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Uncertainty on conventional methods for reverse dosimetry from urinary biomarkers of environmental chemicals

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권 진 현

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지도 교수 김 성 균

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위 원 장 최 경 호 (인)

부위원장 이 승 호 (인)

위 원 김 성 균 (인)

Abstract

Uncertainty on conventional methods for reverse dosimetry from urinary biomarkers of environmental chemicals

Jin Hyun Kwon

Dept. of Environmental Health

The Graduate School of Public Health

Seoul National University

Biomonitoring data is an indicator of internal exposure used in chemical risk assessment. As exposure to environmental chemicals is managed by deriving daily intake, several methods to back calculate biomarker concentration into external dose have been developed. The reverse dosimetry approaches conventionally use urinary excretion fraction (F_{ue}) or a toxicokinetic (TK) model. These methods assume that the concentrations of the biomarker in the biological samples reflect the average exposure when external exposure continuously occurs. However, it is important to consider exposure characteristics of short-lived chemicals, as biomarker levels in the urine samples may vary depending on the half-life of the substance and the interval between actual exposures to the chemical.

In this study, the national biomonitoring data of two representative chemicals, BPS and DEHP were used to estimate oral-equivalent intakes with different reverse

dosimetry methods. After optimizing TK models to fit the urinary excretion profile of controlled human experiments, dose estimates using TK model were compared to those using the F_{ue} values as a golden standard. Also, single, and multi-compartment TK models were compared to show that the distribution of daily intake can vary according to the model structure. As a result, the exposure calculated using the F_{ue} value was likely to overestimate real life exposure, 8-hour interval scenario assumed in each TK model. To further examine the sources of uncertainty, a single compartment model was simulated with varying half-lives and exposure intervals. Overall, simple TK models and simulation data highlighted the importance of identifying exposure characteristics to reduce uncertainty in reverse dosimetry approaches for biomonitoring-based exposure assessment.

Key words: biomonitoring, risk assessment, uncertainty, toxicokinetic model, urinary excretion fraction

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1. Introduction

Biomonitoring is the measurement of environmental chemicals referred to as biomarkers absorbed in the biological system. As biomarker concentration in a biological medium such as blood or urine is assumed to be directly related to chemical exposure, biomonitoring data is widely being used in exposure assessment (DeCaprio, 2006). In risk assessment for chemical exposure, daily intake with the units of mg/kg-bw/day is suggested as various health-based guidance values. Reverse dosimetry approaches have been introduced to estimate daily intake of chemicals corresponding to the measured concentrations from biomonitoring studies. For example, intake dose can be calculated by using urinary excretion fractions (F_{ue}) and human toxicokinetic (TK) models (NRC, 2006).

Urinary excretion fraction (F_{ue}) is the molar ratio between the amount of parent compound ingested and the amount of the parent or measured metabolite excreted in urine. Simply applying this value to an equation, volume or creatinine-based urinary biomarker level can be reconstructed as intake dose of chemical, with an underlying assumption that the concentration in a spot urine sample represents the average 24-hour urinary concentration (Koch et al., 2007). Urinary excretion pattern is also one of the main quantitative explanations of chemicals' toxicokinetic (TK) behavior such as absorption, distribution, metabolism, and elimination (ADME) in humans. Toxicokinetic information of environmental chemicals is collected from controlled in vivo exposure experiments to elucidate the time course of biomarker concentration. TK models are mathematical descriptions for ADME and can be

grouped into two types: classical toxicokinetic and physiologically based toxicokinetic (PBTK) models. Through model simulation, a linear relationship between the concentration of a substance in the body and the amount of exposure can be obtained. Based on this relationship, the oral-equivalent external dose of chemical can be estimated with internal concentration data of exposure biomarkers (Andersen, 2003; Yoon et al., 2022). In this study, the correlation between urinary levels of the biomarkers and estimated daily intake was defined as exposure-concentration relationship (ECR).

