Environmental Research 215 (2022) 114074

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Unravelling sex-specific BPA toxicokinetics in children using a pediatric PBPK model

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ARTICLE INFO

Keywords:
Pediatric PBPK
Pharmacokinetic
Sex-specific risk
Children cohort
Endocrine disruptor
Bisphenol A

ABSTRACT

Bisphenol A (BPA) is a widely known endocrine disruptor (ED) found in many children's products such as toys, feeding utensils, and teething rings. Recent epidemiology association studies have shown postnatal BPA exposure resulted in developing various diseases such as diabetes, obesity, and neurodegeneration, etc., later in their lives. However, little is known about its sex-specific metabolism and consequently internal exposure. The aim of this study was to develop a sex-specific pediatric physiologically based pharmacokinetic model (PBPK) for BPA to compare their toxicokinetic differences. First, the published adult PBPK model was re-validated, and then this model was extended by interpolation to incorporate pediatric sex specific physiological and biochemical parameters. We used both the classical body weight and ontogeny-based scaling approach to interpolate the metabolic process. Then, the pharmacokinetic attributes of the models using the two-scaling approach mentioned above were compared with adult model. Further, a sex-specific PBPK model with an ontogeny scaling approach was preferred to evaluate the pharmacokinetic differences. Moreover, this model was used to reconstruct the BPA exposure from two cohorts (Helix and PBAT Cohort) from 7 EU countries. The half-life of BPA was found to be almost the same in boys and girls at the same exposure levels. Our model estimated BPA children's exposure to be about 1500 times higher than the tolerable daily intake (TDI) recently set by European Food Safety Authority (EFSA) i.e., 0.04 ng/kg BW/day. The model demonstrated feasibility of extending the adult PBPK to sex-specific pediatric, thus investigate a gender-specific health risk assessment.

1. Introduction

Humans are being exposed to the bisphenol A (BPA) through plastic food, beverage containers, thermal receipts, medical devices, canned food, and sealant, with detectable levels occurring in urine worldwide (Harley et al., 2013; Braun and Hauser, 2011; Bushnik et al., 2010). Several human studies have reported BPA exposure is associated with

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https://doi.org/10.1016/j.envres.2022.114074
Received 11 July 2022; Received in revised form 3 August 2022; Accepted 4 August 2022
Available online 19 August 2022

the adverse health outcomes, particularly at young age (Nalbantoğlu et al., 2021; Healy et al., 2015; Eng et al., 2013). Since BPA has an endocrinological activity and can mimic the hormones like estrogen, hormone-regulated pathways are disrupted, affecting normal growth and development (Martínez et al., 2020; Ohore and Zhang, 2019). BPA exposure during childhood has been linked to altered neurodevelopment (Roen et al., 2015), obesity, precocious diabetes, asthma, immunity impairment, and metabolic disorders, among others (Deepika et al., 2020; Ohore and Zhang, 2019; Braun and Hauser, 2011).

BPA has a short half-life (approximately 4–6 h) in adult humans (Sasso et al., 2020; Völkel et al., 2005; Tsukioka et al., 2004) with chronic exposure due to its presence in everyday products (Li et al., 2016). BPA is metabolized in the liver and intestine into two major metabolites, BPA glucuronide (BPAG) and BPA sulfate (BPAS) (Karrer et al., 2018). The formation of BPAG is majorly regulated by the UGT2B15, a uridine diphosphate glucuronosyltransferases enzyme (UGTs), and BPAS is controlled by the SULT1A1, a sulfotransferase enzyme (SULT) (Neumann et al., 2016). The levels of these hepatic enzymes are different in children than in adults, leading to differences in the extent of the metabolism process (Karrer et al., 2018). In addition, the pediatric population is more susceptible to BPA exposure and associated health risk than adults (Bushnik et al., 2010; Lv et al., 2016; Shelby, 2008; Stahlhut et al., 2009). Moreover, several studies have shown that there are gender differences in BPA exposure and its adverse effects (Kim et al., 2003; Takeuchi and Tsutsumi, 2002). For example, BPA exposure in utero was associated with an alteration in the timing of pubertal development (Kasper-Sonnenberg et al., 2017; Miao et al., 2017) and neurotoxicity like autism spectrum disorder only in girls (Hansen et al., 2021). Toxicokinetic differences may exist based on sex due to differences in metabolism (enzyme abundance), absorption kinetics (lower body-weight, low blood flow, less plasma volumes), and the physiological changes (Schwartz, 2003). A study by Caporossi and Papaleo (2015) investigated about different impact of BPA in males and females and concluded that toxicology should be assessed considering the sex differences in BPA. Gender differences in BPA toxicokinetic and exposure can be further explored using a physiologically based pharmacokinetic model (PBPK). The tolerable daily intake (TDI) for BPA was set by EFSA (European Food Safety Authority) based on adverse effects on the immune system. EFSA lowered the TDI from 4 μg/kg BW/day (temporary-TDI) in 2015 to 0.04 ng (ng) per kilogram body weight (BW), taking into account BPA adverse effects (Bisphenol A: EFSA draft opinion proposes lowering the tolerable daily intake 2021). Nevertheless, the question remains whether the TDI should be the same for the adult and pediatric populations. Another debatable aspect is whether there should be a separate TDI for boys and girls? To address this, PBPK model that incorporates the age and gender related change in BPA kinetics can be utilized.

PBPK model is widely used for tissue dosimetry based risk assessment and is recommended for the toxicity testing in the field of the environmental chemicals (Laroche et al., 2018; Schuhmacher et al., 2014; Sharma et al., 2017, 2018a; Wagner et al., 2015). PBPK models have been developed for BPA in monkeys, adults (Fisher et al., 2011; Teeguarden et al., 2005), pregnant females (Sharma et al., 2018b), and generic model from infants to 25 years (Karrer et al., 2018). However, to the best of our knowledge, there are limited PBPK models for BPA that capture the pharmacokinetics and sex differences in growing age children and evaluates health risk. The overall objective of the work is to develop a sex specific pediatric PBPK model for BPA to evaluate the toxicokinetics. The four sub-objectives include: 1) To first extrapolate the adult model based on ontogeny and body-weight scaling for the pediatric population. Further, changes in the biochemical parameters (absorption, distribution and elimination) and sex were incorporated to improve the sex-specific predictive property of the PBPK model. 2) A dosimetry risk assessment was conducted to evaluate exposure in boys and girls. 3) The model was used to compare the changes in pharmacokinetic properties of BPA in children (both boys and girls) with those in adults, suggesting the need for the pediatric PBPK model to improve risk assessment. 4) A sensitivity analysis was conducted to identify the parameters that influence the outcomes when comparing both genders. Pediatric PBPK model can be a valuable tool for predicting target tissue concentration and pharmacokinetic especially where no or sparse data is available. Also, they can aid regulatory bodies for improving decision making regarding environmental chemicals.

List of abbreviations

BPA	Bisphenol A
ED	Endocrine Disruptor
PBPK	Physiologically Based Pharmacokinetic Model
TDI	Total Daily Intake
$t_{1/2}$	Half-life
UGT	Uridine diphosphate glucuronosyltransferases
SULT	Sulfotransferase
EFSA	European Food Safety Authority
AUC	Area under curve
MRT	Mean residence time
F	Bioavailability
BW	Body weight
SF	Scaling Factor
GEC	Gastric emptying rate constant
LN	Log normal
IVIVE	In-vitro to in-vivo extrapolation
Cmax	Maximum Concentration
k_{el}	Elimination rate constant
HBM4EU	Human Biomonitoring for EU
MCMC	Markov Chain Monte Carlo
SA	Sensitivity Analysis
ODE	Ordinary differential equation
BPAG	BPA glucuronide
BPAS	BPA sulfate

2. Methodology

2.1. Adult PBPK model

The pediatric PBPK model with eight compartments was adapted from Sharma et al. (2018a) (Fig. 1). It consists of the following compartments: gut, liver, brain, adipose tissue, kidney, skin, gonads, and rest of the body to describe the kinetics of free BPA and its metabolites (BPAG & BPAS). In the article, total BPA means both free and conjugated whereas free BPA means only the BPA. Biochemical parameters related to partition coefficient and scaling factors have been mentioned in Table 1 whereas other parameters are mentioned in supp file (Table S1). The original fitted adult PBPK model was refined by incorporating dynamic physiological equations published by our group (Deepika et al., 2021). In this model uncertainty was included and monte carlo simulation was performed (Table 1). Physiological equations were provided in the supplementary file (eqs. S1-S23). Then, this model was validated with the human data from Thayer et al. (2015). In the human experimental study, 12 healthy volunteers were administrated a single oral dose of 100 μg/kg BW/day of deuterated BPA (d6-BPA). Blood and urine

