2012). Fourth, we restricted the analysis to term births and also used lipid-adjusted and log-transformed OC concentrations. Furthermore, because PCB-153 and *p,p′*-DDE levels were highly correlated (Spearman correlation coefficients: 0.33 to 1.00, $p < 0.001$) we adjusted the PCB-153 models for *p,p′*-DDE and vice versa to differentiate the role of each pollutant. Finally, to test whether the relationship between prenatal PCB exposure and birth weight was attributable to GWG, acting as confounder or mediator, we adjusted the model for absolute GWG or estimated fat mass in cohorts where data were available (FLEHSI, HUMIS, INMA cord, INMA mat, PCB cohort, PÉLAGIE, and RHEA) (Supplemental material, Table S3). All statistical analyses were conducted with Stata 12.0 statistical software (Stata Corporation, College Station, Texas). DAGs were analyzed using the DAGitty version 2.0 (Textor et al., 2011). All analyses were performed using the imputed datasets except the GAM and effect modification analyses where the non-imputed datasets were used.

3. Results

The mean birth weight and gestational age were 3377 g (standard deviation (SD): 506) and 39.4 weeks (SD: 1.5), respectively (Supplemental material, Table S2). The proportion of preterm births ranged from 1.5% (FAROES3) to 11.7% (RHEA) and of low birth weight babies from 0% (FAROES2) to 6.6% (DUISBURG). The percentage of overweight/obese women exceeded 30% in HUMIS, Greenland, and RHEA. The proportion of lower educated women was higher in Greenland and Kharkiv compared to the other cohorts. Most of the mothers in each cohort were Caucasian and did not smoke during pregnancy except in Greenland where all mothers were Inuit and more than 70% smoked during pregnancy (Supplemental material, Table S2). The median OC concentrations in the 14 study populations ranged from 15 to 394 ng/L for PCB-153 (combined median: 100.0 ng/L) and from 50 to 1323 ng/L for *p,p′*-DDE (combined median: 447.2 ng/L) (Table 1).

Neither PCB-153 nor *p,p′*-DDE was associated with gestational age (Supplemental material Table S6). The analysis showed an inverse linear relationship between prenatal PCB-153 concentrations and birth weight (Supplemental material, Fig. S3; p-value < 0.001). The GAM only needed one degree of freedom, i.e. the function fitted by the model was linear. The unadjusted pooled analysis showed a statistically significant inverse association between cord serum PCB-153 concentrations and birth weight [$\beta = -0.23$ (95% CI: -0.37, -0.08) per 1 ng/L PCB-153 increase], equivalent to a 225 g reduction (95% CI: -371, -78) of birth weight per 1 μg/L increase in cord serum PCB-153 (data not shown). After adjustment the coefficient declined to 194 g reduction (95% CI: -314, -74) of birth weight per 1 μg/L increase in cord serum PCB-153 (Table 2). A statistically significant trend (p-value < 0.001) was also shown after comparing quintiles of PCB-153 concentrations (data not shown). When excluding the 1%

Table 1
Concentration of exposure biomarkers PCB-153 and *p,p′*-DDE (ng/L) in cord serum (original and obtained by conversion).

