보건학석사 학위논문

Construction of a physiologically based pharmacokinetic model for some environmental phenols

일부 환경성페놀계열 물질의 인체 생리학적 약물속도론 모델 구축

2018년 2월

서울대학교 보건대학원
환경보건학과 환경보건학 전공
최 정 원

Abstract

Construction of a physiologically based pharmacokinetic model for some environmental phenols

Jeong Weon Choi
Department of Environmental Health
The Graduate School of Public Health
Seoul National University

It is important to know the exposure levels of environmental phenolic compounds considering their exposure frequency and toxicity. Physiologically based pharmacokinetic (PBPK) model is one of the tools for predicting the daily intake value. Most of the PBPK models were developed for single chemical so several models are required to do exposure assessment for several chemicals. A simple PBPK model was developed for several environmental phenols (methyl paraben, ethyl paraben, propyl paraben, benzophenono-3, triclosan, bisphenol A, bisphenol S) that provides a description of kinetics of those chemicals in human. Since those phenolic compounds share similar chemical structure and pharmacokinetic characteristics, constructing a unified model for them would reduce the cost and time. Structure of the developed model consists of liver, skin, rest-of-the-body and blood compartments. Once the chemical comes into the liver compartment, metabolism happens and the metabolites excretes into

feces or urine after moving to the blood compartment. The model parameters were optimized using data of published pharmacokinetic studies in humans. Then to confirm the validity, the model was applied to other human kinetic data not used in the model calibration except benzophenone-3. Model simulations were visually fitted well to the experimental data of most of the target chemicals except propyl paraben. It appears that the model under-predicted accumulated urinary amount of total propyl paraben. The results of this study is meaningful that the constructed model can be applied to various phenolic compounds with one model structure and it can be used to predict more elaborate intake values that can reflect the physiochemical characteristics of human body. In addition, the result of this study implicated that the model structure could explain pharmacokinetic behavior of various phenols so it could be considered that the extended application of the model to other phenols sharing similar pharmacokinetic properties.

Key words: PBPK, environmental phenols, human model, oral administration

Student No.: 2016-24060

Contents

List of Tables

List of Figures

1. Introduction

Environmental phenol is a group of phenolic compounds widely used in many consumer products, personal care products, and food packaging. Parabens are used as antimicrobial preservatives in cosmetics, personal care products, foodstuffs, and pharmaceuticals (Guo and Kannan, 2013; Mortensen et al., 2014). Triclosan (TCS) also has antimicrobial activity so they used in personal care products, household items, medical devices, and clinical settings (Fang et al., 2010). Benzophenone-3 (BP3) is mainly used as sunscreen agents found in cosmetic products (Janjua et al., 2008; Kim and Choi, 2014) and plastic surface coatings for food packaging as sunscreen agents (Kim et al., 2016). Bisphenol A (BPA) is used to manufacture polycarbonate plastic and epoxy resins and thermal paper (Liu et al., 2017). As BPA is known to be harmful, the production and application of BPA analogues such as bisphenol S (BPS), and –F (BPF) are on the rise these days (Chen et al., 2016). Therefore, general exposure route of environmental phenols is ingestion of food, beverages, and dermal contact of consumer products and personal care products. In addition, oral mucosal exposure through dental care products (e.g., toothpaste, mouthwash) is another route of exposure for phenols (Geens et al., 2009). In addition, many environmental phenols are known as endocrine disruptors based on *in vitro* and *in vivo* studies (Dekant and Völkel, 2008; Skledar et al.; 2016; Kim and Choi, 2014).

These environmental phenols mentioned above share similar pharmacokinetic behavior and metabolic pathway. Human *in vivo* and *in vitro* studies have been conducted to investigate the metabolism and pharmacokinetic profiles of these compounds. The common metabolic pathway

is phase II metabolism in the liver, yielding glucuronided and sulfated conjugates. Once the chemicals absorbed into the body, most of them are rapidly metabolized and eliminated within 24 h. Urinary excretion of the metabolites is the main elimination route in humans (Ye et al., 2007; Moos et al., 2016; Gonzalez et al., 2002; Sandborgh-Englund et al., 2006; Thayer et al., 2015; Völkel et al., 2002; Oh et al., 2018).

Due to the ubiquitous nature and toxicity of the environmental phenols, it is important to know the exposure levels of them in the population. Human exposure to environmental phenols can be estimated by measuring urinary concentrations of these compounds and their metabolites. The advantage of using biomonitoring data is that it can reflect internal exposure. Physiologically-based pharmacokinetic (PBPK) model can be a useful tool to convert urinary concentrations of the compounds into daily intake values. Shin et al. (2010) predict the oral BPA intake of Korean pregnant women using the median blood BPA concentration of the population. Yang et al. (2015) also estimated daily oral intake of BPA for adult humans using their model. They conducted Monte Carlo simulation to evaluate the inter-individual variability of model predicted internal dose metrics (C_{max} and AUC) of serum unconjugated BPA at steady state in the general adult U.S. population.

According to the report of Ministry of Food and Drug Safety (MFDS) of Korea, PBPK models developed for a hundred of chemicals (MFDS, 2011). Several PBPK models have been developed to describe the pharmacokinetic behavior, metabolism and disposition of phenolic compounds (Yang et al., 2015; Fisher et al., 2011; Kawamoto et al., 2007; Teeguarden et al., 2005; Shin et al., 2004; Campbell et al., 2015; Maharjan et al., 2015). Each model has a variety of structures depending on each purpose. Most of the PBPK models are developed for individual chemicals or same group of chemicals, like parabens

(Campbell et al., 2015). However, constructing a model that can encompass a certain class of chemicals with similar structure and pharmacokinetic properties can save the cost and time required for exposure assessment.

The objective of this study is to construct the PBPK core model for seven environmental phenols; methyl paraben (MP), ethyl paraben (EP), propyl paraben (PP), BP3, TCS, BPA, BPS. These chemicals share a similar structure of phenolic ring (Figure 1), metabolic pathway and pharmacokinetic behavior. The purpose of the model is to describe the pharmacokinetic behavior of phenols in humans with single model structure. Model calibration and validation were performed using human pharmacokinetic data (MFDS, 2013, 2016; Sandborgh-Englund et al., 2006; Thayer et al., 2015; Oh et al., 2018).

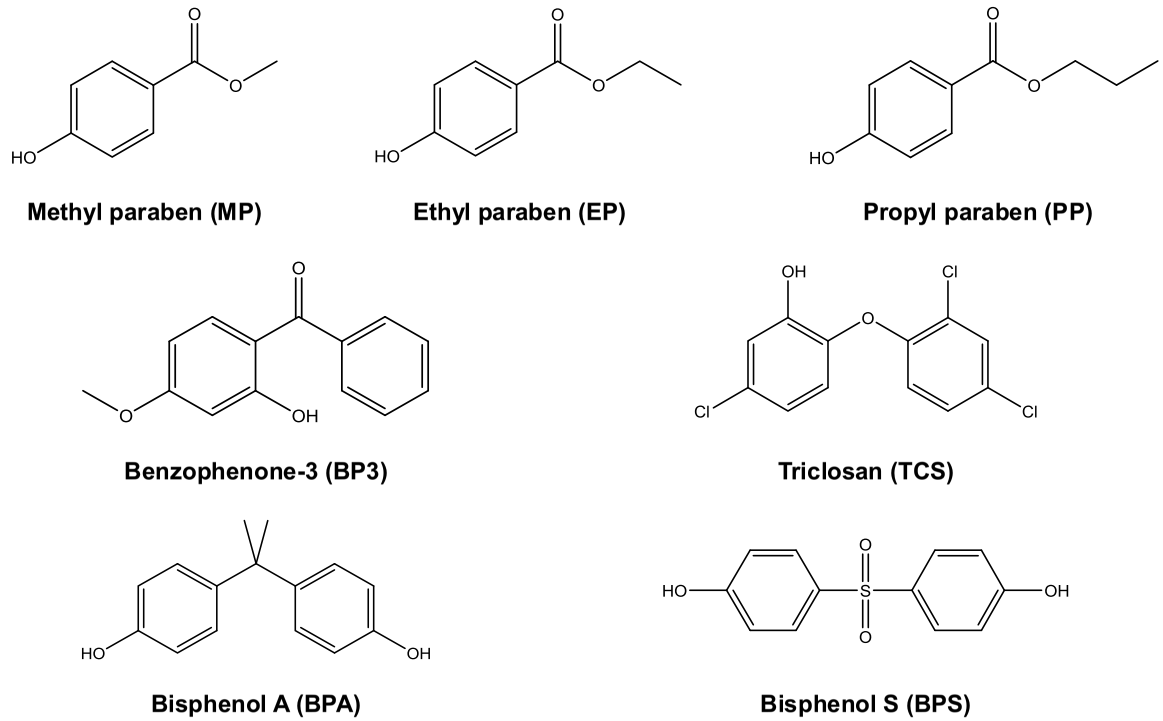

Figure 1. Chemical structures of environmental phenols used to develop the PBPK model in the present study

2. Materials and Methods

2.1. Datasets

In case of MP, EP and PP, time-course kinetic datasets for oral exposure were used to develop the model. MFDS (2013) reported the data of 7 male volunteers orally exposed to 2.5 mg/kg of isotope labeled MP, EP and PP (d_4-MP, d_4-EP, d_4-PP) respectively. Serum was collected from 0 to 8 h after exposure and urine was collected from 0 to 24 h after exposure. MFDS (2013) dataset was used to optimize the oral exposure of the model and the other dataset was used to validate the model. MFDS (2016) reported the data of 7 volunteers orally exposed to 40 mg of d_4-PP. Serum and urine samples were collected and the sample collection time was much longer than MFDS (2013), from 0 to 72 h after exposure. For MP and EP, MFDS (2013) data of three subjects without missing data points were used to calibrate the model and data from remaining four subjects were used to evaluate the model. For PP, MFDS (2013) data was used for model calibration and MFDS (2016) data was used for model evaluation.

For BP3, MFDS (2016) reported serum and urine data after single oral exposure. Five male volunteers were exposed to 2 mg of deuterated BP3 (d_5-BP3) via the oral route of exposure. At this time, serum and urine samples were collected at certain time intervals during 0-72 h after exposure. In the serum time course data, most of them were below the limit of detection (LOD) (0.5 ng/mL) after 8 h so they were excluded from the analysis.

For TCS, MFDS (2016) reported serum and urine data obtained from oral exposure experiments. One adult male was exposed to 4 mg of deuterated TCS

(d_3-TCS) and both serum and urine were collected during 0-72 h after exposure. Sandborgh-Englund et al. (2006) reported the TCS in plasma and urine after single oral administration of 4 mg TCS by swallowing an oral mouthwash solution from 10 Swedish people. The samples were collected before and up to 8 days after exposure. Data from one adult male was used for model calibration and data from 10 Swedish people were used for model evaluation.

Datasets of bisphenols were also from controlled dosing studies. Thayer et al. (2015) gave a single oral dose of 100 μg/kg deuterated BPA (d_6-BPA) to 14 volunteers. After dosing, the serum and urine samples were conducted until 24 h after exposure. Oh et al. (2018) reported the BPS in serum and urine after single oral administration of 0.00875 mg/kg deuterated BPS (d_4-BPS) from seven volunteers. The samples were collected before and up to 72 h after exposure. For BPA, data from five subjects with more time points and longer sample collection time were used for model calibration and the others were used for model evaluation. For BPS, data of four subjects without missing data points were used to optimize the model and data from remaining three subjects were used to evaluate the model.

2.2. Model construction

2.2.1. Model construction procedure

The overall procedure of PBPK model construction is illustrated in Figure 2. Each step before the model formulation was to construct the model structure, which can reflect the appropriate absorption, distribution, metabolism, and excretion (ADME) of the target compound. Information of toxic mechanisms, biochemical properties, and physiological properties of the target compound were gotten from the literatures. Then model structure was described in differential equations and model parameters were estimated using human pharmacokinetic (PK) datasets. Finally, model simulation performed and evaluated with the other PK datasets. Details of each step of the workflow are described in following sections. Coding, all parameter fits and simulations were conducted using Berkeley Madonna ver.8.3.23.0 (University of California).

2.2.2. Model compartments

The structure of the human PBPK model for environmental phenols is shown in Figure 3. Tissue compartments include liver, skin, blood and rest-of-the-body compartments. The selection of compartments was based on both kinetic and metabolic considerations and model's potential use for dose reconstruction and exposure assessment of environmental phenols.

A liver compartment is involved to reflect the metabolism of phenols, and describe the oral exposure. Considering that exposure to environmental phenols via the skin is one of the important route, a skin compartment was included to describe the dermal absorption. A blood compartment was also included because it describes the systemic circulation and excretion through the urine,

the commonly used biological fluid to measure the phenol exposure. The rest-of-the-body compartment (all other organs and tissues not considered individually) was included to complete mass balance. Each compartment was interconnected by the systemic circulation and described as flow limited.

