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A B S T R A C T
Background: Biobank serum samples from longitudinal mother-child cohorts have been used to estimate prenatal exposures to endocrine disrupting chemicals (EDCs). However, the knowledge about variations in serum concentrations of non-persistent chemicals during pregnancy is limited.

Objective: To describe the within- and between-person variations in serum concentrations of non-persistent chemicals and changes over trimesters, including phthalate metabolites, parabens, phenols, and UV filters.

Design: Longitudinal study with repeated blood samples from 128 healthy pregnant women during pregnancy.


Methods: 503 repetitive prenatal serum samples from 128 pregnant women taken at approximately gestational week 12, 20, 30 and 40 were analyzed for 7 UV filters, 32 metabolites of 15 phthalate diesters, 8 phenols and 7 parabens by LC-MS/MS.

Results: Ten of 32 phthalate metabolites from six out of 15 phthalate diesters, two of seven parabens, two of eight phenols and three of seven UV filters were measurable in more than half of the serum samples. Of these chemicals, mono-ethyl phthalate (MEP), mono-iso-nonyl phthalate (MiNP), mono-iso-decyl phthalate (MiDP), 4-methylbenzophenone (4-MBP), 4-hydroxybenzophenone (4-HBP) and n-propyl paraben (nPrP) had intra-class correlation coefficients (ICC) above 0.4 in both adjusted and unadjusted analyses (0.427–0.795), indicating low within-person variation. The serum concentration of UV filters 4-MBP and 4-HBP significantly increased throughout pregnancy, also after adjusting for seasonal variation (4-HBP: effect estimates 0.142–0.437, p < 0.001. 4-MBP: effect estimates 0.156–0.458, p < 0.002.).

Conclusion: MEP, MiNP, MiDP, 4-MBP, 4-HBP and nPrP were measurable in > 50% of serum samples and showed low within-person variation. Thus, it is possible with acceptable accuracy to evaluate maternal exposure during pregnancy for these non-persistent chemicals using one or more biobank serum samples. The here presented adjusted ICC values can in addition be applied as adjustment of residual variation in future studies that evaluate outcomes related to prenatal exposures.

1. Introduction

Humans are exposed to a wide range of chemicals with endocrine disrupting effects (EDGs), some of which are classified to be non-persistent, i.e. phthalates, parabens, phenols and UV filters, and widely used as plasticizers, antibacterial agents, antimicrobial preservatives and absorbers or as UV blocking agents in personal care products, building materials and textiles. Non-persistent chemicals are defined by their short in vivo half-life as they are rapidly metabolized and excreted through urine or feces over the course of 1–5 days. This complicates a robust exposure assessment of these chemicals. Concentrations in one sample may only reflect recent exposures, which may vary from day to day and e.g. over the course of the pregnancy period. Nevertheless, Frederiksen et al. (2014) observed a widespread exposure to non-persistent chemicals measured in several population-based cohorts of all age groups in Denmark, indicating a continuous exposure to several non-persistent chemicals over the life span due to frequent exposures. Even low exposure to some chemicals can be of concern due to so-called
mixture effects with other chemicals (Christiansen et al., 2008; Diamanti-Kandarakis et al., 2009; Studies, 2008). Findings of a potential long-term accumulation of chemicals classified as non-persistent, has also previously been published (Artacho-Cordón et al., 2017). Benzophenone-3 (BP-3), methylparaben (MeP), bisphenol-A (BPA) and 2-phenylphenol (2-PP) were found in human adipose tissue and concentrations in general were similar between serum and adipose tissue (Artacho-Cordón et al., 2017).

Concentrations of phthalates, parabens, phenols and UV filters are, with a few exceptions, known to be generally 10–100 times lower in serum compared with urine (Frederiksen et al., 2011, 2010; Krause et al., 2018; Vandenberg et al., 2014). However, many historical population-based cohorts have serum and not urine stored, making serum highly valuable for long-term and two-generation studies of prenatal EDC exposure. Limited knowledge is available about serum concentrations of non-persistent chemicals measured during pregnancy (Adibi et al., 2008; Blumberg et al., 2011; Johansson et al., 2017; Krause et al., 2018; Philippat et al., 2013; Sathyanarayana et al., 2014).