Cohort	Matrix	PCB-153[a]					*p,p′*-DDE[a]				
		N	Mean ± SD	Median	p25	p75	N	Mean ± SD	Median	p25	p75
DUISBURG[b]	MW	227	132.9 ± 88.6	115.2	79.2	172.8	227	284.3 ± 365.5	194.4	126.0	295.2
FAROES2[b]	MS	173	526.9 ± 469.4	394.4	214.3	664.8	173	1862.8 ± 1557.8	1322.8	848.2	2284.6
FAROES3[b]	BM	587	405.4 ± 362.1	310.7	194.7	507.6	587	711.1 ± 792.6	502.2	295.5	829.5
FLEHSI	CP	1061	73.3 ± 56.7	60.0	30.0	104.3	1107	316.4 ± 346.2	220.0	131.8	378.1
GRD	CP/CS	523	170.6 ± 99.7	150.0	110.0	210.0	–	–	–	–	–
HUMIS[b]	BM	418	43.2 ± 19.9	39.3	30.7	51.1	418	74.6 ± 109.8	49.9	34.6	79.9
INMA cord	CS	1254	157.3 ± 113.5	135.2	91.0	193.6	1559	1409.3 ± 2350.7	603.0	307.3	1509.9
INMA mat[b]	MS	868	106.7 ± 69.9	93.8	62.4	134.2	869	395.2 ± 1549.8	198.7	124.7	311.9
Greenland[b]	MS	546	206.8 ± 278.7	126.4	69.8	233.3	546	694.8 ± 749.2	477.1	261.7	843.7
Warsaw[b]	MS	199	17.7 ± 13.9	15.3	8.4	23.8	199	857.6 ± 539.0	695.5	499.0	1096.8
Kharkiv[b]	MS	575	34.8 ± 27.7	28.2	18.2	43.7	575	1145.2 ± 794.2	952.6	673.9	1329.1
PCB cohort	CS	1055	392.5 ± 456.3	271.4	169.8	448.1	1055	1325.2 ± 1328.2	1015.3	556.7	1667.8
PÉLAGIE	CS	396	126.1 ± 77.7	110.0	75.0	160.0	395	253.3 ± 335.8	180.0	98.0	300.0
RHEA[b]	MS	1115	57.5 ± 41.6	47.4	32.2	71.7	1115	932.5 ± 1092.6	623.6	361.1	1103.3
Combined	CS	8997	166.6 ± 251.7	100.0	47.4	190.0	8825	846.8 ± 1410.2	447.2	200.0	1000.0

Abbreviations: BM: breast milk; CS: cord serum; CP: cord plasma; MS: maternal serum; MW: maternal whole blood; SD: standard deviation; p: percentile. The INMA cohort was represented by two (INMA cord and INMA mat) because OCs were determined in different matrices. The INUENDO cohort was divided into three populations: Greenland, Kharkiv and Warsaw. The PCB cohort included Michalovce and Svidnik.

[a] Calculated based on datasets on PCB-153 or *p,p′*-DDE and birth weight (Supplemental Material, Table S4).

[b] See Supplemental Material, p. 1–5 and Table S1 for more information on conversions from maternal serum/whole blood and breast milk to cord serum concentrations.

most extreme values of PCB-153 concentrations, i.e. restricting to those below 1180 ng/L, the analysis also showed an inverse linear relationship (Fig. 1; *p*-value: 0.001) and the reduction in birth weight appeared to be slightly stronger [−215 g (95% CI: −349, −81)] (Table 2). The GAM showed effects on birth weight over the entire exposure range, even at low levels. The meta-analysis including all PCB-153 concentrations showed a reduction in birth weight of −171 g per 1 μg/L PCB-153 (95% CI: −271, −70) (Table 2 and Supplemental material, Fig. S4). No association was found between cord serum *p,p′*-DDE concentrations and birth weight (Table 2).

Further analyses showed evidence for interactions between some covariates and the PCB-153 association on birth weight (Table 3). The greatest reductions were found in non-Caucasian mothers (*p*-interaction < 0.001) and smokers (*p*-interaction < 0.001). Even though the interaction was not significant, girls and the highest education strata showed the greatest reduction in birth weight (Table 3). There was no indication of modification of the PCB-153 effect on birth weight by maternal weight status, GWG categories, time of sampling collection, and geographical distribution of cohorts (Table 3). Given these results, we explored the following two-way interactions: i) smoking × sex, ii) smoking × education, and iii) sex × education. We did not explore the two-way interaction of the ethnicity variable with other covariates due to the high heterogeneity of the non-Caucasian group. Significant interactions (*p*-interaction < 0.05) were shown for smoking × sex and smoking × education. Therefore, we examined three-way interactions between the PCB-153 effect and each of these two-way interactions. The three-way interaction PCB-153 × smoking × sex resulted borderline statistically significant (*p*-interaction = 0.06) and the interaction of PCB-153 × smoking × education was statistically significant (*p*-interaction = 0.01). The greatest reduction in birth weight was shown among girls born from smoking

Table 2
Adjusted regression coefficients (β — 95% Confidence Interval) of cord serum PCB-153 and *p,p′*-DDE (ng/L) with birth weight (g).

