Full length article

Evaluating the neurotoxic effects of lactational exposure to persistent organic pollutants (POPs) in Spanish children

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ABSTRACT

Although the brain continues developing in the postnatal period, epidemiological studies on the effects of postnatal exposure to neurotoxic POPs through breast-feeding remain mostly inconclusive. Failure to detect associations between postnatal exposure and health outcomes may stem from the limitations of commonly employed approaches to assess lactational exposure. The aim of the present study was to assess whether lactational exposure to polychlorinated biphenyl-153 (PCB-153), dichlorodiphenyldichloroethylene (DDE), or hexachlorobenzene (HCB) as estimated with a physiologically based pharmacokinetic (PBPK) model, is associated with decrements in mental and psychomotor development scores of the Bayley Scales of Infant Development (BSID) test in children aged around 14-months of a subsample (N = 1175) of the Spanish INMA birth cohort, and to compare this with the effects of prenatal exposure. Although in the present study population PCB-153, DDE and HCB exposure increased within the first months of postnatal life, no associations were found between different periods of postnatal exposure to these compounds and mental or psychomotor scores. Increasing prenatal PCB-153 concentrations were associated with worse mental and psychomotor scores, although significance was only reached for psychomotor development ([β [95%CI] = −1.36 [−2.61, −0.11]). Indeed, the association between exposure and effects observed during prenatal life weakened gradually across periods of postnatal life. Results of the present study suggest that, although breastfeeding increases children’s blood persistent organic pollutants (POPs) levels during postnatal life, deleterious effects of PCB-153 on neuropsychological development are mainly attributable to prenatal exposure.

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1. Introduction

Many studies suggest that prenatal exposure to persistent organic pollutants (POPs), such as polychlorinated biphenyls (PCBs), dichlorodiphenyldichloroethylene (DDE), or hexachlorobenzene (HCB), can disrupt neuropsychological development (Eskenazi et al., 2009; Ribas-Fito et al., 2001, 2007). Although the brain continues developing in the postnatal period (Rice and Barone, 2000; Selevan et al., 2000), epidemiological studies on
postnatal exposure to POPs through breastfeeding remain inconclusive (Gladen et al., 1988; Huisman et al., 1995; Jorissen, 2007; Koopman-Esseboom et al., 1996; Pan et al., 2009; Wilhelm et al., 2008a, b). In these previous studies, postnatal exposure assessments have mostly relied on metrics of overall exposure, such as multiplying the level of POPs in breast milk by the duration of breastfeeding. Where specific postnatal windows of susceptibility to neurotoxicants may exist, these measures may not permit the detection of associations with neuropsychological development outcomes.

In order to refine postnatal exposure assessment, a physiologically based pharmacokinetic (PBPK) model was developed to estimate infant blood POP concentration profile over the first year of life (Verner et al., 2009). When using the PBPK-derived estimates of postnatal exposure in a birth cohort of Inuits from Northern Quebec (Canada), an association was detected between blood PCB-153 levels around the 4th month of life and infants’ ability to control their activity (Behaviour Rating Scale of the Bayley Scales of Infant Development (BSID) test) at the age of 11 months (Verner et al., 2010), suggesting the existence of postnatal windows of susceptibility to neurotoxicants. However, in this study of around 170 children, only behavioural outcomes were assessed.

In a previous study, which used the same birth cohort than the present study, prenatal exposure to PCBs, but not DDE or HCB, was associated with a psychomotor development impairment of the children at the age of 14 months (Forns et al., 2012). The aim now is to evaluate whether lactational exposure to DDE, HCB and PCB-153, as estimated with a PBPK model, is associated with decrements in mental and psychomotor functions and to compare this with the effects of prenatal exposure.

