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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

Table 1
Intraclass correlation coefficients (ICC, 95% confidence intervals, CI) reported in previous studies assessing the variability of phthalate metabolites, phenols, organophosphate (OP) pesticide metabolites, and cotinine in pregnant women.[a]

	Adibi et al. (2008)	Ferguson et al. (2014)	Cantonwine et al. (2014) Meeker et al. (2013) Lewis et al. (2015)	Braun et al. (2012) Millenson et al. (2017)[c]	Fisher et al. (2015) Weiss et al. (2015)	Guidry et al. (2015) Bertelsen et al. (2014)	Jusko et al. (2014) Spaan et al. (2015)	Philippat et al. (2013)	Braun et al. (2011)
Country	US	US	Puerto Rico	USA	Canada	Norway	Netherlands	USA	USA
N of subjects	32	482	139[b]	137	80	45	120[d]	71	332
Age (years)	26.0 ± 5.0	–	27.5 ± 5.2	35 ± 4.1	32.3	20–41	31.9 ± 4.4	35.5	< 25: 25% 25–34: 59% > 35: 16%
Number and timing of urine samples collection	2 to 4 voids during pregnancy	4 voids during pregnancy	3 voids during pregnancy	3 voids during pregnancy	All voids over 24 h in 2 times in the 1st trimester, 1 void at 2nd and 3rd trimesters, and 1 at 2–3 months post-partum	3 voids during pregnancy	3 voids during pregnancy	3 voids during pregnancy	3 voids during pregnancy
Phthalate metabolites									
MEP	0.21	0.47 (0.42, 0.52)	0.44 (0.34, 0.55)	0.50	Between-trimester: 0.38 (0.27, 0.50)	–	–	–	–
MiBP	0.48	0.52 (0.48, 0.57)	0.34 (0.24, 0.46)	0.38	Within-day: 0.58 (0.45, 0.71)	–	–	–	–
MnBP	0.55	0.57 (0.53, 0.62)	0.42 (0.31, 0.53)	0.45	Between-trimester: 0.32 (0.21, 0.44)	–	–	–	–
MBzP	0.65	0.61 (0.56, 0.65)	0.41 (0.30, 0.52)	0.25	Between-trimester: 0.23 (0.13, 0.36)	–	–	–	–
MEHP	0.25	0.30 (0.25, 0.35)	0.36 (0.26, 0.48)	0.08	Between-trimester: 0.12 (0.05, 0.26)	–	–	–	–
MEHHP	0.23	0.21 (0.17, 0.27)	0.24 (0.14, 0.37)	–	Between-trimester: 0.15 (0.07, 0.29)	–	–	–	–
MEOHP	0.22	0.19 (0.15, 0.25)	0.25 (0.15, 0.38)	–	Between-trimester: 0.20 (0.11, 0.33)	–	–	–	–
MECPP	0.21	0.31 (0.26, 0.36)	0.19 (0.10, 0.33)	–	Within-day: 0.40 (0.28, 0.54)	–	–	–	–
oh-MiNP	–	–	–	–	–	–	–	–	–
oxo-MiNP	–	–	–	–	–	–	–	–	–
Phenols									
MEPA	–	–	0.39 (0.27, 0.53)	–	–	0.24 (0.10, 0.40)	–	0.61	–
ETPA	–	–		–	–	–	–	0.44	–
PRPA	–	–	0.32 (0.20, 0.47)	–	–	0.62 (0.49, 0.72)	–	0.54	–
BUPA	–	–	0.47 (0.35, 0.60)	–	–	0.38 (0.23, 0.53)	–	0.64	–
BPA	–	–	0.24 (0.13, 0.40)	0.12	Between-trimester: 0.07 (0.02, 0.25)	0.04 (−0.07, 0.17)	0.31 (0.16, 0.47)	0.14	0.11
OXBE	–	–	0.62 (0.51, 0.71)	–	–	< 50% detection	–	0.70	–
TCS	–	–	0.47 (0.35, 0.59)	–	Between-trimester: 0.50 Within-day: 0.77–0.79	0.49 (0.31, 0.65)	–	0.61	–
OP pesticide metabolites									
DMP	–	–		–	–	–	0.33	–	–
DMTP	–	–	0.19 (0.06, 0.43)	–	–	–	0.21	–	–
DMDTP	–	–		–	–	–	0.14	–	–
DEP	–	–		–	–	–	0.25	–	–
DETP	–	–	0.21 (0.09, 0.46)	–	–	–	0.25	–	–
DEDTP	–	–		–	–	–	0.38	–	–
Cotinine	–	–	–	–	–	–	–	–	–

Abbreviations: BPA: bisphenol A; BUPA: *n*-butyl-paraben; DEDTP: diethyl dithiophosphate; DEP: diethyl phosphate; DETP: diethyl thiophosphate; DMDTP: dimethyl dithiophosphate; DMP: dimethyl phosphate; DMTP: dimethyl thiophosphate; CI: confidence interval; ETPA: ethyl-paraben; ICC: intraclass-correlation coefficient; MBzP: mono benzyl phthalate; MECPP: mono-2-ethyl 5-carboxypentyl phthalate; MEHHP: mono-2-ethyl-5-hydroxyhexyl phthalate; MEHP: mono-2-ethylhexyl phthalate; MEOHP: mono-2-ethyl-5-oxohexyl phthalate; MEP: monoethyl phthalate; MEPA: methyl-paraben; MiBP: mono-iso-butyl phthalate; MnBP: mono-*n*-butyl phthalate; oh-MiNP: mono-4-methyl-7-hydroxyoctyl phthalate; OP: organophosphate; OXBE: oxybenzone; oxo-MiNP: mono-4-methyl-7-oxooctyl phthalate; PRPA: propyl-paraben; TCS: triclosan.

[a] Only studies that collected ≥three voids per subject during pregnancy and reported an intraclass correlation coefficient (ICC). ICCs were calculated considering creatinine-standardized concentrations.

[b] In Cantonwine et al. (2014), 139 pregnant women were included, in Meeker et al. (2013) 102 women, and in Lewis et al. (2015) 54 women.

[c] In Millenson et al. (2017) the ICC for OP pesticide metabolites are not shown.

[d] In Jusko et al. (2014) 80 women were included and in Spaan et al. (2015) 120 women.

Table 2
Intraclass correlation coefficients (ICC, 95% CI) reported in previous studies assessing the variability of phthalate metabolites, phenols, organophosphate (OP) pesticide metabolites, and cotinine in children.[a]