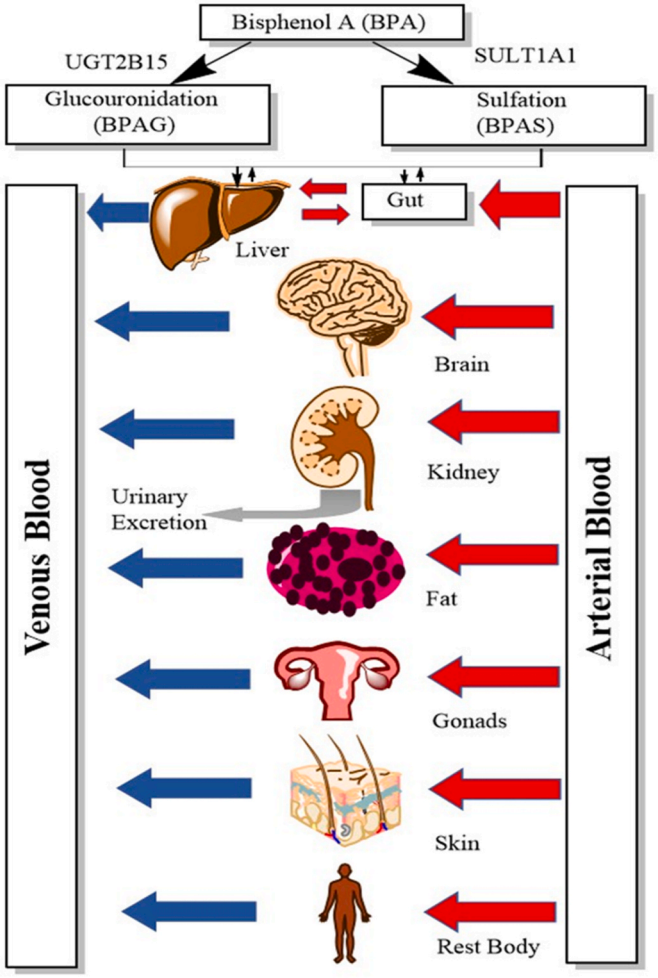

Fig. 1. Physiologically Based Pharmacokinetic (PBPK) Model for Bisphenol A (BPA) in human. Two types of liver and gut enzymes are involved in metabolism of BPA: Isoform of UGT2B15 responsible for glucuronidation (BPAG) and SULT1A1 for sulfation (BPAS). Metabolites are rapidly excreted in urine from human body. UGT stands for uridine diphosphate-glucouronosyl transferase, and SULT for the sulfotransferase.

samples were analyzed for free BPA and its metabolites. After validating the adult model, the same model was adapted for the pediatric population (age 6–12 years). The model was coded in R program version 1.3.1093 with MCSIM version 6.2.0 (Bois, 2009).

2.2. Development of pediatric PBPK model

Dynamic growth was considered for the organs based on the children's body-weight, height, and surface area. These equations were provided in supp file (Eqs. S1-S23), detailed information on equations can be found in the original article published by our group (Deepika et al., 2021). For the biochemical changes, the partition coefficient is provided in Table 1 (Csanády et al., 2002; Doerge et al., 2011; Fisher et al., 2011; Sharma et al., 2018b). The rate of reaction for glucuronidation and sulfation was derived using the in-vitro to in-vivo extrapolation (IVIVE) scaling approach for adults based on Eq. (1). In Eq. (1), MPPGL refers to microsomal protein per gm of the liver. The BPA metabolism was modeled using the non-linear kinetics based on Michaelis-Menten provided in Eq. (2). *V* represents the measured velocity of enzyme-catalyzed reaction, S represents substrate concentration here it is BPA, V_{max} represents maximum reaction velocity per hr for whole body (nM/hr), and K_m (nM) is Michaelis Menten constant (Eq (2)). Based on Eq. (1), Vmax values for glucuronidation and sulfation

Table 1
Partition Coefficient for tissue to plasma and other parameters and their statistical distribution used in PBPK Model for BPA for adult and children. First value in bracket is the mean and second value is standard deviation in LN space. All the parameters were same for adult and children except for parameters with [a] and [b].

Parameter	Value (Distribution)	Reference
Molecular Weight (g/mol)	228.29	(Sharma et al., 2018b)
GEC (hr^{-1})	3.5	(Sharma et al., 2018b)
Vmax gluC[a]	707,537	(Sharma et al., 2018b)
kmliver_glu (nM)	45,800	(Sharma et al., 2018b)
Vmax SulfC[a]	11,657	(Sharma et al., 2018b)
kmliver_sulf (nM)	10,100	(Sharma et al., 2018b)
$SF_{UGT2B15}$[b]	0.67	(Ladumor et al., 2019) [b]
$SF_{SULT1A1}$[b]	1.25	(Ladumor et al., 2019) [b]
Liver: Plasma	LN (0.73, 1.1)	(Doerge et al., 2011; Fisher et al., 2011; Karrer et al., 2018; Sharma et al., 2018b)
Brain: Plasma	LN (2.8, 1.1)	(Doerge et al., 2011; Fisher et al., 2011; Karrer et al., 2018; Sharma et al., 2018b)
Kidney: Plasma	LN (0.858, 1.1)	(Csanády et al., 2002; Doerge et al., 2011; Fisher et al., 2011; Karrer et al., 2018; Sharma et al., 2018b)
Adipose Tissue: Plasma	LN (5.0, 1.1)	(Doerge et al., 2011; Fisher et al., 2011; Karrer et al., 2018; Sharma et al., 2018b)
Skin: Plasma	LN (5.7, 1.1)	(Doerge et al., 2011; Fisher et al., 2011; Karrer et al., 2018; Sharma et al., 2018b)
Gonads: Plasma	LN (2.6, 1.1)	(Sharma et al., 2018b)

[a] Vmax gluC represents glucuronidation of BPA in liver (nm/h/BW) and Vmax SulfC represents sulfation of BPA in liver (nm/h/BW).
[b] SF represents scaling factor calculated in children based on ontogeny changes by Ladumor et al. (2019). GEC: Gastric emptying rate constant. LN refers to log normal.

have been calculated as provided in Table 1.

$$Vmax_{(liver)} = \frac{(Vmax_{(in-vitro)} * MPPGL * Vliver)}{BW^{0.75}} \quad (1)$$

$$V = \frac{V_{max}[S]}{K_m + [S]} \quad (2)$$

Body-weight (Eq (3)) and ontogeny scaling (Eq. (4)) were used to interpolate the metabolic process from adults. Based on the observation reported by Ladumor et al. (2019), a higher fractional contribution of sulfation process over glucuronidation was considered in children metabolizing BPA (Ladumor et al., 2019). In the ontogeny-based model, we integrated this information by using a scaling factor ($SF_{children}$) for the known enzymes involved in BPA metabolism calculated by Ladumor et al. (2019), which for children was 1.25 for SULT1A1 and 0.67 for UGT2B15 using Eq. (4) relative to adult for V_{max}. It was calculated based on selective quantitative proteomic analysis of UGTs in the human liver samples from 137 pediatric and 37 adult samples and studying SULT1A1 by a robust LC-MS/MS proteomics methodology by Ladumor et al. (2019).

$$Adjusted\ V_{max1} = V_{maxadult} * BW^{0.75} \quad (3)$$

$$Adjusted\ V_{max2} = V_{maxadult} * SF_{children} \quad (4)$$

Here, Adjusted Vmax2 is Vmax of children based on ontogeny scaling (nM/hr), $V_{maxadult}$ refers to maximum rate of reaction in adults (nM/hr) and $SF_{children}$ refers to scaling factor based on age dependent enzyme abundance.

2.3. Pharmacokinetic analysis for pediatric and adult PBPK

The pediatric PBPK model was used to compare the simulated pharmacokinetic parameters in adults and children from both the scaling techniques. Predicted plasma concentration-time data was used to calculate the maximum concentration (Cmax, nM), and $AUC_{0\text{-}24}$

(nM*h) using trapezoidal rule (eq. five). The half-life ($t_{1/2}$, hr) was calculated using elimination rate constant (K_{el}, hr^{-1}) based on Eq. (6). Bioavailability (F) is the percentage of free BPA that reaches the systemic circulation and is calculated based on Eq. (7). For calculating F, both oral and IV exposure was simulated at the dose of 1 μg/kg BW/day. Mean Residence time (MRT, hr) was defined by the average time a molecule stays in the body (Eq. (8)). In Eq. (8), AUMC represents (Area under the first moment curve), c represents the concentration of chemical in the plasma, and *t* represents the time.

$$AUC_{0-24} = \int_{t1}^{t2} C^{*}dt \tag{5}$$

$$t_{1/2} = \frac{In(2)}{K_{el}} \tag{6}$$

$$F = \frac{AUC_{oral}}{Dose_{oral}} * \frac{Dose_{IV}}{AUC_{IV}} \tag{7}$$

$$MRT = \frac{AUMC}{AUC} = \frac{t^{*}c(t)}{c(t)} \tag{8}$$

AUC: area under curve, t: time, c: concentration, $t_{1/2}$: half-life, In: logarithmic, K_{el}: elimination rate constant, AUC_{IV}: area under curve from intravenous exposure, MRT: mean residence time, and AUMC: area under first moment time curve.