The overall aim of this longitudinal study was to examine whether serum was suitable as a matrix for evaluating non-persistent EDC exposure of women during pregnancy, achieved through analyses of consistency and within- and between-person variations in serum concentrations of a large range of non-persistent environmental chemicals (phenols, parabens, phthalates and UV filters) throughout pregnancy.

2. Materials and methods

During the period of May 1999–October 2001 pregnant women were recruited at their first routine hospital contact (gestational week 6–12) at the Copenhagen University Hospital, Herlev (Chellakooty et al., 2004). The women belonged to the hospital’s primary geographic referral area. Blood samples were taken repetitively throughout pregnancy and gestational age was based on sonographic measurements (Bos et al., 2009; Chellakooty et al., 2004). In the present study, serum samples from 128 healthy pregnant women were analyzed. Samples were not previously thawed. Nine women had fewer than four samples available, and 119 women had 4 samples available for chemical analyses throughout pregnancy, which were selected as closely to week 12 (time point 1), 20 (time point 2), 30 (time point 3) and 40 (time point 4) of pregnancy as possible.

2.1. Serum analyses of phthalates, UV-filters, parabens and phenols

Serum was stored in aliquots at −20 °C. Serum samples were analyzed for 32 metabolites from 15 phthalate diesters (n = 503), 7 UV filters (n = 501), 7 parabens (n = 502) and 8 phenols (n = 503) by isotope-diluted online Turboflow liquid chromatography-tandem mass spectrometry (LC-MS/MS), preceded by enzymatic deconjugation. All included chemicals, their abbreviations and limits of detection (LODs) are listed in Tables 1a–1d. Preparation of samples, standard solutions, quality control, instrumental analyses and method validation has been previously described in detail for all four chemical groups (Frederiksen et al., 2016, 2013, 2011, 2010; Hart et al., 2018).

2.2. Statistics

Concentrations of endocrine disrupting chemicals in serum were reported as 10th, 25th, 75th and 90th percentiles as well as maximum and median values. All chemicals were included in descriptive statistics; chemicals above LOD in > 50% of the samples were included in all other analyses. Metabolites of DEHP and DiNP measured in > 50% of samples were expressed combined as the sum of DEHP metabolites (sumDEHP) and the sum of DiNP metabolites (sumDiNP), respectively: The molar concentrations of each DEHP metabolite and each DiNP metabolite were added and multiplied with the molecular weight of their respective parent compounds DEHP and DiNP. The sum of MBP isomers (sumMBP) were calculated by adding the serum concentrations of MBP and MnBP. Concentrations below LOD were replaced by LOD/√2. For a few women, concentrations of all di-(2-ethyl-hexyl) phthalate metabolites (n = 1) and di-iso-nonyl phthalate metabolites (n = 15) fell below their respective LOD and in these cases sumDEHP was replaced by LOD(MECPP)/√2, sumDiNP was replaced by LOD(MCiOP)/√2.

The Wilcoxon signed-rank test for related samples was used to test seasonal differences in median serum chemical concentrations. To analyze correlations between the concentrations of different chemicals within the same sample, Spearman’s non-parametric test was used. Variability was assessed by calculating the unadjusted intra-class correlation coefficient (ICC) for the serial concentration measurements of all chemicals measurable in more than half of samples. ICCs determine the within-person variation versus the total variation including between-persons variation of concentrations. ICCs typically range from 0 to 1, with a value closer to 1 indicating a relatively low within-person variation in exposure over time compared to the total variation. Mixed effect models were fitted to estimate the variance components adjusted for gestational age and seasonal effect for each of the chemicals. Women were accounted for using random effects and the time point during pregnancy and season were included as fixed effect. Adjusted ICCs are calculated from the standard deviation between persons (std.dev.men) and the standard deviation within persons (std.dev.within) obtained from the adjusted mixed effects models:

\[ \text{ICC adjusted} = (\text{std. dev. men})^2/(\text{std. dev. men})^2 + (\text{std. dev. within})^2 \]

Data analyses were carried out using IBM SPSS Statistics 22.0 for ICC calculations and SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC) for all other analyses. p-Values below 0.05 were considered statistically significant.

2.3. Ethical approval

The study was approved by the Ethical Committee of the Capital Region of Denmark (KF-02-125/95) as well as the Danish Data Protection Agency (1997-1200-074). The study was conducted in accordance with the Helsinki II Declaration. All women received written information, and informed consent was obtained from all participants.