2. Methods

2.1. Study population

This study was based on three Spanish regions (Gipuzkoa – Basque Country, Sabadell – Catalonia, and Valencia – Valencian Country) belonging to the INMA-Infancia y Medio Ambiente (Environment and Childhood) – Project (Guxens et al., 2012a). All regions followed the same protocol and started recruiting pregnant women between 2003 and 2008 (Sabadell N = 657, Valencia N = 855, Gipuzkoa N = 638). Pregnant women coming for their first trimester routine antenatal care visit in the main public hospital or health centre of reference and who fulfilled the inclusion criteria (age above 16 years, to have a single pregnancy, intention to deliver in the reference hospital, and no problems of communication) were invited to participate. Protocol details are described elsewhere (Guxens et al., 2012a). Out of the initial 2150 mother–child pairs enrolled, 339 had no information on maternal POP levels, 247 were not assessed for mental and psychomotor development and 295 had no information on variables needed in the PBPK model (sex, birth weight, type and duration of breastfeeding, maternal age at delivery, maternal age at the time of blood draw, concentration of lipids in maternal serum, age of the child at the time of neuropsychological development assessment, and weight of the child at each month of postnatal life during the 1st year of life). Out of the 1269 remaining children, 10 were diagnosed with pathologies and were excluded, as well as those flagged by psychologists because of difficulties and suboptimal cooperation at the time of the evaluation (N = 75).

Finally, 9 children had missing information on co-variables used in the adjusted models, so these were excluded as well, resulting in a total of 1175 participants in the present study. This study was conducted with the approval of the hospital ethics committees in the participating regions and written informed consent was obtained from the parents of all children.

2.2. Child neuropsychological assessment

Children’s mental and psychomotor development was assessed at around 14 months of age (range 11–21 months) using the BSID-I (Bayley, 1977). The mental scale consisted of 163 items that assessed age-appropriate cognitive development in areas such as performance ability, memory, and first verbal learning. The psychomotor scale consisted of 81 items assessing fine and gross motor development. All testing was done in the health care centre in the presence of the mother by eight specially trained psychologists who were blind to exposure levels or any other information. To limit inter-observer variability, we applied a strict protocol, including training sessions where inter–observer differences were quantified and three sets of quality controls (inter-observer-reliability-tests) undertaken during the fieldwork. A high inter-rater reliability, estimated in 12 children through intra-class correlation analyses, was observed with coefficients of 0.90 for mental test scores, and 0.91 for psychomotor test scores. Raw scores were standardized for child’s age in days at test administration using a parametric method for the estimation of age-specific reference intervals. The parameters of the distribution were modelled as a fractional polynomial function of age and estimated by maximum likelihood. Residuals were then standardized to a mean of 100 points with a standard deviation of 15 points to homogenize the scales (Guxens et al., 2012b).

2.3. Prenatal exposure assessment

Concentrations of PCB-153 (in the present study used as a marker of PCBs exposure since it is the PCB congener with the highest levels and detection rate in the present cohort), DDE and HCB were measured in maternal serum samples taken between the 7th and the 26th week of pregnancy (median = 12.9 weeks) from peripheral veins. Serum samples were stored in crystal tubes at −20 °C (Sabadell and Gipuzkoa) or at −80 °C (Valencia) and analyzed by gas chromatography using methods described elsewhere (Goni et al., 2007). The limits of detection (LOD) were 0.071 ng/ml in Sabadell and Gipuzkoa and between 0.01 and 0.071 ng/ml in Valencia. International intercalibration exercises showed that differences of levels between regions were not due to lab differences. For comparison purposes, values in Valencia below 0.071 ng/ml were set as non-detected. Samples with non-detectable levels were then set at a value below the LOD using univariate simple imputation sampling. Exposures were expressed on a lipid basis in ng/g lipid using the method described in Phillips et al. (1989).

2.4. Postnatal exposure estimation – PBPK modelling

The PBPK model used to simulate postnatal exposure to POPs in this study is detailed in a previous paper (Verner et al., 2009). In a nutshell, this PBPK model is a mathematical representation of the absorption, distribution, metabolism and excretion of POPs in both the mother and child. For any exposure scenario and individual physiology, the model can generate blood and tissue level vs time profiles. Tissue volumes and lipid composition, blood flows and breast milk composition and daily intake were scaled according to each mother and children weight, height, age and gender. Breast milk POP levels are estimated based on the maternal blood POP levels measured during the prenatal period. Maternal daily oral dose throughout her life is estimated through an iterative optimization process so that simulated blood levels match those measured in the study. This oral daily dose continues during the postnatal period. Both the duration of exclusive (period during which the child is only fed with breast milk) and partial breastfeeding (period during which the child is fed both breast
milk and other types of food) were abstracted from questionnaires administered at the time of neuropsychological testing. In order to characterize breast milk intake during partial breastfeeding in this population, we used data from 382 mother–child pairs enrolled in the region of Sabadell for which we collected information on the percentage of food intake attributable to breastfeeding during the period when children were fed both breast milk and other solids/liquids. In this subset of the population, breast milk represented 71% of total food intake during the first month of the partial breastfeeding period and 5% during the last month. These percentages were independent of the duration of partial breastfeeding. Therefore, we defined breast milk intake during this period as a constant decrease from 71 to 55% of the daily intake in exclusively breastfed children over the period of partial breastfeeding.