2.4. Ontogeny based pediatric PBPK model based on sex

After developing the pediatric PBPK Model for boys, the same model was further refined for girls. The physiological parameters were changed based on dynamic equations (mentioned in supp file, Eqs. S1-S20). In biochemical parameters, only metabolic parameters were changed keeping rest of the parameters similar to the adult model. The metabolic sex differences present in girls, can be understood by changes in Phase II metabolism, especially UGTs and SULTs. For instance, a study by Gallagher et al., 2010 took human liver specimens (n = 103) and analyzed mRNA expression of seven UGT2B genes in males and females. Some UGT genes like UGT2B7, UGT2B15, were expressed more in men with other UGTs expressed significantly in females. UGT2B7 and UGT2B15 are mainly responsible for the glucuronidation of BPA in human beings (Gallagher et al., 2010). For SULT enzymes, the SULT1A1 expression varies among sexes and also by season as studied by several authors (Nowell and Falany, 2006; Marazziti et al., 1998). Based on literature evidence, it was observed that glucuronidation could be higher in boys and sulfation in girls (Gallagher et al., 2010; Kim et al., 2003; Kurebayashi, 2003; Neumann et al., 2016). Taking these evidences into account, scaling factor was set for girls (Table 1 supp. File). Further, pharmacokinetic parameters (Bioavailability, MRT, AUC and half-life) were calculated similarly as mentioned before in Section 2.3. These pharmacokinetic parameters calculated by ontogeny-based girls PBPK model was compared with ontogeny-based boys PBPK model.

2.5. Exposure reconstruction using child cohorts

Reverse dosimetry computes the external exposure from internal organ/plasma concentration or biomarker level in urine (Lin et al., 2020). In this study, the PBPK model was used to reconstruct daily exposure from two cohorts. The HELIX (Human Early-Life Exposome, http://www.projecthelix.eu/es) cohorts include 6 population-based birth cohorts in Europe (Spain, France, Greece, UK, Norway, and Lithuania). Details about this cohort can be found here (Maitre et al., 2018; Magnus et al., 2016; Vrijheid, 2013). From this cohort, the data of children were used for the present study, which was collected from 1999 to 2010. Measured BPA concentrations were extracted for 1357 children (753 boys and 604 girls) at 6–11 years of age after excluding outliers. For the two cohorts, only data for BPA levels in urine was available. There was no data available for BPA level in blood of the children. Total BPA (conjugated and free) was determined in a pool of equal amounts of two spot urine samples collected at bedtime and in the morning. Creatinine concentration was measured for all urinary samples to conduct adjustment with respect to urinary dilutions. Details of the analytical procedure can be found elsewhere (Tamayo-Uria et al., 2019; Haug et al., 2018). BPA urinary concentrations, and the child's weight and height measured using regularly calibrated instruments (Maitre et al., 2018), were considered for reverse dosimetry in the PBPK Model. The other cohort used was the Austrian PBAT cohort in which data was collected from 2010 to 2012, that is part of the Human Biomonitoring for EU (HBM4EU) project. Aggregate data from this cohort was available for boys and girls aged 6–10 years (n = 253, 138 boys and 115 girls) and was downloaded from the website and further used for reconstructing the exposure from total BPA (HBM4EU, 2021).

For calculating cumulative urine, Eq. (9) was considered which include spot urine, spot creatinine, and total urinary creatinine. Value for total urinary creatinine was obtained from the article published by Remer et al. (2002) in which the author has calculated the values based on sex, body weight and the height of children. Reconstructed exposure (μg/kg BW/day) was calculated using the Markov Chain Monte Carlo (MCMC) simulation considering cumulative urine. Oral dose was considered as a parameter to be estimated by the model and it was randomly distributed using uniform distribution. Total BPA urine concentration was used as a likelihood parameter that follows a normal distribution with 10 percent variation (Table S3 supp file). Individual simulation was run for each child considering their specific BW, height, sex information, and cohorts' urine concentration (total number of participants: 1359). Then, from the individual output, which is the reconstructed exposure, median, 5th and 95th percentiles value was calculated separately for boys and girls in case of Helix cohort. For the PBAT cohort, since there was no individual data, the variation in 24-h urinary creatinine was taken for capturing the distribution (B: 4.47 ± 0.092 mmol/d, g: 5.04 ± 1.22 mmol/d) (Remer et al., 2002). The reconstructed exposure for both boys and girls was compared with TDI set by EFSA for BPA. The simulation was performed using the MCSIM version 6.2.0. Correlation between data (experimental data point) and predicted was checked by calculating r^2 for all the individual simulations.

$$Cumulative\ Urine = \frac{Spot\ Urine}{Spot\ Creatinine} * Total\ Urinary\ Creatinine \tag{9}$$

2.6. Sensitivity analysis

We performed the sensitivity analysis for both boys and girls PBPK model using the R package FME. FME package allows to run the complex model containing ODE (ordinary differential equation), producing output as a function of input parameter (Soetaert and Petzoldt, 2010). This package allows for varying the input parameter by 1% up and down, keeping all other parameters constant. In FME, the sensitivity matrix contains dimensionless sensitivity of the parameter to the model output whose $(i,j)^{th}$ element $S_{i,j}$ contains:

$$\frac{\partial y_i}{\partial \Theta_j} = \frac{w\Theta_j}{wy_i} \tag{10}$$

Here, y_i is the output variable, Θ_j is the parameter, wy_i is the scaling of variable y_i which is usually equal to its value and $w\Theta_j$ is thr scaling of variable j which is usually equal to parameter value. Also, the parameters can be ranked based on importance of the parameter for the output variable. The higher is the absolute sensitivity value, the higher will be the ranking.

3. Results

3.1. Age dynamic based adult PBPK model showed good accuracy

The refined adult PBPK model predictions of free BPA and its metabolite concentration in plasma were compared with plasma data from the 12 healthy volunteers after a single oral administration, obtained from Thayer et al. (2015) (see Supp Fig. S8). The predictive accuracy of the model was calculated by the Pearson correlation, which showed that the simulated data fits well with the observed data, within a 2-fold deviation from observed values with r value $\geq$ 0.95 and p value less than 0.05 (Supp file, Fig. S9).

3.2. An ontogeny scaling based pediatric PBPK model showed the critical differences in pharmacokinetic characteristics vs classical body-weight scaling

Pharmacokinetic parameters were calculated and compared with the adult PBPK and the two different pediatric PBPK models: 1) the classical body-weight scaling and 2) the ontogeny scaling. The plasma concentration of free BPA for the same amount of exposure was comparatively higher in children with ontogeny scaling than in adults, and however, the body-weight-based scaling predicted free BPA for the same amount of exposure almost as much as in adults (Fig. S10 in supplementary file). However, BPAG plasma concentration were almost similar in the adult and two pediatric models but BPAS plasma concentration was significantly higher in children with ontogeny-based scaling than with body-weight based scaling and the adult PBPK model (Supplementary Fig. S10). Fig. 2 showed pharmacokinetic parameters like AUC, $t_{1/2}$, bioavailability, and MRT for free BPA for different organs. The trend for half-life was adult > pediatric PBPK with ontogeny scaling > pediatric PBPK with body-weight scaling. An increased terminal half-life was seen in gonads compared to other organs for both children and adults ($t_{1/2}$ = 6–9 h in gonads, $t_{1/2}$ = 4.5–6 h for plasma) (Fig. 2 A). The AUC for ontogeny was highest followed by adult and body-weight scaling in all the organs (Fig. 2B): in case of plasma, the AUC for ontogeny based pediatric model was approximately 17% higher, and the classical body-weight-based model was approximately 13% lower than the adult model (Fig. 2B). Bioavailability was also high in children with ontogeny scaling followed by body-weight and adult model (Fig. 2C), but mean residence time was highest in adults compared to children (Fig. 2C). Overall, the pediatric PBPK model based on ontogeny showed the critical differences in pharmacokinetic of short-acting chemical (BPA), which could not have been explained by simply considering the body-weight-based scaling.

3.3. Impact of sex difference on pharmacokinetics characteristic

Further, the ontogeny-based PBPK model for boys and girl (UGT, SULT, and physiology changes) was taken for sex-specific differences in pharmacokinetics for similar exposure. Plasma concentration of free BPA was higher in girls than boys (Supplementary Fig. S11).