3. Results

Serum concentrations of four groups of chemicals were measured (Tables 1a–1d). Thirty-two phthalate metabolites were analyzed, and of these ten metabolites (MEP, MiBP, MnBP, MHB, MEHP, MECPP, MCMHP, MiNP, MCGiP and MiDiP) representing six different diester phthalates were measured in levels above LOD in more than half of the serum samples. Two out of seven parabens (MeP and n-PrP), two out of eight phenols (BPA and 2-PP) and three out of seven UV filters (BP-3, 4-HBP and 4-MBP) were measured in levels above LOD in more than half of the serum samples. Large total variation in serum concentrations within the population of pregnant women in general was seen for phthalate metabolites MEP, MiBP, MnBP, MEHP, MCMHP and MiDiP, as well as for MeP, BPA, TCS and BP-3 (Tables 1a–1d).

Within phthalates, the strongest correlations were found among metabolites of DEHP and DiNP: MCGiP was significantly positively correlated with MEHP, MECPP and MCMHP (r = 0.254–0.391, p < 0.001). MiNP correlated with MEHP (r = 0.173, p = 0.001). MiDiP correlated with MiNP and MCGiP (r = 0.091–0.323, p = 0.001–0.045), as well as with MHB (r = 0.179, p < 0.001). Selected correlations between primary (hydrolyzed) and secondary (oxidized) phthalate mono-esters of the same phthalate diester are shown in Table 2. Within parabens and UV filters, correlations were also seen: MeP and n-PrP (r = 0.218, p < 0.001), 4-MBP and 4-HBP (r = 0.606, p < 0.001), BP-2 and both 4-MBP and 4-HBP (r = 0.097–0.106, p = 0.019–0.034). No significant correlations were found among phenols. Correlations between primary and secondary phthalate metabolites were also seen: MEP and n-PrP (r = 0.218, p < 0.001), 4-MBP and 4-HBP (r = 0.606, p < 0.001), BP-2 and both 4-MBP and 4-HBP (r = 0.097–0.106, p = 0.019–0.034). No significant correlations were found among phenols. Correlations...
between different chemical groups are shown in Supplementary Tables 1–2.

MEP, MiNP, MiDP, n-PrP, 4-HBP and 4-MBP had an ICC above 0.4, i.e. showed a relatively low within-person variance (Table 3). For each chemical group, the variation of repetitive measurements for each individual woman is plotted against her own median concentration for chemicals with the highest ICC values (Fig. 1).

Analyses of seasonal variation for individual measurements were included in Supplementary Table 3. No systematic differences were seen between adjusted and unadjusted analyses. For the UV filters 4-MBP and 4-HBP significant increases were seen throughout pregnancy in analyses adjusted for season (Table 4). For all other chemicals, no systematic significant differences in serum concentrations were seen across gestational weeks. For 4-MBP and 4-HBP, results for adjusted ICC and within- and between-person variation are shown in Table 5.

### 4. Discussion

This is to our knowledge the largest study of serum samples from pregnant women, which were analyzed for a total of 35 non-persistent chemicals to assess consistency and within- and between-person variation. Seventeen chemicals (ten metabolites of six phthalate diesters, two parabens, two phenols and three UV filters) were detectable in more than half of the serum samples. Six of these (MEP, MiNP, MiDP, n-PrP, 4-HBP and 4-MBP) had furthermore unadjusted ICC values above 0.4, showing a pattern of exposure with relatively low within-person variation. However, gestational timing of blood sampling may play a role for exposure assessment to some chemicals, as serum concentrations of 4-HBP and 4-MBP increased significantly throughout pregnancy. Adjusted ICCs were calculated for the latter two chemicals based on within- and between-persons standard deviation. Our results indicated that a single blood sample taken during pregnancy may be
assessment than serum measurements (Frederiksen et al., 2010). phthalate metabolites is in general considered a more reliable exposure sampling and storage. For the same reason, measurement of urinary serum are a potential challenge due to risk of contamination during Angerer, 2007; Koch et al., 2004). Measurements of metabolites in measurements of MCMHP, a secondary metabolite of MEHP (Koch and two.