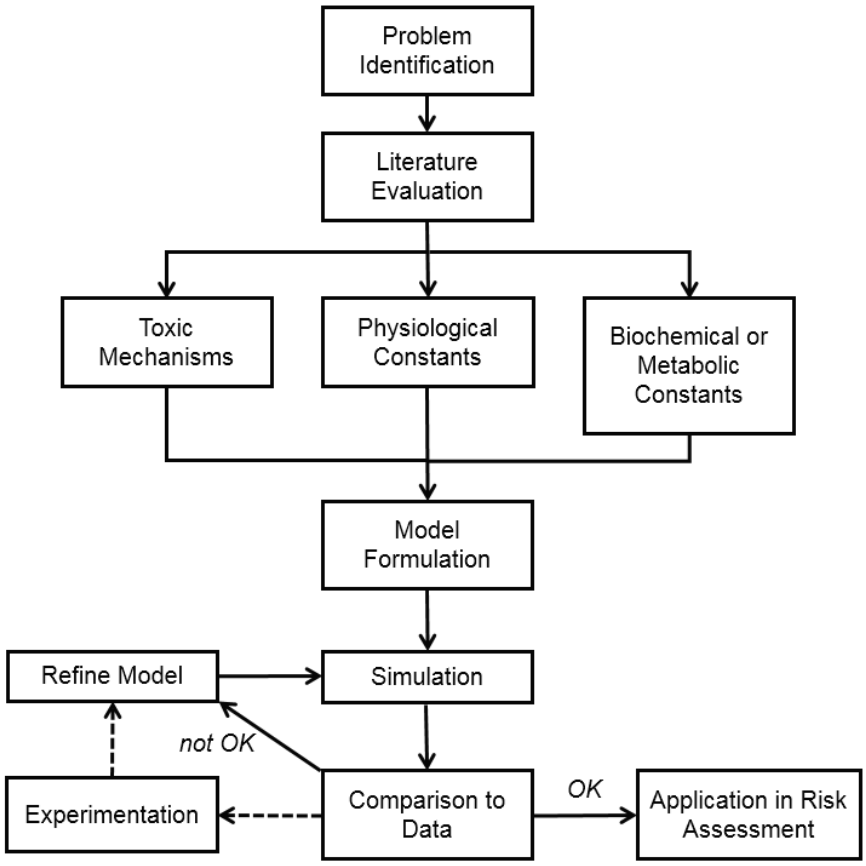

Figure 2. Overall procedure of PBPK model construction. After making the model structure and equations, the model was fitted into the human PK data. Then the calibrated model was validated by the other datasets.

2.2.3. Model parameters

The physiological parameters such as tissue volumes and blood flows (Table 1) were obtained from the literatures (Brown et al.,1997; Corley et al., 2000). Fractional tissue values and blood flows were scaled using body weight.

Kinetic parameters about metabolism were all visually fitted value. All of the phenolic compounds included in this model are commonly conjugated with glucuronide or sulfate in the liver. This phase II metabolism is major metabolic pathway of some bisphenol derivatives and TCS, however, in the case of parabens and BP3, other metabolic processes (e.g., hydrolysis, demethylation) occur mainly (Abbas et al., 2010; Kim and Choi, 2014). Therefore, kinetic parameters related to metabolism were divided into two types. Once metabolites are formed in the liver compartment, they are either transferred to the blood compartment or excreted into the feces by first order rate constant (KfM1b, KfM2b, KfM1f, KfM2f). The transferred metabolites in blood are then excreted into urine and these processes were also described in first order rate constant (KeM1u, KeM2u).

Tissue:blood partition coefficients (PCs) were obtained from the literatures (Campbell et al., 2015; Doerge et al., 2011; Maharjan et al., 2015) or predicted. Campbell et al. (2015) and Maharjan et al. (2015) predicted the PCs of MP, PP, and TCS in humans using the computational method. Doerge et al. (2011) analyzed BPA concentration in multiple tissues and serum from adult rats and calculated PC. PCs of liver could be obtained from the literatures but PCs of skin and rest-of-the-body were based on the values of other slowly-perfused-tissue compartments and modified to fit visually well. The model estimated the PCs of EP, BP3, and BPS but initial values were based on the PCs of MP, PP or BPA, which are belonging to similar groups. Skin:vehicle PCs were obtained

from Roy et al. (1996).

Skin and oral mucosal permeability coefficient were derived from other studies (Seo et al., 2017; MFDS, 2013, 2016) or predicted. The studies evaluated the permeation of MP, PP, BP3, and TCS in human cadaver epidermis using a Franz diffusion cell method. Since EP, BPA, and BPS did not have skin permeability coefficient data, the values were set to MP.

2.2.4. Chemical uptake and metabolism

Oral absorption was based on a pseudo-physiological compartment description representing gastrointestinal (GI) tract. Absorption from the GI tract was modeled using a first-order rate constant. The equation for the GI tract compartment is as follows:

$$\frac{dAGI}{dt} = -(K_a \times AGI + K_{ef} \times AGI)$$

where Ka is the oral absorption rate constant (/hr), AGI is the amount of phenol in GI tract, and Kef is the fecal excretion rate constant (/hr) of parent compound.

Phase II metabolism and other metabolic reaction of the phenols were described using first-order rate equations to minimize the number of model parameter. All parameter values were fitted with human PK data considering the metabolic characteristic of each compound. For example, major metabolite of BP-3 is BP-1 produced by O-demethylation, while the metabolites produced by phase II metabolism are produced at a low rate. Therefore, the values of the parameters related to the phase II metabolism are smaller than those of other metabolism related parameters.

Dermal absorption was described as a rate of penetration through the skin

(Fick's law of diffusion) and the rate of delivery and clearance via systemic blood circulation (Corley et al., 2000). Dermal mass flux is most naturally described by Fickian diffusion equation and passive diffusion is fundamental mechanism of dermal mass transport (Roy, 1998). The equation for the skin compartment is as follows:

$$\frac{dAS}{dt} = (K_p \times \frac{A_e}{1000}) \times (\frac{DMx}{MW} - \frac{C_s}{P_{s_v}}) + QS \times (C_a - CvS)$$

where Kp is the skin permeability constant for each phenolic compounds (cm/h), Ae is the surface area exposed (cm^2), DMx is the concentration of phenol in vehicle (mg/L), MW is the molecular weight of the phenol (g/mol), Cs is the concentration of the phenol in skin (mmol/L), Ps_v is the skin:vehicle partition coefficient, QS is the blood flow to the skin (L/h), Ca is the concentration of phenol in arterial blood, and CvS is the concentration of phenols in venous blood draining the skin.

Oral mucosal absorption was based on a pseudo-physiological one compartment description representing oral mucous. Oral mucosa exposure, actually, is not a major route of exposure like ingestion, contact, and inhalation. However, considering the need of oral mucosa exposure assessment of paraben and TCS by oral care products (e.g., toothpaste, mouthwash), the oral mucosa exposure route was reflected in the model. Intra oral administration could avoid first-pass metabolism and other interactions in the GI tract. Moreover, as the oral mucosa is highly vascular region, transmucosal absorption could provide fast access directly to the systemic circulation (Patel et al., 2012; Xia et al., 2015) and it occurs only by passive diffusion (Boroujerdi, 2001). To reflect the physiological characteristic, when the chemical absorbed via oral mucous, the passive diffusion happens into the oral mucous compartment and the first order

absorption occurred in the blood compartment. The equation for the oral mucous compartment is as follows:

$$\frac{dARO}{dt} = (K_{p_o} \times \frac{A_o}{1000}) \times \frac{OMx}{MW} - K_{a\_o} \times ARO$$

where Kp_o is the oral mucous permeability constant for each phenolic compounds (cm/h), Ao is the surface area exposure (cm^2), OMx is the concentration of phenol in vehicle (mg/L), MW is the molecular weight of the phenol (g/mol), Cv is the concentration of the phenol in venous blood (mmol/L), Po_v is the oral mucous:vehicle partition coefficient, Ka_o is the absorption rate constant of phenol to blood compartment, and ARO is amount of phenol in oral mucous (mmol).

Table 1. Physiological parameters of model

Parameters		Values	Source
Tissue volumes			
BW	Body weight (kg)		Subject-specific where provided
VBc	Blood (%BW)	0.0428	Brown et al., 1997
VLc	Liver (%BW)	0.026	Brown et al., 1997
VSc	Skin (%BW)	0.051	Corley et al., 2000
Blood flows			
QCc	Cardiac output (1/hr/kg)	16.5	Brown et al., 1997
QSc	Skin (%QC)	0.058	Brown et al., 1997
QLc	Liver (%QC)	0.226	Brown et al., 1997

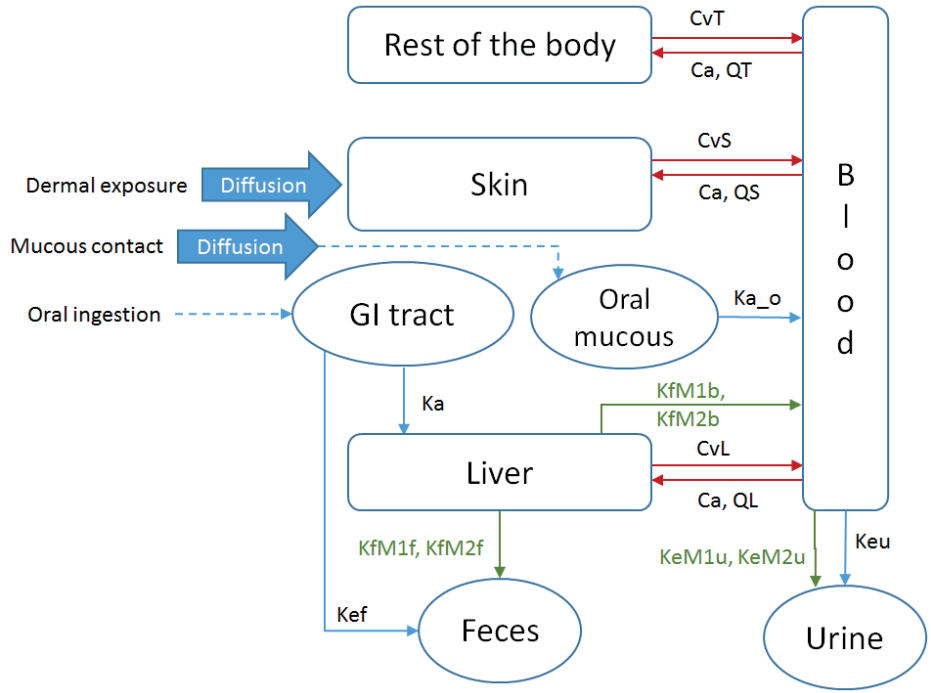

Figure 3. Structure of the human PBPK model for environmental phenols. Orally administered phenols metabolize in the liver, resulting in the formation of two categories of metabolites or excreted into feces. Metabolized phenols are taken up into the blood compartment and excreted into urine or circulate throughout the body.

2.2.5. Urinary and fecal excretion

The absorbed compounds are excreted from the body through urine or feces. Urinary and fecal excretion of phenolic compounds and their metabolites were described using first-order rate equation. Free form of the compound in the feces was excreted directly from the GI tract (Kef) and metabolized forms (KfM1f, KfM2f) were excreted via bile from the liver compartment. In this model, enterohepatic recirculation was not considered because of a high threshold for biliary elimination in humans (Völkel et al., 2002). Both free (Keu) and metabolized form (KeM1u, KeM2u) of the compound in the urine exit through kidney and it described as excreting from the blood compartment. The value of the parameters related to metabolites could consider the metabolic characteristic of each compound. The constants of each compounds were determined by visual fitting to achieve agreement with time-course data of each compound.

2.3. Sensitivity analysis

A local sensitivity analysis was implemented to assess the impact of individual model parameter changes on the model output. The normalized sensitivity coefficient (NSC) was calculated by the following equation (Yang et al., 2015):

$$\mathrm{NSC} = \frac{(O_i - O)/O}{(P_i - P)/P}$$

where O is the model output resulting from the original parameter value, O_i is the model output resulting from the 1% increase in the parameter value, P is the original parameter value, and P_i is the parameter value increased by 1%. Parameters with maximum absolute NSC values exceeding 0.1 is considered sensitive. If absolute NCS values are greater than 1, it indicates that the parameters with the values have a high impact on model output. Positive NCS values mean direct correlation between the model output and each parameter, while negative NCS values suggest that the model output is inversely correlated with each parameter. The sensitivity analysis was performed assuming the adult received a single oral dose of 100 μg/kg target compounds. The model output was the accumulated amount of total compound (parent compound plus conjugated compound) in urine for 72 h. Time course data of target compounds showed that the half-life of the longest half-life was about 10 h, so it was estimated that the chemicals were almost excreted in the body within 72 h.

3. Results

3.1. Model calibration

Most of the kinetic parameters were manually adjusted to arrive at a visually best-fit for the observed data. Terminology and values of chemical specific parameters are shown in Tables 2-8 for MP, EP, PP, BP3, TCS, BPA and BPS. Most of them are fitted and optimized values using the experimental data. Because Ka_o and Kp_o are the parameters related to oral mucosal exposure, the values did not fitted and it did not affect the simulations.

