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Probing the relationship between external and internal human exposure of organophosphate flame retardants using pharmacokinetic modelling☆

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ABSTRACT

Human external exposure (i.e. intake) of organophosphate flame retardants (PFRs) has recently been quantified, but no link has yet been established between external and internal exposure. In this study, we used a pharmacokinetic (PK) model to probe the relationship between external and internal exposure data for three PFRs (EHDPHP, TNBP and TPHP) available for a Norwegian cohort of 61 individuals from 61 different households. Using current literature on metabolism of PFRs, we predicted the metabolite serum/urine concentrations and compared it to measured data from the study population. Unavailable parameters were estimated using a model fitting approach (least squares method) after assigning reasonable constraints on the ranges of fitted parameters. Results showed an acceptable comparison between PK model estimates and measurements (<10-fold deviation) for EHDPHP. However, a deviation of 10–1000 was observed between PK model estimates and measurements for TNBP and TPHP. Sensitivity and uncertainty analysis on the PK model revealed that EHDPHP results showed higher uncertainty than TNBP or TPHP. However, there are indications that (1) current biomarkers of exposure (i.e. assumed metabolites) for TNBP and TPHP chemicals might not be specific and ultimately affecting the outcome of the modelling and (2) some exposure pathways might be missing. Further research, such as *in vivo* laboratory metabolism experiments of PFRs including identification of better biomarkers will reduce uncertainties in human exposure assessment.

1. Introduction

Flame retardants (FRs) are chemical additives used to inhibit or delay the spread of fire in order to meet fire safety regulations (EHC-192, 1997). One of the most common groups of FRs are polybrominated diphenyl ethers (PBDEs), which were used as flame retardants in a wide range of commercial products (Alves et al., 2014; Cequier et al., 2014; Xu et al., 2016). Due to human health and environmental concerns, PBDEs are in the process of global phase out, especially after hexa-BDE, hepta-BDE (commercial octa-BDE) (in 2009) and deca-BDE (in 2017) were listed under Annex A of the Stockholm Convention on Persistent Organic Pollutants (UN, 2011). Organophosphate flame retardants (PFRs), which are substitutes for PBDEs, had an annual production volume of about 90,000 tonnes in Europe in 2006 (van der Veen and de Boer, 2012). PFRs have a wide range of applications, including in plastics, rubber, cable coatings, foams, textiles and paints, while some are also used in floor waxes, nail polishes and food packaging (Mendelsohn et al., 2016; Poma et al., 2017; van der Veen and de Boer, 2012; Xu et al., 2016). Although rapidly metabolized in the human body, some PFRs have been reported to cause negative effects in animal and *in vitro* studies, such as carcinogenicity, neurotoxicity and reproductive toxicity (Pillai et al., 2014; van der Veen and de Boer, 2012). Throughout the lifetime of the commercial products, PFRs, similar to PBDEs, may be emitted into the ambient environment where they eventually pose a threat to human health. Studies have

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reported their presence in various matrices, such as indoor air, dust, food and biota (Eulaers et al., 2014; van der Veen and de Boer, 2012; Xu et al., 2015). Recently, PFRs and their metabolites were found in humans, including urine, blood and breast milk (Kim et al., 2014; Van den Eede et al., 2015b; Zhao et al., 2016) and temporal data show an increasing exposure trend to some PFRs based on urinary metabolite concentrations (Hoffman et al., 2017).

Further information on human exposure to PFRs is still very limited. So far, their major intake pathway remains in debate. Until recently, dust ingestion was considered to be the major pathway of PFR intake for humans (de Boer et al., 2016), but the latest results suggest that different PFRs may have distinct pathways of exposure (Xu et al., 2017, 2016). Food ingestion can be similar or more important than dust exposure, for example for 2-ethylhexyl diphenyl phosphate (EHDPHP) (Poma et al., 2017; Xu et al., 2017; Zheng et al., 2016). Also, Xu et al. (2016) reported that humans may have higher exposure to tris(chloropropyl) phosphate (TCPP), tris(2-chloroethyl) phosphate (TCEP) and tri-n-butyl phosphate (TNBP) via inhalation than via dust ingestion.

On the other hand, most of the PFR internal exposure studies focused on urine (Butt et al., 2016; Dodson et al., 2014; Van den Eede et al., 2015b), while few recent studies detected them or their metabolites in serum, hair and nails (Alves et al., 2016; Kucharska et al., 2015; Zhao et al., 2016). However, the internal exposure of PFRs in humans is still poorly understood and information on metabolism of PFRs is currently limited. Available studies have investigated the metabolism of PFRs either using human hepatocytes and subcellular fractions *in vitro* or *in vitro*. At present, such data are available for triphenyl phosphate (TPHP), TCPP, EHDPHP and tris(1,3-dichloro-2-propyl) phosphate (TDCIPP), indicating di-esters to be the main metabolites (Cooper and Stapleton, 2011; Su et al., 2014; Treon et al., 1953; Van den Eede et al., 2016a; WHO, 1998). Moreover, *in vivo* studies are available for TNBP (Suzuki et al., 1984) and TCEP (Burka et al., 1991). An *in vitro* study was also performed for TPHP and TNBP (Greaves et al., 2016). Recently, *in vitro* studies of human liver microsomes improved the understanding of the metabolism of PFRs in human (Ballesteros-Gómez et al., 2015a, 2015b, Van den Eede et al., 2016b, 2016c, 2015a, 2013).

