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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.