	Teitelbaum et al. (2008)	Watkins et al. (2014) Stacy et al. (2016) Stacy et al. (2017)	Heffernan et al. (2014)	Bradman et al. (2013)	Griffith et al. (2011)
Country	USA	USA	Australia	USA	USA
N of subjects	35	Annual: 283/Short-term: 61	25	25	44
Age (years)	6–9	1–8	2–4	3–6	2–5
Number and timing of urine samples collection	6 voids over 6 months	Annual: at least 2 voids over 5 years Short-term: 2 voids/year 2 weeks apart over 3 years	4 voids over 48-hours	Spot voids over 7 days; 24-hrs over 2 days	10–26 biweekly urines over 21 months
Phthalate metabolites					
MEP	0.26	Annual: 0.35 (0.22, 0.44) Short-term: 0.29 (0.00, 0.52)	–	–	–
MiBP	0.28	Annual: 0.31 (0.06, 0.50)	–	–	–
MnBP	0.35	Annual: 0.20 (0.01, 0.39)	–	–	–
MBzP	0.62	Annual: 0.25 (0.18, 0.35) Short-term: 0.39 (0.19, 0.57)	–	–	–
MEHP	0.29	–	–	–	–
MEHHP	0.24	–	–	–	–
MEOHP	0.23	–	–	–	–
MECPP	–	–	–	–	–
ohMiNP	–	–	–	–	–
oxoMiNP	–	–	–	–	–
Phenols					
MEPA	–	–	–	–	–
ETPA	–	–	–	–	–
PRPA	–	–	–	–	–
BUPA	–	–	–	–	–
BPA	0.35	Annual: 0.11 (~0.02, 0.20) Short-term: 0.49 (~0.18, 0.75)	0.51 (0.32–0.70)	–	–
OXBE	0.46	–	–	–	–
TCS	0.39	Annual: 0.14 (0.22, 0.44) Short-term: 0.29 (0.00, 0.52)	–	–	–
OP pesticide metabolites					
DMP	–	–	–	Weekly total DM = 0.37 24-hrs voids total DM = NQ	0.08 (0.03, 0.16)
DMTP	–	–	–		0.06 (0.03, 0.11)
DMDTP	–	–	–		0.06 (0.03, 0.13)
DEP	–	–	–	Weekly total DE = 0.11 24-hrs voids total DE = 0.16	0.05 (0.02, 0.13)
DETP	–	–	–		0.08 (0.04, 0.14)
DEDTP	–	–	–		–
Cotinine	–	–	–	–	–

Abbreviations: BPA: bisphenol A; BUPA: *n*-butyl-paraben; DE: three diethyl phosphates including DEP, DETP, and DEDTP; DEDTP: diethyl dithiophosphate; DEP: diethyl phosphate; DETP: diethyl thiophosphate; DM: three dimethyl phosphate metabolites including DMP, DMTP, and DMDTP; DMDTP: dimethyl dithiophosphate; DMP: dimethyl phosphate; DMTP: dimethyl thiophosphate; CI: confidence interval; ETPA: ethyl-paraben; ICC: intraclass-correlation coefficient; MBzP: mono benzyl phthalate; MECPP: mono-2-ethyl 5-carboxypentyl phthalate; MEHHP: mono-2-ethyl-5-hydroxyhexyl phthalate; MEHP: mono-2-ethylhexyl phthalate; MEOHP: mono-2-ethyl-5-oxohexyl phthalate; MEP: monoethyl phthalate; MEPA: methyl-paraben; MiBP: mono-iso-butyl phthalate; MnBP: mono-*n*-butyl phthalate; NQ: not quantifable; oh-MiNP: mono-4-methyl-7-hydroxyoctyl phthalate; OP: organophosphate; OXBE: oxybenzone; oxo-MiNP: mono-4-methyl-7-oxooctyl phthalate; PRPA: propyl-paraben; TCS: triclosan.

[a] Only studies that collected ≥three voids per subject during childhood and reported an intraclass correlation coefficient (ICC). ICCs were calculated considering creatinine-standardized concentrations.

collection prior to storage in a domestic freezer (typically at −20 °C). Only the two last samples collected in children were stored in the fridge because these samples corresponded to those collected as part of the HELIX subcohort visit (see Supplemental material, Fig. S1). On day 8, all samples (pregnant women and children) were transported to each study centre, using cooler boxes with ice packs to prevent thawing, and were stored in −80 °C freezers. Urines were defrosted overnight at 4 °C and then placed at room temperature for 30 min prior to aliquoting. All urines from each subject were processed at the same time. Samples were inverted gently 2–3 times and from each sample three aliquots of 1.75 ml in a 2 ml cryovial (Sarstedt: 72.379) were made.

We made within-subject pools of all urines collected in a week by

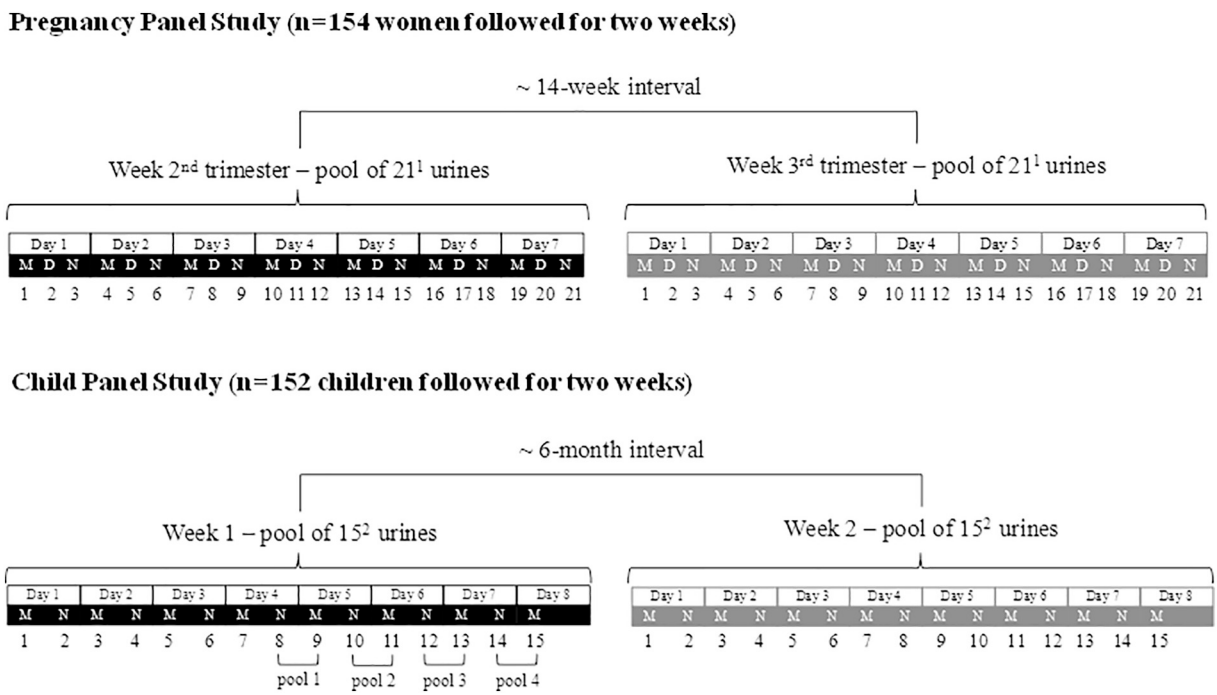

Fig. 1. Study design of the Pregnancy and Child Panel Studies.
Abbreviations: D: midday void; M: morning void; N: nighttime void
[1]mean: 20.0 urines per week; standard deviation: 1.7.
[2]mean: 14.7 urines per week; standard deviation: 0.7.
*In children, cotinine was only analyzed in the last pool of two urines of week 1 (pool 4) and in the two weekly pools.

taking 0.5 ml from each aliquot; i.e. around 20 samples for pregnant women and 15 for children. In children, we also made four pools of two urines (nighttime sample with the following morning sample) collected during the last four days of the first follow-up week (Fig. 1). The last pool of two urines corresponded to the pool that was collected in all the HELIX subcohort children (n = 1301, including panel children) (Maitre et al., 2018). In total, we analyzed 308 pooled samples from pregnant women, corresponding to 6174 voids, and 912 pooled samples from children corresponding to 4090 voids. Collection and processing of the samples were performed in a completely harmonized way, using the same protocols and equipment in all centres.

