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Variability of urinary concentrations of non-persistent chemicals in pregnant women and school-aged children

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ABSTRACT

Background: Exposome studies are challenged by exposure misclassification for non-persistent chemicals, whose temporal variability contributes to bias in dose-response functions.
Objectives: We evaluated the variability of urinary concentrations of 24 non-persistent chemicals: 10 phthalate metabolites, 7 phenols, 6 organophosphate (OP) pesticide metabolites, and cotinine, between weeks from different pregnancy trimesters in pregnant women, and between days and between seasons in children.
Methods: 154 pregnant women and 152 children from six European countries were enrolled in 2014–2015. Pregnant women provided three urine samples over a day (morning, midday, and night), for one week in the 2nd and 3rd pregnancy trimesters. Children provided two urines a day (morning and night), over two one-week periods, six months apart. We pooled all samples for a given subject that were collected within a week. In children, we also made four daily pools (combining morning and night voids) during the last four days of the first follow-up week. Pools were analyzed for all 24 metabolites of interest. We calculated intraclass-correlation coefficients (ICC) and estimated the number of pools needed to obtain an ICC above 0.80.
Results: All phthalate metabolites and phenols were detected in > 90% of pools whereas certain OP pesticide metabolites and cotinine were detected in < 43% of pools. We observed fair (ICC = 0.40–0.59) to good (0.60–0.74) between-day reliability of the pools of two samples in children for all chemicals. Reliability was poor (< 0.40) to fair between trimesters in pregnant women and between seasons in children. For most chemicals, three daily pools of two urines each (for weekly exposure windows) and four weekly pools of 15–20 urines each

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would be necessary to obtain an ICC above 0.80.
Conclusions: This quantification of the variability of biomarker measurements of many non-persistent chemicals during several time windows shows that for many of these compounds a few dozen samples are required to accurately assess exposure over periods encompassing several trimesters or months.

1. Introduction

Exposome studies, which aim to characterize the totality of human environmental exposures from conception onward, are challenged by exposure misclassification, particularly for non-persistent chemical contaminants. Phthalates, parabens, phenols, and organophosphate (OP) pesticides are non-persistent chemicals for which there are concerns regarding human health risks because of their widespread use and potential toxicity (Braun, 2017). Also, pregnancy and childhood are exposure periods of specific concern for each of these chemicals because the fetus and infant are particularly vulnerable to such potential hazards (Braun, 2017). Non-persistent chemicals are rapidly cleared from the body, with biological half-lives ranging from few hours to days (e.g., Meeker et al., 2009). Hence, information provided by urinary concentrations measured in one or two spot urine samples, as available in most former population-based birth cohort studies, may contribute to exposure misclassification (i.e. measurement error). This exposure misclassification, which likely corresponds to classical-type error, is expected to cause attenuation bias in exposure-response functions. In the case of a chemical with high temporal variability (i.e. with an intraclass correlation coefficient (ICC) of 0.2), the expected (attenuation) bias in studies relying on a spot urine sample is about 80% (Perrier et al., 2016). Collecting repeated biospecimens per subject is an efficient method to decrease bias but this approach is sometimes logistically cumbersome and cannot be applied to existing studies without repeated biospecimens collection. Approaches that would limit bias in epidemiological studies without requiring repeated biospecimen collection exist (Perrier et al., 2016; Pleil and Sobus, 2016, 2013), such as the a posteriori disattenuation approach (Perrier et al., 2016); these approaches require having an estimate of the chemical specific ICC, a measure of the temporal within-subject variability of the biomarkers' levels. Providing an estimate of the within-subject variability (e.g., as quantified by the ICC) of a large number of chemicals is of particular relevance at the era of exposome research. Exposome studies might indeed suffer from exposure misclassification in amounts differing between compounds (Slama and Vrijheid, 2015), making any health effect of non-persistent chemicals less likely to be identified compared to that of more persistent chemicals, for which one spot biospecimen does a better job of estimating exposure over a long-time period.