To examine whether this correlation is suitable for short half-life chemicals, temporal variation should be considered. For example, biomarker concentration in matrix varies greatly when the elimination half-life is short, and exposures are not frequent (Aylward et al., 2014). The elimination half-lives explain the terminal exponential decay of a chemical in biological samples. These inter- and intra-individual variability of concentrations in urine samples for short term chemicals have been discussed in relevant studies (Aylward et al., 2017; Aylward et al., 2012). However, few studies have reported the uncertainty of reverse dosimetry methods using biological concentrations (Brown et al., 2015; Pleil et al., 2007; Ring et al., 2017; Spaan et al., 2010; Tan et al., 2012).

While the variability of biological samples can only be characterized and is not reducible by further experiment, characterization of uncertainty regarding default assumptions can help reduce uncertainty in risk assessment (Asante-Duah, 2002; NRC, 2009). Therefore, TK model was regarded as a golden standard to evaluate conventional reverse dosimetry using F_{ue} in this study. Then, additional sources of

uncertainty related to model itself, and model parameters based on exposure interval and elimination half-life were reviewed.

Firstly, the differences between dose reconstruction results estimated by the ECR based method and the F_{ue} based method were discussed using the representative biomonitoring data of specific environmental chemicals with short term half-life. Then, the intake doses from TK simulation were examined to characterize the degree of variation due to different combinations of exposure intervals and elimination half-lives. Here, model simulations were performed with deterministic values for variables such as volume of distribution and daily urine excretion volume based on representative characteristics of the population (Jang et al., 2014; Valentin, 2002; Yoon et al., 2020).

This study aimed to identify the sources of uncertainty in risk assessment for chemicals with short half-lives by comparing two conventional approaches and showing the impact of exposure characteristics. These results will enable better interpretation of biomonitoring data and related exposure assessment of environmental chemicals.

2. Methods

2.1. Dose reconstruction using TK model

2.1.1. Simple TK model structures and simulation

Simple toxicokinetic (TK) models of the substance were constructed to simulate multiple dosing in oral ingestion route (Figure 2). Based on each model structure, it was assumed that the rate of absorption (k_a) from the gastrointestinal (GI) tract and the rate of elimination (k_e) via the urinary void can be explained as first-order kinetics. Urinary excretion data was resolved into various exponential components by the method of residuals (Boroujerdi, 2001; Gibaldi and Perrier, 1982).

The one-compartment model was employed to illustrate the urinary concentration versus time curve by the biexponential equation, assuming that k_a is greater than k_e (Equation 1). Furthermore, the following equation was used to resolve the toxicokinetic characteristics of a two-compartment model, where α and β are the apparent first-order fast and slow disposition rate constants, respectively. A, B, C are coefficients that correspond to the zero-time intercepts of each phase (Equation 2).

$$\frac{dA_u}{dt} = \frac{Dose \times k_e}{(k_a - k_e)} \times (e^{-k_e \cdot t} - e^{-k_a \cdot t}) \qquad \textbf{Equation 1}$$

$$\frac{dA_u}{dt} = A \times e^{-\alpha \cdot t} + B \times e^{-\beta \cdot t} + C \times e^{-k_a \cdot t} \qquad \textbf{Equation 2}$$

The daily average concentration of chemicals in urine sample was calculated using Equation 3, where t_{start} and t_{stop} are the start and stop time during the exposure period. The physiological variables of age group, body weight, and daily urinary excretion rate (V_{24}), for children (7-12 yrs), adolescents (13-18 yrs) and adults (19-64 yrs) were uniformly set to derive an exposure-concentration relationship (ECR) as shown in Table S1. Model simulations were performed using Berkeley Madonna version 8.3.18 (University of California at Berkeley, USA). Differential equations were used to describe the model and were solved using the fixed step size integration algorithm, and the fourth-order Runge-Kutta (RK4) method available in the program.

$$\boldsymbol{c_{urine} = \frac{\int_{t_{start}}^{t_{stop}} (k_e * A_c) dt}{\frac{(t_{stop} - t_{start})}{24}} \times V_{24}} \qquad \textbf{Equation 3}$$