2.3. Chemical analyses

Samples were analyzed at the Department of Environmental Exposure and Epidemiology at the Norwegian Institute of Public Health (NIPH), in Norway. This study focused on the least persistent compounds considered in the HELIX project. We analyzed a total of 10 phthalate metabolites: monoethyl phthalate (MEP), mono-iso-butyl phthalate (MiBP), mono-*n*-butyl phthalate (MnBP), mono benzyl phthalate (MBzP), mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5-hydroxyhexyl phthalate (MEHHP), mono-2-ethyl-5-oxohexyl phthalate (MEOHP), mono-2-ethyl 5-carboxypentyl phthalate (MECPP), mono-4-methyl-7-hydroxyoctyl phthalate (oh-MiNP), and mono-4-methyl-7-oxooctyl phthalate (oxo-MiNP); 7 phenols: methyl-paraben (MEPA), ethyl-paraben (ETPA), propyl-paraben (PRPA), and *n*-butyl-paraben (BUPA), BPA, oxybenzone (OXBE), and triclosan (TCS); 6 dialkyl phosphate (DAP) metabolites: dimethyl phosphate (DMP), dimethyl thiophosphate (DMTP), dimethyl dithiophosphate (DMDTP), diethyl phosphate (DEP), diethyl thiophosphate (DETP), and diethyl dithiophosphate (DEDTP); and cotinine. The methods are described in detail elsewhere (Haug et al., 2018). Briefly, phthalate metabolites were quantified using liquid chromatography coupled with mass spectrometry (LC-MS/MS) (Sabaredzovic et al., 2015), phenols concentrations using ultra-high performance liquid chromatography - tandem mass spectrometry (UPLC-MS/MS) (Sakhi et al., under review), and OP pesticide metabolites using ultra-high performance liquid chromatography-time-of-flight mass spectrometry (UHPLC-TOF) (Cequier et al., 2016). Cotinine and creatinine were measured at Fürst Medisinsk Laboratorium (Norway) by using the Immulite® 2000 Nicotine Metabolite (Cotinine) 600 Test on an Immulite 2000 XPi from Siemens Healthineers and the AU680 Chemistry System form Beckman Coulter using DRI® Creatinine-Detect® Test, respectively. The limits of detection (LOD) for the various methods ranged from 0.03 for most of phenols 3.03 μg/l for cotinine (Supplemental material, Table S1). All samples from the same subject were analyzed in the same batch. All samples from the same subject were analyzed in the same batch. Procedural blanks were prepared in the same way as the samples and were analyzed along with each batch of samples. For almost all compounds, the blanks were below or equal to the LODs. In some few sample preparation batches, the DEP concentrations in the procedural blanks were higher than the LOD, and thus the mean blank level was subtracted from the sample concentrations for the samples included in these batches. For all methods, we included internal quality control samples in each batch to ensure high quality of the determinations throughout the project. Furthermore, Standard Reference Materials were available for phthalate metabolites and phenols, which were analyzed at regular intervals. NIPH also participated in at least one inter-laboratory comparison for phenol measurements during the period when HELIX samples were analyzed. The relative standard deviation of the internal and external (standard reference materials) quality controls was below 30% for almost all the compounds. The results from the standard reference material and available interlaboratory comparison were found satisfactory (Supplemental material).

2.4. Population characteristics

In the Pregnancy Panel Study, information on socio-demographic characteristics was obtained by questionnaires completed by women and during face-to-face interviews conducted by trained interviewers at

the beginning of the first follow-up week. Women provided information on age, pre-pregnancy body mass index (BMI), smoking status during pregnancy, and parity. In the Child Panel Study, maternal characteristics were obtained from the mother of the child through self-reported questionnaires administered during pregnancy (age, education, country of birth, parity) (Maitre et al., 2018). When children were approximately 8 years of age, mothers also completed a questionnaire regarding second-hand-tobacco smoke exposure and current employment status. Weight and height of the child were measured at the end of the first follow-up week.

2.5. Estimation of the ICCs

For observations below the LOD, values were imputed using a quantile regression approach for the imputation of left-censored missing data implemented in the *imputeLOD* function available in the *rexposome* package in the R software (R Core, 2016). Supplemental material, Fig. S2 illustrates how the distribution of imputed data mimics observed raw data distribution. Concentrations of all compounds were log-transformed to improve normality of their distribution. In order to estimate the within-person variation, we used linear mixed models (with random effect on woman or child) adjusted for cohort and creatinine concentrations (continuous, non-transformed) to decompose the total variability of concentrations and estimate: i) the between-trimester (or between-week) variability of the two weekly pools in pregnant women; ii) the between-day (or within-week) variability of the four pools of two urines of consecutive days in children; and iii) the between-season (or between-week) variability of the two weekly pools in children. For each type of sample, we calculated the ICCs, defined as the ratio of the between-subject variance to total variance, as a measure of reliability of measurements in the respective time periods:

$$ICC = \frac{\sigma_\alpha^2}{\sigma_\alpha^2 + \sigma_\varepsilon^2}$$

where

$\sigma_\alpha{}^2$ = between-subject variance.

$\sigma_\varepsilon{}^2$ = within-subject variance.

For each compound and time-period, we characterized reliability as being poor (ICC < 0.40), fair (ICC = 0.40–0.59), good (ICC = 0.60–0.74) or excellent (ICC ≥ 0.75) (Rosner, 2011). For chemicals for which > 70% of samples were below the LOD (DEDTP, DMDTP, and cotinine in pregnant women; DEDTP and cotinine in children), we created a categorical variable to classify subjects as having undetected or detected concentrations in urine and calculated the *Kappa* (*K*) coefficient (0 = poor; 0.01–0.20 = slight; 0.21–0.40 = fair; 0.41–0.60 = moderate; 0.61–0.80 = substantial; 0.81–1.00 = almost perfect). Finally, in children, we estimated whether the last pool of two urines of the first follow-up week (pool 4, Fig. 1) was a good measure of the mean annual concentration. We chose this specific urine pool because it corresponded to the pool of urines that was collected in all the 1301 HELIX subcohort children. To do that, we used the average of the two weekly pools of 15 urines as the gold standard, and computed the square correlations between pool 4 and the gold standard (Armstrong, 1996).

2.6. Estimation of the number of pools needed to limit exposure misclassification

In case of a low ICC, reliability can be improved by collecting additional samples in each subject during the time period of interest. We estimated the number of pools *m* needed to obtain an ICC ≥ 0.80 by calculating the reliability coefficient of *m* pools by using the Spearman-Brown equation (Lachin, 2004):

Table 3
Characteristics of pregnant women and children in HELIX panel studies, as well as of HELIX subcohort children not included in the panel study.