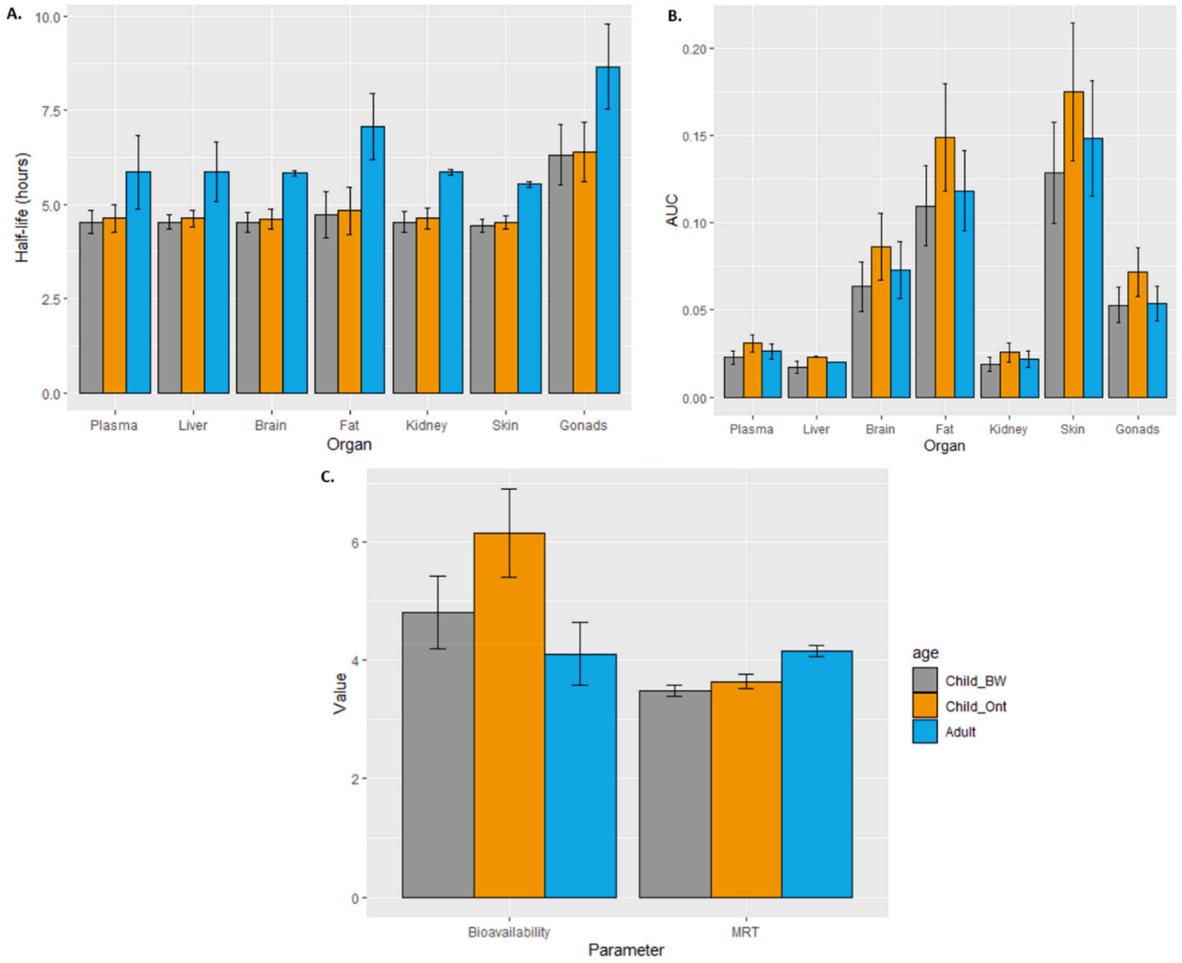

Fig. 2. Comparison for different pharmacokinetic parameters in children (based on body-weight and ontogeny scaling) and adults at the dose of 1 μg/kg BW/day. 3 A. represents half-life ($t_{1/2}$) for different organs, B. represents area under curve (AUC) for 7 organs (plasma, liver, brain, fat, kidney, skin and gonads), and C. represents bioavailability (F) and mean residence time (MRT) for free BPA in children and adult. Bioavailability (F) is in % and MRT is in hours in Fig. 2C.

Glucuronidation of BPA was slightly higher in boys, however sulfation was comparatively more in girls (Supplementary Fig. S11). Free BPA half-life was almost similar in boys and girls (girls, $t_{1/2} = 4.38$ h vs. boys, $t_{1/2} = 4.63$ h) in plasma and all other organs (Fig. 3). The trend followed by half-life was gonads > fat > kidney > liver > plasma > brain > skin. The mean residence time was slightly higher in boys, but bioavailability and AUC were found to be slightly more in girls (Supplementary Figs. S12 and S13).

3.4. Daily exposure in boys and girls: reverse dosimetry

The ontogeny-based gender-specific PBPK model was used to calculate daily exposure to total BPA for both the boys and girls. Fig. 4 represents the daily dose calculated from the HELIX and the PBAT cohorts for different countries in Europe. Exposure was found to be a little higher in girls than boys for all countries except Greece and Norway. The median daily intake was lowest in France (girls: 0.045, boys: 0.040 μg/kg BW/day) and highest in Austria (girls: 0.254, boys: 0.218 μg/kg BW/day). Average daily intake estimates for all the cohorts ranged from 0.0138 to 0.294 (P5:P95) with a median of 0.0723 μg/kg BW/day. The P95 value was approximately thirteen times lower than the temporary total daily intake (t-TDI) set by EFSA in 2015, which was 4 μg/kg BW/day (EFSA Panel on Food Contact Materials Flavourings and Processing Aids (CEF) 2015). In 2021, EFSA drastically decreased the TDI for BPA to 0.04 ng/kg BW/day recently opened for comments. Now, median value of daily intake is comparatively 1500 times higher than recent TDI established by EFSA (Bisphenol A: EFSA draft opinion proposes lowering the tolerable daily intake 2021). For the model verification we again checked the model with forward dosimetry taking the predicted reconstructed exposure as an input and simulated the total cumulative urine and compared with the cohort data. Correlation was checked by calculating the r^2, which was found to be 0.95 (Fig. S15, Supp file).

3.5. Sensitivity analysis

Sensitivity analysis has been carried out for all the biochemical parameters used for developing the pediatric PBPK Model for both boys and girls. Table S4 (Supp file) represents the statistics of parameter sensitivity results along with ranking. Ranking for sensitivity varies in boys and girls for many parameters like conjugation, fat and gonads partition coefficient etc. but the mean value for the parameters was quite similar. Fig. 5 represents the mean sensitivity coefficient for boys and girls respectively. Liver_plasma partition coefficient is highly sensitive for both sex with a sensitivity coefficient of −1 suggesting that 10% increase in the partition may reduce the plasma concentration by 10%. Fat_plasma partition coefficient is more sensitive in girls than boys. The mean sensitivity coefficient of Vmax is negative, and Km is positive for both sexes, implicating both the parameters have opposite impact on the output plasma concentration.

4. Discussion

This study was the first to investigate the pharmacokinetic differences between pediatric population considering sex differences with different scaling approaches and adults using the PBPK model for BPA. The development of pediatric PBPK model based on adult model considering 2 approaches: 1) body-weight scaling and 2) ontogeny Scaling. In the present study, data from two different cohort studies was taken and used to estimate daily exposure for boys and girls. Overall, the pediatric PBPK model with ontogeny scaling greatly improves the understanding of toxicokinetic and risk assessment for short-acting molecules like BPA based on sex and age.

The adult model was validated and then extrapolated for the pediatric population following the classical approach of building PBPK. Overall, free BPA metabolizes and eliminates faster in adults as increased levels of BPAS and BPAG were seen. Individual adult PBPK simulations showed not much difference in plasma time profile of free BPA, indicating physiological parameters have little impact on BPA elimination. However, for two subjects, the data did not fit well which could be explained by enzymatic polymorphism leading to high variability of the glucuronidation and sulfation metabolic processes (Skledar et al., 2015; Hanioka et al., 2008). It can be overcome by optimizing the excretion rate for metabolites for those individuals, but this was outside the scope of this paper.

In the pediatric PBPK model, AUC for plasma and all other organs was higher in ontogeny-based scaling representing the underestimation of risk from short-acting chemicals in the case of children with body weight-based scaling. A higher AUC of the free BPA indicates higher systemic exposure to the chemical and comparatively lower metabolism. As mentioned already in the methodology that glucuronidation is lower in children, and sulfation is comparatively higher in children than adults, but the important point is glucuronidation is the major metabolic pathway for BPA (Karrer et al., 2018), which may be responsible for higher AUC in children. Overall, the model indicated that the

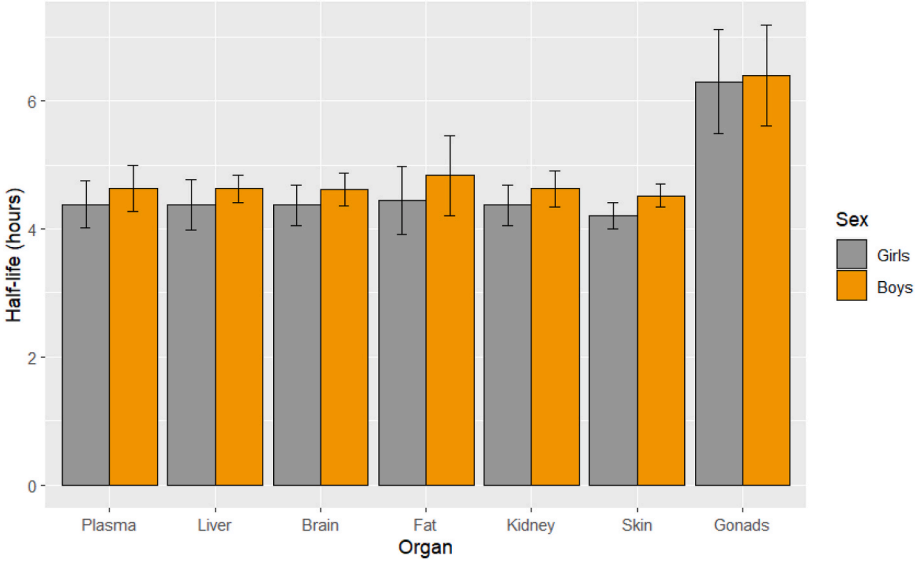

Fig. 3. Half-life for boys and girls based on ontogeny scaling PBPK Model at the dose of 1 μg/kg BW/day.