Single measures intra-class correlation coeﬃcients (ICC) for the within-person variance of repeated measures for all chemicals above LOD in > 50% of the samples. 

**Table 1c**

Concentration of phenols in maternal serum (ng/mL), n = 503.

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Abbreviation</th>
<th>LOD</th>
<th>N &gt; LOD</th>
<th>1p</th>
<th>25p</th>
<th>50p</th>
<th>75p</th>
<th>90P</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphenol A</td>
<td>BPA</td>
<td>0.18</td>
<td>282</td>
<td>&lt; LOD</td>
<td>0.30</td>
<td>1.17</td>
<td>2.19</td>
<td>28.10</td>
<td></td>
</tr>
<tr>
<td>Triclosan</td>
<td>TCS</td>
<td>0.22</td>
<td>236</td>
<td>&lt; LOD</td>
<td>6.64</td>
<td>18.77</td>
<td>237.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triclocarban</td>
<td>TCC</td>
<td>0.27</td>
<td>0</td>
<td>&lt; LOD</td>
<td></td>
<td>&lt; LOD</td>
<td>&lt; LOD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,4-Dichlorophenol</td>
<td>2,4-DCP</td>
<td>0.18</td>
<td>19</td>
<td>&lt; LOD</td>
<td>1.48</td>
<td>1.03</td>
<td>0.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,5-Dichlorophenol</td>
<td>2,5-DCP</td>
<td>0.11</td>
<td>2</td>
<td>&lt; LOD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,4,5-Trichlorophenol</td>
<td>2.4-5-TCP</td>
<td>0.29</td>
<td>1</td>
<td>&lt; LOD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-Phenylphenol</td>
<td>2-PP</td>
<td>0.13</td>
<td>286</td>
<td>&lt; LOD</td>
<td>0.14</td>
<td>0.24</td>
<td>0.35</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>4-Phenylphenol</td>
<td>4-PP</td>
<td>0.12</td>
<td>7</td>
<td>&lt; LOD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Serum phenol concentrations (ng/ml) in prenatal maternal serum samples from 128 Danish women given as percentiles. LOD – level of detection.

**Table 1d**

Concentration of UV filters in maternal serum (ng/mL), n = 501.

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Abbreviation</th>
<th>LOD</th>
<th>N &gt; LOD</th>
<th>10p</th>
<th>25p</th>
<th>50p</th>
<th>75p</th>
<th>90P</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzenophene-1</td>
<td>BP-1</td>
<td>0.13</td>
<td>94</td>
<td>&lt; LOD</td>
<td></td>
<td></td>
<td></td>
<td>0.23</td>
<td>9.76</td>
</tr>
<tr>
<td>Benzenophene-2</td>
<td>BP-2</td>
<td>0.08</td>
<td>128</td>
<td>&lt; LOD</td>
<td>0.08</td>
<td>0.21</td>
<td>0.10</td>
<td>0.21</td>
<td>0.10</td>
</tr>
<tr>
<td>Benzenophene-3</td>
<td>BP-3</td>
<td>0.12</td>
<td>495</td>
<td>0.28</td>
<td>0.40</td>
<td>0.53</td>
<td>0.67</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>Benzenophene-4</td>
<td>BP-4</td>
<td>0.24</td>
<td>34</td>
<td>0.63</td>
<td>0.87</td>
<td>1.16</td>
<td>1.49</td>
<td>1.87</td>
<td>3.19</td>
</tr>
<tr>
<td>4-Hydroxybenzophenone</td>
<td>4-HPB</td>
<td>0.18</td>
<td>498</td>
<td>0.63</td>
<td>0.87</td>
<td>1.16</td>
<td>1.49</td>
<td>1.87</td>
<td>3.19</td>
</tr>
<tr>
<td>4-Methylbenzophenone</td>
<td>4-MBP</td>
<td>0.27</td>
<td>481</td>
<td>0.51</td>
<td>0.99</td>
<td>1.71</td>
<td>2.42</td>
<td>3.23</td>
<td>5.40</td>
</tr>
<tr>
<td>4-Methylbenzyldine camphor</td>
<td>4-MBC</td>
<td>0.18</td>
<td>104</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Serum concentrations (ng/ml) of UV filters in prenatal maternal serum samples from 128 Danish women given as percentiles. LOD – Level of detection.