Characteristics	Pregnant women	Children	
	N = 154[a]	Panel study N = 152	Non-panel N = 877[b]
Study setting %			
France	28.0	16.5	19.7
Greece	–	19.1	19.4
Lithuania	–	19.7	19.8
Norway	37.3	–	–
Spain	34.7	26.3	20.9
United Kingdom	–	18.4	20.2
Age of the study participant (years) mean (SD)	33.0 (4.2)	7.8 (1.7)	7.8 (1.7)
Age of participant's mother (years) mean (SD)	NA	30.8 (4.8)	30.1 (5.0)
Sex %			
Female	100.0	43.4	45.0
Male	–	56.6	55.0
Body mass index %			
< 25 kg/m^2	86.0	72.0	67.4
25–29.9 kg/m^2	11.2	16.7	20.8
≥ 30 kg/m^2	2.8	11.3	11.8
Parity[c] %			
0 previous pregnancy	41.6	43.2	45.8
≥ 1 previous pregnancy	58.4	56.9	54.2
Country of birth %			
Europe	90.3	NA	NA
South America	7.6	NA	NA
Others	2.1	NA	NA
Country of origin of parents %			
Both from other country	NA	5.4	9.6
One parent from other country	NA	4.0	6.7
Both parents from country of cohort	NA	90.6	83.7
Maternal smoking during pregnancy %			
Yes	4.2	14.5	18.8
No	95.8	85.5	81.2
Passive smoking %			
Yes	NA	41.2	39.1
No	NA	58.8	60.9
Maternal education %			
Low	2.0	10.9	18.5
Middle	8.0	39.5	37.7
High	90.0	49.7	43.8
Current maternal occupational status %			
Employed	88.4	74.0	72.3
Unemployed	6.1	16.7	10.0
Other	5.4	9.3	17.7

Abbreviations: NA: not available; SD: standard deviation.

[a] Pregnant women from the pregnancy panel were volunteer women from outside the HELIX cohorts; therefore, there were not "non-panel women".

[b] 1301 taking out the children panel study (N = 152) and the MoBa subjects (N = 272) because they did not perform the panel study. Differences between covariates distribution in panel and non-panel children were estimated by using One-Way Anova, Wilcoxon or Chi-square tests. None of the p-values were < 0.05.

[c] For children, we report the parity of the mother before the child's birth.

$$\rho_m = \frac{m * \rho}{1 + (m - 1)\rho}$$

where:

ρ = reliability coefficient of one pool (the ICC).

m = number of pools.

ρ_m = targeted reliability coefficient of *m* pools (set at 0.80).

This was done for each chemical and for each type of pool (daily and

weekly) in women and children.

Statistical analyses were conducted with Stata (Stata Corporation, 2015) and R softwares (R Core, 2016).

3. Results

3.1. Study population

Characteristics of pregnant women and children are shown in Table 3. Women who participated in the Pregnancy Panel Study were on average 33 years old (SD: 4.2). Most women had a BMI in the 20–25 kg/m^2 range (mean: 22.3 kg/m^2, SD: 3.2), were multiparous (58%), born in Europe (90%), did not smoke during pregnancy (96%), had a high education level (90%), and worked during pregnancy (88%). Children from the Child Panel Study were on average 8 years old (SD: 1.7). Fifty-seven percent were boys, 28% were overweight or obese, 91% of children had both parents born in the country of cohort, and 41% of children were exposed to tobacco smoke. Mothers of children included in the panel study had a mean age at delivery of 31 years (SD: 4.8), were more likely to be multiparous (57%), to have a high education level (50%) and currently working (74%). Children in the panel did not differ from the rest of HELIX subcohort children not included in the Child Panel Study in terms of socio-demographic characteristics (Table 3).

3.2. Urinary concentrations of non-persistent chemicals

Phthalate metabolites were detected in all samples from pregnant women and children (Table 4 and Supplemental material, Tables S1 and S2 and Figs. S3 and S4). Phenols were detected in over 90% of samples in both populations. DMTP and DEP were the most detected OP pesticide metabolites (≥87% samples) whereas for DMDTP and DEDTP most samples (≥57%) were below the LOD. Cotinine was detected in < 18% of samples in both pregnant women and children. In pregnant women, MEP concentrations were the highest and MEHP and oxo-MiNP the lowest among the phthalate metabolites; in children MEP, MiBP, and MECPP concentrations were the highest and MEHP and oxo-MiNP the lowest (Table 4 and Supplemental material, Figs. S3 and S4). Concentrations of phenols were higher in pregnant women than in children, except for BPA. Among all seven phenols assessed, MEPA concentrations were the highest and BUPA the lowest in both groups. Concentrations of OP pesticide metabolites were of similar magnitude in pregnant women and children. In both groups, the highest OP pesticide metabolites concentrations corresponded to DMP, DMTP, and DEP while the secondary metabolites DMDTP and DEDTP corresponded to the lowest concentration. Among samples with detectable levels of cotinine, pregnant women had higher concentrations than children. There were no differences in urinary concentrations of non-persistent chemicals between children included and not included in the panel study; cotinine was more frequently detected in children not included in the panel (Supplemental material, Table S3).

3.3. Between-trimester variability of urinary concentrations in pregnant women

Table 5 shows the ICCs of repeated urinary concentrations of phthalate metabolites, phenols, OP pesticide metabolites, and cotinine in pregnant women. Supplemental material, Table S4 shows the corresponding components of variance. Between-trimester reliability of phthalate metabolites and phenols weekly pools ranged from 0.23 for BPA to 0.67 for MnBP. The reliability was poor for all DAP metabolites (ICC < 0.31) with the exception of DEP metabolite (ICC = 0.51). There was no agreement between the proportion of detected samples across trimesters for DMDTP and DEDTP ($K = -0.02$ and -0.01, respectively). Reliability of cotinine between trimesters was good (ICC = 0.73) as well as the agreement in the proportion of samples with detected levels between trimesters ($K = 0.79$).

Table 4
Urinary concentrations[a] (average of the two weekly pools, μg/g creatinine) of phthalate metabolites, phenols, OP pesticide metabolites, and cotinine in pregnant women and children.

Biomarkers	Pregnant women				Children			
	p25	p50	p95	Max	p25	p50	p95	Max
Phthalate metabolites								
MEP	18.9	27.0	33.4	161.8	32.2	52.1	81.8	220.4
MiBP	11.7	15.8	22.2	69.4	16.2	23.0	35.7	282.5
MnBP	2.6	3.8	7.0	104.7	3.8	6.2	9.9	99.5
MBzP	2.0	3.1	5.2	74.8	2.5	3.3	5.5	29.3
MEHP	7.1	9.1	12.6	208.1	16.1	24.1	35.0	178.8
MEHHP	4.8	6.0	8.0	111.1	9.2	14.1	20.4	95.1
MEOHP	12.4	15.6	19.8	213.7	27.4	43.3	64.9	344.2
MECPP	3.8	6.9	12.1	241.1	4.4	6.9	10.3	42.9
oh-MiNP	2.2	3.6	7.5	64.8	3.0	4.0	5.5	27.8
oxo-MiNP	18.9	27.0	33.4	161.8	32.2	52.1	81.8	220.4
Phenols								
MEPA	17.7	57.7	141.0	5600.2	8.4	29.7	97.7	2676.4
ETPA	0.7	1.9	12.3	155.0	0.6	1.0	2.0	76.3
PRPA	2.9	10.8	31.7	1232.9	0.4	2.0	11.7	359.9
BUPA	0.1	0.2	0.6	22.3	0.1	0.1	0.2	13.6
BPA	2.6	3.9	5.5	24.3	3.3	4.5	6.7	47.4
OXBE	2.6	7.2	29.2	3873.0	1.3	2.9	8.2	1176.5
TCS	0.5	1.3	16.3	683.6	0.5	0.9	2.4	496.6
OP pesticide metabolites								
DMP	2.3	4.1	6.0	16.8	0.4	2.2	6.2	55.5
DMTP	3.0	4.7	7.2	32.9	3.6	5.1	8.8	72.4
DMDTP[b]	0.3	1.0	2.8	11.8	0.0	0.1	0.5	41.1
DEP	2.5	3.9	5.5	36.1	2.3	3.8	6.3	37.5
DETP	0.6	1.3	2.7	38.9	0.5	1.4	3.1	11.8
DEDTP[b]	0.2	0.2	0.2	0.2	0.3	0.4	0.5	0.6
Cotinine[b]	11.1	19.7	441.7	9776.0	11.3	15.2	20.5	116.8