Cohort	PCB-153		*p,p′*-DDE	
	N	Adjusted[a] β (95% CI)	N	Adjusted[a] β (95% CI)
DUISBURG	227	−0.817 (−1.596, −0.038)	227	−0.081 (−0.260, 0.098)
FAROES2	173	−0.063 (−0.203, 0.076)	173	−0.016 (−0.057, 0.025)
FAROES3	587	−0.038 (−0.133, 0.057)	587	−0.021 (−0.065, 0.022)
FLEHSI	1061	−0.658 (−1.108, −0.207)	1107	0.037 (−0.030, 0.104)
GRD	523	−0.391 (−0.760, −0.022)	–	–
HUMIS	418	−1.034 (−3.455, 1.388)	418	−0.149 (−0.558, 0.260)
INMA cord	1254	−0.362 (−0.556, −0.168)	1559	−0.008 (−0.017, 0.001)
INMA mat	868	−0.006 (−0.395, 0.383)	869	0.012 (−0.004, 0.028)
Greenland	546	−0.218 (−0.371, −0.065)	546	−0.058 (−0.114, −0.001)
Warsaw	199	−0.149 (−4.895, 4.597)	199	−0.101 (−0.214, 0.012)
Kharkiv	575	0.874 (−0.236, 1.983)	575	0.015 (−0.023, 0.054)
PCB cohort	1055	−0.042 (−0.093, 0.010)	1055	−0.018 (−0.037, 0.000)
PÉLAGIE	396	−0.364 (−0.901, 0.172)	395	0.014 (−0.099, 0.127)
RHEA	1115	−0.305 (−0.928, 0.317)	1115	−0.016 (−0.037, 0.005)
Combined effect — pooled analysis (multiple imputation)	8997	−0.194 (−0.314, −0.074)	8825	−0.009 (−0.019, 0.007)
Excluding high concentrations[b]	8907	−0.215 (−0.349, −0.081)	8737	−0.010 (−0.025, 0.045)
Combined effect — pooled analysis (complete case)	8512	−0.174 (−0.280, −0.068)	8035	−0.008 (−0.019, 0.004)
Excluding high concentrations[c]	8427	−0.196 (−0.314, −0.079)	7988	−0.012 (−0.025, 0.014)
Combined effect — meta-analysis (multiple imputation)	8997	−0.171 (−0.271, −0.070)	8825	−0.008 (−0.019, 0.003)

Greenland, Kharkiv and Warsaw are part of the INUENDO cohort.

[a] Adjusted for cohort, maternal age at delivery, parity, child's sex, maternal pre-pregnancy BMI, maternal height, maternal smoking during pregnancy, maternal education, time of sample collection, gestational age, and the square of gestational age. Cohort and PCB-153 or *p,p′*-DDE were included as random effects.

[b] PCB-153 concentrations ≥ 1180 ng/L (n = 90); *p,p′*-DDE concentrations ≥ 6050 ng/L (n = 88).

[c] PCB-153 concentrations ≥ 1180 ng/L (n = 85); *p,p′*-DDE concentrations ≥ 6050 ng/L (n = 47).