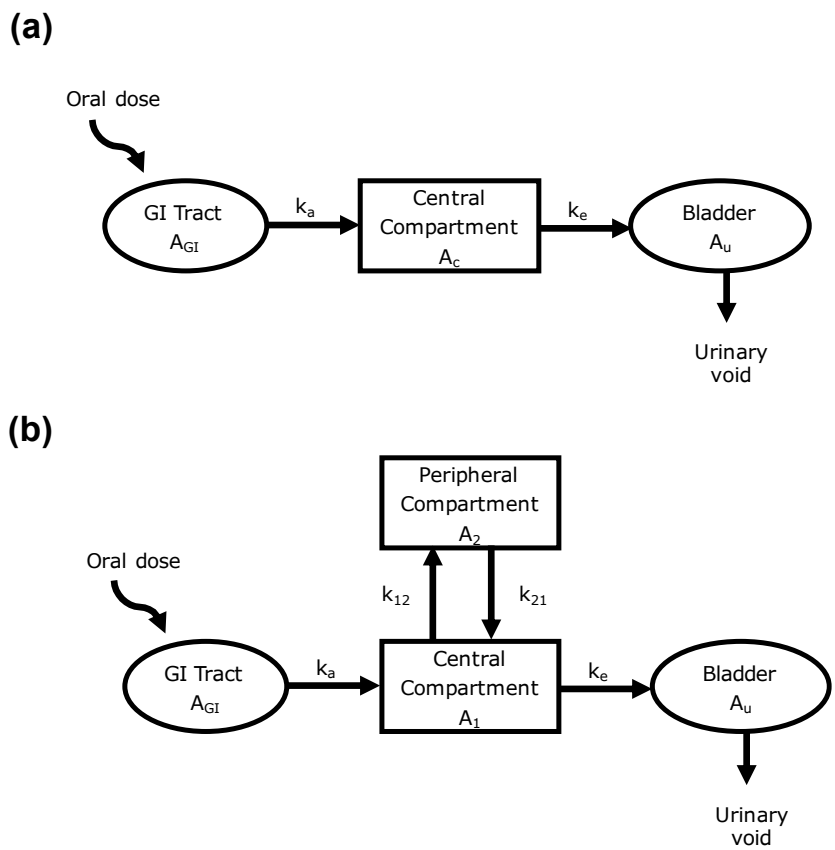

Figure 1. Simple (a) 1-compartment and (b) 2-compartment models for oral ingestion route used in this study (modified from Aylward et al., 2012).

Abbreviations: GI tract – gastrointestinal tract; A_{GI} – amount of substance in GI tract; k_a – absorption rate constant; A_c – amount of substance in central compartment (blood); k_{12} – elimination rate constant from central compartment to peripheral compartment ; k_{21} – elimination rate constant from peripheral compartment to central compartment; k_e – elimination rate constant from central compartment (blood) to bladder (urinary excretion); A_u – amount of substance in bladder.

2.1.2. Model optimization for environmental chemicals

Bisphenol S (BPS) and Bis(2-ethylhexyl phthalate) (DEHP) were selected as model chemicals to compare reverse dosimetry methods of short-lived environmental chemicals, which have human toxicokinetic (TK) profiles (Koch et al., 2004; Koch et al., 2005; Oh et al., 2018), and average urinary excretion fractions (F_{ue}) as shown in Table 1. The simple compartment models from Figure 2 were fitted to the urinary data, where each parameter was optimized using the concentration of the parent compound and its metabolites using Berkeley Madonna program. Oral bioavailability for both BPS and DEHP was set at unity, assuming that 100% of an administered dose reached the systemic circulation. Compartment models for BPS were compared using Akaike's Information Criteria (AIC) from the log-likelihood ratio between models to elucidate a best-fit model (Kim et al., 2009).

Table 1. Toxicokinetic studies in humans for model development

Chemicals	Dose regimen	Matrix	References
Bisphenol S	Singe oral dose at 8.75 μg/kg-bw	Plasma; urine	Oh et al. (2018)
DEHP	Singe oral dose at 48.5 mg	Plasma; urine	Koch et al. (2004); Koch et al. (2005)

2.2. Dose reconstruction using urinary excretion fractions

To calculate the estimated daily intake (EDI) using urinary excretion fraction (F_{ue}), Equation 4 was applied using average values from Table 3 (Koch et al., 2007). Body weight (BW), and daily urinary excretion rate (V_{24}) values used for each population are listed in Table S1. Also, the molar concentration of the analyte (UE) and molecular weight of the parent compound (MW) from Table 2 were used to estimate the chemical intake dose. Biomonitoring data of urinary BPS and metabolites of DEHP was taken from the Korean National Environmental Health Survey (KoNEHS) Cycle 3 (Ministry of Environment, National Institute of Environmental Research).