**Table 2**

Correlations (Spearman’s rho) among serum concentrations of primary and secondary phthalate mono-esters.

<table>
<thead>
<tr>
<th>Primary phthalate mono-esters</th>
<th>Secondary phthalate mono-esters</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEP</td>
<td>MCBP</td>
</tr>
<tr>
<td>MBP</td>
<td>MnBP</td>
</tr>
<tr>
<td>MEHP</td>
<td>MNP</td>
</tr>
<tr>
<td>MCBP</td>
<td>MiBP</td>
</tr>
<tr>
<td>MnBP</td>
<td>MCiOP</td>
</tr>
<tr>
<td>MEHP</td>
<td>MiNP</td>
</tr>
<tr>
<td>MCBP</td>
<td>MDP</td>
</tr>
</tbody>
</table>

* Significant correlation, p-value 0.01–0.05.
** Significant correlation, p-value 0.001–0.01.
*** Significant correlation, p-value < 0.001.

**Table 3**

Single measures intra-class correlation coefficient (ICC) for the within-person variance of repeated measures for all chemicals above LOD in > 50% of the samples.

<table>
<thead>
<tr>
<th>Chemicals</th>
<th>Phthalates</th>
<th>MEP</th>
<th>MBP</th>
<th>MnBP</th>
<th>MCBP</th>
<th>MEHP</th>
<th>MECBP</th>
<th>MCMBP</th>
<th>MNP</th>
<th>MiNP</th>
<th>MiOP</th>
<th>MDCP</th>
<th>MDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single measures ICCs (p-value)</td>
<td>0.476</td>
<td>0.111</td>
<td>0.014</td>
<td>0.351</td>
<td>0.115</td>
<td>0.025</td>
<td>0.133</td>
<td>0.496</td>
<td>0.092</td>
<td>0.427</td>
<td>0.047</td>
<td>0.029</td>
<td></td>
</tr>
<tr>
<td>(&lt; 0.001)</td>
<td>(0.003)</td>
<td>(0.638)</td>
<td>(&lt; 0.001)</td>
<td>(0.002)</td>
<td>(0.250)</td>
<td>(&lt; 0.001)</td>
<td>(&lt; 0.001)</td>
<td>(0.001)</td>
<td>(0.010)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chemicals</th>
<th>Parabens</th>
<th>Phenols</th>
<th>UV filters</th>
<th>Phthalate sums</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-PrP</td>
<td>BPA</td>
<td>2-PP</td>
<td>BP-3</td>
<td>4-HBP</td>
</tr>
<tr>
<td>MeP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single measures ICCs (p-value)</td>
<td>0.027</td>
<td>0.586</td>
<td>0.007</td>
<td>0.149</td>
</tr>
<tr>
<td>(0.235)</td>
<td>(0.417)</td>
<td>(0.001)</td>
<td>(0.001)</td>
<td>(0.001)</td>
</tr>
</tbody>
</table>

Informative about individual exposures to some but not all non-per-
sistent chemicals; while keeping in mind that repeating chemical measurements twice, reduces the within-person variance by a factor of two.