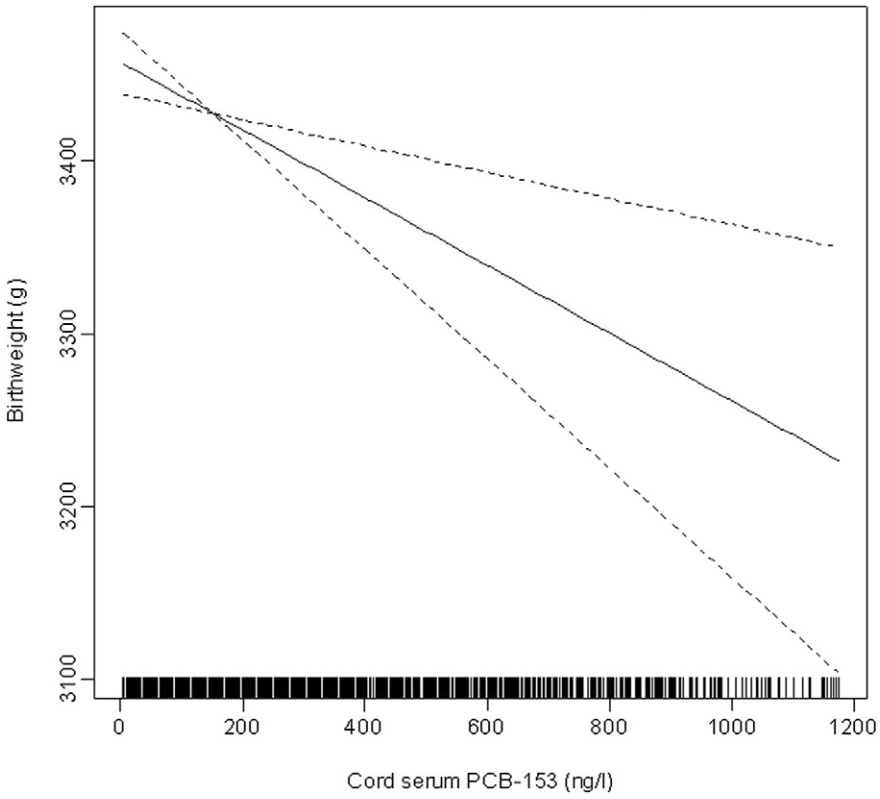

Fig. 1. General additive models of the association between cord serum PCB-153 (ng/L) and birth weight (g) (n = 8427). The continuous line is the smoothed function for PCB-153 and discontinuous lines are the 95% CIs. Adjusted for maternal age at delivery, parity, child's sex, maternal pre-pregnancy BMI, maternal height, maternal smoking during pregnancy, maternal education, time of sample collection, gestational age, and the square of gestational age. Cohort and PCB-153 were included as random effects. Complete case analysis excluding PCB-153 concentrations ≥ 1180 ng/L. GAM model only needs 1 degree of freedom, i.e. the function fitted by the model is linear.

mothers (β per 1 ng/L PCB-153 increase: Boys/Maternal non-smoking: −0.148; Boys/Maternal smoking: −146.43; Girls/Maternal non-smoking: −141.03; Girls/Maternal smoking: −228.19) (Fig. 2).

The association between PCB-153 and birth weight did not change after leaving out one population each time (data not shown). Results did not change substantially when another cohort-specific conversion factor was taken for Greenland, Warsaw, Kharkiv, and RHEA, and after applying the conversion factors used by Govarts et al. (2012) (data not shown). Restricting the analysis to term births did not change the coefficient. Associations were also comparable when modeling lipid-adjusted and log-transformed PCB-153 concentrations. When *p,p′*-DDE was included in the model, the beta coefficient for the PCB-153 association did not change (data not shown). Adjustment for absolute GWG or estimated fat mass in cohorts where available [equivalent pooled analysis n = 4266: −260 g (95% CI: −470, −50)], reduced the coefficient for PCB-153 by 48% [−135 g (95% CI: −298, 27)] and 34% [−182 g (95% CI: −363, −0)] (Supplemental material Table S7), respectively.

4. Discussion

This study suggests that there is an inverse linear exposure–response relationship between prenatal exposure to PCB-153 and birth weight in a sample of more than 9000 pregnant women of 11 birth cohorts in Europe. This reduction in birth weight related to PCB-153 exposure seems to be stronger among children of mothers who were non-Caucasian or had smoked during pregnancy. We also identified that girls whose mothers smoked during pregnancy were the most susceptible subgroup. In addition, we found that although GWG may potentially confound the association between PCB-153 and birth weight, we still saw a large reduction in birth weight with an increase in PCB-153 levels. Infants with low birth weight, generally defined as a weight below 2500 g, have an increased risk of morbidity and mortality in the first year of life and an increased risk of cardiovascular and other diseases later in life (Barker, 2007; Elgen et al., 2002; Iliadou et al., 2004; McCormick, 1985); therefore, our results may have public health implications for infant and later adult health.

