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Estimating uptake of phthalate ester metabolites into the human nail plate using pharmacokinetic modelling

Thuy T. Bui [a,d,*], Andreia Alves [b,c], Anna Palm-Cousins [a], Stefan Voorspoels [b], Adrian Covaci [c], Ian T. Cousins [d]

[a] IVL Swedish Environmental Research Institute, SE-100 31 Stockholm, Sweden
[b] VITO NV Flemish Institute for Technological Research, Boeretang 200, 2400 Mol, Belgium
[c] Toxicological Center, Department of Pharmaceutical Sciences, University of Antwerp, Universiteitplein 1, B-2610 Wilrijk, Belgium
[d] Department of Environmental Science and Analytical Chemistry (ACES), Stockholm University, SE-106 91 Stockholm, Sweden

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ABSTRACT

There is a lack of knowledge regarding uptake of phthalate esters (PEs) and other chemicals into the human nail plate and thus, clarity concerning the suitability of human nails as a valid alternative matrix for monitoring long-term exposure. In particular, the relative importance of internal uptake of phthalate metabolites (from e.g. blood) compared to external uptake pathways is unknown. This study provides first insights into the partitioning of phthalate-metabolites between blood and nail using pharmacokinetic (PK) modelling and biomonitoring data from a Norwegian cohort. A previously published PK model (Lorber PK model) was used in combination with measured urine data to predict serum concentrations of DEHP and DnBP/DiBP metabolites at steady state. Then, partitioning between blood and nail was assessed assuming equilibrium conditions and treating the nail plate as a tissue, assuming a fixed lipid and water content. Although calculated as a worst-case scenario at equilibrium, the predicted nail concentrations of metabolites were lower than the biomonitoring data by factors of 44 to 1300 depending on the metabolite. It is therefore concluded that internal uptake of phthalate metabolites from blood into nail is a negligible pathway and does not explain the observed nail concentrations. Instead, external uptake pathways are more likely to dominate, possibly through deposition of phthalates onto the skin/nail and subsequent metabolism. Modelling gaseous diffusive uptake of PEs from air to nail revealed that this pathway is unlikely to be important. Experimental quantification of internal and external uptake pathways of phthalates and their metabolites into the human nail plate is needed to verify these modelling results. However, based on this model, human nails are not a good indicator of internal human exposure for the phthalate esters studied.

1. Introduction

Phthalate esters (PEs) are the di-alkyl or alkyl aryl esters of phthalic acid and have been used worldwide, mainly as plasticizers, in a wide range of consumer products for almost a century. High molecular weight PEs can be found in PVC polymer applications (e.g. clothing, wires and cables, toys, furniture, car interiors) whereas the low molecular weight PEs are usually used in non-PVC products (e.g. personal-care products, paints, adhesives) (Wittassek et al., 2011).

Human health effects, such as decreased anogenital index, have been associated with exposure to certain PEs (Bustamante-Montes et al., 2013). Although PEs are a class of chemicals with a wide range of physicochemical and toxicological properties, developmental and reproductive toxicity and endocrine disrupting effects are commonly observed for some PEs (Culty et al., 2008; Ventrice et al., 2013; Wittassek et al., 2011; Wittassek and Angerer, 2008). Moreover, diethyl phthalate (DEP) and DEHP are suspected carcinogens (Kluwe et al., 2009; Lopez-Carrillo et al., 2010). Although legislation is still lacking regarding the maximum allowed levels of PEs in many consumer products, actions were already taken to restrict or even ban some PEs, depending on the particular use. For instance if bis(2-ethylhexyl) phthalate (DEHP), benzylbutyl phthalate (BBzP) or di-n-butyl phthalate (DnBP) are to be incorporated or can have direct contact with food, health and/or personal care products, childcare articles or medical devices, a ban or restriction to a maximum level was introduced (EP and CoEU, 2005; EU, 2007; Health and Food, 2001).

