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Persistent organic pollutants in infants and toddlers: Relationship between concentrations in matched plasma and faecal samples

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ABSTRACT

Early-childhood biomonitoring of persistent organic pollutants (POPs) is challenging due to the logistic and ethical limitations associated with blood sampling. We investigated using faeces as a non-invasive matrix to estimate internal exposure to POPs. The concentrations of selected POPs were measured in matched plasma and faecal samples collected from 20 infants/toddlers (aged 13 ± 4.8 months), including a repeat sample time point for 13 infants (~5 months apart). We observed higher rates of POP quantification in faeces (2 g dry weight) than in plasma (0.5 mL). Among the five chemicals that had quantification frequencies over 50% in both matrices, except for HCB, log concentration in faeces (C_f) and blood (C_b) were correlated ($r > 0.74$, $P < 0.05$) for *p,p′*-dichlorodiphenyldichloroethylene (*p,p′*-DDE), 2,3′,4,4′,5-pentachlorobiphenyl (PCB118), 2,2′,3,4,4′,5′-pentachlorobiphenyl (PCB138) and 2,2′,4,4′,5,5′-pentachlorobiphenyl (PCB153). We determined faeces:plasma concentration ratios (K_{fb}), which can be used to estimate C_b from measurements of C_f for infants/toddlers. For a given chemical, the variation in K_{fb} across individuals was considerable (CV from 0.46 to 0.70). Between 5% and 50% of this variation was attributed to short-term intra-individual variability between successive faecal samples. This variability could be reduced by pooling faeces samples over several days. Some of the remaining variability was attributed to longer-term intra-individual variability, which was consistent with previously reported observations of a decrease in K_{fb} over the first year of life. The strong correlations between C_f and C_b demonstrate the promise of using faeces for biomonitoring of these compounds. Future research on the sources of variability in K_{fb} could improve the precision and utility of this technique.

1. Introduction

The burden of chronic diseases has been rapidly increasing during the past decades (IHME, 2013) and risk factors occurring during the developmental period are now recognized to play an important role (Barker, 2004). The mechanisms implicated in developmental programming of chronic disorders are poorly understood, but epigenetic mechanisms are likely involved (Hanson and Gluckman, 2015). Exposure to environmental xenobiotics is suggested to be one of the triggers for epigenetic changes, especially during sensitive early life stages (Nickerson, 2006; Kortenkamp et al., 2011; Vaiserman, 2015). Persistent organic pollutants (POPs) including polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs) and polybrominated diphenyl ethers (PBDEs), are a group of environmental xenobiotics that are resistant to degradation and bioaccumulate in humans, and have been shown to induce epigenetic changes (Herbstman et al., 2010; Valvi et al., 2012; Eskenazi et al., 2013).

All POPs that are listed on the Stockholm Convention have been banned or substantially restricted in their use in many countries. For many POPs like PCBs, OCPs, tetrabromodiphenyl ether and pentabromodiphenyl ether, a decrease in exposure and associated body burden has been observed in some parts of the world (Law et al., 2014; Mikeš et al., 2012). Nonetheless, exposure and accumulation will continue for decades to come (Hung et al., 2016; Ryan and Rawn, 2014; Sharma et al., 2014; Toms et al., 2012). Therefore, research continues into whether adverse effects from POPs are occurring at the current levels of

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exposure and whether extra actions should be taken to reduce exposure (Nickerson, 2006). In order to answer these questions, it is vital to be able to quantify exposure during critical exposure windows, including during the early stages of life (La Merrill et al., 2013).

For infants and toddlers, individual and longitudinal data on POP concentrations in blood samples are scarce, due to the logistic and ethical constraints regarding sampling blood in these age groups (Needham et al., 2005). Faeces can be obtained from infants/toddlers less invasively and more conveniently than blood, and therefore may be useful for early-life biomonitoring. In toddlers, significant correlations between congener-specific concentrations in faeces and serum were found for seven of nine PBDE congeners studied (Sahlstrom et al., 2015). Concentrations of *p,p′* DDE and PCB153 in faeces collected from one infant over a period of one year were reported to be more reflective of estimated body burden than of rate of dietary intake at the time of faecal sample collection (Chen et al., 2016). Those results are in accordance with findings from studies of POPs in adults that showed that POP levels in faeces are not influenced by current dietary intake levels, but are instead governed by levels in the body (Rohde et al., 1999; To-Figueras et al., 2000; Moser and McLachlan, 2001).

Furthermore, it has been demonstrated in adults that the POP concentration in faeces is highly correlated with the POP concentration in blood, while the influence of the mass of faeces excreted each day on POP concentration in faeces is minor in comparison (Moser and McLachlan, 2001). On the basis of this work, Moser and McLachlan (2001) suggested that the ratio of POP concentrations in faeces to blood (K_{fb}) is a parameter of considerable practical value for estimating the concentrations of POPs in the body. However, before this method can be reliably used to estimate infants and toddlers POP body burden, more data regarding how K_{fb} varies during the early years are required. Although variations in K_{fb} have been observed between individuals (Sahlstrom et al., 2015), between chemicals and between pre- and post-weaning in the same individual (Chen et al., 2016), no studies have quantified the relative contributions of intra- and inter-individual variability to the overall variation in K_{fb}.