Abbreviations: BPA: bisphenol A; BUPA: *n*-butyl-paraben; DEDTP: diethyl dithiophosphate; DEP: diethyl phosphate; DETP: diethyl thiophosphate; DMDTP: dimethyl dithiophosphate; DMP: dimethyl phosphate; DMTP: dimethyl thiophosphate; ETPA: ethyl-paraben; MBzP: mono benzyl phthalate; MECPP: mono-2-ethyl 5-carboxypentyl phthalate; MEHHP: mono-2-ethyl-5-hydroxyhexyl phthalate; MEHP: mono-2-ethylhexyl phthalate; MEOHP: mono-2-ethyl-5-oxohexyl phthalate; MEP: monoethyl phthalate; MEPA: methyl-paraben; MiBP: mono-iso-butyl phthalate; MnBP: mono-*n*-butyl phthalate; oh-MiNP: mono-4-methyl-7-hydroxyoctyl phthalate; OP: organophosphate; OXBE: oxybenzone; oxo-MiNP: mono-4-methyl-7-oxooctyl phthalate; PRPA: propyl-paraben; TCS: triclosan.

[a] Concentrations below the LOD have been imputed.

[b] Since many samples had concentrations below the LOD, we reported the distribution of concentrations above the LOD: DMDTP, DEDTP, and cotinine for pregnant women and DEDTP and cotinine for children. The percentage of samples below the LOD in each weekly pool is indicated in Supplemental material, Tables S1 and S2.

3.4. Between-day and between-season variability of urinary concentrations in children

Table 5 and Supplemental material Table S4 show the ICCs and the corresponding components of variance of urinary concentrations in children. To illustrate the between-day and between-season variability of these chemicals, Fig. 2 shows the distribution of urinary concentrations of MEP, MEHHP, BPA, OXBE, and DEP in five random children. Between-day and between-season reliability of phthalate metabolites MiBP, MBzP, MEHP, MEHHP, MEOHP, and MECPP was fair to good (ICC ranging from 0.51 to 0.70, Table 3). Reliability of MEP and MnBP was higher between-day (ICC = 0.63 and 0.60, respectively) than between seasons (ICC = 0.38 and 0.36, respectively). The between-day and between-season reliability of oh-MiNP and oxo-MiNP was poor to fair (ICC < 0.46). Reliability of OXBE was the highest among phenols

Table 5
Intraclass correlation coefficients[a] (ICC, 95% CI) of urinary concentrations of phthalate metabolites, phenols, OP pesticide metabolites, and cotinine in pregnant women and children.

Biomarkers	Pregnant women		Children				
	Between-trimester reliability		Between-day reliability[c]		Between-season reliability		Reliability coefficient (95% CI) of pool of 2 consecutive urines[d]
	N[b] samples/N women	ICC (95% CI)	N[b] samples/N children	ICC (95% CI)	N[b] samples/N children	ICC (95% CI)	
Phthalate metabolites							
MEP	297/153	0.59 (0.48, 0.69)	608/152	0.63 (0.55, 0.69)	304/152	0.38 (0.26, 0.52)	0.51 (0.39, 0.62)
MiBP	308/154	0.57 (0.47, 0.68)	608/152	0.61 (0.54, 0.68)	304/152	0.51 (0.39, 0.62)	0.76 (0.69, 0.82)
MnBP	308/154	0.66 (0.56, 0.74)	608/152	0.58 (0.50, 0.65)	304/152	0.36 (0.23, 0.50)	0.63 (0.53, 0.72)
MBzP	305/154	0.59 (0.48, 0.69)	608/152	0.6 (0.52, 0.67)	304/152	0.55 (0.44, 0.66)	0.57 (0.46, 0.66)
MEHP	298/153	0.45 (0.33, 0.58)	599/151	0.64 (0.57, 0.70)	299/151	0.70 (0.61, 0.78)	0.67 (0.57, 0.75)
MEHHP	307/154	0.32 (0.19, 0.47)	608/152	0.48 (0.40, 0.57)	304/152	0.52 (0.41, 0.63)	0.65 (0.56, 0.73)
MEOHP	308/154	0.32 (0.20, 0.48)	608/152	0.51 (0.43, 0.59)	304/152	0.54 (0.42, 0.65)	0.69 (0.60, 0.77)
MECPP	308/154	0.41 (0.29, 0.55)	608/152	0.52 (0.44, 0.60)	304/152	0.56 (0.45, 0.67)	0.69 (0.60, 0.76)
oh-MiNP	308/154	0.31 (0.19, 0.47)	608/152	0.46 (0.38, 0.55)	304/152	0.30 (0.18, 0.46)	0.30 (0.19, 0.43)
oxo-MiNP	308/154	0.32 (0.20, 0.47)	608/152	0.28 (0.20, 0.37)	304/152	0.22 (0.11, 0.41)	0.24 (0.13, 0.36)
Phenols							
MEPA	307/154	0.38 (0.25, 0.52)	608/152	0.58 (0.51, 0.66)	304/152	0.17 (0.07, 0.38)	0.37 (0.25, 0.49)
ETPA	307/154	0.53 (0.25, 0.64)	604/152	0.62 (0.55, 0.69)	304/152	0.31 (0.19, 0.47)	0.42 (0.29, 0.53)
PRPA	306/154	0.36 (0.24, 0.51)	588/152	0.61 (0.54, 0.68)	296/152	0.28 (0.15, 0.45)	0.50 (0.38, 0.61)
BUPA	307/154	0.54 (0.43, 0.65)	608/152	0.68 (0.61, 0.74)	304/152	0.27 (0.15, 0.44)	0.32 (0.20, 0.45)
BPA	305/154	0.24 (0.11, 0.43)	592/152	0.47 (0.39, 0.56)	291/151	0.09 (0.01, 0.45)	0.41 (0.29, 0.53)
OXBE	308/154	0.65 (0.55, 0.73)	608/152	0.88 (0.85, 0.91)	304/152	0.54 (0.42, 0.65)	0.69 (0.60, 0.76)
TCS	308/154	0.41 (0.29, 0.55)	608/152	0.84 (0.80, 0.87)	304/152	0.14 (0.04, 0.37)	0.46 (0.34, 0.57)
OP pesticide metabolites							
DMP	308/154	0.12 (0.03, 0.37)	608/152	0.22 (0.15, 0.32)	304/152	0.13 (0.04, 0.38)	0.05 (0.01, 0.14)
DMTP	308/154	0.16 (0.06, 0.37)	607/152	0.26 (0.19, 0.36)	304/152	0.33 (0.21, 0.49)	0.23 (0.12, 0.35)
DMDTP	50/46[e]	−0.02 (0.09)[f]	487/152	0.28 (0.20, 0.39)	304/152	0.14 (0.04, 0.37)	0.01 (0.08, 0.18)
DEP	308/154	0.52 (0.41, 0.63)	608/152	0.37 (0.29, 0.46)	303/152	0.25 (0.13, 0.43)	0.32 (0.20, 0.44)
DETP	298/153	0.23 (0.11, 0.42)	597/152	0.37 (0.29, 0.46)	290/151	0.35 (0.22, 0.51)	0.29 (0.17, 0.42)
DEDTP	2/2[e]	−0.01 (0.08)[f]	459/152	0.16 (0.09, 0.27)	4/4[e]	−0.01 (0.07)[f]	0.25 (−)
Cotinine	37/22[e]	0.79 (0.08)[f]	NA	NA	52/34[e]	0.63 (0.08)[f]	0.30 (0.03, 0.61)