We traced body weight profiles for the first year of life based on month-by-month weight data. Participants were weighed on average 6 times (ranging from 2 to 12) between birth and 12 months of age during their visits to the paediatrician. Missing birth weight values were estimated by linear regression based on weight at 1 month (n = 3). The Jens–Bayley (van Dommelen et al., 2005) growth model was used to estimate missing monthly weight data based on available measurements. Height profiles were based on standard growth curves and children’s height at 13.8 months of age (range = 11.4–19.5). For each child, we simulated blood POP level profiles for the first year of life. We extracted the blood concentration at each month for a total of 12 exposure estimates. The PBPK model was coded in ACSLX software (Aegis Technologies Group, Inc., Huntsville, AL, USA). A script was developed to extract data from databases and compile results in Microsoft Excel 2010 spreadsheets (Microsoft, Redmond, WA, USA).

2.5. Other variables

Information on co-variables was extracted from the questionnaires answered by the mothers during the 1st and the 3rd trimester of pregnancy and 14 months after delivery: maternal age, education and region of birth, maternal smoking during pregnancy, parity (first child or not), day care attendance, maternal consumption of total fish during pregnancy and maternal and paternal social class (defined using the UK Registrar General’s 1990 classification according to occupation by ISCO88 code: non-manual – professionals, managers and technicians, other non-manual – skilled manual and non-manual jobs, manual – semiskilled and unskilled jobs). Maternal pre-pregnancy body mass index (BMI), gestational age and weight at birth were collected from clinical records or reported by mothers.

2.6. Statistical methods

We log-transformed POP concentrations for statistical analyses. Coefficients for the association between the different POPs concentrations and the BSID’s mental and psychomotor scores were estimated using linear regression models, where each exposure was introduced individually. Given the high correlation of simulated children’s blood levels between contiguous months of postnatal life, four periods of three months were created, where monthly levels were averaged to better untangle the importance of each period of exposure and to be able to adjust one exposure for the other (multi-exposure model) whilst avoiding problems of collinearity. However, we also assessed the role of postnatal exposure at each month during the first 12 months. Linearity of the association between POPs and BSID mental and psychomotor scores was assessed by using Generalized Additive Models (GAM); associations between DDE and mental and psychomotor test scores were not linear (p-gain for non-linearity < 0.05 and 0.13, respectively). For this reason, DDE levels were included in the models as a binary variable, where the median was used as a cut-off. Covariates were considered using a backward selection procedure; those showing associations with p-value < 0.05 with mental or psychomotor test scores or those that resulted in a change in estimate of ≥10% in the linear regression models, were retained in the models. All the analyses were done with STATA 10 (Stata Corporation, College Station, TX, USA).

3. Results

There were no differences in POPs levels between participants and non-participants. However, they differed for almost all the socio-demographical characteristics as shown in Supplemental material, Table 1 (p < 0.05). For instance, participants were born to mothers of a higher social class and educational level. Also, none of the participants had a gestational age below 37 weeks and the percentage of children with low birth-weight (≤2500 g) was much lower. Participants were breastfed for a longer period and had better mental and psychomotor BSID scores.