In this study, the concentrations of several OCPs, PCB congeners and PBDE congeners were measured in matched plasma and faecal samples from 20 infants/toddlers at two time points. The relationship between the concentrations in plasma (C_b) and the concentrations in faeces (C_f) was then assessed via both linear regression and variability analysis of K_{fb}. The study was designed to allow comparison of the intra- and inter-individual variation in K_{fb}, with the goal of investigating further the potential utility of faeces as a non-invasive matrix for biomonitoring POPs in infants and toddlers.

2. Methods

2.1. Study participants

The participants (infants/toddlers [n = 20]) in this study were recruited from the ongoing study “A phase 2, single-centre, double blind, randomized, placebo-controlled study testing the primary prevention of persistent asthma in high risk children by protection against acute respiratory infections during early childhood using OM-85” (OMPAC). The inclusion/exclusion criteria for the OMPAC study are shown in Table S1.

For the analysis of the long-term variation in K_{fb}, participants were asked to donate samples twice for the present study. The first sample collection occurred in April 2014 while the second occurred in September 2014. At each sampling time, one plasma sample of ~0.5 mL and faecal samples from 1 to 2 bowel movements (~2 g dry weight [dw]) were collected from each participant, and a questionnaire regarding living and eating habits was completed by their parents. Participants were not required to fast before the blood samples were conducted. Thirteen participants completed two sample periods. Four participants provided a sample only in the first sample period, while three participated only in the second.

If a faeces sample was smaller than 1 g dw, it was combined with the other faeces sample from the same sampling day prior to extraction. Otherwise the two faeces samples from the same sampling day (from participants No. 5, 20 and 22 from the first sampling, and participants No. 2, 3, 8, 10, 15 and 16 from the second sampling) were analysed separately to provide information regarding the short-term variation in K_{fb}.

This study received ethics approval by the University of Queensland Ethics Committee (approval number H/308NRCET/00) and Children's Health Services Queensland Human Research Ethics Committee (HREC reference number: HREC/12/QRCH/119). The Centers for Disease Control and Prevention (CDC) were determined not to be engaged in human subject research since no personally identifiable information was made available to CDC researchers.

2.2. Sampling

Blood was collected into a polypropylene tube with 100 units of preservative free heparin. It was then processed as follows to obtain plasma: (i) centrifuging at 700 × *g* for 10 min at room temperature; (ii) collecting the plasma layer down to within 0.5–1.0 cm of the top of the red cell layer (avoiding disturbance of white cells) using a sterile transfer pipette; (iii) centrifuging the plasma again at 700 × *g* for 10 mins to remove platelets; (iv) transferring the plasma sample into a brown Eppendorf tube and storing at −80 °C.

Faecal samples for each participant were collected from one to two defecation events directly before and after the blood sampling. At each sampling point, only faecal material that had not been in contact with the inner liner of the diaper was transferred to a sheet of aluminium foil. The folded aluminium foil sheet was then sealed inside a plastic re-sealable bag and stored in a freezer at the participant's home until transportation to the laboratory (on ice, in a cool bag). A detailed description of faecal sample collection and transportation has been provided previously (Chen et al., 2015). Faecal samples were stored at −20 °C until analysis.

2.3. Analysis

Analysis included four chlorinated pesticides (*p,p′* DDE, HCB, β-HCH, γ-HCH), five PCB congeners (PCB28, 118, 138, 153 and 180) and five PBDE congeners (PBDE 47, 99, 100, 153 and 154) in plasma and faecal samples. All brown Eppendorf tubes containing plasma samples were sent to the Centers for Disease Control and Prevention (CDC), USA, on dry ice for analysis. POPs were measured in individual plasma samples using a methodology published previously (Jones et al., 2012; Sjodin et al., 2004). POPs were measured in faeces using a previously described method (Chen et al., 2015). Detailed description of the methods can be found in the Table S2.

2.4. Quality control

Quality control procedures for plasma and faeces samples included method blanks and spiked samples. Additional details of quality control procedures and determination of limits of detection (LOD) and quantification (LOQ) are provided in Table S3. The average recoveries of the labelled standards ranged from 61% to 93% for all chemicals (Table S4). Only results that were above the LOQ were used in the regression analysis. A more conservative criterion for quantification was used for faecal samples because the variability in matrix properties contributes to a higher uncertainty in the measurements. For summarizing data, results for plasma below the LOQ were imputed as $LOQ/(2)^{1/2}$; results for faeces below the LOD were imputed as $LOD/(2)^{1/2}$ and for faeces between the LOD and the LOQ were imputed as the average of LOD and LOQ.

Concentrations of target POPs in faeces were determined on both a