Figures 4-6 show model predictions and observations of serum time courses and accumulated urinary excretion of d_4-MP, d_4-EP, and d_4-PP in adult humans after a single oral dosing of 2.5 mg/kg d_4-MP, d_4-EP, and d_4-PP (MFDS, 2013). The model was generally capable of tracking accumulated excretion profile of parabens into urine, but serum time-concentration profiles of d_4-MP and d_4-EP at later time points were somewhat underestimated. Figure 7 shows model predictions and observations of serum time courses and accumulated urinary excretion of d_5-BP3 in adult humans after a single oral dose of 2 mg d_5-BP3 (MFDS, 2016). The predictions did not fit well with the urine and blood data, but the tendency of the time course seemed to be good. Figures 8 shows model predictions and observations of serum time courses and accumulated urinary excretion of d_3-TCS in one adult human after a single oral dosing of 4 mg d_3-TCS (MFDS, 2016). Simulations of accumulated urinary excretion profiles after oral exposure in general tracked experimental data. Serum d_3-TCS concentration time courses of oral exposure did not fitted well but it provides a good description of the time course for TCS in the serum. Figure 9 shows model

predictions and observations of serum time courses and accumulated urinary excretion of d_6-BPA in adult humans after a single oral dosing of 100 μg/kg d_6-BPA (Thayer et al., 2015). Simulation of both serum concentration and urine excretion profile generally tracked observed data. Figure 10 shows model predictions and observations of serum time courses and accumulated urinary excretion of d_4-BPS in adult humans after a single oral dosing of 0.00875 mg/kg d_4-BPS. Simulation of urinary excretion profile accurately tracked experimental data. In case of the serum concentration profile, simulation showed a tendency to follow the trend of the experimental data.

Table 2. Chemical specific parameters for methyl paraben

Parameters		Values	Source
Partition coefficients (unitless)			
PL	Liver/blood	1.8	Campbell et al., 2015
PS	Slowly perfused tissue/blood	1.8	Campbell et al., 2015
PT	Rest of the body/blood	0.55	Fit[a]
Ps_v	Skin/vehicle	1.94	Roy et al., 1996
Kinetic parameters (/hr)			
Ka	Absorption from GI tract	1.5	Fit[a]
Ka_o	Absorption from oral mucous	-	
Kp	Skin permeability coefficient	9.0e-5	Seo et al., 2017
Kp_o	Oral mucosal permeability coefficient	-	
Keu	Urinary excretion rate (free form)	0.01	Fit[a]
Kef	Fecal excretion rate (free form)	0.03	Fit[a]
KfM1b	Forming of conjugated metabolites (glu./sulf.) into blood	0.5	Fit[a]
KfM2b	Forming of other metabolites into blood	1.0	Fit[a]
KeM1u	Excretion of conjugated metabolites (glu./sulf.) into urine	6.0	Fit[a]
KeM2u	Excretion of other metabolites into urine	10.0	Fit[a]
KfM1f	Forming of conjugated metabolites (glu./sulf.) into feces	0.8	Fit[a]
KfM2f	Forming of other metabolites into feces	1.6	Fit[a]

[a] Visual fit were obtained by optimizing the value for each parameter in question against available data with all other parameters held constant.

Table 3. Chemical specific parameters for ethyl paraben

Parameters		Values	Source
Partition coefficients (unitless)			
PL	Liver/blood	1.85	Campbell et al., 2015 *(Estimated)*[a]
PS	Slowly perfused tissue/blood	1.85	Campbell et al., 2015 *(Estimated)*[a]
PT	Rest of the body/blood	0.5	Fit[b]
Ps_v	Skin/vehicle	1.94	Roy et al., 1996
Kinetic parameters (/hr)			
Ka	Absorption from GI tract	1.8	Fit[b]
Ka_o	Absorption from oral mucous	-	
Kp	Skin permeability coefficient	9.0e-5	Seo et al., 2017[c]
Kp_o	Oral mucosal permeability coefficient	-	
Keu	Urinary excretion rate (free form)	0.2	Fit[b]
Kef	Fecal excretion rate (free form)	0.01	Fit[b]
KfM1b	Forming of conjugated metabolites (glu./sulf.) into blood	0.3	Fit[b]
KfM2b	Forming of other metabolites into blood	0.5	Fit[b]
KeM1u	Excretion of conjugated metabolites (glu./sulf.) into urine	5.0	Fit[b]
KeM2u	Excretion of other metabolites into urine	7.0	Fit[b]
KfM1f	Forming of conjugated metabolites (glu./sulf.) into feces	0.3	Fit[b]
KfM2f	Forming of other metabolites into feces	4.0	Fit[b]

[a] Initial value was based on the value of the MP and PP and then adjusted.
[b] Visual fits were obtained by optimizing the value for each parameter in question against available data with all other parameters held constant.
[c] Values were set to MP.

Table 4. Chemical specific parameters for propyl paraben

Parameters		Values	Source
Partition coefficients (unitless)			
PL	Liver/blood	1.88	Campbell et al., 2015
PS	Slowly perfused tissue/blood	1.88	Campbell et al., 2015
PT	Rest of the body/blood	0.5	Fit[a]
Ps_v	Skin/vehicle	1.94	Roy et al., 1996
Kinetic parameters (/hr)			
Ka	Absorption from GI tract	3.0	Fit[a]
Ka_o	Absorption from oral mucous	-	
Kp	Skin permeability coefficient	9.0e-5	Seo et al., 2017
Kp_o	Oral mucosal permeability coefficient	-	
Keu	Urinary excretion rate (free form)	0.3	Fit[a]
Kef	Fecal excretion rate (free form)	0.01	Fit[a]
KfM1b	Forming of conjugated metabolites (glu./sulf.) into blood	0.5	Fit[a]
KfM2b	Forming of other metabolites into blood	6.0	Fit[a]
KeM1u	Excretion of conjugated metabolites (glu./sulf.) into urine	0.7	Fit[a]
KeM2u	Excretion of other metabolites into urine	5.0	Fit[a]
KfM1f	Forming of conjugated metabolites (glu./sulf.) into feces	2.0	Fit[a]
KfM2f	Forming of other metabolites into feces	7.0	Fit[a]

[a] Visual fit were obtained by optimizing the value for each parameter in question against available data with all other parameters held constant.

Table 5. Chemical specific parameters for benzophenonone-3

Parameters		Values	Source
Partition coefficients (unitless)			
PL	Liver/blood	1.88	Campbell et al., 2015 *(Estimated)*[a]
PS	Slowly perfused tissue/blood	1.83	Campbell et al., 2015 *(Estimated)*[a]
PT	Rest of the body/blood	1.5	Fit[b]
Ps_v	Skin/vehicle	1.94	Roy et al., 1996
Kinetic parameters (/hr)			
Ka	Absorption from GI tract	3.5	Fit[b]
Ka_o	Absorption from oral mucous	-	
Kp	Skin permeability coefficient	1.21e-4	MFDS, 2016
Kp_o	Oral mucosal permeability coefficient	-	
Keu	Urinary excretion rate (free form)	2.5	Fit[b]
Kef	Fecal excretion rate (free form)	1.0	Fit[b]
KfM1b	Forming of conjugated metabolites (glu./sulf.) into blood	3.5	Fit[b]
KfM2b	Forming of other metabolites into blood	6.0	Fit[b]
KeM1u	Excretion of conjugated metabolites (glu./sulf.) into urine	1.0	Fit[b]
KeM2u	Excretion of other metabolites into urine	5.0	Fit[b]
KfM1f	Forming of conjugated metabolites (glu./sulf.) into feces	0.8	Fit[b]
KfM2f	Forming of other metabolites into feces	2.5	Fit[b]

[a] Initial value was based on the value of the PP and then adjusted.
[b] Visual fit were obtained by optimizing the value for each parameter in question against available data with all other parameters held constant.

Table 6. Chemical specific parameters for triclosan

Parameters		Values	Source
Partition coefficients (unitless)			
PL	Liver/blood	0.55	Maharjan et al., 2015
PS	Slowly perfused tissue/blood	0.77	Maharjan et al., 2015
PT	Rest of the body/blood	5.3	Fit[a]
Ps_v	Skin/vehicle	1.94	Roy et al., 1996
Kinetic parameters (/hr)			
Ka	Absorption from GI tract	1.2	Fit[a]
Ka_o	Absorption from oral mucous	-	
Kp	Skin permeability coefficient	1.37e-3	MFDS, 2016
Kp_o	Oral mucosal permeability coefficient	-	
Keu	Urinary excretion rate (free form)	0.01	Fit[a]
Kef	Fecal excretion rate (free form)	0.01	Fit[a]
KfM1b	Forming of conjugated metabolites (glu./sulf.) into blood	5.0	Fit[a]
KfM2b	Forming of other metabolites into blood	1.2	Fit[a]
KeM1u	Excretion of conjugated metabolites (glu./sulf.) into urine	0.4	Fit[a]
KeM2u	Excretion of other metabolites into urine	0.2	Fit[a]
KfM1f	Forming of conjugated metabolites (glu./sulf.) into feces	4.2	Fit[a]
KfM2f	Forming of other metabolites into feces	1.2	Fit[a]

[a] Visual fit were obtained by optimizing the value for each parameter in question against available data with all other parameters held constant.

Table 7. Chemical specific parameters for bisphenol A

Parameters		Values	Source
Partition coefficients (unitless)			
PL	Liver/blood	0.73	Doerge et al., 2011
PS	Slowly perfused tissue/blood	2.7	Doerge et al., 2011
PT	Rest of the body/blood	2.0	Fit[a]
Ps_v	Skin/vehicle	1.94	Roy et al., 1996
Kinetic parameters (/hr)			
Ka	Absorption from GI tract	3.0	Fit[b]
Ka_o	Absorption from oral mucous	-	
Kp	Skin permeability coefficient	9.0e-5	Seo et al., 2017 [c] *(Set to MP)*
Kp_o	Oral mucosal permeability coefficient	-	
Keu	Urinary excretion rate (free form)	1.5	Fit[b]
Kef	Fecal excretion rate (free form)	0.01	Fit[b]
KfM1b	Forming of conjugated metabolites (glu./sulf.) into blood	8.5	Fit[b]
KfM2b	Forming of other metabolites into blood	1.0	Fit[b]
KeM1u	Excretion of conjugated metabolites (glu./sulf.) into urine	3.0	Fit[b]
KeM2u	Excretion of other metabolites into urine	1.0	Fit[b]
KfM1f	Forming of conjugated metabolites (glu./sulf.) into feces	1.0	Fit[b]
KfM2f	Forming of other metabolites into feces	0.1	Fit[b]

[a] The initial value was set as brain value (2.8 ± 0.8) and adjusted within the standard deviation range.
[b] Visual fit were obtained by optimizing the value for each parameter in question against available data with all other parameters held constant.
[c] Value was set to MP (Seo et al., 2017)

Table 8. Chemical specific parameters for bisphenol S

Parameters		Values	Source
Partition coefficients (unitless)			
PL	Liver/blood	0.73	Doerge et al., 2011 *(Set to BPA)*[a]
PS	Slowly perfused tissue/blood	2.7	Doerge et al., 2011 *(Set to BPA)*[a]
PT	Rest of the body/blood	3.2	Fit[b]
Ps_v	Skin/vehicle	1.94	Roy et al., 1996
Kinetic parameters (/hr)			
Ka	Absorption from GI tract	1.3	Fit[b]
Ka_o	Absorption from oral mucous	-	
Kp	Skin permeability coefficient	9.0e-5	Seo et al., 2017[c] *(Set to MP)*
Kp_o	Oral mucosal permeability coefficient	-	
Keu	Urinary excretion rate (free form)	2.2	Fit[b]
Kef	Fecal excretion rate (free form)	0.01	Fit[b]
KfM1b	Forming of conjugated metabolites (glu./sulf.) into blood	5.0	Fit[b]
KfM2b	Forming of other metabolites into blood	0.6	Fit[b]
KeM1u	Excretion of conjugated metabolites (glu./sulf.) into urine	7.0	Fit[b]
KeM2u	Excretion of other metabolites into urine	2.0	Fit[b]
KfM1f	Forming of conjugated metabolites (glu./sulf.) into feces	1.0	Fit[b]
KfM2f	Forming of other metabolites into feces	0.1	Fit[b]

[a] Value was set to BPA (Doerge et al., 2011)
[b] Visual fit were obtained by optimizing the value for each parameter in question against available data with all other parameters held constant.
[c] Value was set to MP (Seo et al., 2017)