PCB-153, DDE and HCB were detected in a high proportion of maternal serum samples (95.1%, 99.5% and 91.2% of the samples, respectively). DDE was the compound present in the highest concentrations in maternal serum, approximately three times higher than PCB-153 or HCB (Table 1). Monthly estimations obtained with the PBPK model show that the highest levels of POPs were reached around the 3rd month of life for DDE (GM = 206.6 ng/g lipid) and HCB (GM = 63.9 ng/g lipid) and within the 4th month of life for PCB153 (GM = 62.9 ng/g lipid) (full data not shown). When calculating these estimations by three-month periods (Table 1), DDE and HCB highest levels were reached during the first period (GM = 199.17 and 62.29 ng/g lipid, respectively), whereas highest levels of PCB-153 were reached during the second period (GM = 60.85 ng/g lipid). The correlation between prenatal and estimated postnatal concentrations of the different POPs decreased with increasing child age (Supplemental material, Table 2). Correlations between different compounds showed that prenatal DDE concentrations were poorly correlated to PCB-153 or HCB concentrations (r = 0.11 and 0.22, respectively), whereas the correlation between PCB-153 and HCB was 0.45. However, the correlation between compounds increased across subsequent months of exposure; at 12 months of age there was a correlation of 0.74 and 0.72, respectively, between DDE and PCB-153 between DDE and HCB, whereas the correlation between PCB-153 and HCB was 0.82 (data at each month not shown).

The associations between postnatal estimates of exposure and BSID mental and psychomotor test scores were not statistically significant for any of the three-month periods assessed (Table 2), whereas increasing prenatal PCB-153 concentrations were significantly associated to a lower psychomotor score (adjusted β coefficient [95%CI] = −1.36 [−2.61, −0.11]). Associations observed between PCB-153 during prenatal life and psychomotor test scores weakened gradually across periods of postnatal life (1st period: = −0.41 [−1.37, 0.54]; 2nd period: = −0.07 [−0.79, 0.65]; 3rd period: = 0.02 [−0.63, 0.68]; 4th period: = 0.05 [−0.58, 0.68]). This same pattern was observed with the mental test scores, although no significant association with pre- or postnatal exposure was found (Table 2). Similar results were obtained when analyses were performed using monthly blood levels (Fig. 1). No association was found between postnatal exposure to DDE or HCB and any of the two scores assessed (Table 2), neither with prenatal exposure.

Models including prenatal and postnatal PCB-153 exposures jointly showed similar results to those obtained when only one of
these exposures was included in the model. For instance, when the 1st period of postnatal exposure was included in the model together with prenatal exposure the association between prenatal exposure and psychomotor score was $\beta_{(95\% CI)} = -2.24$ (−4.18, −0.31) compared to $\beta_{(95\% CI)} = -1.36$ (−2.61, −0.11) when postnatal exposure was left out of the model, whereas no association with postnatal exposure was found (data not shown). The same occurred when including prenatal and the 2nd, the 3rd or the 4th period of postnatal exposure in the model (data not shown).

### 4. Discussion

#### 4.1. Postnatal exposure estimations to PCB153, DDE and HCB

On average, children’s estimated blood POP levels were higher during the first months of postnatal life than those measured during their prenatal life; due to breastfeeding, levels increased during the first 3 to 4 months of life, and started to decrease from the 4th to 5th month; in Spain, it is around this time when most of the mothers return to work and thus stop breastfeeding or start to

### Table 1

Geometric mean (GM) and the 25th and the 75th concentrations (ng/g lipid) of the exposure to PCB153, DDE and HCB during prenatal (measured in maternal blood) and postnatal life (estimated through PBPK modelling).

<table>
<thead>
<tr>
<th></th>
<th>PCB153</th>
<th></th>
<th></th>
<th>DDE</th>
<th></th>
<th></th>
<th>HCB</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GM</td>
<td>25th</td>
<td>75th</td>
<td>GM</td>
<td>25th</td>
<td>75th</td>
<td>GM</td>
<td>25th</td>
</tr>
<tr>
<td>Prenatal exposure</td>
<td>39.81</td>
<td>28.19</td>
<td>60.65</td>
<td>132.47</td>
<td>76.61</td>
<td>204.57</td>
<td>42.74</td>
<td>24.60</td>
</tr>
<tr>
<td>Postnatal exposure estimations</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st three-month period</td>
<td>60.32</td>
<td>34.69</td>
<td>115.48</td>
<td>199.17</td>
<td>107.16</td>
<td>356.48</td>
<td>62.29</td>
<td>34.64</td>
</tr>
<tr>
<td>2nd three-month period</td>
<td>60.85</td>
<td>26.86</td>
<td>148.14</td>
<td>199.11</td>
<td>94.39</td>
<td>447.22</td>
<td>60.49</td>
<td>26.51</td>
</tr>
<tr>
<td>3rd three-month period</td>
<td>54.87</td>
<td>20.97</td>
<td>152.51</td>
<td>177.86</td>
<td>72.86</td>
<td>463.17</td>
<td>52.41</td>
<td>20.53</td>
</tr>
<tr>
<td>4th three-month period</td>
<td>49.63</td>
<td>18.32</td>
<td>144.91</td>
<td>159.28</td>
<td>61.27</td>
<td>417.79</td>
<td>45.45</td>
<td>17.00</td>
</tr>
</tbody>
</table>