Abbreviations: BPA: bisphenol A; BUPA: *n*-butyl-paraben; DEDTP: diethyl dithiophosphate; DEP: diethyl phosphate; DETP: diethyl thiophosphate; DMDTP: dimethyl dithiophosphate; DMP: dimethyl phosphate; DMTP: dimethyl thiophosphate; CI: confidence interval; ETPA: ethyl-paraben; ICC: interclass-correlation coefficient; MBzP: mono benzyl phthalate; MECPP: mono-2-ethyl 5-carboxypentyl phthalate; MEHHP: mono-2-ethyl-5-hydroxyhexyl phthalate; MEHP: mono-2-ethylhexyl phthalate; MEOHP: mono-2-ethyl-5-oxohexyl phthalate; MEP: monoethyl phthalate; MEPA: methyl-paraben; MiBP: mono-iso-butyl phthalate; MnBP: mono-*n*-butyl phthalate; NA: not applicable; oh-MiNP: mono-4-methyl-7-hydroxyoctyl phthalate; OP: organophosphate; OXBE: oxybenzone; oxo-MiNP: mono-4-methyl-7-oxooctyl phthalate; PRPA: propyl-paraben; SD: standard deviation; TCS: triclosan.

[a] Models were adjusted for cohort and creatinine concentrations (g/l) except the reliability coefficient that was based on the creatinine-corrected concentrations of compounds (ng/g).

[b] Concentrations below the LOD have been imputed. Missing subjects/samples were those that were non-quantifiable (qualifier/quantifier ratio out of range); see Supplemental material Tables S1 and S2.

[c] Based on four pools of two consecutive urines collected within the same week.

[d] Based on the squared correlation between pool 4 of week 1 (pool collected in the HELIX subcohort) and the average of the weekly pools of 15 urines (as gold standard).

[e] Number of samples/subjects with detectable levels in both trimesters/seasons.

[f] Kappa coefficient as a measure of the agreement between the number of samples undetected and detected in each trimester/season.

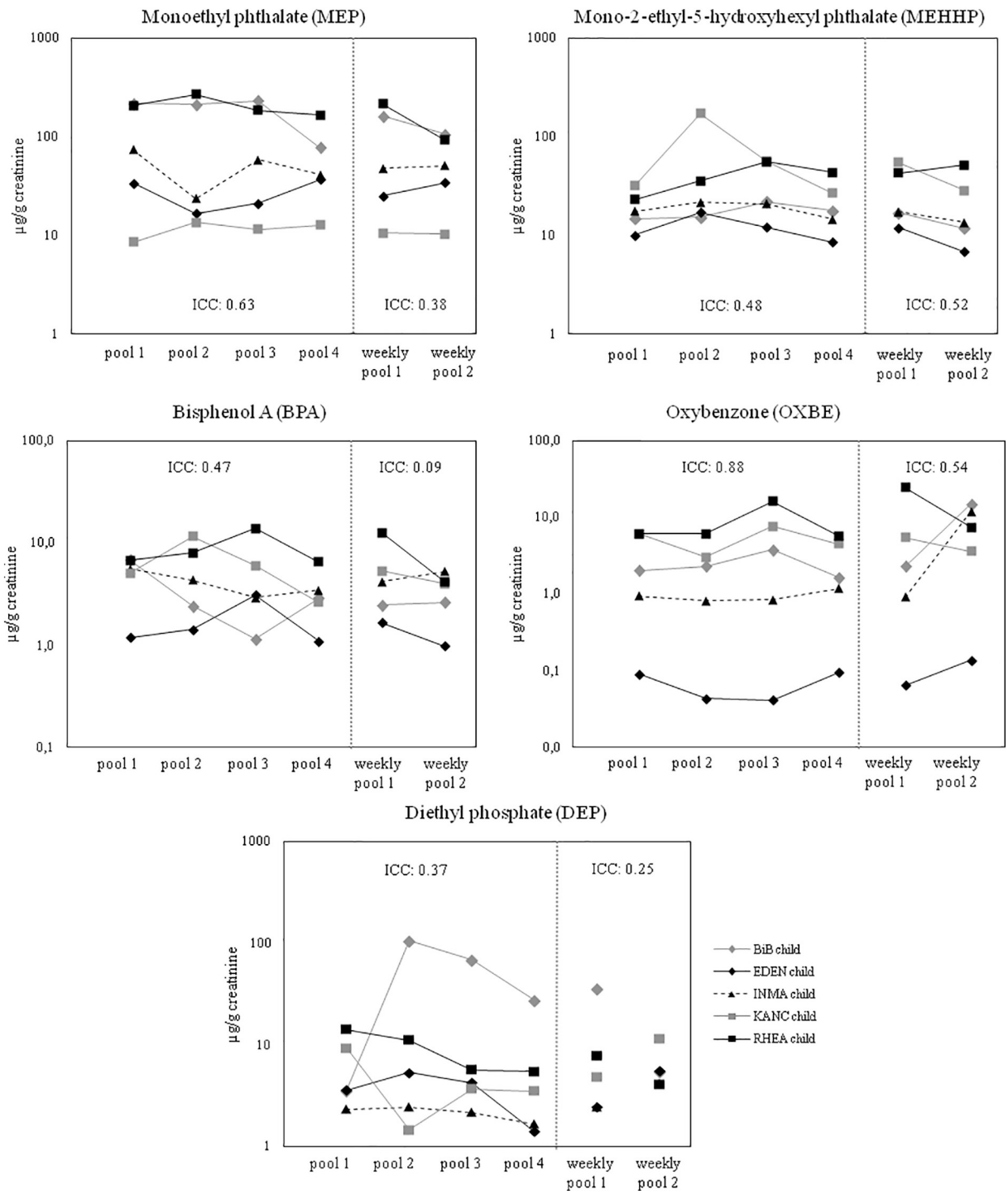

Fig. 2. Urinary concentrations (µg/g creatinine) of two phthalate metabolites, bisphenol-A, oxybenzone, and diethyl phosphate in five random children from the Child Panel Study.
Abbreviations: ICC: intraclass correlation coefficient.

(within week ICC = 0.88; between seasons ICC = 0.52) whereas BPA had the lowest reliability (between-day ICC = 0.49; between-season ICC = 0.10). OP pesticide metabolites were highly variable within week and between seasons, with ICCs ranging from 0.13 to 0.37. In the case of DEDTP, with a high number of samples below the LOD, there was no agreement in the proportion of detected samples between seasons ($K = -0.01$). Between-season reliability of cotinine was fair (ICC = 0.41) while the agreement in the proportion of samples above the LOD between seasons was substantial ($K = 0.63$).

3.5. Reliability of pool of two consecutive urines in children

In children, the last pool of two urines of the first follow-up week was a good estimate of concentration over a year (computed as the average of the two weekly pools of 15 urines) for the majority of phthalate metabolites and OXBE, with reliability coefficients from 0.57

to 0.76 (Table 5). This pool was not a good measure of variability over a year for the other phenols, all OP pesticide metabolites, nor for cotinine (reliability coefficients from 0.01 to 0.51).