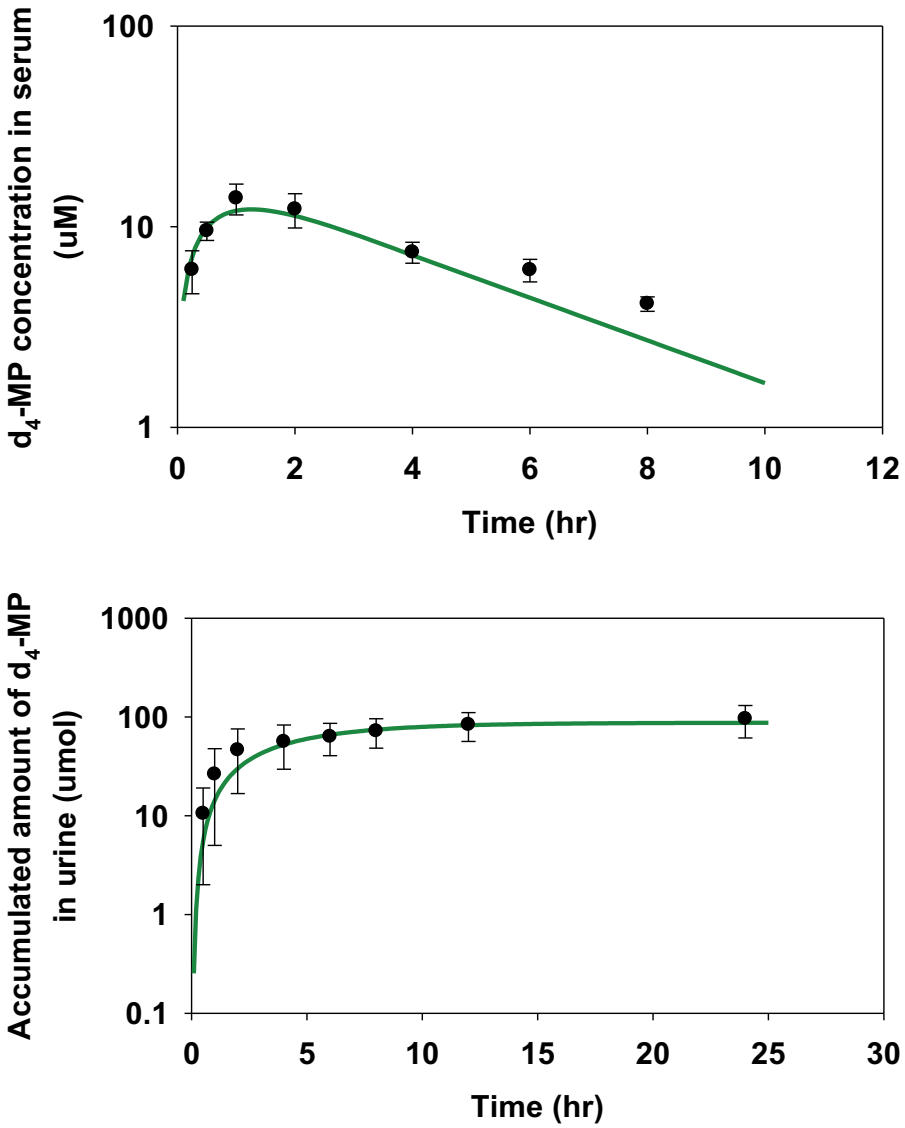

Figure 4. Model calibration of d_4-methyl paraben. Observed (mean ± SD) urinary excretion profiles and serum concentration-time profiles (n=3) and simulated values (solid line) after single oral dosing of 2.5 mg/kg d_4-MP to adult humans.

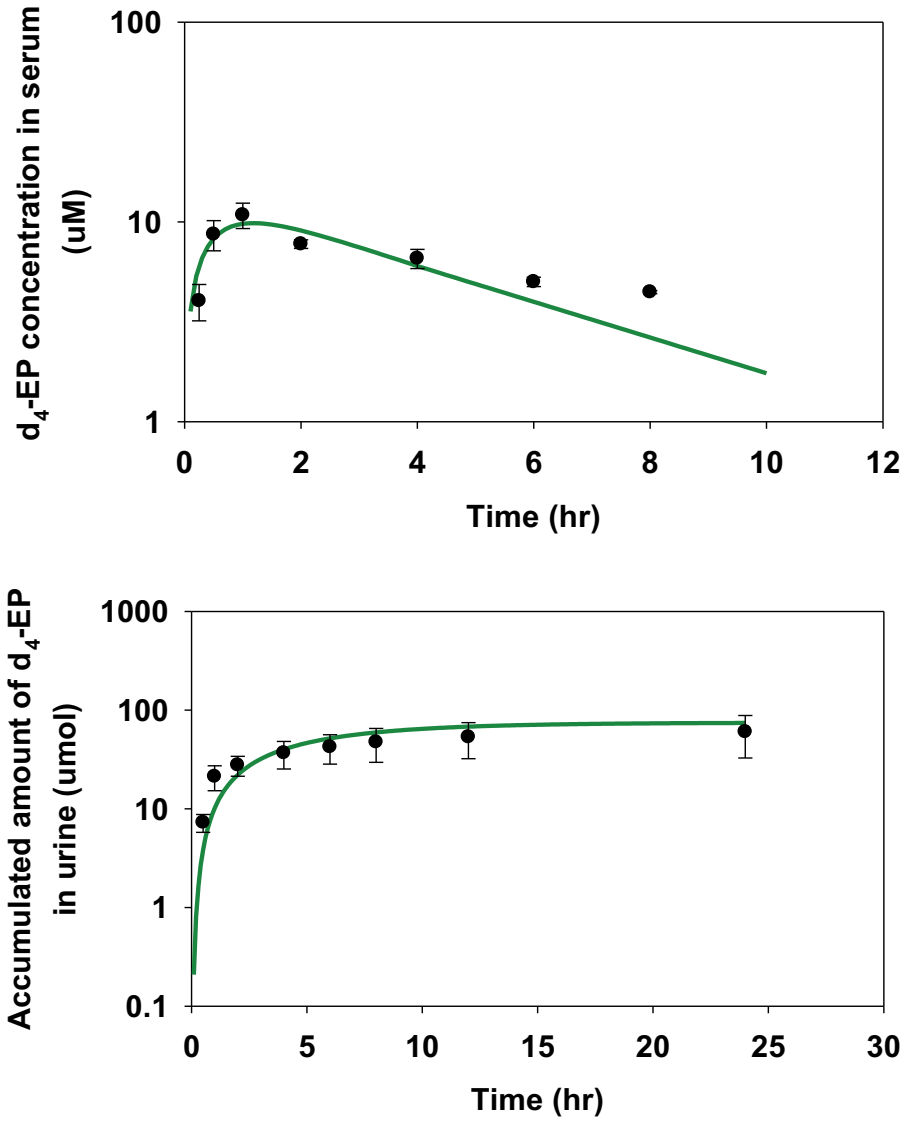

Figure 5. Model calibration of d_4-ethyl paraben. Observed (mean ± SD) urinary excretion profiles and serum concentration-time profiles (n=3) and simulated values (solid line) after single oral dosing of 2.5 mg/kg d_4-EP to adult humans.

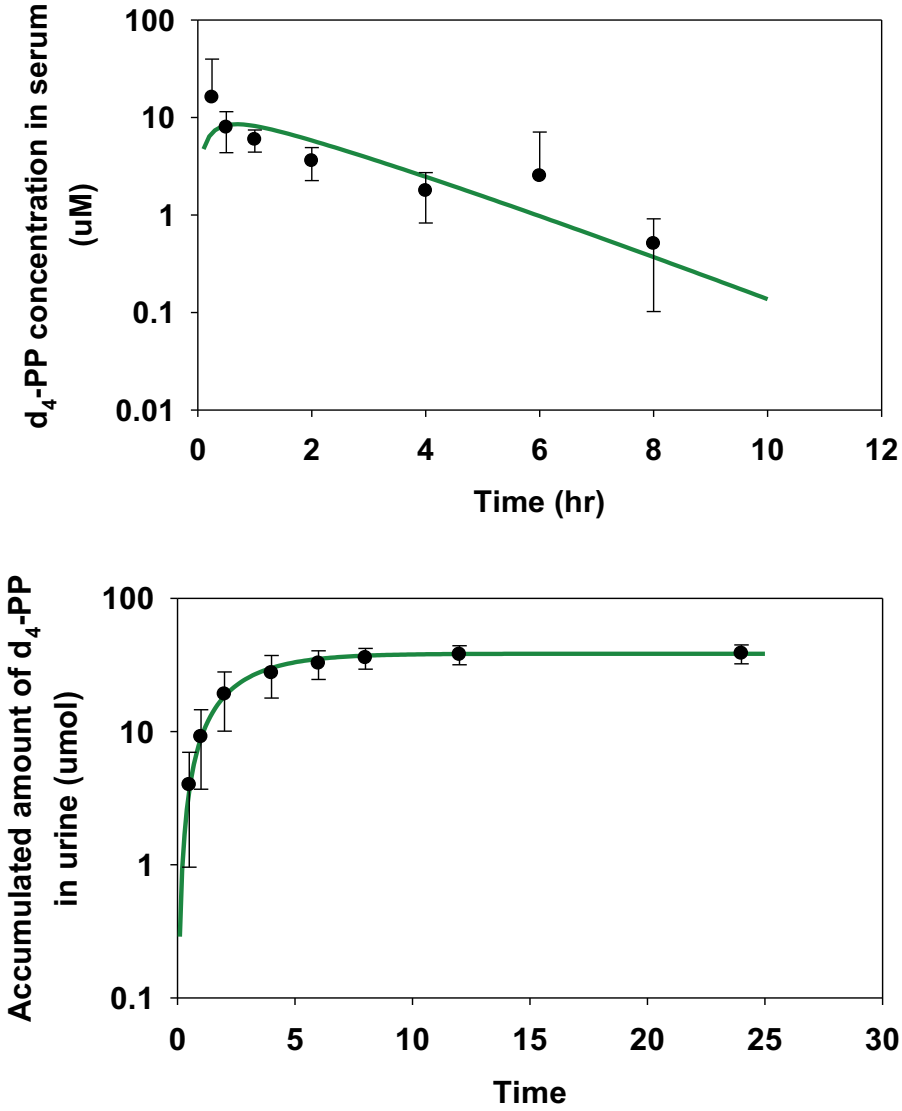

Figure 6. Model calibration of d_4-propyl paraben. Observed (mean ± SD) urinary excretion profiles and serum concentration-time profiles (n=7) and simulated values (solid line) after single oral dosing of 2.5 mg/kg d_4-PP to adult humans.

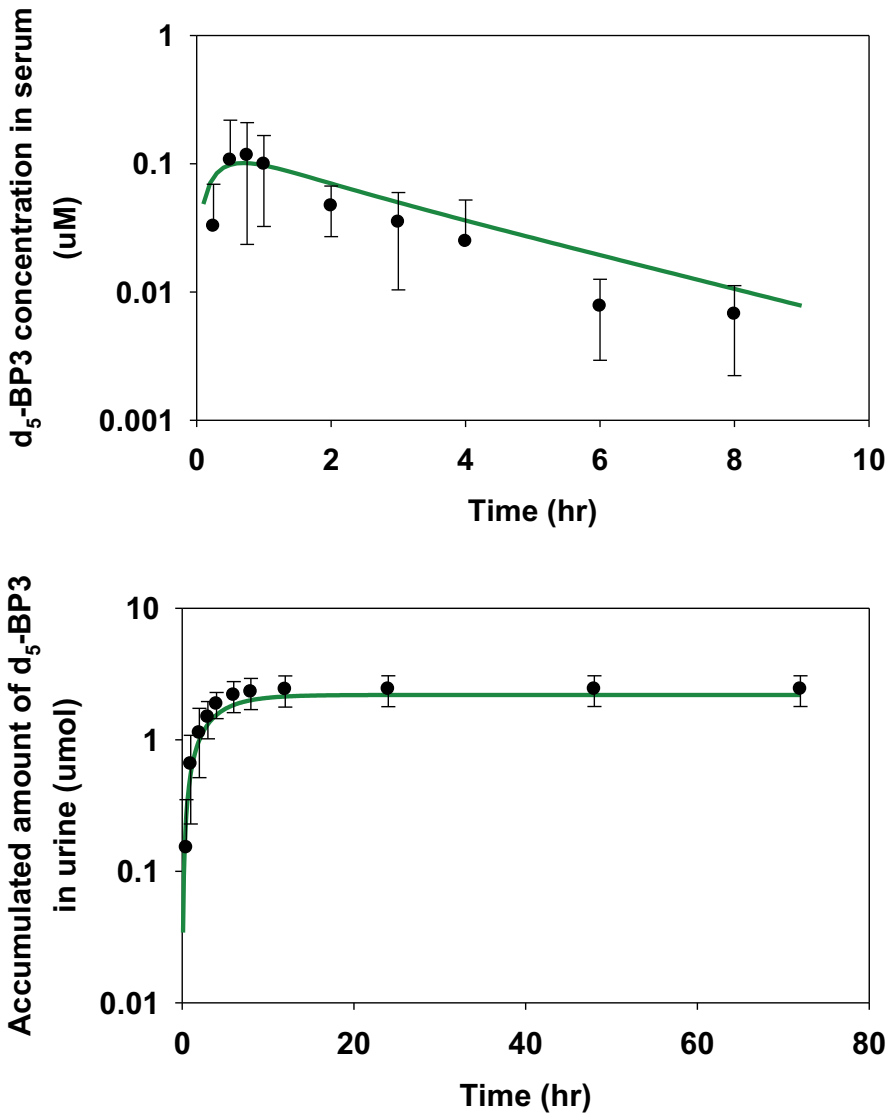

Figure 7. Model calibration of d_5-benzophenone-3. Observed (mean ± SD) urinary excretion profiles and serum concentration-time profiles (n=5) and simulated values (solid line) after single oral dosing of 2 mg d_5-BP3 to adult humans