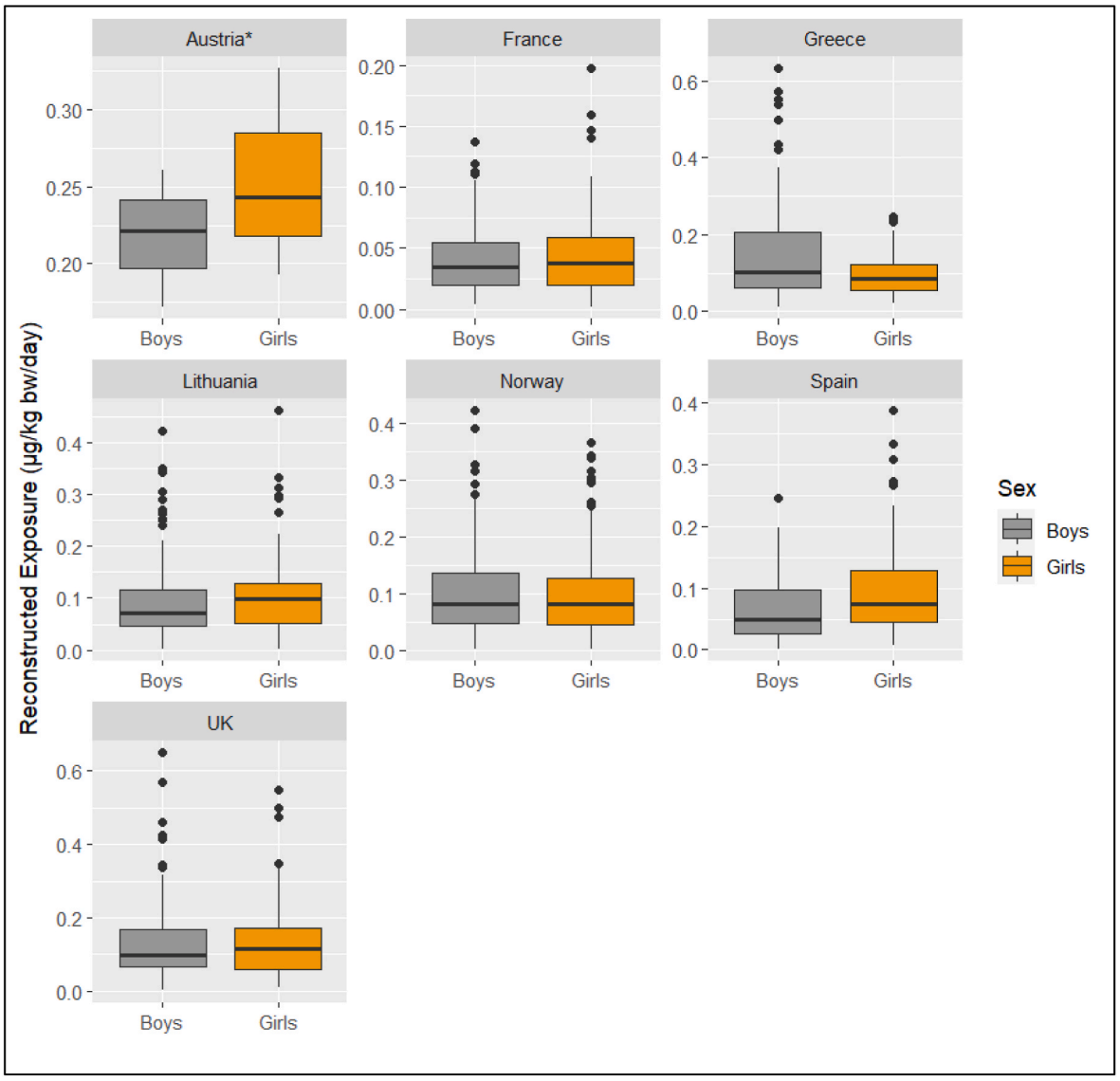

Fig. 4. Reconstructed exposure for boys and girls for two different cohorts (HBM4EU and Helix Cohort). Data from Austria is from PBAT cohort from HBM4EU and for rest other countries, it is from Helix cohort. Upper whisker represents P95 and lower whisker represents P5 confidence interval. For Helix cohort, the percentiles are from combining the individual output results. *represents the aggregated data downloaded from HBM4EU website and the distribution represent changes in creatinine levels. X-axis represents country and y-axis represents daily intake levels (µg/kg BW/day) for boys and girls.

body-weight scaling approach might lead to an underestimation of the risk.

The estimated half-life was found to be higher in the gonads followed by adipose tissue and other organs, for both pediatric and adult model. This estimate could be correlated with other research finding that gonads are highly sensitive to the BPA exposure, which is known to be an endocrine disruptor (Berger et al., 2018; Braun and Hauser, 2011; Ferguson et al., 2014; Forner-Piquer et al., 2020; Santangeli et al., 2016). This suggests that BPA has potential to affect the developing female and male reproductive systems in children. This finding is in accordance with literature in which Ferguson et al. demonstrated an association between BPA exposure and increased sex hormone-binding globulin (SBHG) levels and reduced free and total testosterone levels in boys (8–14 years) along with several other studies finding links between BPA exposure and varying onset of puberty (Berger et al., 2018; Braun and Hauser, 2011; Ferguson et al., 2014; Forner-Piquer et al., 2020; Santangeli et al., 2016). In all the organs, shorter half-life in children than in adults was in correlation with MRT, emphasizing on the importance of calculating the PK parameters. Nevertheless, bioavailability and AUC were higher in children with ontogeny scaling than in adults. A higher AUC and bioavailability mean that a greater amount of chemical is present in systemic circulation and hence more risk. The possible reason for increased bioavailability may be due to decreased extent of metabolic capabilities in the liver and intestine in children than adults which was also seen in case of the infant PBPK model for BPA (Karrer et al., 2018). This points towards the question: Should we set a separate TDI for children and adults as children may be more susceptible to risk? However, further research is needed in this area to reach a conclusion.

Sex differences in growing children were represented by PK parameters with half-life ($t_{1/2}$), bioavailability, AUC, MRT and plasma concentration-time curve. The model simulated that bioavailability, AUC and plasma concentration were higher in girls than in boys based on ontogeny-scaling PBPK model. All these parameters are correlated and the reason behind higher value in girls may be the relatively slower conversion of free BPA to BPAG. The elimination half-life was found to be similar in boys and girls in almost all organs. However, further experimental studies are needed to understand in detail the human sex toxicokinetic differences. The model predicted a comparatively higher