Several studies have assessed the temporal variability of non-persistent chemical contaminants in pregnant women and children (Adibi et al., 2008; Bertelsen et al., 2014; Bradman et al., 2013; Braun et al., 2012, 2011; Cantonwine et al., 2014; Ferguson et al., 2014; Fisher et al., 2015; Griffith et al., 2011; Guidry et al., 2015; Heffernan et al., 2014; Jusko et al., 2014; Lewis et al., 2015; Meeker et al., 2013; Millenson et al., 2017; Philippat et al., 2013; Spaan et al., 2015; Stacy et al., 2017, 2016; Teitelbaum et al., 2008; Watkins et al., 2014; Weiss et al., 2015) (Tables 1 and 2). The majority of studies in pregnant women only collected three spot urines samples over pregnancy; in children, most studies were relatively small (N < 61). These studies focused on a narrow range of chemicals; there is relatively little information on phenols other than BPA and none on parabens and cotinine in children (Tables 1 and 2). Generally, ICCs and variability patterns are expected to differ at different time scales (days, weeks, trimesters) but very few studies have provided comparative estimates at different time scales.

Here, we aimed to evaluate between-trimester variability in pregnant women and between-days and between-season variability in school-aged children of urinary concentrations of phthalate metabolites, phenols, OP pesticide metabolites, and cotinine; we also aimed to calculate the number of biospecimens needed to obtain excellent reliability (defined as an ICC of 0.80 or more) of each chemical.

2. Methods

2.1. Study participants

During 2014 and 2015, two panel studies were conducted within the HELIX (Human Early-Life Exposome) project (Vrijheid et al., 2014). The Pregnancy Panel Study included 154 pregnant women from three European countries under study in HELIX: 52 women from Barcelona (Spain), 46 from Grenoble (France), and 56 from Oslo (Norway). In Grenoble, women were part of SEPAGES cohort (Suivi de l'Exposition à la Pollution Atmosphérique pendant la Grossesse et Effets sur la Santé [Assessment of Air Pollution Exposure during Pregnancy and Effects on Health]). Pregnant women were recruited between 2014 and 2015. Criteria for inclusion were: a) singleton pregnancy; b) age ≥ 18 years at the time of start of pregnancy; c) first visit to be conducted before 20 weeks of pregnancy; and d) residence in the study area covered by the cohort.

From the six existing European longitudinal population-based birth cohorts studies participating in HELIX, a subcohort of 1301 mother-child pairs was selected to be fully characterized for a broad suite of environmental exposures and “omics” data, to be clinically examined, and to have biological samples collected (Maitre et al., 2018). From this subcohort, 152 children were selected to be part of the Child Panel Study: 28 from BiB (Born in Bradford; United Kingdom), 25 from EDEN (Etude des Determinants pre et postnatals du developpement et de la sante de l'ENfant; France), 40 from INMA Sabadell (INfancia y Medio Ambiente; Spain), 30 from KANC (Kaunus Cohort; Lithuania), and 29 from RHEA (Greece) (Vrijheid et al., 2014). Children from MoBa (Norwegian Mother and Child Cohort Study; Norway) were not included in this panel study. The Child Panel Study had the same inclusion criteria as the HELIX subcohort: a) age 6–11 years at the time of the visit, with a preference for ages 7–9 years if possible; b) sufficient stored pregnancy blood and urine samples; c) complete address history available; and d) no serious health problem. Pregnant women participating in the Pregnancy Panel Study were not the mothers of the HELIX children since the pregnancies of HELIX children mothers had occurred several years before (between 1999 and 2010).

All research protocols were approved by the Ethics Committee of each country and informed consent was obtained from all subjects.

2.2. Urine collection and pooling procedure

All subjects were followed during a normal week (i.e., working week for pregnant women and a school week for children) in two time periods: in the 2nd (mean: 18.0 gestational weeks, standard deviation (SD): 2.6) and 3rd (mean: 32.2, SD: 2.4) trimesters for pregnant women and two one-week periods six months apart (mean: 6.2 months, SD: 2.1; Fig. 1) for children. Urine samples were collected three times per day (first morning, afternoon, and bed time voids) in the Pregnancy Panel and two times per day (first morning and bedtime voids) in the Child Panel. Urine samples were collected in 70 ml polypropylene containers (Sarstedt: 75.9922.744). Following the protocol, each pregnant woman collected around 20 urines per week (mean: 20.0 urines per week; SD: 1.7) and each child collected 15 urines per week (mean: 14.7 urines per week; SD: 0.7) (Fig. 1). Participants recorded the date and time of each