$$\mathbf{EDI} = \frac{\mathbf{UE}\ (\boldsymbol{\mu mole/day}) \times \mathbf{V_{24}}(\boldsymbol{L/day})}{\mathbf{F_{ue}} \times\ \mathbf{BW}\ (\boldsymbol{kg})} \times \mathbf{MW}(\boldsymbol{g/mole}) \qquad \textbf{Equation 4}$$

Table 2. The fraction of urinary excretion fraction (F_{ue}) of selected analytes

Chemicals	Analytes	Molecular weight [a] (g/mol)	Average F_{ue} (unitless)	References
Bisphenol S	Total BPS	250.28	0.82	Oh et al. (2018)
DEHP	MEHHP	294.34	0.25	Koch et al. (2004); Koch et al. (2005)
	MEOHP	292.33	0.15	
	MECPP	278.09	0.22	

[a] Deuterium labelled chemicals were used in the controlled exposure experiments.

Abbreviations: MEHHP – Mono(2-ethyl-5-hydroxyhexyl) phthalate, MEOHP – Mono(2-ethyl-5-oxohexyl) phthalate, MECPP – Mono(2-ethyl-5-carboxypentyl) phthalate

2.3. TK model simulation with varying exposure related parameters

At the individual level, reverse dosimetry requires interpretation of biomonitoring data, including the elimination half-life (HL) and exposure routes (Clewell et al., 2008). For non-persistent chemicals, terminal plasma half-lives are on the order of hours. Exposure characteristics simulated by the TK model in this study are shown in Table 3. These characteristics depict several chemicals from national biomonitoring surveys, such as propyl paraben with HL of 2.9 hours (Shin et al., 2019), Bisphenol S (BPS) with HL of 6.8 hours (Oh et al., 2018), Bis(2-ethylhexyl phthalate (DEHP) with HL of 2-10 hours (Koch et al., 2004), and triclosan with HL of 21 hours (Sandborgh-Englund et al., 2006).

To investigate the differences in dose estimates due to exposure frequency, the exposure intervals (τ) were set accordingly to the total exposure period of 5 days. The absorption rate constant (k_a) was set to a uniform value of 0.8 based on the distribution observed in drugs and other chemicals (Poulin et al., 2011; Wambaugh et al., 2018). The elimination rate constant (k_e) was estimated by dividing 0.693 by the elimination half-life.

Table 3. Exposure characteristics simulated by TK model in this study

Case	HL (hours)	τ/HL (unitless)
A	2	0.5 - 24
B	5	0.2 – 9.6
C	10	0.1 – 2.4
D	20	0.1 - 2

Abbreviations: HL – elimination half-life; τ – exposure interval

3. Results and discussion

3.1. Comparison of estimated daily intake by reverse dosimetry methods

For BPS, the toxicokinetic profile of the parent compound was fitted to urinary excretion data as shown in Figure S2. The dose estimates from the simple mathematical equation with the urinary excretion fraction (F_{ue}) of BPS were similar to those from TK models with continuous exposure scenarios. The overall daily intake for the 95th percentile population was highest in adolescents followed by children and adults, whereas mean exposure to BPS was highest in adolescents, then adults and children.

Next, the oral equivalent dose calculated with F_{ue} overestimated the amount calculated using the TK model for an 8-hour interval of exposure by approximately 1.5 to 3-fold. The range of daily intake simulated with 8-hour interval exposure in the 1-compartment TK model was as follows: 0.21-4.59 ng/kg-bw/day for male children, 0.11-4.04 ng/kg-bw/day for female children, 3.50-8.79 ng/kg-bw/day for male adolescents, 0.32-12.11 ng/kg-bw/day for female adolescents, 0.23-2.96 ng/kg-bw/day for male adults, and 0.21-2.57 ng/kg-bw/day for female adults. (Table 4).

Although the 1-compartment TK model showed a lower Akaike information criteria (AIC) value due to the smaller number of parameters, the 2-compartment TK model showed a lower log-likelihood function (Table 5).