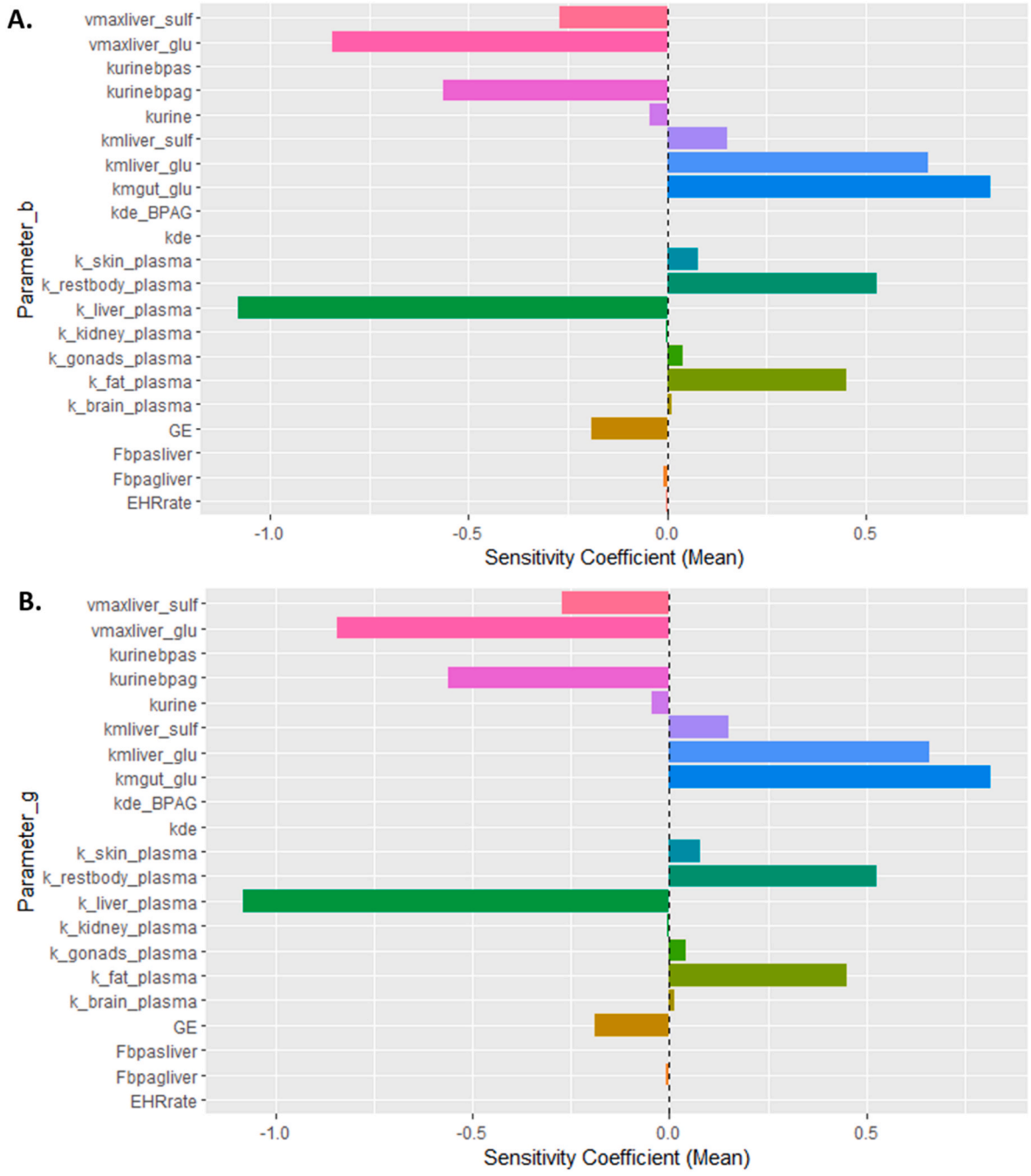

Fig. 5. Sensitivity Coefficient for boys and girls. A) Sensitivity plot for boys, B) Sensitivity plot for girls. All the biochemical parameter used for developing PBPK Model has been used for the sensitivity analysis. Analysis has been done with FME Package.

half-life in the gonads than in other organs, which is consistent with literature findings demonstrating BPA exposure associated with variation in puberty onset in girls (Berger et al., 2018), highlighting the advantage of such a model in tissue dosimetry based risk assessment.

Two biomonitoring studies reported higher urine BPA levels in school age children that adults (Abraham and Chakraborty, 2019; Covaci et al., 2015). Study by Covaci et al. has shown 5 out of 6 countries in Europe with having more than 87% population exposed to BPA above the limit of quantification (LOQ) and children with higher exposure than adults (Covaci et al., 2015). Exposure reconstruction through model for these two cohorts showed that exposure is slightly higher in girls than boys for most countries. One possible reason behind this higher exposure can be that girls are getting more exposed than boys through everyday use products. A recent study by Robles-Aguilera et al., 2021 showed sex-related differences in exposure concluding that a higher risk of dietary exposure in boys was not from BPA but other analogues, but the girls aged under 14 years were at higher risk for increased BPA dietary exposure, especially overweight and obese girls. A critical finding from the pediatric PBPK model is that even with similar exposure in boys and girls, the risk can be slightly higher in girls due to less metabolism in younger girls than boys. The study by Sonnenberg et al. has reported pre-pubertal exposure with phthalates and BPA associated with pubertal timing in girls (mean age: 8.8 years) observed in 472 subjects with no association for boys (Kasper-Sonnenberg et al., 2017). An important outcome of developing ontogeny and sex-specific pediatric models is to better understand the toxicity, metabolic pathway and exposure in

children of growing age.

At last, the reconstructed exposure by the PBPK model for children was compared with the t-TDI established by EFSA in 2015 for BPA (4 μg/kg BW/day) and it was found to be lower than the t-TDI (EFSA Panel on Food Contact Materials Flavourings and Processing Aids (CEF) 2015). It points towards that there may not be any risk or adverse effects involved with the exposure of BPA in human beings. This may not be true. Several epidemiological studies published over the years showed positive associations between BPA exposure and health outcome in children (Healy et al., 2015). But, recent drastic lowering of TDI by EFSA in 2021 (0.04 ng/kg BW/day) which is open for comments, reconstructed exposure by PBPK is approximately 1500 times higher in children pointing towards multiple health concerns ranging from immune effects to neurotoxicity (Bisphenol A: EFSA draft opinion proposes lowering the tolerable daily intake 2021). Further, pediatric PBPK Model can be combined with toxicodynamic to understand the signaling mechanism involving estrogen, aryl hydrocarbon and thyroid hormone receptors (Sharma et al., 2017). This could help in improving the understanding towards adverse effects involved with BPA exposure taking into account toxicokinetic for children.

Interpolation of the pediatric PBPK model from an adult is the most widely used and preferred approach by scientists and regulatory bodies, based on body-weight scaling. In this model, we tried to incorporate ontogeny-specific metabolic parameters to improve the model. This is the first model to consider sex-specific differences in children for BPA. We did not see major differences between genders but, more metabolic and absorption data on sex-specific differences is required to further confirm this. This model also aids in calculating the external exposure which can be from various sources, which is often difficult to calculate during experimental studies. Simulating daily exposure through urine data is another strength of the pediatric PBPK model replacing blood collection for short acting chemicals. PBPK models can predict the aggregate exposure which may be from multiple sources. However, the limitation of these models is the inability to predict route of exposure (oral, dermal, inhalational or sublingual exposure). Further refinement of the model by including separate exposure sources and dermal compartments can help overcome some of the limitations. Overall, the pediatric PBPK model provides a framework to integrate the sex differences and consider pediatric population for the risk assessment in case of such short-acting chemicals. Also, toxicologists should take into account sex-related differences while developing research protocols for environmental chemicals since boys and girls may have quite different effects on the health even with the same exposure.

5. Conclusion

In summary, the BPA pediatric PBPK model was developed for dosimetry assessment and predicting the tissue concentration-time profile in plasma and other organs. At the same exposure, the ontogeny-based pediatric PBPK model showed children might be at higher risk than adults (higher AUC and higher bioavailability in all the organs), which could not be explained by classical body-weight scaling. AUC and bioavailability were slightly higher in girls than boys suggesting free BPA is more present in girls for the same exposure. Further, the reconstructed daily exposure was found to be higher than the TDI recently established by EFSA and reconstructed daily exposure from a large cohort was found to be slightly higher in girls than boys. Overall, this study presents an example of how ontogeny based pediatric PBPK model can show a larger difference in kinetics than traditional approach which further warrants using this kind of model would improve the risk assessment. Also, it is one step forward towards incorporating sex-specific differences in the PBPK model improving the translation of risk.

Credit roles

Deepika Deepika: Conceptualization, Methodology, Formal analysis and simulation, and writing; Raju Prasad Sharma: Supervision, Conceptualization, Methodology, writing, review and revision; Marta Schuhmacher: Supervision, Review and revision; Amrit Kaur Sakhi: Provided Cohort Data and reviewing; Cathrine Thomsen: Provided Cohort Data and reviewing; Leda Chatzi: Provided Cohort Data and reviewing; Marina Vafeiadi: Provided Cohort Data and reviewing; Remy Slama: Provided Cohort Data and reviewing; Joane Quentin: Provided Cohort Data and reviewing; Sandra Andrušaitytė; : Provided Cohort Data and reviewing; Regina Grazuleviciene: Provided Cohort Data and reviewing; Tiffany C Yang: Provided Cohort Data and reviewing; John Wright: Provided Cohort Data and reviewing; Dagmar Waiblinger: Provided Cohort Data and reviewing; Martine Vrijheid: Provided Cohort Data and reviewing; Jose Urquiza: Provided Cohort Data and reviewing; Maribel Casas: Provided Cohort Data, Writing, Review and revision; José L. Domingo: Supervision, Review and revision; Vikas Kumar: Supervision, Conceptualization, Methodology, Formal analysis and simulation, writing, review and revision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgment

This study was financially supported by Marie Skłodowska-Curie “Neurosome Project” under the grant agreement No. 766251, the European Community funded H2020 HBM4EU project under Grant Agreements no. 733032, and the Instituto de Salud Carlos III (PI17/01194), and the European Community’s Seventh Framework Programme (FP7/2007–206) under grant agreement no 308333 (HELIX project). Maribel Casas holds a Miguel Servet fellowship (CP16/00128) funded by Instituto de Salud Carlos III and co-funded by European Social Fund “Investing in your future”. We acknowledge support from the Spanish Ministry of Science and Innovation through the “Centro de Excelencia Severo Ochoa 2019–2023” Program (2018-000806-S), and support from the Generalitat de Catalunya through the CERCA Program. This publication reflects only the authors’ views. The Community and other funding organizations are not liable for any use made of the information contained therein. Born in Bradford is only possible because of the enthusiasm and commitment of the children and parents in Born in Bradford. We are grateful to all participants, health professionals and researchers who have made Born in Bradford happen. BiB receives core infrastructure funding from the Wellcome Trust (WT101597MA) and a joint grant from the UK Medical Research Council (MRC) and Economic and Social Science Research Council (ESRC) (MR/N024397/1). This study has received support from European Research Council under the European Union’s Seventh Framework Programme (FP7/2007–2013)/ERC grant agreement no 669545 and National Institute for Health Research Applied Research Collaboration Yorkshire and Humber (NIHR200166). The Norwegian Mother, Father and Child Cohort Study is supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research. We are grateful to all the participating families in Norway who take part in this on-going cohort study. The views expressed are those of the author(s), and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. Jose Urquiza is supported by Spanish regional program PERIS (Ref.: SLT017/20/000119), granted by Departament de Salut de la Generalitat de Catalunya.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.114074.

References

Abraham, A., Chakraborty, P., 2019. A review on sources and health impacts of bisphenol A. Rev. Environ. Health 1–10. https://doi.org/10.1515/reveh-2019-0034.