*a* Postnatal exposure was estimated month by month from the 1st until the 12th month of postnatal life, however, in the present table estimations have been grouped into four-month periods (N=1175), which are the periods used in the main analysis.

### Table 2

Associations between prenatal and postnatal exposure*a* (divided into three-month periods) and mental and psychomotor scales (N=1175).

<table>
<thead>
<tr>
<th></th>
<th>Mental scale*b</th>
<th>Psychomotor scale*c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude $\beta$ coefficient (95% CI)</td>
<td>Adjusted $\beta$ coefficient (95% CI)</td>
</tr>
<tr>
<td>PCB153 Prenatal exposure</td>
<td>0.20 (−1.08, 1.48)</td>
<td>−0.39 (−1.83, 1.06)</td>
</tr>
<tr>
<td>Postnatal exposure estimations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st three-month period</td>
<td>0.21 (−0.75, 1.18)</td>
<td>−0.23 (−1.25, 0.78)</td>
</tr>
<tr>
<td>2nd three-month period</td>
<td>0.27 (−0.45, 1.00)</td>
<td>−0.03 (−0.77, 0.72)</td>
</tr>
<tr>
<td>3rd three-month period</td>
<td>0.31 (−0.34, 0.97)</td>
<td>0.06 (−0.62, 0.73)</td>
</tr>
<tr>
<td>4th three-month period</td>
<td>0.34 (−0.30, 0.97)</td>
<td>0.10 (−0.56, 0.75)</td>
</tr>
<tr>
<td>DDE Prenatal exposure</td>
<td>0.60 (−1.23, 2.23)</td>
<td>0.86 (−0.92, 2.63)</td>
</tr>
<tr>
<td>Postnatal exposure estimations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;199.79 vs ≥199.79)</td>
<td>0.14 (−1.61, 1.87)</td>
<td>0.27 (−1.49, 2.03)</td>
</tr>
<tr>
<td>2nd three-month period</td>
<td>0.44 (−2.16, 1.28)</td>
<td>−0.50 (−2.24, 1.24)</td>
</tr>
<tr>
<td>3rd three-month period</td>
<td>0.32 (−2.24, 1.51)</td>
<td>−0.43 (−2.17, 1.31)</td>
</tr>
<tr>
<td>4th three-month period</td>
<td>0.06 (−1.67, 1.78)</td>
<td>−0.03 (−1.77, 1.71)</td>
</tr>
<tr>
<td>HCB Prenatal exposure</td>
<td>0.79 (−0.22, 1.18)</td>
<td>0.66 (−0.44, 1.76)</td>
</tr>
<tr>
<td>Postnatal exposure estimations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st three-month period</td>
<td>0.68 (−0.20, 1.56)</td>
<td>0.43 (−0.49, 1.34)</td>
</tr>
<tr>
<td>2nd three-month period</td>
<td>0.57 (−0.12, 1.27)</td>
<td>0.35 (−0.36, 1.07)</td>
</tr>
<tr>
<td>3rd three-month period</td>
<td>0.57 (−0.07, 1.20)</td>
<td>0.37 (−0.28, 1.02)</td>
</tr>
<tr>
<td>4th three-month period</td>
<td>0.57 (−0.04, 1.19)</td>
<td>0.39 (−0.24, 1.01)</td>
</tr>
</tbody>
</table>

*a* PCB153 and HCB were introduced in the model as continuous variables, whereas DDE was introduced as a categorical variable (median as a cut-off).