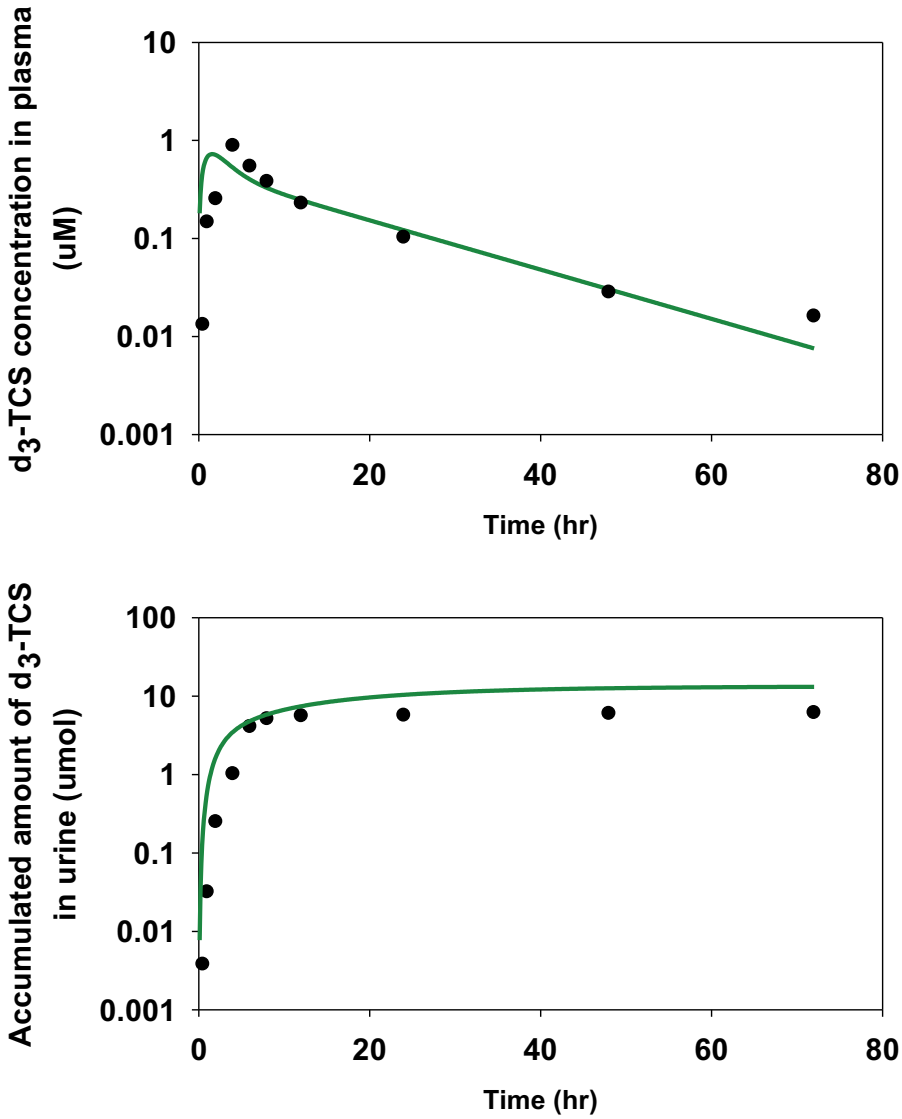

Figure 8. Model calibration of d_3-triclosan. Observed urinary excretion profiles and serum concentration-time profiles (n=1) and simulated values (solid line) after single oral dosing of 4 mg d_3-TCS to adult humans.

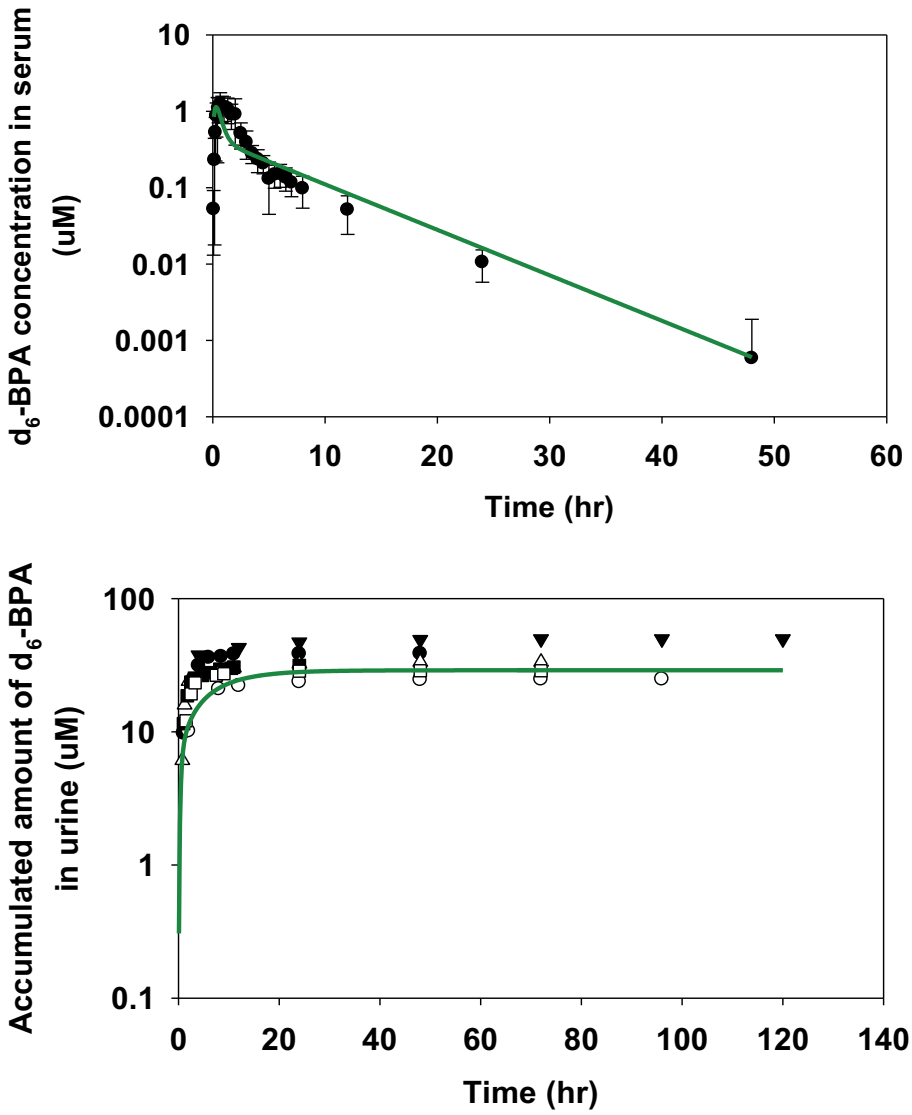

Figure 9. Model calibration of d_6-bisphenol A. Observed (mean ± SD) urinary excretion profiles and serum concentration-time profiles (n=5) and simulated values (solid line) after single oral dose of 100 µg/kg d_6-BPA in mouthwash to adult humans.

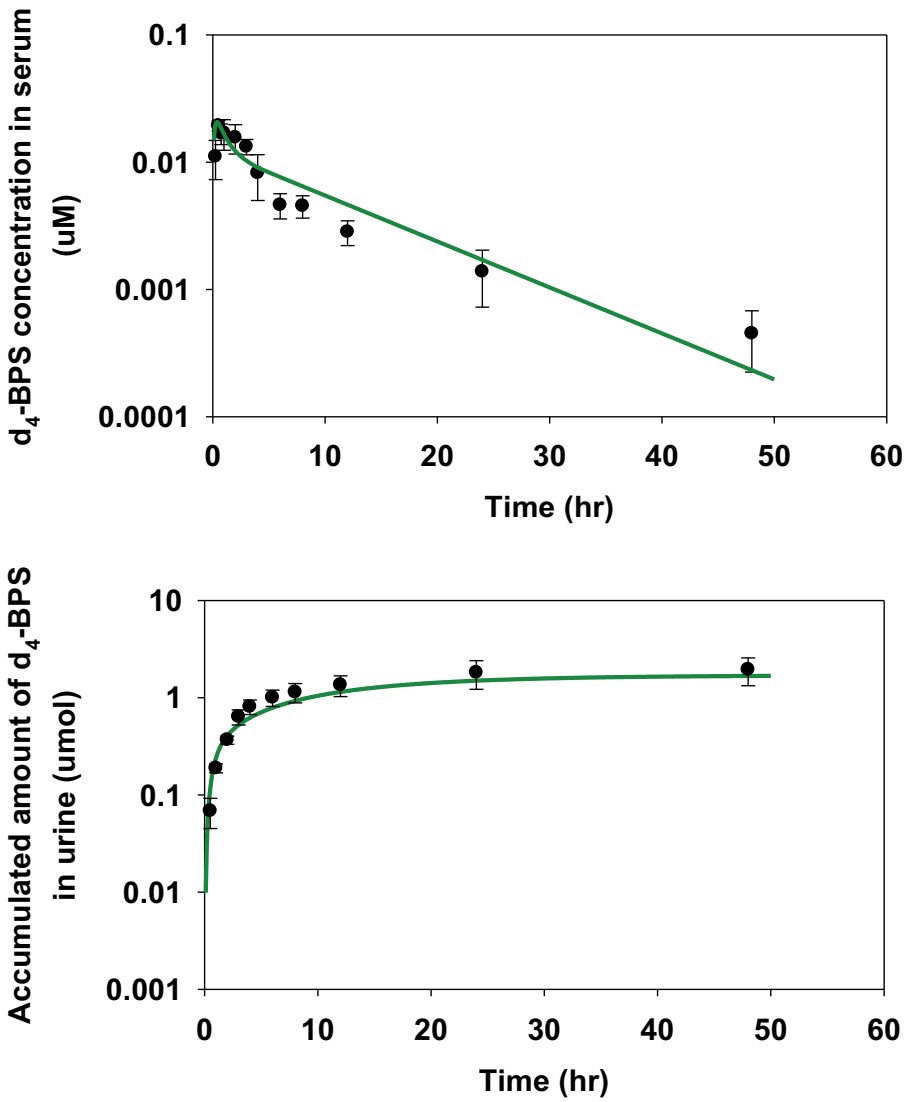

Figure 10. Model calibration of d_4-bisphenol S. Observed (mean ± SD) urinary excretion profiles and serum concentration-time profiles (n=4) and simulated values (solid line) after single oral dose of 0.00875 mg/kg d_4-BPS to adult humans.

3.2. Model validation

After fitting the model, the model was applied to the blood time courses and accumulated excretion profile in urine of other groups of people. If the model predictions and the observed values did not match, the model parameters have been refined.

Figure 11, 12 show model predictions and observations of blood time courses and accumulated urinary excretion of d_4-MP and d_4-EP in adult humans after a single oral dosing of 2.5 mg/kg d_4-MP and d_4-EP. While the model provided good descriptions of accumulated urinary excretion amount of d_4-MP and d_4-EP, observations of serum time courses at later time points were somewhat underestimated. Figure 13 shows model predictions and observations of blood time courses and accumulated urinary excretion of d_4-PP in adult humans after a single oral dosing of 40 mg d_4-PP. Observations of urine data were a bit underestimated and predictions of serum time courses eliminated faster than observations at later time points.

Figure 14 shows model predictions and observations of blood time courses and accumulated urinary excretion of TCS in adult humans after a single oral dosing. Simulations of accumulated excretion of total TCS in urine showed that TCS was eliminated more slowly than the observed value, but within the standard deviation range except one point of 12 hours. On the other hand, predictions of blood time course showed similar trend with observations.

Figure 15 shows model predictions and observations of blood time courses and accumulated urinary excretion of d_6-BPA in adult humans after a single oral dosing of 0.1 mg/kg d_6-BPA. Simulations of urine d_6-BPA excretion profiles in

general tracked experimental data, but serum d_6-BPA concentration profiles were slightly underestimated at the early time points and final time point.

Figure 16 shows model predictions and observations of blood time courses and accumulated urinary excretion of d_4-BPS in adult humans after a single oral dosing of 0.00875 mg/kg d_4-BPS. Model predictions of accumulated urinary excretion and serum concentration profiles were in good agreement with collected data.