The impact of prenatal PCB exposure on birth weight has been investigated in nearly 20 studies (El Majidi et al., 2012). El Majidi et al. (2012) performed a systematic analysis of all these studies to verify the plausibility of a causal relationship between PCB exposure and low birth weight. First, they standardized PCB concentrations per kg of lipids in maternal plasma and afterwards, they compared 'standardized biological concentration–birth weight' relationship across studies by applying the Bradford Hill criteria (Hill, 1965). They concluded that it is unlikely that PCBs at current exposure levels in the European population are associated with low birth weight (<2500 g). However, the lack of harmonization of PCB concentrations (i.e. different methods, matrices, units), the measurement of different congeners among cohorts, and the small study population size (a thousand subjects the largest) may explain why this relationship could not be demonstrated. In our large study, with measurements of the same PCB congener in all cohorts, and using cohort-specific conversion factors to compare between matrices, we identified an inverse linear exposure–response relationship. We have to consider, however, that due to the high uncertainty of the estimate at the end of exposure distribution (n = 90 PCB-153 ≥ 1180 ng/L), it is difficult to make conclusions at this high level of exposure. Our meta-analysis results were consistent with those reported by Govarts et al. (2012). We also found no indications that fetal exposure to PCB-153 was related to gestational age. In contrast, Kezios et al. (2012) found evidence of a reduction in gestational age associated with prenatal PCBs exposure. This study included 600 Californian pregnant women

Table 3
Effect modification[a] (β − 95% Confidence Interval) of the association between cord serum PCB-153 (ng/L) and birth weight (g).

Characteristics	N	Adjusted[b] β (95% CI)	*p* for interaction
Base model			
PCB-153 and birth weight (complete case)	8512	−0.174 (−0.280, −0.068)	–
Effect modifiers			
Child's sex			0.069
Boy	4413	−0.119 (−0.256, 0.019)	
Girl	4099	−0.157 (−0.258, −0.056)	
Maternal pre-pregnancy BMI			0.193
<25 kg/m^2	6393	−0.128 (−0.218, −0.039)	
≥25 kg/m^2	2119	−0.213 (−0.408, −0.019)	
Gestational weight gain[c]			0.099
Low	1037	−0.168 (−0.445, 0.108)	
Recommended	1657	0.035 (−0.058, 0.128)	
High	1572	−0.118 (−0.350, 0.114)	
Maternal education			0.006
Low	1897	−0.121 (−0.213, −0.029)	
Medium	3966	−0.124 (−0.207, −0.041)	
High	2649	−0.185 (−0.386, 0.016)	
Maternal ethnicity[d]			<0.001
Caucasian	6666	−0.104 (−0.198, −0.010)	
Non-Caucasian	799	−0.199 (−0.312, −0.087)	
Maternal smoking during pregnancy[e]			<0.001
No	6427	−0.095 (−0.179, −0.011)	
Yes	2085	−0.204 (−0.339, −0.068)	
Maternal alcoholic beverages during pregnancy[f]			0.598
No	6379	−0.144 (−0.239, −0.049)	
Yes	1838	−0.174 (−0.353, 0.005)	
Time of sample collection			0.056
1st trimester	759	0.133 (−0.281, 0.546)	
2nd trimester	698	−0.311 (−0.518, −0.105)	
3rd trimester	2808	−0.037 (−0.083, 0.009)	
Postnatal	4247	−0.274 (−0.450, −0.098)	
Geographical region[g]			0.667
Northern–Western cohorts	3377	−0.194 (−0.337, −0.050)	
Southern–Eastern cohorts	5135	−0.164 (−0.322, −0.006)	

Abbreviations: BMI: body mass index; GWG: Gestational Weight Gain.
[a] Complete case analysis.
[b] Adjusted for cohort, maternal age at delivery, parity, child's sex, maternal pre-pregnancy BMI, maternal height, maternal smoking during pregnancy, maternal education, time of sample collection, gestational age, and the square of gestational age. Cohort and PCB-153 were included as random effects.
[c] Pooled analysis (complete case) for the subset of population with GWG data available (N = 4266): −0.260 (95% CI: −0.470, −0.050).
[d] Information on ethnicity was not available in FLEHSI. Pooled analysis (complete case) for the subset of population with ethnicity variable available (N = 7465): −0.156 (95% CI: −0.256, −0.055).
[e] Smokers were included in one category (≤10 cigarettes/day + >10 cigarettes/day). Pooled analysis (complete case) for 2 categories of smoking (no/yes): −0.192 (95% CI: −0.308, −0.079).
[f] Pooled analysis (complete case) for the subset of population with alcohol consumption data available (N = 8217): −0.165 (95% CI: −0.269, −0.060).
[g] Northern–Western cohorts: DUISBURG, FAROES2, FAROES3, FLEHSI, Greenland, GRD, and HUMIS; Southern–Eastern cohorts: INMA cord, INMA mat, Kharkiv, Warsaw, PCB cohort, PÉLAGIE, and RHEA.

enrolled between 1959 and 1966 and with a median PCB-153 concentration of 650 ng/L. Our larger population, including pregnant women enrolled after 1990 and with lower PCB-153 concentrations than those reported in Kezios et al. (2012) (median: 100 ng/L) may explain the different results.