Berger, K., Eskenazi, B., Kogut, K., Parra, K., Lustig, R.H., Greenspan, L.C., et al., 2018. Association of prenatal urinary concentrations of phthalates and bisphenol A and pubertal timing in boys and girls. Environ. Health Perspect. 126, 097004 https://doi.org/10.1289/EHP3424.

Bisphenol, A., 2021. EFSA Draft Opinion Proposes Lowering the Tolerable Daily Intake. Available: https://www.efsa.europa.eu/en/news/bisphenol-efsa-draft-opinion-proposes-lowering-tolerable-daily-intake.

Bois, F.Y., 2009. GNU MCSim: bayesian statistical inference for SBML-coded systems biology models. Bioinformatics 25, 1453–1454. https://doi.org/10.1093/bioinformatics/btp162.

Braun, J.M., Hauser, R., 2011. Bisphenol A and children's health. Curr. Opin. Pediatr. 23, 233–239. https://doi.org/10.1097/MOP.0b013e3283445675.

Bushnik, T., Haines, D., Levallois, P., Levesque, J., Van Oostdam, J., Viau, C., 2010. Lead and bisphenol A concentrations in the Canadian population. Heal reports 21, 7—18.

Caporossi, L., Papaleo, B., 2015. Exposure to bisphenol A and gender differences: from rodents to humans evidences and hypothesis about the health effects. J Xenobiotics 5, 15–19. https://doi.org/10.4081/xeno.2015.5264.

Covaci, A., Hond, E Den, Geens, T., Govarts, E., Koppen, G., Frederiksen, H., et al., 2015. Urinary BPA measurements in children and mothers from six European member states: overall results and determinants of exposure. Environ. Res. 141, 77–85. https://doi.org/10.1016/j.envres.2014.08.008.

Csanády, G.A., Oberste-Frielinghaus, H.R., Semder, B., Baur, C., Schneider, K.T., Filser, J. G., 2002. Distribution and unspecific protein binding of the xenoestrogens bisphenol A and daidzein. Arch. Toxicol. 76, 299–305. https://doi.org/10.1007/s00204-002-0339-5.

Deepika, D., Sharma, R.P., Schuhmacher, M., Kumar, V., 2020. An integrative translational framework for chemical induced neurotoxicity–a systematic review. Crit. Rev. Toxicol. 50, 424–438. https://doi.org/10.1080/10408444.2020.1763253.

Deepika, D., Sharma, R.P., Schuhmacher, M., Kumar, V., 2021. Risk assessment of perfluorooctane sulfonate (PFOS) using dynamic age dependent physiologically based pharmacokinetic model (PBPK) across human lifetime. Environ. Res. 199, 111287 https://doi.org/10.1016/j.envres.2021.111287.

Doerge, D.R., Twaddle, N.C., Vanlandingham, M., Brown, R.P., Fisher, J.W., 2011. Distribution of bisphenol A into tissues of adult, neonatal, and fetal Sprague–Dawley rats. Toxicol. Appl. Pharmacol. 255, 261–270. https://doi.org/10.1016/j.taap.2011.07.009.

EFSA Panel on Food Contact Materials Flavourings and Processing Aids (CEF) E, 2015. Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. EFSA J. 13, 3978. https://doi.org/10.2903/j.efsa.2015.3978.

Eng, D.S., Lee, J.M., Gebremariam, A., Meeker, J.D., Peterson, K., Padmanabhan, V., 2013. Bisphenol A and chronic disease risk factors in us children. Pediatrics 132, e637–e645. https://doi.org/10.1542/peds.2013-0106.

Ferguson, K.K., Peterson, K.E., Lee, J.M., Mercado-García, A., Blank-Goldenberg, C., Téllez-Rojo, M.M., et al., 2014. Prenatal and peripubertal phthalates and bisphenol A in relation to sex hormones and puberty in boys. Reprod. Toxicol. 47, 70–76. https://doi.org/10.1016/j.reprotox.2014.06.002.

Fisher, J.W., Twaddle, N.C., Vanlandingham, M., Doerge, D.R., 2011. Pharmacokinetic modeling: prediction and evaluation of route dependent dosimetry of bisphenol A in monkeys with extrapolation to humans. Toxicol. Appl. Pharmacol. 257, 122–136. https://doi.org/10.1016/j.taap.2011.08.026.

Forner-Piquer, I., Beato, S., Piscitelli, F., Santangeli, S., Di Marzo, V., Habibi, H.R., et al., 2020. Effects of BPA on zebrafish gonads: focus on the endocannabinoid system. Environ. Pollut. 264, 114710 https://doi.org/10.1016/j.envpol.2020.114710.

Gallagher, C.J., Balliet, R.M., Sun, D., Chen, G., Lazarus, P., 2010. Sex differences in UDP-glucuronosyltransferase 2B17 expression and activity. Drug Metab. Dispos. 38, 2204–2209. https://doi.org/10.1124/dmd.110.035345.

Hanioka, N., Naito, T., Narimatsu, S., 2008. Human UDP-glucuronosyltransferase isoforms involved in bisphenol A glucuronidation. Chemosphere 74, 33–36. https://doi.org/10.1016/j.chemosphere.2008.09.053.

Hansen, J.B., Bilenberg, N., Timmermann, C.A.G., Jensen, R.C., Frederiksen, H., Andersson, A.-M., et al., 2021. Prenatal exposure to bisphenol A and autistic- and ADHD-related symptoms in children aged 2 and5 years from the Odense Child Cohort. Environ. Health 20, 24. https://doi.org/10.1186/s12940-021-00709-y.

Harley, K.G., Gunier, R.B., Kogut, K., Johnson, C., Bradman, A., Calafat, A.M., et al., 2013. Prenatal and early childhood bisphenol A concentrations and behavior in school-aged children. Environ. Res. 126, 43–50. https://doi.org/10.1016/j.envres.2013.06.004.

Haug, L.S., Sakhi, A.K., Cequier, E., Casas, M., Maitre, L., Basagana, X., et al., 2018. In-utero and childhood chemical exposome in six European mother-child cohorts. Environ. Int. 121, 751–763. https://doi.org/10.1016/j.envint.2018.09.056.

Hbm4Eu, 2021. HBM4EU - science and policy for a healthy future. Available: https://www.hbm4eu.eu/deliverables/.

Healy, B.F., English, K.R., Jagals, P., Sly, P.D., 2015. Bisphenol A exposure pathways in early childhood: reviewing the need for improved risk assessment models. J. Expo. Sci. Environ. Epidemiol. 25, 544–556. https://doi.org/10.1038/jes.2015.49.

Karrer, C., Roiss, T., von Goetz, N., Skledar, D.G., Mašič, L.P., Hungerbühler, K., 2018. Physiologically based pharmacokinetic (PBPK) modeling of the bisphenols BPA, BPS, BPF, and BPAF with new experimental metabolic parameters: comparing the pharmacokinetic behavior of BPA with its substitutes. Environ. Health Perspect. 126, 077002 https://doi.org/10.1289/EHP2739.

Kasper-Sonnenberg, M., Wittsiepe, J., Wald, K., Koch, H.M., Wilhelm, M., 2017. Pre-pubertal exposure with phthalates and bisphenol A and pubertal development. PLoS One 12, 1–18. https://doi.org/10.1371/journal.pone.0187922.

Kim, Y.-H., Kim, C.-S., Park, S., Han, S.Y., Pyo, M.-Y., Yang, M., 2003. Gender differences in the levels of bisphenol A metabolites in urine. Biochem. Biophys. Res. Commun. 312, 441–448. https://doi.org/10.1016/j.bbrc.2003.10.135.

Kurebayashi, H., 2003. Disposition of a low dose of 14C-bisphenol A in male rats and its main biliary excretion as BPA glucuronide. Toxicol. Sci. 73, 17–25. https://doi.org/10.1093/toxsci/kfg040.

Ladumor, M.K., Bhatt, D.K., Gaedigk, A., Sharma, S., Thakur, A., Pearce, R.E., et al., 2019. Ontogeny of hepatic sulfotransferases and prediction of age-dependent fractional contribution of sulfation in acetaminophen metabolism. Drug Metab. Dispos. 47, 818–831. https://doi.org/10.1124/dmd.119.086462.

Laroche, C., Aggarwal, M., Bender, H., Benndorf, P., Birk, B., Crozier, J., et al., 2018. Finding synergies for 3Rs – toxicokinetics and read-across: report from an EPAA partners' forum. Regul. Toxicol. Pharmacol. 99, 5–21. https://doi.org/10.1016/j.yrtph.2018.08.006.

Li, Q., Davila, J., Kannan, A., Flaws, J.A., Bagchi, M.K., Bagchi, I.C., 2016. Chronic exposure to bisphenol A affects uterine function during early pregnancy in mice. Endocrinology 157, 1764–1774. https://doi.org/10.1210/en.2015-2031.

Lin, Y.J., Hsiao, J.L., Hsu, H.T., 2020. Integration of biomonitoring data and reverse dosimetry modeling to assess population risks of arsenic-induced chronic kidney disease and urinary cancer. Ecotoxicol. Environ. Saf. 206, 111212 https://doi.org/10.1016/j.ecoenv.2020.111212.

