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Temporal variability of urinary concentrations of phthalate metabolites, parabens and benzophenone-3 in a Belgian adult population

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ABSTRACT

In the present study, we investigated the temporal within-person variability of the exposure biomarker for phthalates, parabens and benzophenone-3 (BP3) in 32 Belgian adults, each providing 11 urine spots during 4 months. We calculated the intraclass coefficient correlation (ICC), the sensitivity and the specificity to assess the temporal reproducibility and to investigate the predictive ability of the spot measurements for these classes of chemicals. Additionally, we explored the temporal variability of the estimation of the cumulative risk of exposure to phthalates (hazard index; HI). We observed fair ICC ranging from 0.55 to 0.68 for parabens, monoethyl phthalate (MEP), mono-iso-butyl phthalate (MiBP) and BP3, but lower ICC, from 0.20 to 0.49, for monobenzyl phthalate (MBzP), mono-n-butyl phthalate (MnBP), mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5-oxo-hexyl phthalate (5-oxo-MEHP) and mono-2-ethyl-5-hydroxy-hexyl phthalate (5-OH-MEHP). The ICC estimated for HI (0.49) reflected a moderate reproducibility. The measurements in spot samples were moderate to good predictor of the 4-month level of exposure for parabens, MEP, MnBP, MiBP, BP3 and HI (sensitivity ranging from 0.67 to 0.77), but lower predictor for MEHP, 5-oxo-MEHP, 5-OH-MEHP and MBzP (sensitivity ranging from 0.58 to 0.63). The sensitivity could be increased when several spot urinary levels were averaged to predict the long-term level of exposure. Globally, our results indicate that a single spot measurement seems to correctly represent the long-term exposure for parabens, BP3, MEP, MiBP and HI. Additional spot samples seemed to be needed for the proper exposure assessment of the other target compounds.

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1. Introduction

Phthalates are used as plasticizers and solvents in numerous daily life items, such as food contact materials, clothes, toys, construction materials, personal care products (PCP), medical and pharmaceutical products. Since phthalates are not chemically bound to polymers in which they are included, e.g. PVC, they could be released in the environment. Consequently, humans are ubiquitously exposed through inhalation, oral or dermal pathways (Wittassek et al., 2011). Once absorbed, phthalate diesters are rapidly metabolized to the corresponding monoesters and oxidized-monoesters, and are then eliminated in the urine (Anderson et al., 2001). Therefore, the human exposure assessment is commonly performed by measuring the phthalate metabolite concentrations in the urine (Wittassek et al., 2011; Anderson et al., 2001). Several phthalates are known to be endocrine-disrupting chemicals (Howdeshell et al., 2008). Through the wide spectrum of phthalate effects, the toxicity of these compounds on male offspring has currently received the most attention (Wittassek et al., 2011; Howdeshell et al., 2008). Several phthalates have been demonstrated to act in male laboratory animals as anti-androgenic compounds through the inhibition of the fetal testosterone synthesis during the development stage. They could therefore induce genital malformations, low sperm quality and signs of feminization, constituting the phthalate syndrome (Howdeshell et al., 2008). Consistently, human phthalate exposure has already been associated with several pathologies, such as the reduction of the anogenital distance (Swan et al., 2005) or the reduction of sperm quality (Hauser et al., 2007).

Similarly to phthalates, parabens can be found in PCP, but also in foods and pharmaceutical products. Parabens are employed for their antimicrobial properties in a large range of consumer products (Cosmetic Ingredient Review Expert Panel, 2008). They also

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present some endocrine-disrupting properties acting as weak estrogenic and anti-androgenic compounds, but up to now contradictory results have been reported (Darbre and Harvey, 2008; Hoberman et al., 2008). It is widely suspected that humans are mainly exposed through the dermal pathway after skin application of PCP (Darbre and Harvey, 2008). After crossing the skin barrier, parabens are degraded by esterases into unspecific metabolites and eliminated in the urine (Darbre and Harvey, 2008). However, a small fraction is also eliminated as unchanged species and can be monitored to quantify the individual exposure (Ma et al., 2013).

BP3 is a UV-filter mainly used in sunscreens, but also in polymers and packaging to protect their content from the UV rays (Gonzalez et al., 2006). BP3 is known to exhibit weak estrogenic properties *in vitro* (Schlumpf et al., 2001). Similarly to parabens, the BP3 exposure mainly occurs through the skin (Gonzalez et al., 2006), and is partly metabolized. The different metabolites are eliminated in urine concomitantly with the unchanged compound, which therefore could be measured to assess the individual exposure (Gonzalez et al., 2006).

Phthalates, parabens and BP3 are three chemical classes of non-persistent endocrine-disrupting pollutants eliminated from the human body within a day (Anderson et al., 2001; Ma et al., 2013; Gonzalez et al., 2006). However, since human exposure occurs daily, the question of the temporal representativeness of the urinary biomarker measurements could be raised (Dewalque et al., 2014a). To provide an answer, several studies have been carried out to assess the within-person variability of phthalates, parabens and BP3 biomarkers (Hauser et al., 2004; Smith et al., 2012; Teitelbaum et al., 2008; Frederiksen et al., 2013; Koch et al., 2014; Fromme et al., 2007). However, to our knowledge, only a few studies were performed in European countries (Frederiksen et al., 2013; Koch et al., 2014; Fromme et al., 2007). After more than 10 years of experience in human biomonitoring of phthalates, parabens and BP3, levels as well as patterns of exposure observed differ from one country or specific group of individuals to another according to local specific habits or commercial applications (Suzuki et al., 2009; Frederiksen et al., 2010; Shirai et al., 2013; Braun et al., 2012). Consequently, it cannot be assumed that the within-person variability of these urinary biomarkers will be similar in different targeted populations.