The biological activities of PCBs have been reported to include both estrogenic and antiestrogenic effects in various in vitro and in vivo models (Bonefeld-Jorgensen et al., 2001; Pliskova et al., 2005). Estrogenic activity of PCB-153 could potentially be the underlying mechanism that explains the reduction in birth weight shown here (Welshons et al., 2003). Moreover, there is some evidence that PCB can perturb thyroid function (Takser et al., 2005) but it is still not clear whether this is the mechanism that can impact fetal development (Kezios et al., 2012). We were unable to identify any exposure level at which there was no effect on birth weight; but we have to consider that the GAM analysis might just not be sensitive enough to detect deviations, particularly at low doses. The concept of a 'dose-threshold', however, as a dose below of which the effect is assumed to be zero, is losing support since toxicologists claim that it is impractical since zero effects cannot be determined (Slob, 2007). They state that it is more appropriate to estimate the point of departure index, derived from the benchmark dose approach and equivalent to the dose where the effect is below some effect size (Slob, 2007). Further studies assessing the exposure–response association between OCs and birth outcomes might address this issue, as has been done for intellectual impairment (Jacobson et al., 2002). It should be noted however, that although PCB-153 represents nearly 28% of total PCBs (Hagmar et al., 2006), the exposure–response relationship described here may not apply for other PCB congeners (Bonefeld-Jorgensen et al., 2001; Connor et al., 1997; Kraugerud et al., 2010). Moreover, the estrogenic potency of PCB-153 is 10^3–10^4 times weaker than estradiol (Bonefeld-Jorgensen et al., 2001). If the effect shown here is indeed explained by the estrogenic activity of PCB-153, then it is unlikely that only the measured PCB-153 concentrations can elicit the observed response unless many PCB congeners and related compounds act in concert with additive or synergistic effects, as it has been demonstrated in some animal studies (Christiansen et al., 2012).

A stronger effect of environmental toxicants on birth weight among smokers has also been reported for PCBs (Rylander et al., 1995; Sagiv et al., 2007) and hexachlorobenzene (HCB) (Eggesbo et al., 2009). Cigarette smoking contains a number of toxins that can cause cellular damage and disrupt immune function (Noakes et al., 2003), but the biological mechanisms for the modifying effect of smoking remain unknown. Further analysis in our population allowed us to identify a PCB–smoking–sex interaction and newborn girls whose mothers smoked during pregnancy appeared to be the most susceptible subgroup. Although the two way interaction between PCB-153 and sex was not significant, girls seemed to be more affected by the effect of PCB-153 on birth weight than boys. This contradicts most of the publications reporting sex-specific results frequently indicating a stronger reduction in boys (Hertz-Picciotto et al., 2005; Rylander et al., 1995, 1996; Tsukimori et al., 2012). However, these studies used fish consumption as an indicator of exposure to PCBs during pregnancy (Rylander et al., 1995, 1996) or had a modest sample size [n = 399 (Hertz-Picciotto et al., 2005) and n = 101 (Tsukimori et al., 2012)]. On the contrary, some studies investigating the obesogenic effects of prenatal PCB exposure have indicated a higher risk of overweight in girls (Gladen et al., 2000; Lamb et al., 2006; Valvi et al., 2012). Children with lower weight at birth tend to growth faster during the first years of life than children with higher birth weights and they are at higher risk of obesity later in childhood and adult life (Baird et al., 2005; Labayen et al., 2012; Ong et al., 2000). Thus, the increased risk in girls for childhood obesity linked to prenatal PCB exposure may be mediated, at least partially, by the greatest reduction in birth weight among girls shown here. However, the biological mechanisms underlying the possible interaction between PCB-153 and sex remain to be established. Besides, the reason why coexistence of these two factors (girls and maternal smoking) may increase the PCB effect susceptibility needs to be further explored.