*b* Mental scale model; crude models already adjusted for sex and region of study. Adjusted model for: region of study, sex, gestational age, day-care attendance, birth weight, maternal social class and maternal region of birth. For prenatal exposure the model was also adjusted for predominant breastfeeding.

*c* Psychomotor scale model; crude models already adjusted for region of study. Adjusted model for: region of study, gestational age, paternal social class.
combine breastfeeding with other types of foods. Results in the present cohort also show that the correlation between prenatal and subsequent estimated postnatal concentrations of the different POPs decreased with increasing months of life.

The correlation between prenatal DDE and PCB-153 or HCB in the present population was lower than in previous studies measuring POPs in human tissues (Barr et al., 2006; Dallaire et al., 2006; Glynn et al., 2008; Karmaus et al., 2005). The low correlations in the present study can be explained by the different sources of exposure to these compounds. In Spain, DDE was extensively used in agriculture and for pest control, whereas PCB153 was used in industrial processes. HCB was used as a fungicide in agriculture but has also been released in the environment as an unintended product of industrial combustion processes. Diet is another differential exposure factor; for instance, fish is a major source of PCB-153, but not of DDE, for which meat, fruit and cereals seem to be more important sources of exposure in the present population (Ibarluzea et al., 2011; Llop et al., 2010). However, as the main source of exposure to all these compounds during postnatal life is breastfeeding, the correlation among them increases.

4.2. Neurotoxic effects of exposure to postnatal PCB153, DDE and HCB

With the exception of the study published by Verner et al. (2010), previous studies evaluating neurotoxic effects of postnatal exposure to POPs at around one year of age assessed postnatal exposure by measuring POPs levels in breast milk or, in order to improve exposure estimations, by multiplying the levels measured in breast milk by the number of weeks of breastfeeding (Gladen et al., 1988; Huisman et al., 1995; Koopman-esseboom et al., 1996; Pan et al., 2009; Wilhelm et al., 2008a, b). Levels of POPs measured in previous studies on infant’s neurotoxicology, including those that evaluated postnatal exposure to POPs, are in general lower than those in the present study (Ibarluzea et al., 2011; Longnecker et al., 2003). Despite the higher levels, none of the previous studies observed an association between postnatal exposure to PCBs (Gladen et al., 1988; Huisman et al., 1995; Koopman-esseboom et al., 1996; Pan et al., 2009; Walkowiak et al., 2001; Wilhelm et al., 2008a, b) or DDE (Gladen et al., 1988; Pan et al., 2009) and different domains of neuropsychological development at ages between 6 and 24 months of age. Postnatal effects of HCB have never been assessed in previous studies. In the present study, where postnatal exposure assessment has been improved by applying PBPK models, no associations were found with any of the three-month or month-by-month periods of postnatal exposure. In fact, the associations observed during prenatal life weakened gradually across periods of postnatal life. No association with mental score was found. These results contrast with those obtained by Verner et al. (2010), the only other study applying PBPK models, where an association between blood PCB-153 levels around the 4th month of life and infants’ ability to control their activity (Behaviour Rating Scale of the BSID test) at the age of 11 months was detected. However, there are some methodological differences that could explain this discrepancy; for instance, the domains assessed in this study were different from those evaluated in the present study. Additionally, prenatal and postnatal levels of exposure were higher in the Inuit study population (on average, mothers breastfed their children for 156 days in the Inuit cohort vs 106 days in the present cohort).

On the other hand, we should note that, although BSID is one of the most widely used tools available to assess neuropsychological development at such young ages, it has sometimes shown a low predictive value for later performance on general cognition and intelligence tests (Bayley, 1977). For instance, a study assessing effects of postnatal PCB exposure (calculated by multiplying milk PCB levels by the weeks of breastfeeding) did not observe any
associations with BSID measures at 7, 18 and 30 months of life. However, significant negative effects of postnatal exposure were detected when children were assessed with the Kaufman Assessment Battery for Children at age 42 months (Walkowiak et al., 2001). Thus, evaluation of both pre- and postnatal exposure to these compounds will be interesting at older ages in the present study population, when brain is more developed, phenotypes better expressed and children have acquired more neuropsychological abilities that can be tested with more precise and reliable tests.