For these reasons, we present here the results of a within-person variability study carried out on the urine of 32 Belgian adults over a 4-month period. The target compounds were 7 phthalate metabolites and 4 parabens, namely monoethyl phthalate (MEP), mono-n-butyl phthalate (MnBP), mono-iso-butyl phthalate (MiBP), monobenzyl phthalate (MBzP), mono-2-ethylhexyl phthalate (MEHP), mono-2-ethyl-5-oxo-hexyl phthalate (5-oxo-MEHP), mono-2-ethyl-5-hydroxy-hexyl phthalate (5-OH-MEHP), methylparaben (MP), ethylparaben (EP), n-propylparaben (PP) and n-butylparaben (BP), and also BP3. The aims of this work were, firstly, to investigate the temporal reproducibility of their urinary concentrations to evaluate whether the observed concentrations remained consistent through time or were highly dependent on day-to-day habits. Secondly, we compared the urinary biomarker variability occurring within a week and over months. Thirdly, we investigated the level of confidence which can be attributed to the predictive ability of one or several spot samples to classify the long-term exposure into low, medium, high and very-high levels. Finally, we used the results of this study to evaluate the variability of the estimated hazard index (HI) which commonly quantifies the risk of cumulative exposure of several phthalates exerting similar toxicity (Benson, 2009; Dewalque et al., 2014b). The purpose was to evaluate if HI could reasonably be used to identify individuals with an increased risk of cumulative exposure over time.

2. Material and methods

2.1. Study population and sampling protocol

32 Belgian adults from the general population participating to the previous study (Dewalque et al., 2014a) were asked to provide 11 spot urine samples, collected in polypropylene cups, during 4 months between February and July 2013. The sampling was performed in two phases: firstly, single spot voids were randomly collected each day during a week and were named from D1 to D7. Secondly, from day 30, spots were collected monthly (M1–M4) with a mean interval ($\pm$SD) of 30.2 ($\pm$1.7) days. The timing in urine collection was not taken into consideration. Samples were kept at 5 °C before being shipped within 24 h to the laboratory. Spots were then aliquoted and stored at -20 °C until they were analyzed. The volunteers consisted in 12 males and 20 females aged between 20 and 73 years (mean: 37.7 years; median: 35 years). This study was approved by the Hospital Faculty Ethics Committee of the University of Liege (Belgium).

2.2. Urine analysis

The urinary creatinine content was immediately measured using Architect kits (Abbott, Illinois, USA) before the aliquoting and storage. The samples were analyzed for 12 biomarkers of exposure, namely MEP (metabolite of diethyl phthalate; DEP), MnBP (metabolite of di-n-butyl phthalate; DnBP), MiBP (metabolite of di-iso-butyl phthalate; DiBP), MBzP (metabolite of benzylbutyl phthalate; BBzP), MEHP (metabolite of di-2-ethylhexyl phthalate; DEHP), 5-oxo-MEHP (metabolite of DEHP), 5-OH-MEHP (metabolite of DEHP), MP, EP, PP, BP and BP3. The analytical procedure, consisting in an enzymatic hydrolysis and a solid phase extraction followed by liquid chromatography tandem mass spectrometry, has been previously described (Dewalque et al., 2014c).

2.3. Cumulative risk assessment

The risk of cumulative exposure to phthalates was assessed through the estimation of HI, defined as the sum of the hazard quotients (HQ) of DnBP, DiBP and DEHP based on similar toxicological endpoints (Benson, 2009; Dewalque et al., 2014b; Bekö et al., 2013; Kranich et al., 2014). These HQ were calculated for each participant as the ratio between the estimated daily intake (EDI), based on metabolite urine levels (Anderson et al., 2001; Anderson et al., 2011; Koch et al., 2012), and the corresponding tolerable daily intake (TDI; European Food Safety Authorities, 2005a, 2005b, 2005c). The estimations of HI, HQ and EDI have already been thoroughly detailed elsewhere (Dewalque et al., 2014b) and are summarized in Table S1.

2.4. Statistical analysis

2.4.1. Descriptive analysis

Statistical analyses were performed with JMP 10.0.0 (SAS Institute, Carry, NC), GraphPad Prism 5.0 (GraphPad Software, CA, USA), RStudio 0.98.945 (Rstudio, Boston, MA) and Excel 2003 (Microsoft, Redmond, WA). Measured concentrations below the limits of detection (LOD) were replaced by the corresponding LOD/2 (Dewalque et al., 2014a, 2014c; Hornung and Reed, 1990). All statistical analyses were performed on $\log_{10}$-transformed values to better approximate a normal distribution. Correlations between biomarkers in the same sample were highlighted using Pearson test. The significance limit was set at 0.05. All following variability analyses were performed with both volumetric and creatinine-adjusted concentrations. The variability analyses described in the following sections were also conducted with HI. In that case, this

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