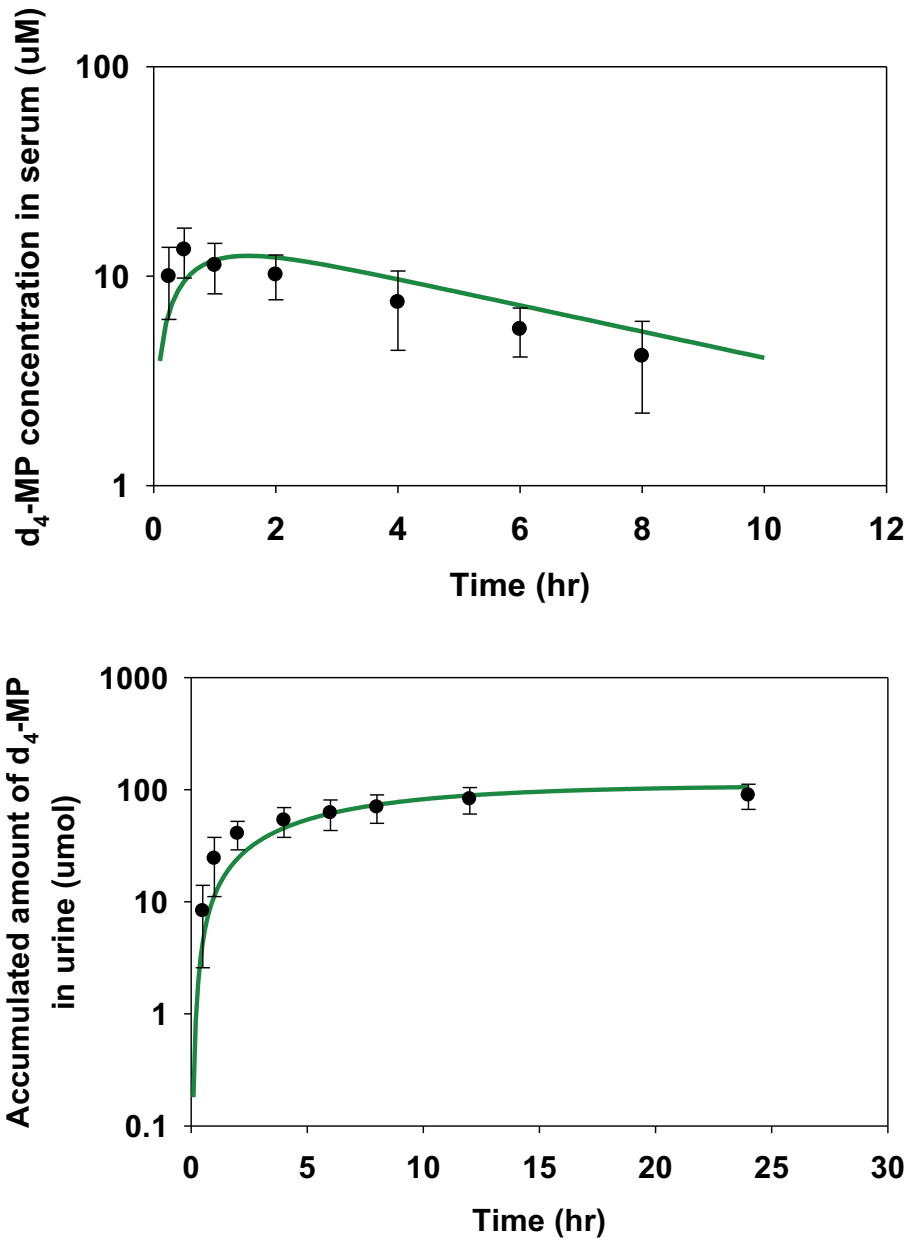

Figure 11. Model validation of d_4-methyl paraben. Observed (mean ± SD) urinary excretion profiles and serum concentration-time profiles (n=4) and simulated values (solid line) after single oral dose of 2.5 mg/kg d_4-MP to adult humans.

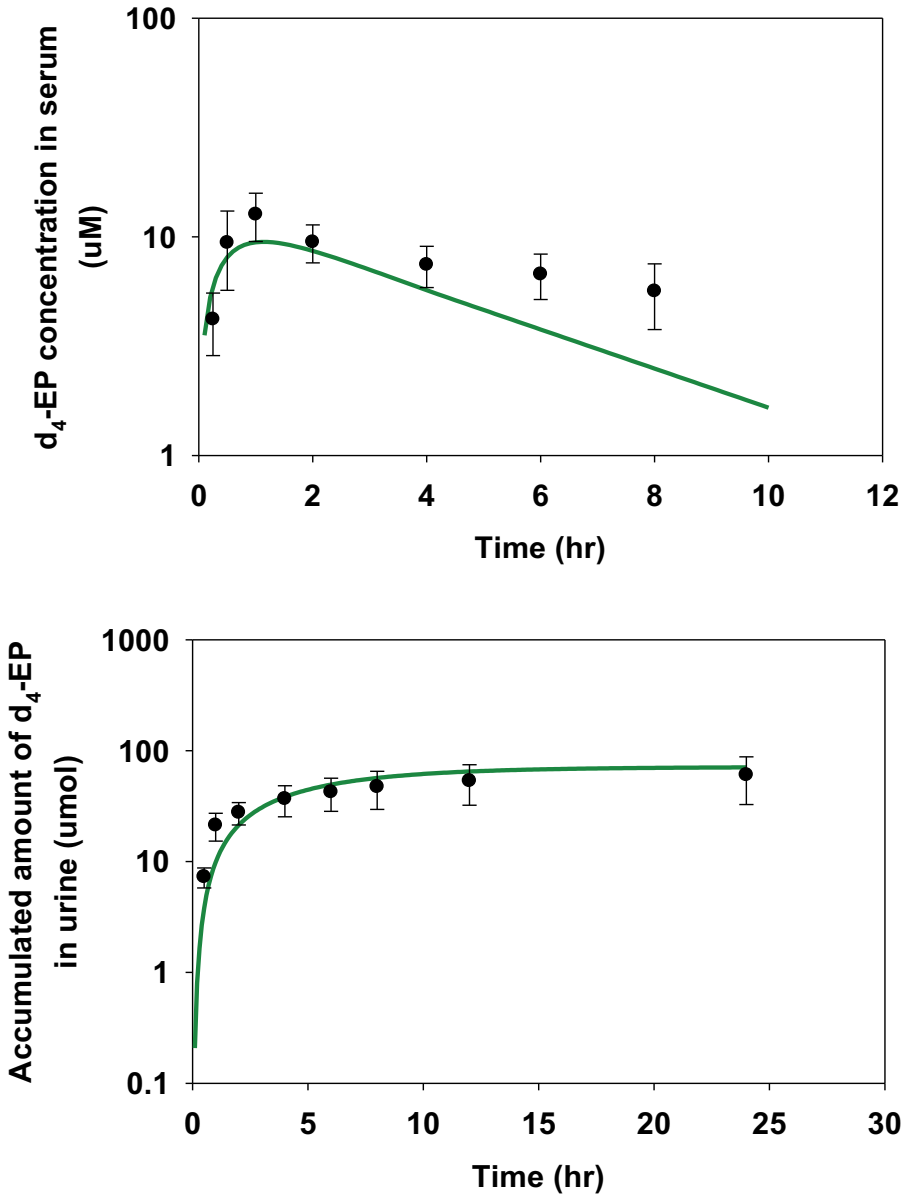

Figure 12. Model validation of d_4-ethyl paraben. Observed (mean ± SD) urinary excretion profiles and serum concentration-time profiles (n=4) and simulated values (solid line) after single oral dose of 2.5 mg/kg d_4-EP to adult humans.

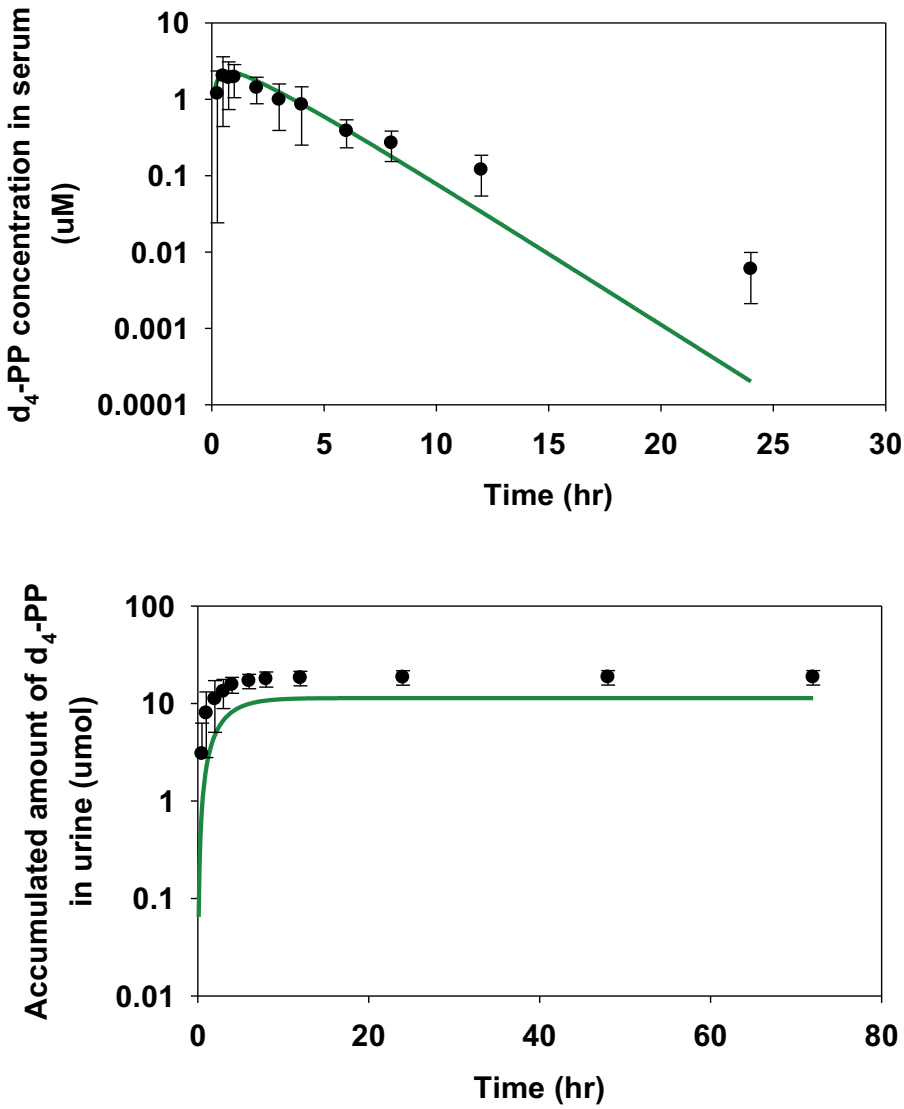

Figure 13. Model validation of d_4-propyl paraben. Observed (mean ± SD) urinary excretion profiles and serum concentration-time profiles (n=5) and simulated values (solid line) after single oral dose of 40 mg d_4-PP to adult humans.

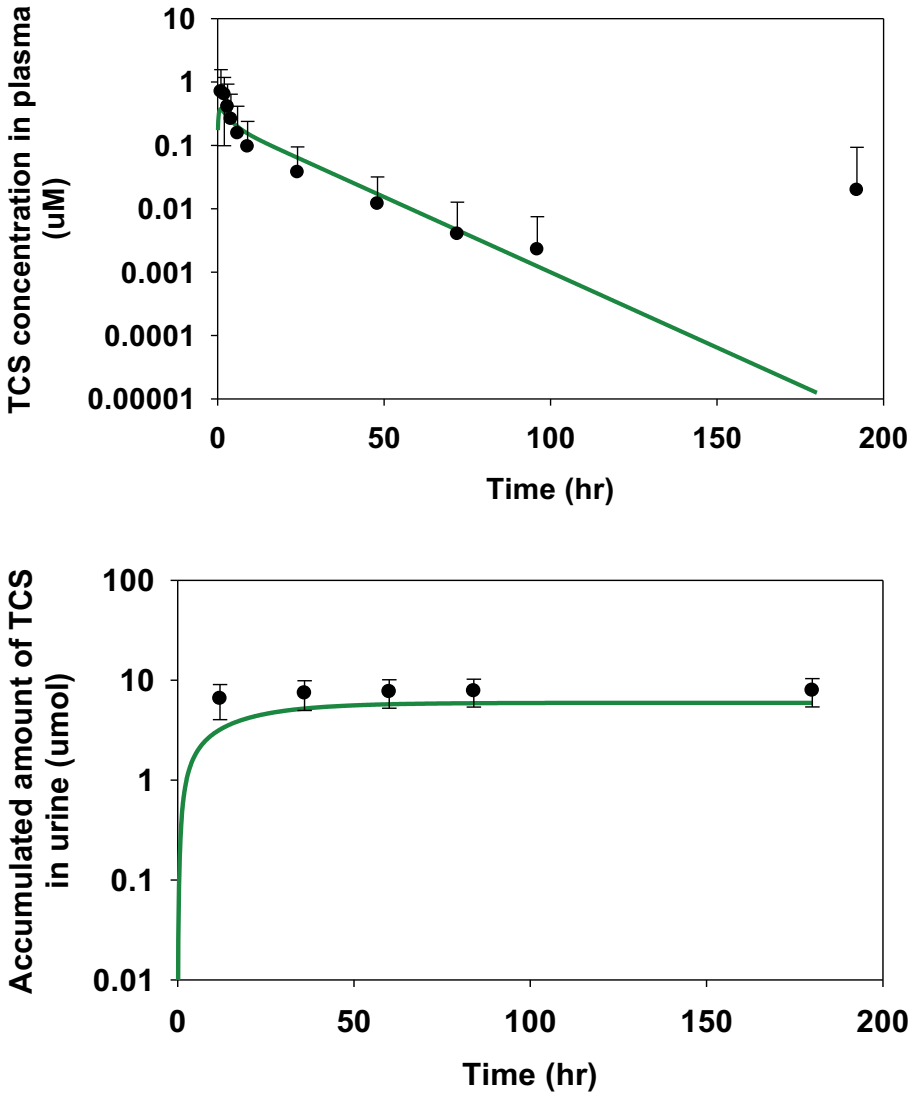

Figure 14. Model validation of triclosan. Observed (mean ± SD) urinary excretion profiles and serum concentration-time profiles (n=10; Sandborgh-Englund et al., 2006) and simulated values (solid line) after single oral dose of 4 mg TCS in mouthwash to adult humans.

