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Using exposure prediction tools to link exposure and dosimetry for risk-based decisions: A case study with phthalates

Marjory Moreau [a], Jeremy Leonard [c], Katherine A. Phillips [e], Jerry Campbell [b], Salil N. Pendse [a], Chantel Nicolas [a], Martin Phillips [a], Miyoung Yoon [a, *], Yu-Mei Tan [e, **], Sherrie Smith [d], Harish Pudukodu [d], Kristin Isaacs [e], Harvey Clewell [a]

[a] Scitovation, 6 Davis Drive, Durham, NC 27709, United States
[b] Ramboll Environ, 6 Davis Drive, Durham, NC 27709, United States
[c] Oak Ridge Institute for Science and Education, 1299 Bethel Valley Rd, Oak Ridge, TN 37830, United States
[d] North Carolina State University, Raleigh, NC 27695, United States
[e] National Exposure Research Laboratory, US Environmental Protection Agency, 109 TW Alexander Dr, Durham, NC 27709, United States

HIGHLIGHTS

- Evaluation of available exposure prediction tools for source-to-outcome modeling.
- Estimation of the human exposure based on PBPK-reverse dosimetry for comparison to predictions.
- Discussion of the utility and areas for improvement of each tool.
- Implication in risk assessment for prioritization and safe exposure decision.

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ABSTRACT

A few different exposure prediction tools were evaluated for use in the new *in vitro*-based safety assessment paradigm using di-2-ethylhexyl phthalate (DEHP) and dibutyl phthalate (DnBP) as case compounds. Daily intake of each phthalate was estimated using both high-throughput (HT) prediction models such as the HT Stochastic Human Exposure and Dose Simulation model (SHEDS-HT) and the ExpoCast heuristic model and non-HT approaches based on chemical specific exposure estimations in the environment in conjunction with human exposure factors. Reverse dosimetry was performed using a published physiologically based pharmacokinetic (PBPK) model for phthalates and their metabolites to provide a comparison point. Daily intakes of DEHP and DnBP were estimated based on the urinary concentrations of their respective monoesters, mono-2-ethylhexyl phthalate (MEHP) and monobutyl phthalate (MnBP), reported in NHANES (2011–2012). The PBPK-reverse dosimetry estimated daily intakes at the 50th and 95th percentiles were 0.68 and 9.58 μg/kg/d and 0.089 and 0.68 μg/kg/d for DEHP and DnBP, respectively. For DEHP, the estimated median from PBPK-reverse dosimetry was about 3.6-fold higher than the ExpoCast estimate (0.68 and 0.18 μg/kg/d, respectively). For DnBP, the estimated median was similar to that predicted by ExpoCast (0.089 and 0.094 μg/kg/d, respectively). The SHEDS-HT prediction of DnBP intake from consumer product pathways alone was higher at 0.67 μg/kg/d. The PBPK-reverse dosimetry-estimated median intake of DEHP and DnBP was comparable to values previously reported for US populations. These comparisons provide insights into establishing criteria for selecting appropriate exposure prediction tools for use in an integrated modeling platform to link exposure to health effects.

1. Introduction

Under the new direction in toxicity testing, *in vitro* and *in silico* tools are recommended for assessing potential risks of chemical

* Corresponding author.
** Corresponding author.
E-mail addresses: myoon@scitovation.com (M. Yoon), tan.cecilia@epa.gov (Y.-M. Tan).

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exposure to humans, with an aim to increase human relevancy and efficiency (NRC, 2007). High-throughput (HT) *in vitro* screening, toxicokinetic and human exposure data have been used in developing metrics of margin of exposure for prioritization of chemicals for risk assessment (Rotroff et al., 2010; Wetmore et al., 2012; Wambaugh et al., 2015; US U.S. EPA, 2014). Margin of exposure analysis can be used to support chemical-specific risk assessment when combined with equivalent exposures inferred via toxicokinetic modeling from fit-for-purpose *in vitro* assays. However, obtaining sufficient data to support human chemical exposure is a major challenge. Several HT exposure estimation/prediction tools are available for use in chemical prioritization to estimate human exposure and intake, each possessing different strengths and uncertainties (Isaacs et al., 2014 Wambaugh et al., 2014). Other chemical-specific data-based approaches are also used, including human biomarker- or environmental level-based estimation methods.

An integrated simulation platform could bridge human exposure and health outcomes efficiently given the availability of information for determining a safe exposure level for humans derives from diverse data sources, especially from *in vitro* and *in silico* methods. The Population Life Course Exposure to Health Effects Modeling (PLETHEM) platform provides a tool that links results from emerging toxicity testing applications to exposure estimates for humans. Exposure and dosimetry simulation models are essential components of such a platform. This study compares pharmacokinetic reverse dosimetry results with exposure predictions from existing exposure models that could potentially be used in such an integrated modeling platform, using phthalates as a case study.