Table 4. Comparison of estimated BPS exposure calculated by TK model simulation and F_{ue} (Biomonitoring data was taken from KoNEHS III, 2015-2017.)

Population		Urinary concentration of total BPS (ng/mL)		Estimated BPS exposure (ng/kg-bw/day)									
				By F_{ue}		By 1-compartment model				By 2-compartment model			
						Continuous exposure		8-hour interval exposure		Continuous exposure		8-hour interval exposure	
		P50	P95	P50	P95	P50	P95	P50	P95	P50	P95	P50	P95
Children	Male	0.027	0.58	0.57	12.38	0.56	12.14	0.21	4.59	1.16	24.97	0.37	7.92
	Female	0.012	0.45	0.29	10.88	0.29	10.67	0.11	4.04	0.59	21.9	0.19	6.96
Adolescents	Male	0.387	0.97	9.44	23.6	9.26	23.2	3.50	8.78	6.48	16.2	2.06	5.15
	Female	0.032	1.23	0.86	32.62	0.84	31.99	0.32	12.11	0.59	22.4	0.19	7.10
Adults	Male	0.022	0.29	0.61	7.97	0.60	7.82	0.23	2.96	0.23	3.08	0.07	0.98
	Female	0.023	0.28	0.56	6.93	0.55	6.79	0.21	2.57	0.38	4.75	0.12	1.51

Table 5. Model comparison statistics

Chemical	Model structure	AIC	(-)2LL	No. of parameter
BPS	1-compartment	-7.2	-11.16	2
	2-compartment	-1.2	-11.20	5

Abbreviations: AIC – Akaike Information Criteria, (-2)LL – - 2Log-likelihood function

For DEHP, the toxicokinetic profile of each metabolite was fitted to urinary excretion data as shown in Figure S3. The dose estimates from the simple mathematical equation with respective urinary excretion fractions (F_{ue}) of metabolites were similar to those from TK models with continuous exposure scenarios. The daily intake was highest when calculated with the urinary biomarker MECPP, but the overall tendency was the same for all metabolites, where the 95th percentile exposure was highest in children and adults, followed by adolescents.

The oral equivalent dose calculated with F_{ue} overestimated the amount calculated using the TK model for an 8-hour interval exposure by approximately 2 to 7-fold. The oral equivalent exposure based on MEHHP concentration using one compartment TK model for 8-hour interval exposure was in following ranges: 1.30-3.69 ng/kg-bw/day for male children, 1.40-4.09 ng/kg-bw/day for female children, 0.77-2.62 ng/kg-bw/day for male adolescents, 0.68-2.82 ng/kg-bw/day for female adolescents, 0.81-3.64 ng/kg-bw/day for male adults, and 0.21-2.57 ng/kg-bw/day. (Table 6).

Also, the overall daily intake was calculated with the sum of molar concentrations for MEHHP, MEOHP, MECPP, and the sum of F_{ue}. The estimated results were higher than those calculated with MEHHP and MEOHP, but lower than those calculated with MECPP (Table 7).

Table 6. Comparison of estimated DEHP exposure calculated by TK model simulation and respective F_{ue} (Biomonitoring data was taken from KoNEHS III, 2015-2017.)