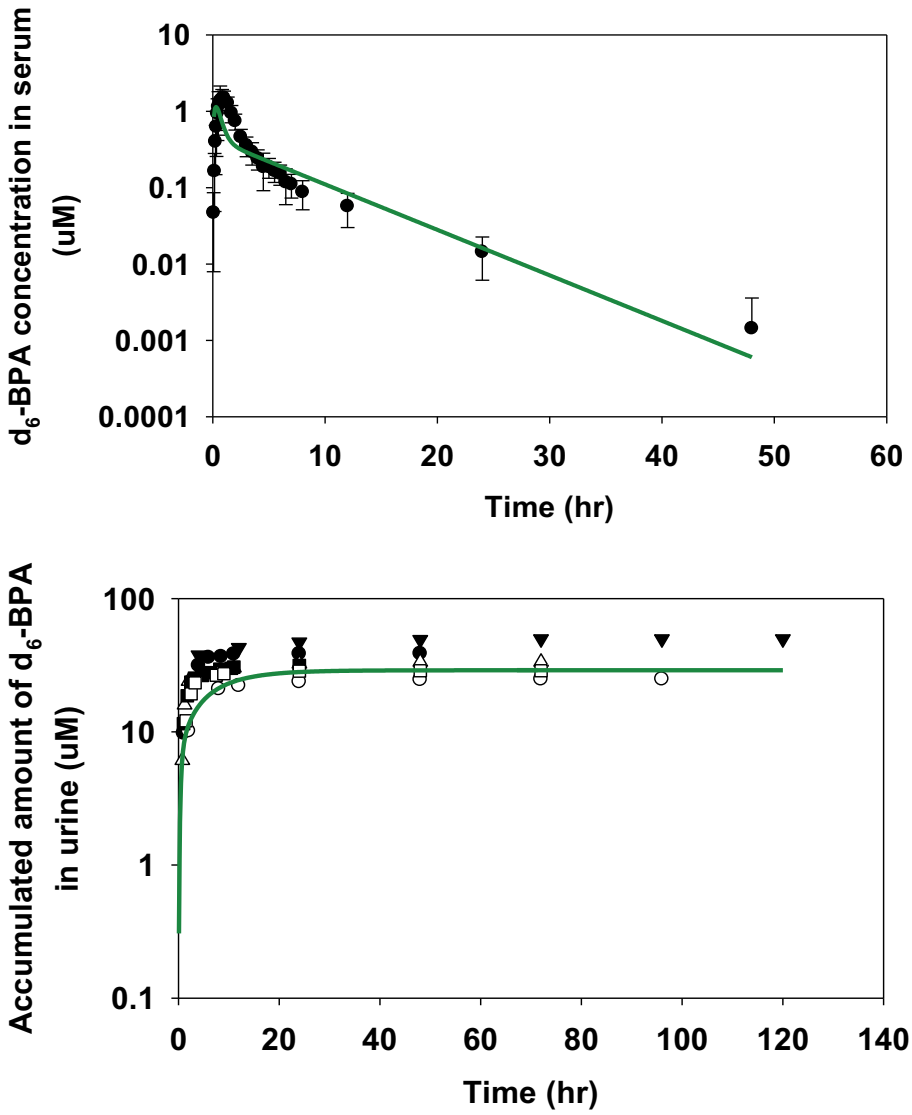

Figure 15. Model validation of d_6-bisphenol A. Observed (mean ± SD) urinary excretion profiles (n=6) and serum concentration-time profiles (n=9) (Thayer et al., 2015) and simulated values (solid line) after single oral dose of 100 µg/kg d_6-BPA to adult humans.

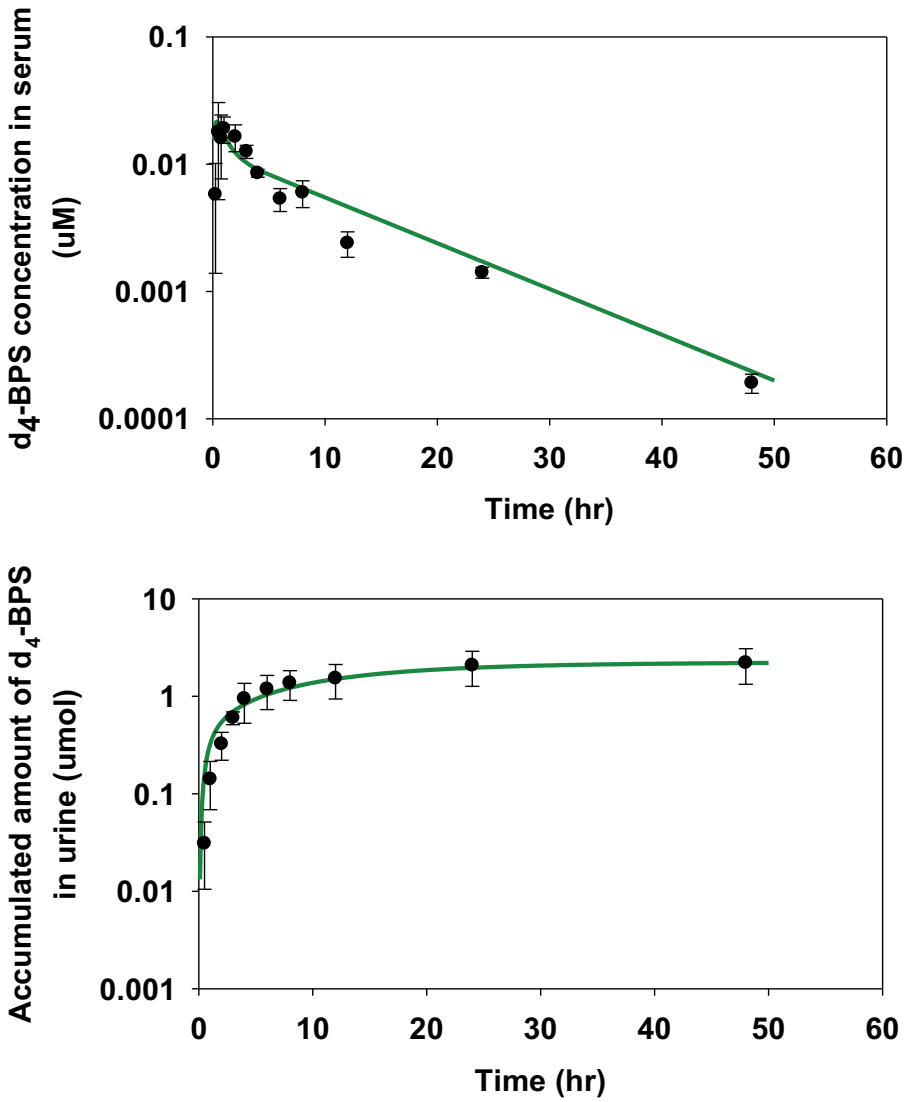

Figure 16. Model validation of d_4-bisphenol S. Observed (mean ± SD) urinary excretion profiles and serum concentration-time profiles (n=3) and simulated values (solid line) after single oral dose of 0.00875 mg/kg d_4-BPS to adult humans.

3.3. Sensitivity analysis

Sensitivity analysis of the PBPK model was performed for all model parameters and parameters for which the calculated absolute values of NSC were greater than 0.1 are shown in Table 9. The output evaluated was accumulated urinary amount of total compound over a period of 72 h in adult humans after single oral dosing of 100 μg/kg. Sensitivity coefficients of less than 0.1 in absolute value were omitted from the table. It can be seen that of the 21 parameters in the model, 8 have less impact on risk predictions based on the dose metric. The parameters related to the metabolism in the liver (KfM1b, KfM2b, KfM1f, KfM2f) were sensitive, and only body weight (BW) was identified to have the most apparent impact on model. However, it needs to be considered that the sensitive analysis performed in this study did not take into account the potential interactions between parameters because the parameters were tested individually.

Table 9. Normalized sensitivity coefficients for PBPK model predictions of accumulated amount total compound in urine

Parameter	MP	EP	PP	BP3	TCS	BPA	BPS
BW	1.0	1.0	1.0	1.0	1.0	1.0	1.0
VBc	–	0.5	0.4	0.3	–	–	0.1
VLc	–	-0.5	-0.5	-0.3	0.1	–	-0.1
VSc	–	–	–	–	–	–	–
QCc	–	–	0.1	0.1	–	–	–
QSc	–	–	–	–	–	–	–
QLc	–	–	0.1	0.1	–	–	–
PL	–	–	–	–	–	–	–
PS	–	–	–	–	–	–	–
PT	–	–	–	–	-0.1	–	–
Ps_v	–	–	–	–	–	–	–
KfM1f	-0.2	-0.1	-0.1	-0.1	-0.3	-0.1	-0.1
KfM2f	-0.4	-0.7	-0.4	-0.2	-0.1	–	–
KfM1b	0.8	0.4	0.5	0.3	0.6	0.1	0.1
KfM2b	-0.3	-0.1	-0.4	-0.4	-0.1	-0.1	-0.1
KeM1u	–	–	–	–	–	–	–
KeM2u	–	–	–	–	–	–	–
Ka	–	–	–	0.2	–	–	–
Keu	–	0.5	0.4	0.3	–	–	0.1
Kp	–	–	–	–	–	–	–
Kef	–	–	–	-0.2	–	–	–

[a] Parent compound plus conjugated compound

–: Less than 0.1 in absolute value.

4. Discussion

Considering the toxicity, usage and exposure frequency of phenolic compounds, it is important to know how much they are exposed. The PBPK model can be used as a tool to predict exposure. In this study, the human PBPK model for seven environmental phenols (MP, EP, PP, BP3, TCS, BPA, BPS) was constructed. The model structure included oral, dermal, and oral mucosal exposures routes to reflect diversity of exposures in environmental phenols. However, only oral exposure route was validated in the present study due to the lack of data. Several PK datasets used for model calibration and evaluation encompass serum concentration and urinary excretion profiles collected in adult humans following a single dose of chemical (MFDS, 2013, 2016; Sandborgh-Englund et al., 2006; Thayer et al., 2015; Oh et al., 2018). Model parameters of each phenol were optimized using the time course data in humans. Because there is not enough human experiment data, most of the chemicals were subdivided into model optimization and evaluation subjects in one experimental group except PP and BP3. PP had datasets from two different populations so one was used to model calibration and the other was used to model validation. On the other hand, BP3 had only one dataset but all data (n=5) was used to estimate model parameter.

Most of the chemicals (MP, EP, TCS, BPA, BPS) were visually well fitted to the simulated and observed data. It demonstrated that the pharmacokinetics of some environmental phenols could be explained by the developed PBPK model structure. However, the simulation of BP3 and PP with optimized parameters could not track the validation dataset (MFDS, 2013, 2016) well (Figure 12, 13). In case of PP, urine data showed a difference of about two times between the

simulation value and the experimental values. In reality, the average fractional urinary excretion (F_{UE}) of total PP in MFDS (2013) data was 3.8% and in MFDS (2016) data was 8.6%. However, considering the F_{UE} of five individuals, the range was 6.8-10%, so if number of the population was larger, it would be acceptable to show the difference of about 2 times. Time-course data of BP3 were used for model calibration and model validation could not be performed. Because the main exposure route of BP3 is dermal contact, most human exposure studies expose the chemical through the skin contact (Gonzalez et al., 2002; Janjua et al., 2008), not ingestion. In addition, it was hard to perform model fitting and validation with only five persons, since the pattern of serum BP3 time-course data were very different for each person. Not only sunscreen but also dust and food are other sources from which BP3 exposure occurs (Frederiksen et al., 2013; Wang et al., 2013; Kim et al., 2016), and further studies on the pharmacokinetic behavior through oral ingestion are needed.

In a strict manner, the PBPK model should be validated using the data not used in the development and parameterization of the model. Each of the model parameters would have been estimated from separate experiments and the model should then be tested using time-course data (Clewell et al., 2000). However, in practice, there were not enough human pharmacokinetic data to use. For this reason, in many cases, PBPK models are developed using animal experimental data and extrapolated to the human. Nevertheless, there are physiological differences between animals and human and it causes the discrepant pharmacokinetic properties. For example, enterohepatic recirculation of BPA glucuronide results in a slow excretion rate (Völkel et al., 2002) and BPA glucuronide excretes predominantly via the bile into the feces in rats (Tominaga et al., 2006). Therefore, this study is worthwhile in terms of being based on human pharmacokinetic data and estimating the human-

optimized parameters for various exposure routes in the target chemicals. The developed PBPK model could be applied to estimate exposure dose and might be contribute to reducing uncertainty in exposure assessment.