4.3. The role of breastfeeding

Postnatal exposure to POPs during the first year of life is primarily due to lactational exposure (Jorissen, 2007). Through breast milk, children are also exposed to beneficial compounds such as long-chain polyunsaturated fatty acid (LC-PUFA), as shown by a previous study including 504 children of the INMA birth cohort study in the region of Sabadell, which revealed mental score to be better among children with higher LC-PUFA levels and longer breastfeeding period. However, psychomotor development was not improved (Guxens et al., 2011). In the present study it is still possible that we see no effect of postnatal exposure to PCB–153 (or other POPs) because of the counterbalancing beneficial effects of breastfeeding, or maybe because the critical window of exposure for these outcomes is, in fact, prenatal life. To test for that, in the present study we adjusted the model for psychomotor scores by including prenatal and postnatal exposures together and results were similar to those obtained with models including one exposure estimate at the time. This seems to indicate that prenatal exposure probably is the most critical window of exposure or, at least, more critical than any other period of postnatal life for these outcomes.

4.4. Strengths and limitations

The present study has some limitations, but also strengths compared to previous papers. As shown in Supplemental material, Table 1, participants differed from excluded children for almost all the characteristics shown in the table. This hampers the generalization of the results to the population, because our study population had more mothers of higher social class and educational level. Also, no preterm children or with low birth weight were represented. However, we do not think this is affecting or biasing the association between the exposure and neuropsychological development of the children. Indeed, it might be helping to better detect the effects of such exposure, because we are avoiding important factors related to worse neuropsychological development such as being a preterm child, with low birth weight, and coming from lower social and educational classes.

The lack of information on sources of exposure other than breast milk may have introduced noise in the exposure-outcome associations. However, previous studies have clearly demonstrated that breastfeeding is the primary determinant of children’s blood levels of POPs from early infancy (Ayotte et al., 2003) up to ~7 years of age (Barr et al., 2006). Although we did not have blood levels in children enrolled in this study to validate the PBPK model simulations, Verner et al. (2009) validated the model in a population of infants where simulated levels were correlated to levels measured in ~6 month old children (range: 1–14 months) with Spearman coefficients of 0.89 for PCB–153, 0.90 for DDE and 0.83 for HCB without accounting for other exposure pathways. Whether including other sources of exposure can increase model accuracy has not yet been evaluated. Anyhow, the PBPK approach provides estimates of POP levels at any time point during the first year of life, a serious advantage over other metrics such as the multiplication of breast milk levels by the weeks of breastfeeding that only give an overall estimate of postnatal exposure. It is thus a potential tool for future epidemiological birth cohort studies evaluating the health effects of POP exposure during the first years of life. However, this model needs to be validated for other POPs such as PBDEs for which substantial postnatal exposure also occurs and may exhibit different chemical properties such as transfer rates from maternal blood to other biological matrices (Costa and Giordano, 2011; Frederiksen et al., 2010).

With an improved method to estimate postnatal exposure, our results are consistent with most of the previous studies so far and also internally; despite the high correlation between pre- and postnatal exposures, when models including prenatal PCB–153 exposure were adjusted for any of the postnatal three-month periods of exposure, associations between psychomotor score and prenatal PCB–153 remained, whereas no association with postnatal exposure was seen. Additionally, although the study population differed a little (N = 1391 vs 1175 in the present study population), we obtained consistent results to those found by Forns et al. (2012) between prenatal PCBs and psychomotor score.

Our study population is the largest so far (N = 1775), since previous studies assessing the effects of postnatal exposure to POPs ranged from 168 (Verner et al., 2010) to 858 participants (Gladen et al., 1988). Additionally, we were able to perform PBPK models because we had complete information on the type and duration of breastfeeding during the first year of life, as well as complete information on other important variables needed to perform such models and to control for potential confounding. Therefore, this is the second and the largest study to apply PBPK models to evaluate the effects of lactational exposure to POPs.

5. Conclusions

Despite the fact that breastfeeding increases children's blood POP levels during postnatal life, results from this study suggest that deleterious effects of PCB–153 on early brain development, particularly on psychomotor development, are mainly attributable to prenatal exposure to low levels of POPs.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

References