In contrast to previous studies, only few other studies include measurements of MCMHP, a secondary metabolite of MEHP (Koch and Angerer, 2007; Koch et al., 2004). Measurements of metabolites in serum are a potential challenge due to risk of contamination during sampling and storage. For the same reason, measurement of urinary phthalate metabolites is in general considered a more reliable exposure assessment than serum measurements (Frederiksen et al., 2010). However, in this study, MCMHP correlated significantly with MEHP, and MCiOP correlated significantly with MiNP, supporting the conclusion that neither MEHP nor MiNP measured in the samples were caused by sample contamination. A general contamination of all samples is thereby not supported by these results, by the number of samples with concentrations below LOD or by the between-person variation. Only few previously published studies include concentrations measured in serum. The detection rates and median serum concentrations of phthalates, parabens and UV filters in our study are comparable to some studies of both pregnant women and other participants (Frederiksen et al., 2011, 2010; Hart et al., 2018; Krause et al., 2018). However,
Fig. 1. Serum concentrations (ng/mL) in individual samples for each woman plotted against the median level (vertical line) of the same woman’s four samples. Graphs shown for chemicals with the highest ICC values within each chemical group (please note differences in scaling of axes). All concentrations are here shown on a logarithmic scale. Samples with concentration < LOD were set to LOD/√2. Vertical lines represent individual women and dots on the lines represent measured concentrations for each individual woman. Dashed lines represent LOD/√2.
et al., 2011, 2010; Krause et al., 2018; Vandenberg et al., 2014). It is yet unclear whether concentrations in urine or serum best reflect relevant exposure associated with health effects in humans. Our findings confirm a considerable and ongoing exposure of pregnant women to a broad mixture of non-persistent chemicals, which has also been shown as urinary excretion in previous studies of pregnant women (Frederiksen et al., 2011; Louis et al., 2014; Sathyanarayana et al., 2017). The large total variation of some chemicals indicated differences in life style among women and may be linked to personal care products, diet and other life style factors. Detectable concentrations of BP-2 in 25% of samples as found in our cohort might be expected in samples collected 15–20 years ago. BP-2 is not used today and is on the EU category 1 list, which includes substances known or strongly presumed to have endocrine-disrupting effects based on in vivo studies (Hass et al., 2012). Despite low ICCs for DEHP metabolites and the sum of these indicating large variation from day to day, there were significant correlations among DEHP metabolites and they were detectable in a high number of samples, which underlines its important role in environmental exposures to chemicals.

The increases in serum concentrations of 4-MBP and 4-HBP across trimesters are to our knowledge a novel observation which we currently do not have an explanation for. This change may reflect changes of personal habits or physiological metabolic changes during pregnancy. Concentrations of 4-MBP and 4-HBP measured in serum are higher for these two chemicals than those measured in urine, which is not accounted for by their hydrophilicity, as 4-HBP is more hydrophilic than other benzophenones and 4-MBP more lipophilic (Krause et al., 2018).

Serial concentration measurements of EDCs in each woman demonstrated a considerable variation. The within-person variation included both the variation in the laboratory measurement as well as the day-to-day variation in the personal exposure and metabolism. Previously published studies of within- and between-person variation found similar ICCs based on urine concentrations for BPA, MEHP, MECPP, propylparaben and MEP (Lassen et al., 2013; Philippat et al., 2013). Thus, the assessment of an individual’s exposure to non-persistent chemicals remains a considerable challenge for research into human health effects of EDCs, independent of which biological matrix is used. Historic cohorts often have serum from pregnant women stored, making serum analyses still highly valuable in the study of long term effects and two-generation studies of prenatal EDC exposure, i.e. for chemicals such as some phthalate metabolites, parabens and UV filters i.e. MEP, MiNP, MiDP, nPrP, 4-HBP and 4-MBP. The quantification of the variation as between- and within-person allowed calculation of ICCs adjusted for season and gestational age. Being able to quantify this variation enables an estimate of the effect of the compound where an adjustment has been made for the fact that the exposure is measured with error.

This corrects for well-known attenuation of an exposure effect in the presence of measurement error in the exposure. The analyses can be performed as a regression calibration approach or a standard regression with subsequent correction of the found effect (Carroll et al., 2006). The estimated ICC indicates that any health effect of an investigated chemical is likely to be underestimated in a cross-sectional study. Adjusted ICCs are also valuable when designing a new study aimed at identifying the effect of e.g. 4-HBP on a subsequent outcome, as measuring 4-HBP concentrations twice rather than once will reduce the within-person variance by a factor of two.

4.1. Conclusions

In conclusion, thirty-nine chemicals and metabolites were measurable in > 50% of samples, and MEP, MiNP, MiDP, 4-MBP, and nPrP showed a lower within-person than total variation. Thus, it was possible with acceptable accuracy to evaluate maternal exposure for these non-persistent chemicals using biobank serum samples. The here presented adjusted ICC values can in addition be applied as adjustment of residual variation in future studies that evaluate outcomes related to prenatal exposures.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.11.047.
Declarations of interest

None.

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Authors’ contributions

AJ, TL and KMM conceptualized the study of pregnant women. MA performed statistical analyses, analyzed data and wrote the manuscript. AJ, KMM, NES and AMA contributed to data analysis and manuscript writing. HF contributed to designing the exposure study, carried out chemical and data analyses and contributed to manuscript writing. JHP contributed to the statistical data analyses and modelling. All authors approved the final manuscript.

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