Di-2(ethylhexyl) phthalate (DEHP) and di-butyl phthalate (DnBP) were selected, as they each have different uses and exposure trends (CDC, 2016). Both phthalates are used in a wide variety of consumer products, household articles and building materials, in addition to being contaminants in foodstuffs. DEHP is a ubiquitous compound that is used as a PVC plasticizer in coatings, adhesives and resins, and it can also be found in cosmetics, liquid soap, and detergents (David et al., 2001; Hauser and Calafat, 2005). DnBP is also used as a plasticizer, but is more often used in a variety of industrial applications such as surface coatings, polymer emulsion for adhesives, and textiles (Wittassek et al., 2011; Hauser et al., 2004; Kamrin, 2009 Otake et al., 2004). The primary route of human exposure to DEHP and DnBP in the general population is through oral consumption, which is mainly due to the transfer of substances from food packaging onto food products as well as dust and soil ingestion (Biryol et al., 2017). After absorption, DEHP is rapidly metabolized to its monoester, mono(2-ethylhexyl) phthalate (MEHP), which is further metabolized by various oxidation reactions to a number of secondary hydrolytic and oxidative metabolites (Fig. 1S, supplemental 2) that are conjugated via glucuronidation and other processes before being eliminated. The three oxidative metabolites of interest here are mono(2-ethyl-5-hydroxyhexyl) phthalate (5OH-MEHP), mono(2-ethyl-5-oxo-hexyl) phthalate (5OXO-MEHP) and mono(2-ethyl-5-carboxy-pentyl) phthalate (5CX-MEPP) (Choi et al., 2013). DnBP is metabolized to its monoester, mono-butylphthalate (MnBP) (Koch et al., 2005; Clewell et al., 2009) (Fig. 2S, supplemental 2). Exposure to phthalate metabolites has been associated with observed infertility and developmental toxicity occurring through testicular effects, malformations, and defects in sexual differentiation in animals (Leung et al. 2015). These metabolites are distributed in all tissues with no evidence of accumulation (Rusyn et al., 2006).

This case study used predictions from two currently available exposure models for population exposure predictions: 1.) the HT Stochastic Human Exposure and Dose Simulation (SHEDS-HT) and; 2.) an empirical heuristics-based model developed under the US Environmental Protection Agency's (US EPA) Exposure Forecasting (ExpoCast) project (Wambaugh et al., 2014). SHEDS-HT is a probabilistic model that estimates the range of chemical exposure in a population from different consumer product pathways over the course of a 24-h period. These 1-day exposure estimates are calculated based on census data, consumer product use patterns, reported compositions of consumer products and activity diaries (Isaacs et al., 2014), which are appropriate for screening-level assessment. The ExpoCast model is designed to screen and classify thousands of chemicals based on their potential for human exposure (Wambaugh et al., 2014). To provide a point of comparison for those estimates from the two exposure prediction models, the daily exposure to these two phthalates was also estimated by reverse dosimetry using previously developed PBPK models. As exposure to a chemical can vary widely due to inherent properties, product usage and other environmental factors, an additional non-HT approach involving the assemblage of exposure data for the two phthalates from literature was also taken, to compare with values generated by the two exposure models and using reverse dosimetry.

2. Methods

2.1. Estimation of phthalates daily dose by reverse dosimetry

The structure of the PBPK model for DEHP and DnBP and their metabolites was adapted from Gentry et al. (2011). The current model (Fig. 1) includes four interconnected sub-models for the diester, the hydrolytic monoester, the oxidative metabolites and the glucuronide conjugate. The three oxidative metabolites of MEHP (i.e., 5OXO-MEHP, 5OH-MEHP and 5CX-MEPP) which had human data available to parameterize their description, were incorporated as a fraction of the total MEHP oxidative metabolism with a volume of distribution approximating body water distribution. The model was manually optimized to simulate kinetic time-course data in human plasma (DEHP and total MEHP) and urine (MEHP, 5OXO-MEHP, 5OH-MEHP and 5CX-MEPP) after oral consumption, based on controlled dosing studies in humans (Kessler et al., 2012; Anderson et al., 2011).

At low exposure concentrations, relevant to human exposure in the environment, kinetics are linear and metabolite concentrations in urine can be used to estimate parent exposure levels. Our reverse dosimetry approach combined the simple PBPK model described above with Monte Carlo simulations and calculations of probability to convert distributions of urine concentration measurements from NHANES into probability distributions of exposure doses. Distributions of daily intake of DEHP and DnBP in a population were generated based on the urine concentrations of their mono-ester metabolites as measured in NHANES, 2011–2012 (CDC, 2016) using a Monte Carlo (MC) analysis to incorporate variability in pharmacokinetics and uncertainty in exposure patterns. All model parameters were randomly sampled, and a distribution of phthalate urine concentrations was generated by running the PBPK model for several iterations. All parameters in the MC analysis either were distributed lognormally (e.g., body weight, cardiac output, metabolism constant, metabolites clearance, partition coefficient and oral absorption constants) or were distributed normally (e.g., blood flow, tissue volumes and fraction of metabolites). To exclude physiologically implausible values, CV was assumed to be 50%. with parameters truncated at ± 1.95 SD (Table 1S, supplemental 2). The “Exposure Conversion Factor” (ECF) approach from Tan et al. (2006) was used to estimate the population's distribution of exposure. Briefly, one thousand urine concentrations were generated for MEHP and its three oxidative metabolites, as