While the general PBPK model can only describe one chemical, the developed model tried to describe several chemicals with similar characteristics as one model structure. Therefore, the model structure has a relatively simple structure, which has fewer compartments than other models and describe common metabolism. For example, Fisher et al. (2011) included gonad and brain compartments to predict the dosimetry in the target organ and used the Michaelis-Menten equation to describe the phase II metabolism of BPA. Campbell et al. (2015) included different hydrolysis rate of each tissue compartments (liver, GI tract, skin) in their model to describe the chemical specific metabolism of paraben by microsomal proteins. In this case, more elaborating description of the chemical behavior would be possible, but it will be difficult to describe a number of chemicals using one model. Despite these limitations, the fitted and simulated value showed generally good agreement with the data considering that the structure of the model was simple compared to the number of applied chemicals and the diversity of exposure routes.

Furthermore, since it has been confirmed that the structure of the developed model could be applied to various phenolic compounds, the applicability of the model to other phenols with similar pharmacokinetic characteristics might be considered.

5. Conclusions

The human PBPK model for seven environmental phenols was developed in this study. Firstly, a simple model structure was constructed to explain the multiple exposure routes and the various chemicals with similar pharmacokinetic properties. Then model parameters for each phenol were optimized and evaluated using urine excretion profile and blood concentration-time data from human. As a result, the model in general tracked the kinetic behavior of target chemicals except PP and BP3. Even though some limitations still exist, the human PBPK model for environmental phenols can be a useful tool for reconstructing exposure dose from human biomonitoring data. Eventually, it can contribute to the more realistic exposure assessment.

6. References

Abbas S, Greige-Gerges H, Karam N, Piet M-H, Netter P, Magdalou J. 2010. Metabolism of parabens (4-hydroxybenzoic acid esters) by hepatic esterases and UDP-glucuronosyltransferases in man. Drug Metabolism and Pharmacokinetics 25:568-577.

Boroujerdi M. 2001. Pharmacokinetics: Principles and Applications:McGraw-Hill.

Brown RP, Delp MD, Lindstedt SL, Rhomberg LR, Beliles RP. 1997. Physiological parameter values for physiologically based pharmacokinetic models. Toxicology and Industrial Health 13:407-484.

Campbell JL, Yoon M, Clewell HJ. 2015. A case study on quantitative in vitro to in vivo extrapolation for environmental esters: Methyl-, propyl-and butylparaben. Toxicology 332:67-76.

Chen D, Kannan K, Tan H, Zheng Z, Feng Y-L, Wu Y, et al. 2016. Bisphenol analogues other than BPA: Environmental occurrence, human exposure, and toxicity: a review. Environmental Science & Technology 50:5438-5453.

Clewell 3rd H, Gentry PR, Covington TR, Gearhart JM. 2000. Development of a physiologically based pharmacokinetic model of trichloroethylene and its metabolites for use in risk assessment. Environmental Health Perspectives 108:283.

Corley RA, Gordon SM, Wallace LA. 2000. Physiologically based pharmacokinetic modeling of the temperature-dependent dermal absorption of chloroform by humans following bath water exposures. Toxicological Sciences 53:13-23.

Dekant W, Völkel W. 2008. Human exposure to bisphenol A by biomonitoring: Methods, results and assessment of environmental exposures. Toxicology and Applied Pharmacology 228:114-134.

Doerge DR, Twaddle NC, Vanlandingham M, Brown RP, Fisher JW. 2011. Distribution of bisphenol A into tissues of adult, neonatal, and fetal Sprague–Dawley rats. Toxicology and applied pharmacology 255:261-270.

EPA. 2006. Approaches for the application of physiologically based pharmacokinetic (PBPK) models and supporting data in risk assessment. EPA/600/R-05/043F. Washington, DC.

Fang J-L, Stingley RL, Beland FA, Harrouk W, Lumpkins DL, Howard P. 2010. Occurrence, efficacy, metabolism, and toxicity of triclosan. Journal of Environmental Science and Health, Part C 28:147-171.

Fang JL, Vanlandingham M, Costa GG, Beland FA. 2016. Absorption and metabolism of triclosan after application to the skin of b6c3f1 mice. Environmental Toxicology 31:609-623.

Frederiksen H, Nielsen JKS, Mørck TA, Hansen PW, Jensen JF, Nielsen O, et al. 2013. Urinary excretion of phthalate metabolites, phenols and parabens in rural and urban Danish mother–child pairs. International Journal of Hygiene and Environmental Health 216:772-783.

Geens T, Roosens L, Neels H, Covaci A. 2009. Assessment of human exposure to bisphenol-A, triclosan and tetrabromobisphenol-A through indoor dust intake in Belgium. Chemosphere 76:755-760.

Guo Y, Kannan K. 2013. A survey of phthalates and parabens in personal care products from the united states and its implications for human exposure. Environmental Science & Technology 47:14442-14449.

Gustavsson Gonzalez H, Farbrot A, Larkö O. 2002. Percutaneous absorption of benzophenone-3, a common component of topical sunscreens. Clinical and Experimental Dermatology 27:691-694.

Harris D, Robinson JR. 1992. Drug delivery via the mucous membranes of the oral cavity. Journal of Pharmaceutical Sciences 81:1-10.

Janjua N, Kongshoj B, Andersson AM, Wulf HC. 2008. Sunscreens in human plasma and urine after repeated whole-body topical application. Journal of the European Academy of Dermatology and Venereology 22:456-461.

Kadry AM, Okereke CS, Abdel-Rahman MS, Friedman MA, Davis RA. 1995. Pharmacokinetics of benzophenone-3 after oral exposure in male rats. Journal of Applied Toxicology 15:97-102.

Kim S, Choi K. 2014. Occurrences, toxicities, and ecological risks of benzophenone-

3, a common component of organic sunscreen products: A mini-review. Environment International 70:143-157.

Kim B, Kwon B, Jang S, Kim P-G, Ji K. 2016. Major benzophenone concentrations and influence of food consumption among the general population in Korea, and the association with oxidative stress biomarker. Science of The Total Environment 565:649-655.

Liu J, Martin JW. 2017. Prolonged exposure to bisphenol A from single dermal contact events. Environmental Science & Technology 51:9940-9949.

Maharjan S, Sharma R, Husøy T, Dirven H, Andreassen M, Lie B. 2015. Modeling and simulation of triclosan kinetics and distribution in humans using a PBPK model.

Marzulli FN, Brown DW, Maibach HI. 1969. Techniques for studying skin penetration. Toxicology and Applied Pharmacology 14:76-83.

MFDS. 2011. 바이오모니터링 자료를 이용한 외적노출량 평가 연구.

MFDS. 2013. Estimation of external and internal dose for paraben risk assessment.

MFDS. 2016. Exposure assessment study of toxic substance using PBPK core model.

Mortensen ME, Calafat AM, Ye X, Wong L-Y, Wright DJ, Pirkle JL, et al. 2014. Urinary concentrations of environmental phenols in pregnant women in a pilot study of the national children's study. Environmental Research 129:32-38.

Moos RK, Angerer J, Dierkes G, Brüning T, Koch HM. 2016. Metabolism and elimination of methyl, iso-and n-butyl paraben in human urine after single oral dosage. Archives of Toxicology 90:2699-2709.

Oh J, Choi JW, Ahn Y-A, Kim S. 2018. Pharmacokinetics of bisphenol S in humans after single oral administration. Environment International 112:127-133.

Patel VF, Liu F, Brown MB. 2012. Modeling the oral cavity: In vitro and in vivo evaluations of buccal drug delivery systems. Journal of Controlled Release 161:746-756.

Roy A, Weisel C, Lioy P, Georgopoulos P. 1996. A distributed parameter physiologically- based pharmacokinetic model for dermal and inhalation exposure to volatile organic compounds. Risk Analysis 16:147-160.

Roy A, Pans G. 1998. Mechanistic modeling of transport and metabolism in physiological systems.

Sandborgh-Englund G, Adolfsson-Erici M, Odham G, Ekstrand J. 2006. Pharmacokinetics of triclosan following oral ingestion in humans. Journal of Toxicology and Environmental Health, Part A 69:1861-1873.

Seo J-E, Kim S, Kim B-H. 2017. In vitro skin absorption tests of three types of parabens using a Franz diffusion cell. Journal of Exposure Science and Environmental Epidemiology 27:320-325.

Shin BS, Hwang SW, Bulitta JB, Lee JB, Yang SD, Park JS, et al. 2010. Assessment of bisphenol A exposure in Korean pregnant women by physiologically based pharmacokinetic modeling. Journal of Toxicology and Environmental Health, Part A 73:1586-1598.

Shin BS, Kim CH, Jun YS, Kim DH, Lee BM, Yoon CH, et al. 2004. Physiologically based pharmacokinetics of bisphenol A. Journal of Toxicology and Environmental Health, Part A 67:1971-1985.

Skledar DG, Mašič LP. 2016. Bisphenol A and its analogs: Do their metabolites have endocrine activity? Environmental Toxicology and Pharmacology 47:182-199.

Thayer KA, Doerge DR, Hunt D, Schurman SH, Twaddle NC, Churchwell MI, et al. 2015. Pharmacokinetics of bisphenol A in humans following a single oral administration. Environment international 83:107-115.

Tominaga T, Negishi T, Hirooka H, Miyachi A, Inoue A, Hayasaka I, et al. 2006. Toxicokinetics of bisphenol A in rats, monkeys and chimpanzees by the LC–MS/MS method. Toxicology 226:208-217.

Völkel W, Colnot T, Csanády GA, Filser JG, Dekant W. 2002. Metabolism and kinetics of bisphenol A in humans at low doses following oral administration. Chemical Research in Toxicology 15:1281-1287.

Wang L, Asimakopoulos AG, Moon H-B, Nakata H, Kannan K. 2013. Benzotriazole, benzothiazole, and benzophenone compounds in indoor dust from the United States and East Asian countries. Environmental Science & Technology 47:4752-4759.

Xia B, Yang Z, Zhou H, Lukacova V, Zhu W, Milewski M, et al. 2015. Development

of a novel oral cavity compartmental absorption and transit model for sublingual administration: Illustration with zolpidem. The AAPS journal 17:631-642.

Yang X, Doerge DR, Teeguarden JG, Fisher JW. 2015. Development of a physiologically based pharmacokinetic model for assessment of human exposure to bisphenol A. Toxicology and Applied Pharmacology 289:442-456.

Ye X, Bishop AM, Reidy JA, Needham LL, Calafat AM. 2007. Temporal stability of the conjugated species of bisphenol A, parabens, and other environmental phenols in human urine. Journal of Exposure Science and Environmental Epidemiology 17:567-572.

국문초록

일부 환경성페놀류의 인체 생리학적 약물속도론 모델 구축

서울대학교 보건대학원
환경보건학과 환경보건전공
최 정 원

파라벤, 벤조페논, 트리클로산, 비스페놀과 같은 환경성페놀류는 그 노출 빈도와 독성을 고려하였을 때 노출 수준이 어느 정도인지 파악하는 것은 중요하다. 이 때 노출량을 예측하기 위한 방법 중 하나로 활용되는 생리학적 약물속도론 (physiologically based pharmacokinetic, PBPK) 모델은 대부분 개별 물질에 대해 구축된 모델로, 다수의 물질에 대해 노출평가를 수행하기 위해서는 각각에 대한 모델이 모두 필요하다. 하지만 환경성페놀 계열 물질들은 화학적 구조와 약동학적 특성이 유사하므로 이를 포괄하는 모델을 확립한다면 모델 개발 및 활용에 드는 비용과 시간을 절감할 수 있을 것이다. 따라서 해당 연구에서는 몇 가지 환경성페놀 계열 물질들 (메틸-, 에틸-, 프로필 파라벤, 벤조페논, 트리클로산, 비스페놀 A, -S)을 포괄할 수 있는 비교적 간단한 구조의 모델을 구축하였다.

모델 구조는 liver, skin, rest of the body, blood 컴파트먼트로 이루어져 있으며, 물질이 liver 컴파트먼트로 유입되면 대사가 일어나 분변으로 배출되거나 blood로 이동한 뒤 전신을 순환하다 소변으로 배출된다. 모델에서는 우선 페놀류의 경구 노출을 반영할 수 있도록 파라미터 최적화와 모델 검증을 수행하였으며, 이때 기존에 발표된 PK time profile data를 이용하였다. 그 결과 프로필 파라벤과 벤조페논-3를 제외한 나머지 모든 물질들에서 모델 시뮬레이션 값과 검증 자료가 비교적 잘 일치하는 것으로 나타났으며, 물질별로 단일 또는 다수의 노출을 반영할 수 있는 최적화된 파라미터를 얻을 수 있었다. 해당 연구 결과는 여러 환경성페놀 계열 물질들에 대해 적용 가능한 통합 모델을 구축하였으며, 이를 이용하여 물질과 인체의 생리 화학적 특성을 반영할 수 있는 보다 정교한 노출 추정치를 산출할 수 있도록 하였다는 점에 의의가 있다. 또한 해당 모델 구조를 다양한 페놀류에 적용 가능하다는 것을 확인하였으므로, 추후 약동학적 성질이 유사한 다른 페놀류에 대한 모델의 확대 적용 가능성도 고려할 수 있다.

주요어: 생리학적 약물속도론(PBPK) 모델, 환경성페놀, 인체 모델, 경구 투여

학번: 2016-24060