On one hand, human exposure to PEs can be dependent on lifestyle, for instance, use of personal care products etc. (Wormuth et al., 2006). On the other hand, exposure to these chemicals can also be dependent on their physicochemical properties, e.g. exposure via inhalation of indoor air is important for low molecular weight PEs due to high volatility (e.g. DEP), whereas food and dust ingestion becomes relatively more important for high molecular weight PEs such as DEHP (Wormuth et

Abbreviations: PE, phthalate ester; PK, pharmacokinetic; PVC, polyvinyl chloride; PCB, polychlorinated biphenyl; BFR, brominated flame retardant; CF, confidence factor.

* Corresponding author.
E-mail address: thuy.bui@ivl.se (T.T. Bui).

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al., 2006). For determining PE exposure and to conduct risk assessments, biomonitoring studies have been shown to be useful tools (Angerer et al., 2007) and many have been performed in the last decade in order to study exposure to PEs. In particular, urine has been the most studied matrix for assessing the short-term exposure to PEs (Barr et al., 2003; Calafat et al., 2011; Giovanoulis et al., 2016; Hines et al., 2009). Although less explored, serum/blood (Hines et al., 2009; Högberg et al., 2008), breast milk (Fromme et al., 2011; Hines et al., 2009; Högberg et al., 2008) or saliva (Hines et al., 2009; Koch et al., 2012) are alternative matrices for biomonitoring. Nevertheless, due to the possible constraints of finding volunteers, ethical issues associated with sampling (e.g. taking blood) and especially due to the short exposure window (24–48 h) that these matrices reflect, other non-invasive matrices such as hair and nails have been suggested recently (Alves et al., 2016a, 2016b, 2016c; Giovanoulis et al., 2016). The advantages on using these matrices instead of urine are various, including a wider exposure window (months to years) reflected, ease of sampling, relative stability of the samples and fewer complications during collection (pain, hematomas).

A literature review covering hair and nail as biomonitoring matrices is given by Alves et al. (2014) and is briefly summarized here. Hair has been mostly used to measure the presence of metals, pharmaceuticals and drugs (Nakahara, 1999; Pragst and Balikova, 2006; Wang et al., 2009), but was also successfully used to monitor DEHP metabolites (Chang et al., 2013). Additionally, more persistent substances have been detected in hair such as dioxins (Nakao et al., 2005), polychlorinated biphenyls (PCBs) and various pesticides (Altshul et al., 2004; Zhao et al., 2008), and brominated flame retardants (BFRs) (Aleksa et al., 2012; Malarvannan et al., 2013; Tadeo et al., 2009). Human nails have been used to measure metals in forensics (Barbosa et al., 2005; Button et al., 2009; Mehra and Thakur, 2010), but have been used to study perfluoroalkyl substances as well (Li et al., 2012, 2013). More recently, some studies explored the potential of nails to reflect long-term exposure to different plasticizers and compared nail concentrations to urine concentrations for the same study population (Alves et al., 2016a, 2016b, 2016c; Giovanoulis et al., 2016). Although both nails and urine reflect human exposure to a specific PE, they may represent different exposure time windows. Urine typically represents exposure within 24–48 h, whereas nails, as slow growing structures, are likely to reflect long-term exposure from up to several months in the past. However, there is a lack of knowledge regarding the kinetics of PE uptake into nails and the relative importance of internal/external exposure and how levels in nail can be correlated with or reflected by urine concentrations.

Pharmacokinetic (PK) models can be designed to estimate concentrations in different body compartments and to understand the links between internal concentrations and external exposure. In order to investigate how PEs partition between different tissues and organs, chemical and tissue specific kinetics such as transfer rates or fractions can be incorporated. Additionally, one can consider the PE metabolism rate in the human body or also further transformation from the monoester to oxidized metabolites, excretion etc. In a study by Lorber et al. (2010), a simple pharmacokinetic model was used to predict the levels in urine and serum of DEHP metabolites in humans following ingestion of DEHP. In another study by Lorber and Koch (2013), the same method was used to estimate DnBP and DiBP metabolites in serum and urine. This model was further validated using urine data from 5 individuals in fasted state over 48 h, showing a good fit for all metabolites, except for 3-carboxy-mono-propylphthalate (MCPP).