3.6. Number of urine pools per subject required to reduce exposure misclassification

In pregnant women, between two (e.g., cotinine) and six (e.g., DMDTP) weekly pools of 20 urines each collected during pregnancy would be needed to properly classify women (defined as an ICC ≥ 0.80) in terms of phthalate metabolites, phenols, OP pesticide metabolites, and cotinine levels (Table 6). In children, one would need between one (e.g., OXBE) and four pools (e.g., all DAP metabolites) of two consecutive urines to obtain appropriate weekly exposure estimation for phthalate metabolites, phenols, and OP pesticide metabolites. Between three (e.g., OXBE, cotinine) and five (e.g., BPA, DMP) weekly pools of 15 urines each collected during a year would be required to obtain an accurate annual exposure estimation in children.

4. Discussion

We evaluated the variability of urinary concentrations of non-persistent chemical contaminants between trimesters in pregnant women and between days and between seasons in school-aged children. In both populations, phthalate metabolites and phenols were detected in > 90% of pools whereas certain OP pesticide metabolites and cotinine were detected in < 43% of pools. In pregnant women, for the majority of chemicals, we observed poor to fair between-trimester (i.e., between weeks from different pregnancy trimesters) reliability of biomarker urinary concentrations in spite of the fact that we relied on a weekly pool to assess mean concentration. Only for certain phthalate metabolites, OXBE, and cotinine the reliability between trimesters was good. Overall in children, we observed fair to good between-day reliability but, as in women, poor to fair between-season reliability; MEHP was the least variable chemical over a year. Urinary cotinine concentrations were stable during pregnancy in pregnant women and over a year in children. The pool of two urines available in the HELIX subcohort children predicted well the annual exposure of most phthalate metabolites and OXBE but not the mean annual concentration of other phenols, of the OP pesticide metabolites, nor of cotinine. For most chemicals, three daily pools of two urines would be necessary to obtain excellent reliability for weekly exposure windows. Similarly, four weekly pools of 15 to 20 urines would be needed to achieve excellent reliability for a pregnancy or yearly exposure window.

4.1. Comparison with previous studies

Because of differences in study designs, time periods, or population settings, the comparability of results with previous studies is limited. A total of nine studies have assessed the temporal variability of these chemicals among pregnant women (Table 1). These studies collected between three to five spot urines samples during pregnancy; except the studies of Fisher et al. (2015) and Weiss et al. (2015) that collected many more samples during pregnancy. The ICCs of phthalate metabolites and phenols of previous studies were similar to our ICCs. Philippat et al. (2013) however, collecting three urines voids over pregnancy, reported higher reliability for the majority of phenols than in the present study, with the exception of BPA for which the reliability was lower than ours. Only two studies assessed the temporal variability of DAP metabolites in pregnant women (Lewis et al., 2015; Spaan et al., 2015) and reported very high variability, similarly to our study, although urinary concentrations of DAP among our women showed a lower degree of variability than pregnant women from the Generation R study (Spaan et al., 2015).

Regarding children, five previous studies have evaluated the temporal variability of these chemicals over periods ranging from days to years (Table 2). Compared with the long-term variability across months and years reported by Teitelbaum et al. (2008) and Watkins et al. (2014), respectively, our seasonal reliability is higher for phthalate metabolites and OXBE but lower for BPA and TCS. Even though the study of Heffernan et al. (2014) did not follow the same study design as us (i.e., they collected 4 voids over 48 h), they reported very similar short-term variability of BPA (ICC = 0.51) as us (ICC = 0.49). The two studies that assessed the reliability of DAP metabolites also showed very high variability between days and months (Bradman et al., 2013; Griffith et al., 2011).

4.2. Interpretation of results

Phthalates are found in polyvinyl chloride (PVC) applications such as food containers and building materials, and also in personal care products and some medications. Phthalates have short biological half-lives, from hours to days (Meeker et al., 2009). Reliability of phthalates present in personal care products (i.e., diethyl phthalate (DEP) – parent of MEP, di-*n*-butyl phthalate (DnBP) – parent of MnBP) was high in our

Table 6
Estimation of the number of urine pools needed to limit exposure misclassification of phthalate metabolites, phenols, OP pesticide metabolites, and cotinine in pregnant women and children based on the intraclass correlation coefficients of Table 5.

Biomarkers	Pregnant women	Children	
	N of pools of 20 urines needed for between-trimester ICC ≥ 0.80	N of pools of two urines needed for between-week ICC ≥ 0.80	N of pools of 15 urines needed for between-season ICC ≥ 0.80
Phthalate metabolites			
MEP	3	3	4
MiBP	3	3	3
MnBP	2	3	4
MBzP	3	3	3
MEHP	3	3	2
MEHHP	4	3	3
MEOHP	4	3	3
MECPP	3	3	3
oh-MiNP	4	3	4
oxo-MiNP	4	4	4
Phenols			
MEPA	4	3	4
ETPA	3	3	4
PRPA	4	3	4
BUPA	3	3	4
BPA	4	3	5
OXBE	3	1	3
TCS	3	1	5
OP pesticide metabolites			
DMP	4	4	5
DMTP	4	4	4
DMDTP	6	4	4
DEP	3	4	4
DETP	4	4	4
DEDTP	4	4	4
Cotinine	2	–	3

Abbreviations: BPA: bisphenol A; BUPA: *n*-butyl-paraben; DEDTP: diethyl dithiophosphate; DEP: diethyl phosphate; DETP: diethyl thiophosphate; DMDTP: dimethyl dithiophosphate; DMP: dimethyl phosphate; DMTP: dimethyl thiophosphate; CI: confidence interval; ETPA: ethyl-paraben; ICC: intraclass-correlation coefficient; MBzP: mono benzyl phthalate; MECPP: mono-2-ethyl 5-carboxypentyl phthalate; MEHHP: mono-2-ethyl-5-hydroxyhexyl phthalate; MEHP: mono-2-ethylhexyl phthalate; MEOHP: mono-2-ethyl-5-oxohexyl phthalate; MEP: monoethyl phthalate; MEPA: methyl-paraben; MiBP: mono-iso-butyl phthalate; MnBP: mono-*n*-butyl phthalate; oh-MiNP: mono-4-methyl-7-hydroxyoctyl phthalate; OP: organophosphate; OXBE: oxybenzone; oxo-MiNP: mono-4-methyl-7-oxooctyl phthalate; PRPA: propyl-paraben; TCS: triclosan.

population of women, indicating that these women may tend to apply personal care products in similar amounts throughout the whole pregnancy. Our population of women showed low between-trimester reliability of phthalates present in PVC (i.e., DEHP metabolites); this could be attributable to changes in diet during pregnancy or in the time spent in the different indoor environments (e.g. home versus work). Children presented similar between-day and between-season reliability for all phthalate metabolites, which may indicate a regular use of products that contain phthalates between seasons.