Non-Caucasian mothers including Inuit (100% Greenland), Romanian (21.0% PCB cohort), Latin American (3.0% INMA mat and cord), African (0.4% DUISBURG), Asian/Eastern European (3.1% DUISBURG), and Asian (1.9% HUMIS) had a greater PCB-associated reduction in birth weight than Caucasian mothers. Since individual interactions per cohort did not reach the level of statistical significance (data not shown), we did not investigate whether this high susceptibility was for the overall group of non-Caucasian or only for some specific subgroups. This race vulnerability to PCB effects has been suggested in

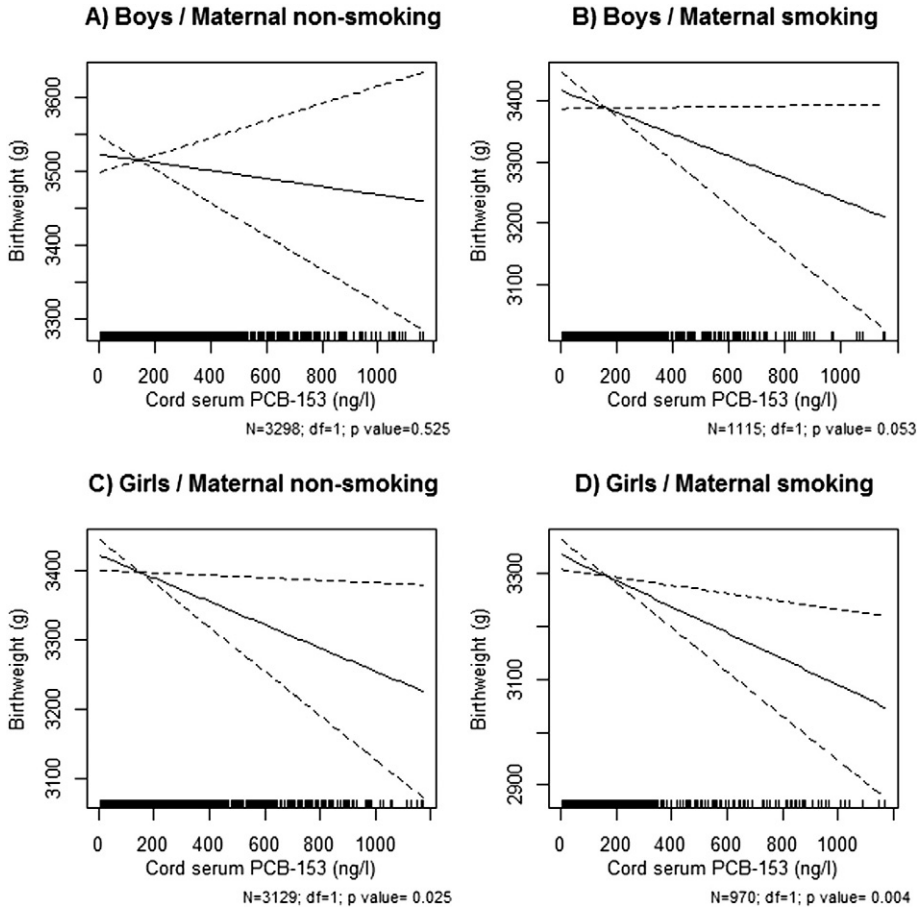

Fig. 2. General additive models of the association between cord serum PCB-153 (ng/L) and birth weight (g): Boys/Maternal non-smoking (*A*), Boys/Maternal smoking (*B*), Girls/Maternal non-smoking (C), and Girls/Maternal smoking (D). The continuous line is the smoothed function for PCB-153 and discontinuous lines are the 95% CIs. Adjusted for cohort, maternal age at delivery, parity, maternal pre-pregnancy BMI, maternal height, maternal education, time of sample collection, gestational age, and the square of gestational age. Cohort and PCB-153 were included as random effects. Complete case analysis excluding PCB-153 concentrations ≥ 1180 ng/L. In all cases GAM models only needs 1 degree of freedom (df), i.e. the function fitted by the model is linear.

various studies on birth weight and other health effects (Sonneborn et al., 2008; Wojtyniak et al., 2010). Non-Caucasian mothers from our population had higher PCB-153 levels and lower education level, and tended to smoke more during pregnancy compared to Caucasian mothers. These particular characteristics of non-Caucasian mothers and others not included in our analysis may have led to an enhanced susceptibility in this population. Finally, we also found a greater reduction in birth weight among the highest education strata. Although we tried to harmonize this variable among cohorts as best as possible, there may still be country differences in educational levels and hence it becomes difficult to draw conclusions.