Lv, Y., Rui, C., Dai, Y., Pang, Q., Li, Y., Fan, R., et al., 2016. Exposure of children to BPA through dust and the association of urinary BPA and triclosan with oxidative stress in Guangzhou, China. Environ Sci Process Impacts 18, 1492–1499. https://doi.org/10.1039/c6em00472e.

Magnus, P., Birke, C., Vejrup, K., Haugan, A., Alsaker, E., Daltveit, A.K., et al., 2016. Cohort profile update: the Norwegian mother and child cohort study (MoBa). Int. J. Epidemiol. 45, 382–388. https://doi.org/10.1093/ije/dyw029.

Maitre, L., de Bont, J., Casas, M., Robinson, O., Aasvang, G.M., Agier, L., et al., 2018. Human Early Life Exposome (HELIX) study: a European population-based exposome cohort. BMJ Open 8, e021311. https://doi.org/10.1136/bmjopen-2017-021311.

Marazziti, D., Palego, L., Rossi, A., Cassano, G.B., 1998. Gender-related seasonality of human platelet phenolsulfotransferase activity. Neuropsychobiology 38, 1–5. https://doi.org/10.1159/000026509.

Martínez, M., Blanco, J., Rovira, J., Kumar, V., Domingo, J.L., Schuhmacher, M., 2020. Bisphenol A analogues (BPS and BPF) present a greater obesogenic capacity in 3T3-L1 cell line. Food Chem. Toxicol. 140, 111298 https://doi.org/10.1016/j.fct.2020.111298.

Miao, M., Wang, Z., Liu, X., Liang, H., Zhou, Z., Tan, H., et al., 2017. Urinary bisphenol A and pubertal development in Chinese school-aged girls: a cross-sectional study. Environ. Health 16, 80. https://doi.org/10.1186/s12940-017-0290-9.

Nalbantoğlu, A., Çelikkol, A., Samancı, N., Günaydın, N.C., Nalbantoğlu, B., 2021. Bisphenol A as a risk factor for allergic rhinitis in children. Hum. Exp. Toxicol. 40, 395–402. https://doi.org/10.1177/0960327120958105.

Neumann, E., Mehboob, H., Ramírez, J., Mirkov, S., Zhang, M., Liu, W., 2016. Age-Dependent hepatic UDP-glucuronosyltransferase gene expression and activity in children. Front. Pharmacol. 7, 1–7. https://doi.org/10.3389/fphar.2016.00437.

Nowell, S., Falany, C.N., 2006. Pharmacogenetics of human cytosolic sulfotransferases. Oncogene 25, 1673–1678. https://doi.org/10.1038/sj.onc.1209376.

Ohore, O.E., Zhang, S., 2019. Endocrine disrupting effects of bisphenol A exposure and recent advances on its removal by water treatment systems. A review. Sci African 5, e00135. https://doi.org/10.1016/j.sciaf.2019.e00135.

Remer, T., Neubert, A., Maser-Gluth, C., 2002. Anthropometry-based reference values for 24-h urinary creatinine excretion during growth and their use in endocrine and nutritional research. Am. J. Clin. Nutr. 75, 561–569. https://doi.org/10.1093/ajcn/75.3.561.

Robles-Aguilera, V., Gálvez-Ontiveros, Y., Rodrigo, L., Salcedo-Bellido, I., Aguilera, M., Zafra-Gómez, A., et al., 2021. Factors associated with exposure to dietary bisphenols in adolescents. Nutrients 13, 1553. https://doi.org/10.3390/nu13051553.

Roen, E.L., Wang, Y., Calafat, A.M., Wang, S., Margolis, A., Herbstman, J., et al., 2015. Bisphenol A exposure and behavioral problems among inner city children at 7–9 years of age. Environ. Res. 142, 739–745. https://doi.org/10.1016/j.envres.2015.01.014.

Santangeli, S., Maradonna, F., Gioacchini, G., Cobellis, G., Piccinetti, C.C., Dalla Valle, L., et al., 2016. BPA-induced deregulation of epigenetic patterns: effects on female zebrafish reproduction. Sci. Rep. 6, 21982 https://doi.org/10.1038/srep21982.

Sasso, A.F., Pirow, R., Andra, S.S., Church, R., Nachman, R.M., Linke, S., et al., 2020. Pharmacokinetics of bisphenol A in humans following dermal administration. Environ. Int. 144, 106031 https://doi.org/10.1016/j.envint.2020.106031.

Schuhmacher, M., Fàbrega, F., Kumar, V., García, F., Nadal, M., Domingo, J.L., 2014. A PBPK model to estimate PCDD/F levels in adipose tissue: Comparison with experimental values of residents near a hazardous waste incinerator. Environ. Int. 73, 150–157. https://doi.org/10.1016/j.envint.2014.07.020.

Schwartz, J.B., 2003. The influence of sex on pharmacokinetics. Clin. Pharmacokinet. 42, 107–121. https://doi.org/10.2165/00003088-200342020-00001.

Sharma, R.P., Schuhmacher, M., Kumar, V., 2017. Developing integrated PBPK/PD coupled mechanistic pathway model (miRNA-BDNF): an approach towards system toxicology. Toxicol. Lett. 280, 79–91. https://doi.org/10.1016/j.toxlet.2017.08.003.

Sharma, R.P., Schuhmacher, M., Kumar, V., 2018a. Development of a human physiologically based pharmacokinetic (PBPK) model for phthalate (DEHP) and its metabolites: a bottom up modeling approach. Toxicol. Lett. 296, 152–162. https://doi.org/10.1016/j.toxlet.2018.06.1217.

Sharma, R.P., Schuhmacher, M., Kumar, V., 2018b. The development of a pregnancy PBPK Model for Bisphenol A and its evaluation with the available biomonitoring data. Sci. Total Environ. 624, 55–68. https://doi.org/10.1016/j.scitotenv.2017.12.023.

Shelby, M.D., 2008. NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A. NTP CERHR MON v, pp. 1–64 passim vols. ii–ix.

Skledar, D.G., Troberg, J., Lavdas, J., Mašič, L.P., Finel, M., 2015. Differences in the glucuronidation of bisphenols F and S between two homologous human UGT enzymes, 1A9 and 1A10. Xenobiotica 45, 511–519. https://doi.org/10.3109/00498254.2014.999140.

Soetaert, K., Petzoldt, T., 2010. Inverse modelling, sensitivity and Monte Carlo analysis in R using package FME. J. Stat. Software 33, 1–28. https://doi.org/10.18637/jss.v033.i03.

Stahlhut, R.W., Welshons, W.V., Swan, S.H., 2009. Bisphenol A data in nhanes suggest longer than expected half-life, substantial nonfood exposure, or both. Environ. Health Perspect. 117, 784–789. https://doi.org/10.1289/ehp.0800376.

Takeuchi, T., Tsutsumi, O., 2002. Serum bisphenol a concentrations showed gender differences, possibly linked to androgen levels. Biochem. Biophys. Res. Commun. 291, 76–78. https://doi.org/10.1006/bbrc.2002.6407.

Tamayo-Uria, I., Maitre, L., Thomsen, C., Nieuwenhuijsen, M.J., Chatzi, L., Siroux, V., et al., 2019. The early-life exposome: description and patterns in six European countries. Environ. Int. 123, 189–200. https://doi.org/10.1016/j.envint.2018.11.067.

Teeguarden, J.G., Waechter, J.M., Clewell, H.J., Covington, T.R., Barton, H.A., 2005. Evaluation of oral and intravenous route pharmacokinetics, plasma protein binding, and uterine tissue dose metrics of bisphenol A: a physiologically based pharmacokinetic approach. Toxicol. Sci. 85, 823–838. https://doi.org/10.1093/toxsci/kfi135.

Thayer, K.A., Doerge, D.R., Hunt, D., Schurman, S.H., Twaddle, N.C., Churchwell, M.I., et al., 2015. Pharmacokinetics of bisphenol A in humans following a single oral administration. Environ. Int. 83, 107–115. https://doi.org/10.1016/j.envint.2015.06.008.

Tsukioka, T., Terasawa, J., Sato, S., Hatayama, Y., Makino, T., Nakazawa, H., 2004. Development of analytical method for determining trace amounts of BPA in urine samples and estimation of exposure to BPA. J Environ Chem 14, 57–63. https://doi.org/10.5985/jec.14.57.

Völkel, W.V., Bittner, N., Dekant, W., 2005. Quantitation of bisphenol A and bisphenol A glucuronide in biological samples by high performance liquid chromatography-tandem mass spectrometry. Drug Metab. Dispos. 33, 1748–1757. https://doi.org/10.1124/dmd.105.005454.

Vrijheid, M., 2013. The human early life exposome (HELIX): project rationale and design. In: ISEE Conf Abstr 2013:5849. https://doi.org/10.1289/isee.2013.s-2-32-05.

Wagner, C., Zhao, P., Pan, Y., Hsu, V., Grillo, J., Huang, S.M., et al., 2015. Application of physiologically based pharmacokinetic (PBPK) modeling to support dose selection: report of an FDA public workshop on PBPK. CPT Pharmacometrics Syst. Pharmacol. 4, 226–230. https://doi.org/10.1002/psp4.33.