Analytes	Population		Urinary concentration of DEHP metabolites (ng/mL)		Estimated DEHP exposure (ng/kg-bw/day)									
					By F_{ue}		By 1-compartment model				By 2-compartment model			
							Continuous exposure		8-hour interval exposure		Continuous exposure		8-hour interval exposure	
			P50	P95	P50	P95	P50	P95	P50	P95	P50	P95	P50	P95
MEHHP	Children	Male	30.43	86.02	2.88	8.13	2.85	8.05	1.30	3.69	2.72	7.69	1.18	3.34
		Female	28.58	83.496	3.09	9.02	3.06	8.93	1.40	4.09	2.92	8.53	1.27	3.70
	Adolescents	Male	15.77	53.5	1.70	5.78	1.69	5.72	0.77	2.62	1.61	5.46	0.70	2.37
		Female	13.86	57.58	1.63	6.79	1.48	6.16	0.68	2.82	1.55	6.42	0.67	2.79
	Adults	Male	14.51	65.06	1.79	8.03	1.77	7.95	0.81	3.64	1.70	7.60	0.74	3.30
		Female	12.75	59.82	1.38	6.46	1.36	6.40	0.62	2.93	1.30	6.11	0.57	2.65
MEOHP	Children	Male	19.68	68.49	3.11	10.81	3.11	10.83	1.46	5.09	2.92	10.15	1.40	4.86
		Female	19.09	63.88	3.44	11.52	3.45	11.54	1.62	5.43	3.23	10.81	1.55	5.18
	Adolescents	Male	10.34	35.48	1.86	6.40	1.87	6.41	0.88	3.01	1.75	6.00	0.84	2.88
		Female	9.99	40.78	1.97	8.02	1.81	7.37	0.85	3.46	1.85	7.54	0.88	3.61
	Adults	Male	10.96	50.54	2.26	10.42	2.26	10.44	1.06	4.91	2.12	9.77	1.02	4.68
		Female	10.33	51.72	1.86	9.33	1.87	9.35	0.88	4.39	1.75	8.75	0.84	4.19

(Continued.)

Analytes	Population		Urinary concentration of DEHP metabolites (ng/mL)		Estimated DEHP exposure (ng/kg-bw/day)									
					By F_{ue}		By 1-compartment model				By 2-compartment model			
							Continuous exposure		8-hour interval exposure		Continuous exposure		8-hour interval exposure	
			P50	P95	P50	P95	P50	P95	P50	P95	P50	P95	P50	P95
MECPP	Children	Male	44.09	144.1	5.01	16.69	4.87	16.21	1.99	6.64	3.50	11.45	0.67	2.20
		Female	43.1	143.5	4.49	14.67	4.36	14.25	1.79	5.84	3.91	13.04	0.75	2.51
	Adolescents	Male	31.28	97.24	3.64	11.31	3.53	10.98	1.45	4.50	2.84	8.83	0.55	1.70
		Female	26.57	84.07	3.37	10.67	3.00	9.50	1.23	3.89	2.63	8.33	0.51	1.60
	Adults	Male	22.46	126.8	2.99	16.85	2.90	16.37	1.19	6.70	2.33	13.15	0.45	2.53
		Female	20.84	138.6	2.42	16.12	2.35	15.65	0.96	6.41	1.89	12.59	0.36	2.42

Table 7. Comparison of estimated DEHP exposure calculated by TK model simulation and sum of respective F_{ue} (Biomonitoring data was taken from KoNEHS III, 2015-2017.)

Population		Molar concentration sum of urinary metabolites [a] (nmol/mL)		Estimated DEHP exposure (㎍/kg-bw/day)									
				By F_{ue}		By 1-compartment model				By 2-compartment model			
						Continuous exposure		8-hour interval exposure		Continuous exposure		8-hour interval exposure	
		P50	P95	P50	P95	P50	P95	P50	P95	P50	P95	P50	P95
Children	Male	0.315	0.998	3.51	11.11	3.51	11.12	1.51	4.80	3.32	10.51	1.09	3.44
	Female	0.304	0.972	3.86	12.36	3.86	12.37	1.67	5.35	3.66	11.71	1.21	3.89
Adolescents	Male	0.191	0.621	2.43	7.90	2.43	7.90	1.05	3.41	2.30	7.49	0.76	2.49
	Female	0.168	0.610	2.33	8.47	2.33	8.47	1.01	3.66	2.21	8.03	0.73	2.65
Adults	Male	0.160	0.809	2.33	11.75	2.33	11.75	1.01	5.09	2.20	11.08	0.73	3.68
	Female	0.147	0.833	1.87	10.60	1.87	10.60	0.81	4.58	1.77	10.04	0.59	3.33

[a] Molar concentration sum of MEHHP, MEOHP, and MECPP.