Changes in the weight gain of the mother can potentially confound the association between PCB-153 and birth weight. Pregnancy weight gain can both increases the volume of lipids, thereby diluting PCB levels in blood (Glynn et al., 2011), and increases the birth weight of the offspring (Siega-Riz et al., 2009). However, GWG can also be considered a mediator because PCBs may act as obesogens and increase weight (Tang-Peronard et al., 2014). In our analysis, after adjusting the model for absolute GWG or estimated fat mass the PCB-153 coefficient was reduced significantly; however, a large reduction in birth weight associated with an increase in PCB-153 levels was still present, particularly after including estimated fat mass which is a more precise surrogate of maternal lipid gain during pregnancy. The reduction was still present after subtracting birth weight from GWG (data not shown). These findings suggest that GWG may confound this association or maybe partially mediate it since a direct effect of PCB-153 on birth weight still exists. If this is a partial mediation, we must consider the possibility of omitted mediators in the direct relationship between PCBs and birth weight (Zhao et al., 2010). To elucidate whether GWG is a potential confounder or partial mediator, further studies with repeated measurements throughout pregnancy are needed.

One of the main limitations of this study is that only one PCB congener 153 was measured in all cohorts. There are 209 PCB congeners which differ in structure and mechanism of action and hence may have different health outcomes (Yorita Christensen and White, 2011). Although PCB-153 is the major PCB congener and is highly correlated with other congeners and with the total sum of PCBs (Hagmar et al., 2006), the magnitude of the correlations varies. In our population for example, in cohorts where data on various PCB congeners were available, the Spearman correlation coefficients between them ranged from 0.23 to 1.00. Also, there is likely to be different mixtures of congeners within the different cohorts. Recently, the RHEA cohort conducted a multipollutant model including concentrations of 6 PCB congeners, *p,p′*-DDE, and HCB and showed that the association with birth weight was mainly driven by HCB (Vafeiadi et al., 2014). We did not have HCB concentrations available at the moment of the study; further studies should add more congeners and other persistent organic pollutants in the analysis. Moreover, in a multipollutant model including DDT and *o,p′*-DDT, Kezios et al. (2013) found a reduction in birth weight and gestational age of 153 g and 0.5 days associated with prenatal *p,p′*-DDE exposure, respectively. When DDT and *o,p′*-DDT were not considered, *p,p′*-DDE was not associated neither with birth weight nor gestational age. However, we have to consider that this study was done in an old population with much

higher *p,p′*-DDE levels (median: 38,700 ng/L) than our population (median: 447 ng/L). Further research is needed to disentangle whether the reduction in birth weight and the susceptible subgroups identified could be accounted for other individual PCB congeners, for the mixture of them or for other environmental contaminants.

We were able to harmonize common potential confounders; however, this implies the loss of some particular and valuable cohort characteristics. Differences in the coefficient of association between PCB-153 and birth weight in this paper compared to those reported by Govarts et al. (2012) were mainly due to the increase in sample size in the RHEA cohort: from 30 to 1115 mother–child pairs (Vafeiadi et al., 2014). The coefficient in this cohort changed substantially from 11.27 (95% CI: −20.89, 43.44) to −0.31 (95% CI: −0.93, 0.32), which is more consistent with the other cohorts. The strength of this study relies on its large sample size that allowed us to better describe the shape of the relationship and to identify effect modifiers. Compared with the previous study (Govarts et al., 2012), we performed multiple imputation using chained equations to deal with missing values in covariates (Spratt et al., 2010). No significant differences in covariate distributions were shown between observed and imputed data of each dataset (PCB-153 and birth weight dataset, Supplemental material, Table S8). Furthermore, we calculated cohort-specific conversion factors rather than general conversion factors, providing more valid comparisons of OC measurements in the different matrices within each cohort.

5. Conclusion

This study suggests that the association between low-level exposure to PCB-153 and birth weight exists and follows an inverse linear exposure–response relationship, with effects even at low levels, and that maternal smoking and ethnicity modify this association.

Conflict of interest

Nothing to declare.

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Appendix A. Supplementary data

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