Phenols are used in personal care products including cosmetics (i.e., parabens), toothpastes (i.e., TCS), and sunscreen (i.e., OXBE), and in food packaging and polycarbonates (in the case of BPA). Their biological half-life is < 24 h (Meeker et al., 2009; Sandborgh-Englund et al., 2006). All phenols except OXBE presented high variability between trimesters and between seasons, but less variability between-day, probably indicative of seasonal variations of exposure sources. BPA presented the lowest reliability among phenols, where > 70% of the total variance was attributable to within-person variance in samples collected between trimesters and between seasons (Supplemental material, Table S4). High OXBE concentrations have been found in human adipose tissue and have been positively correlated with donor's age (Wang et al., 2015); this may explain the high reliability of this phenol observed in both pregnant women and children.

DAP are non-specific urinary markers of OP pesticides and each DAP can be generated from more than one OP pesticide; hence, urinary concentrations of DAP metabolites reflect exposure to a wide range of OP pesticides. They are primarily used as insecticides, mostly in agriculture but also to fight pests in residential and institutional settings. They have biological half-lives of hours to days (Bradman et al., 2013). In our study, we observed very high variability of all DAPs in both populations. This may suggest that exposure to these chemicals through contaminated food or pesticide used at home is intermittent over time.

Cotinine has a short biological half-life of around 9 h in pregnant women (Dempsey et al., 2002). In our population, 73% of the total variance corresponded to between-women variance, indicating that, with repeated samples, we can classify pregnant women as smokers, passive smokers, or non-smokers based on their cotinine levels in weekly urine pools. In children, the within- and between-child variance contributed equally to total variance, indicating that they are probably sporadically exposed to tobacco smoke (at home or in other places) and that the half-life is short (~20 h; Bono et al., 2005).

4.3. Implications for epidemiological studies

Exposure to many non-persistent chemicals has been described to be chronic but highly variable over the life course; therefore, one of the main challenges in understanding their health effects is the characterization of the long-term exposure, i.e. during critical sensitive windows that depend on the health or biological outcomes considered. For many diseases such as childhood obesity, diabetes, neurobehavioural disorders, or asthma, exposure estimates months or years before the outcome occurrence are relevant considering (Fénichel et al., 2015). A study with data on repeated urinary concentrations of TCS over a week for example, a chemical with good between-day but poor between-season reliability, would only provide information on exposure in the recent week(s), which would not be relevant if the toxicologically relevant time window is much longer than a week. Accurately characterizing potential long-term effects would require collecting a larger number of samples over a year (i.e., five pools of 15 urines each). Moreover, knowing the ICC of a particular exposure allows correcting the observed estimates of association (Hofmann et al., 2011; Perrier et al., 2016; Rosner et al., 1992). To provide an example, if we consider a true relative risk of 1.20 associated with prenatal exposure to phenols, the corresponding observed relative risks would range from 1.04 for the lowest ICC of 0.23 for BPA, to 1.13 for the highest ICC of 0.65 for OXBE (considering that $RR_{obs} = \exp[ICC \times \ln(RR_{true})]$ (Hofmann et al., 2011; Rosner et al., 1992).

Many ICCs have been reported in the literature for several chemicals (Table 1); however, the recommended study design to obtain the ICCs for a particular population and time window of exposure would be an internal reliability study (Spiegelman, 2010), as the one conducted in HELIX. The sample size and the number of biospecimens per subject collected in this internal reliability study will mainly depend on the fieldwork and storage capacities and the available budget. Increasing the number of urines per subject does not necessarily translate into an important increase in the budget, which is mainly dependent on the number of chemical assays done. Collecting two urines per day during three weeks instead of three spot urines during pregnancy would increase the fungible costs but not the analytical costs since only three urinary pools will be analyzed. In terms of logistics, a fieldworker would have to bring all urine containers to participants at the beginning of the week and pick them up at the end of the week. It is worth mentioning that in our study the majority of women and children collected 21 (> 65%) and 15 (> 80%) urines per week, respectively, with no major complaints. If resources are an issue, increasing the number of subjects and reducing the number of biospecimens per subject may not be the best option. Perrier et al. (2016) have shown that, for the most variable compounds, a study with a given number of subjects with a spot biospecimen in each subject can be less efficient in terms of bias or power than a study with half as many subjects in whom two samples are collected.

Most of the previous etiological studies relied on concentrations of non-persistent chemicals assessed in very few spot biospecimens per subject, based on biosample collection strategies that were not originally designed to assess exposure to these compounds. Our study aimed to propose an alternative sampling strategy to better characterize exposure to these compounds. However, even our pooling strategy did not result in excellent reliability for compounds with very high temporal variability such as BPA. Therefore, future etiological studies should consider a thoughtful sampling design based on many pooled urines rather than using the conventional one of a few spot biospecimen per subject.

Exposure misclassification is of particular concern in exposome studies, which aim at simultaneously assessing the effect of multiple chemicals. If they ignore the high temporal variability of the non-persistent chemicals, exposome studies relying on spot biospecimens may fail to identify associations for those chemicals for which a spot biospecimen does not accurately reflect exposure during the toxicologically relevant window, such as those considered here (Slama and Vrijheid, 2015). For example, Agay-Shay et al. (2015) only observed associations between prenatal exposure to organochlorine compounds (which are generally very persistent in the body) and childhood overweight although they considered a total of 27 endocrine-disrupting chemicals, 11 of them with a high temporal variability. If repeated exposure assessment is available, measurement error models, such as simulation extrapolation and regression calibration (Carroll et al., 2006), can be used in single exposure studies to limit bias. Possible extensions exist for the situation of multiple exposures (Vasquez et al., 2017).

4.4. Strengths and limitations

The main strength of this study relies on the collection of multiple biospecimens per subject during one week in two periods during pregnancy in women and over a year in children. An additional strength is that multiple chemicals from multiple chemical classes were measured in each subject. Moreover, ICCs obtained in the child panel study can be directly transferred to the rest of the HELIX subcohort children (n = 1301), which will allow correcting for exposure misclassification in future HELIX studies. However, caution is required in generalizing our findings to other populations due to differences in study design, sampling procedure, and exposure patterns. Pregnant women from the panel were mostly European and highly educated. It has been reported

that urinary concentrations of these chemicals can differ based on socioeconomic and lifestyle characteristics (e.g., Casas et al., 2013; Valvi et al., 2015); this would be an issue if these characteristics affect their temporal variability; i.e., the higher the magnitude of the concentration the higher the variability. Also, our results should not be generalized to other age groups and populations such as adult men, non-pregnant women, or adolescents, since dietary patterns, use of personal care products, metabolism, and critical windows of exposure are expected to differ across groups. We thus encourage researchers to estimate the ICCs specific for the population they study and to apply the Spearman-Brown equation to estimate the number of samples required, or to collect a large number of samples (30–40) in the exposure window of interest, in case it is not possible to estimate the ICCs before the study start. Another limitation of the present study is that we did not collect urine samples in the first trimester or before pregnancy; conducting studies focused on these periods, that may be more critical to the adverse effects of these chemicals than late pregnancy, would be relevant in the future. We should also consider that our children were followed over a year and it is possible that the length of the study and the number of samples collected were not enough to accurately characterize the within-person variability exhibited over a longer time period.

5. Conclusions

There is substantial concentration variability for the majority of phthalate metabolites, phenols, and OP pesticide metabolites during pregnancy as well as over a year in school-aged children. This leads to studies interested in assessing exposures over time periods spanning over several trimesters or months to require the collection of generally several dozen biospecimens per subject. Our quantification of the variability of biomarker measurements of many non-persistent chemicals during several time windows can be used to optimize sampling designs in future biomonitoring and exposome studies and limit exposure misclassification.

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Competing financial interest declaration

Nothing to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.09.046.

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