A recent study of a human cohort of 61 adult participants from 61 households in Norway, sampled during the Winter of 2013/2014 (Papadopoulou et al., 2015), generated monitoring data for PFRs in house dust, indoor air, hand-wipes (Xu et al., 2016) and food (Xu et al., 2017), as well as data on PFR metabolites in urine and serum (see Supplementary information). Apart from studying PFRs, the study population is currently used to investigate human exposure to other groups of indoor contaminants, namely phthalate esters (PEs), emerging brominated flame retardants (EBFRs) and per- and polyfluoroalkyl substances (PFASs).

The aim of this work is to exploit this dataset to: 1) establish a pharmacokinetic (PK) model for PFRs that quantitatively links external exposure (intake) with internal levels of PFRs and metabolites, 2) derive parameters needed to estimate human metabolism of PFRs and 3) use the modelling approach to explore uncertainties and data gaps in our understanding of human exposure of PFRs. To the best of our knowledge, this is the first study that attempts a quantitative link between external exposure (intakes) and internal exposure (biomonitoring data) for the same study population. The comprehensive nature of the study population, in particular the availability of biomonitoring data, measured concentrations in external media and other cohort information (eating habits, indoor data, personal care product use etc.) makes it possible to provide a comprehensive picture regarding internal and external exposure of PFRs to humans. Moreover, since PFRs are regarded as rapidly eliminated compounds in humans (indicated by the fact that biomonitoring studies measure their metabolites in urine as mentioned above), we can directly link body burdens to concentrations in exposure sources. PK modelling of PFRs has not been previously attempted due to the scarcity of 1) data needed for model inputs and 2) exposure and biomonitoring data needed for model evaluation.

2. Materials and methods

2.1. Compounds of interest

After careful examination of PFR data in our cohort study, we determined EHDPHP, TNBP and TPHP to be suitable study compounds due to the availability of metabolite measurements in both urine and serum (Table 1). Their measured metabolites were 5-hydroxy-2-ethylhexyl-diphenyl phosphate (5-OH-EHDPHP), di-n-butyl phosphate (DNBP) and diphenyl phosphate (DPHP), respectively. Other PFRs and metabolites are not included in this model due to lack of sufficient data, in particular metabolite levels above the LOQ in serum.

2.2. Biomonitoring and intake data

The Norwegian study population was recruited in 2013 and sampling was performed for 24 h during the winter of 2013/2014. The participants were recruited from the staff of the Norwegian Institute of Public Health (NIPH) and included 16 males and 45 females from the age of 20–66 years. Both external exposure matrices/probes (air, dust, food, hand-wipes) and human samples (urine and serum) were sampled. Details of the sampling procedures for all substance groups can be found in Papadopoulou et al. (2015).

Biomonitoring data includes metabolite measurements in urine and serum (see SI). Among 61 participants, only those with metabolite levels above detection limits in both serum and urine were selected for modelling. The detection frequencies of three PFR metabolites in urine were above 70%, but were only 20–40% in serum. Non-detects, which mainly concerned serum measurements, were excluded from this study in order to avoid bias during the model fitting. Thus, the number of individual measurement was 12, 21 and 24 for EHDPHP, TNBP and TPHP, respectively (Fig. 2).

Human intake estimations were based on measurements of the parent PFRs in air, dust, hand-wipes and food and calculated in earlier studies (Xu et al., 2017, 2016). The total daily intake was calculated by adding dietary intake, dust ingestion, inhalation (stationary air) and dermal uptake (dust or hand-wipes). Concentrations in any of the external matrices (food, air, dust, hand wipes) which were below the limit of quantification (LOQ) were set to LOQ multiplied by the detection frequency as a fraction. Furthermore, no hand wipe measurements for TPHP were available so dermal uptake was solely based on dust. An overview of the cohort data is given in the SI (Table A1 and A2).

2.3. Pharmacokinetic model

Pharmacokinetic (PK) models are well-established tools to study the intake, distribution and excretion of chemicals in living organisms. The approach used in this study is structurally similar to a dynamic PK model by Lorber et al. (2010) and Lorber and Koch (2013) used to study phthalates. This model has a relatively high level of simplicity due to the low number of compartments and processes (Fig. 1). Because literature information is scarce, the advantage in using a simple model lies in the low number of parameters. A physiologically based approach would have to consider, in addition to metabolic parameters, partitioning behaviors of the