To judge the suitability of human nail as a matrix to monitor human exposure, we need to better understand the uptake processes of chemicals into nails. Currently, the relative importance of internal and external uptake pathways of PEs into the nail is unknown. However, not only do we lack experimental data regarding uptake of PEs (or their metabolites) into the human nail plate, no PK modelling has been attempted to assess this issue. Several studies have measured or estimated nail permeation coefficients for various chemicals (Baswan et al., 2016; Kobayashi et al., 2004; Saner et al., 2014; Walters and Flynn, 1983), but none of them addressing PEs. Theoretically, the presence of PEs in the human nail can result from internal sources (i.e. mass transfer from blood) and/or external sources (i.e. via application of personal care products, diffusion of volatile PEs from the air). However, measured concentrations of certain PE metabolites in nails are available for a human cohort for which external intakes of PEs are well quantified (Giovanoulis et al., 2016). If these measured nail concentrations mostly reflect internal uptake (partitioning between blood and nail), nails might be a suitable matrix to assess total exposure of PEs over a long period of time. However, if external exposure dominates, measuring concentrations in nail is more prone to uncertainties and current concentrations do not only depend on long-time exposure but also on recent (i.e. cumulative) exposure. Thus, they are more susceptible to variations when assessing the total exposure.

In this work, we study DnBP, DiBP (both low molecular weight phthalates) and DEHP (a high molecular weight phthalate) as PK models have been developed and validated for all three substances (Lorber et al., 2010; Lorber and Koch, 2013). These models were calibrated using only oral doses, however, Wormuth et al. (2006) and Clark et al. (2011) performed multi-pathway exposure assessments of several PEs included the three mentioned above and have found dietary ingestion to be the dominant exposure pathway for the PEs of interest here. The aims of this study were 1) to understand the relative importance of internal uptake of phthalates into the human nail plate and 2) to discuss implications for the suitability of human nails as a biomonitoring matrix. To our knowledge, this study is the first to address this matter. Therefore, we formulate the following hypothesis: For DEHP and DnBP/DiBP, where ingestion of food has been found to dominate total exposure, nail concentrations of their metabolites are mainly a result of internal uptake from blood and thus, human nails can be used for biomonitoring internal exposure for these phthalates. Using a PK model for DEHP and DnBP/DiBP, we first calculated the serum concentration of their metabolites based on the intake rate estimated from urine measurements of a Norwegian study cohort and then used a nail-blood equilibrium partitioning model to predict nail concentrations, which were then compared to measure nail concentrations of the same study population.

2. Methods

In order to test the study hypothesis, we: 1) used daily intake estimates of DEHP, DnBP and DiBP based on metabolites measured in urine for a Norwegian cohort of 61 adults (Giovanoulis et al., 2016) as input to the Lorber PK model (Lorber et al., 2010; Lorber and Koch, 2013) to estimate serum concentrations; 2) applied the PK model estimated serum concentrations to compare predicted and measured nail levels of PE metabolites and 3) based on our findings, discussed the implications for the use of human nail for biomonitoring purposes. The overall concept of the study is depicted in Fig. 1. In the first step, we used biomonitoring data from Giovanoulis et al. (2016) (PE metabolite concentrations in urine) and other data from a Norwegian cohort such as daily intake, body weight and urination volume to modify the human pharmacokinetic model (Lorber model) for the Norwegian cohort. Steady-state serum concentrations were then estimated using the Lorber model. In the second step, nail concentrations were estimated using a simple equilibrium partitioning model and compared with measurements for the Norwegian cohort.

2.1. Experimental data

Measured urine and nail concentrations were taken from a Norwegian cohort study consisting of 61 adult participants (Giovanoulis et al., 2016). Sampling of both matrices was performed according to the method described in Papadopoulou et al. (2015). For urine, 3 sample