To evaluate the method using F_{ue} values, the results were compared with those from the TK model simulation. Conventional method using F_{ue} has limitation that the values are based on a controlled study where all participants are adults, and there are not many human exposure data. Urinary excretion data of total BPS, which measured the parent compound as a single exposure biomarker, resulted in different F_{ue} between genders (Oh et al., 2018). Also, the estimates of DEHP exposure using F_{ue} varied depending on which urinary metabolite was used, due to the different levels of metabolism and conjugation among substances (EFSA Panel on Food Contact Materials et al., 2019; Koch et al., 2003; Wittassek et al., 2011). Further research on the exposure assessment method using F_{ue} can be investigated to lower the uncertainty level of the result.

F_{ue} values of urinary biomarkers are estimated based on the assumption that the human body consists of a single compartment and that exposure occurs constantly. Therefore, BPS and DEHP intake by continuous oral exposure concurs with the intake using F_{ue}, while the intake by ingestion every 8 hours was estimated to be lower. In this study, TK models were optimized with the TK profiles from controlled studies that reported F_{ue} values. Both methods used same values of bodyweight, and daily urinary excretion rate for each population when back calculating.

However, there are limitations in a single compartment TK model since the time courses of chemical concentration were only explained as a single first-order decay. For many chemicals, elimination can occur through a biphasic or multiphasic process which results in more than one half-life (HL), shorter initial HL followed by

a longer terminal HL (Sayre et al., 2020; Tan et al., 2018). It can be suggested that the difference in dose estimates between TK models is determined by the parameters set in TK models, as they elaborately describe the ADME of each chemical.

3.2. Simple TK model simulation with varying exposure events

To evaluate the impact of exposure events on the dose estimation, a single compartment TK model was simulated for exposure intervals (τ) of 1, 4, 8, 12, 24, 36, and 48 hours. A total exposure period of 120 hours was simulated to reach a pseudo steady state. Multiple dosing was simulated for each case where the elimination half-life (HL) of chemicals is 2, 5, 10, or 20 hours, and the exposure-biomarker concentration relationship (ECR) was derived accordingly. To compare the simulation results of different age groups, physiological variables were fixed: the values for children was 30 kg, 0.7 L/day, 55 kg, 1.2 L/day for adolescents, and 70 kg, 1.6 L/day for adults, respectively.

ECR is the linear equation between intake dose and the biomarker concentration derived from TK model simulation of multiple dosing. Smaller ECR slope indicates a larger intake dose for the same urinary concentration of the biomarker. As ECR slope increases when exposure frequency decreases, the relative changes in ECR slope were calculated to quantify the differences between each exposure event. There were no significant differences in overall results for each age group, and the simulation results for adults were presented in this study (Figure 3).

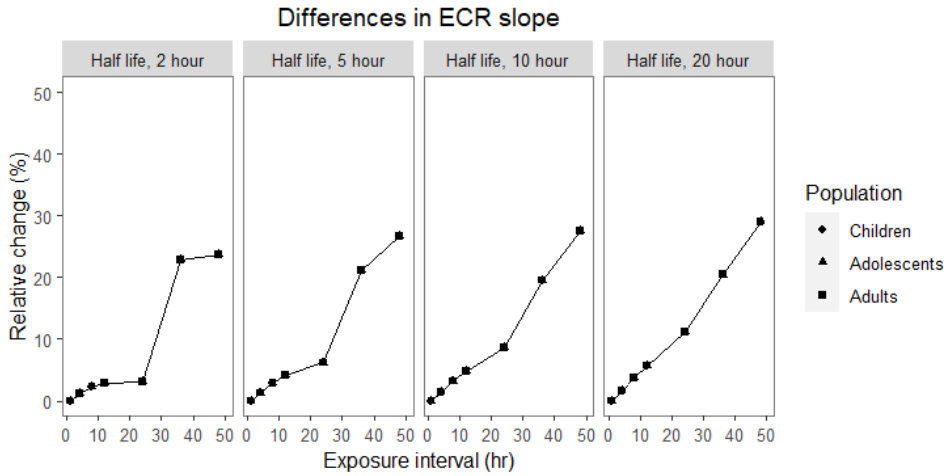

Figure 2. Relative changes in ECR slope of substances according to each exposure event simulated for all population.

The importance of elimination half-life (HL) and exposure interval (τ) to explain the variability of biomarker concentration was first introduced in the study regarding population exposure assessment (Aylward et al., 2017; Aylward et al., 2012). In this study, the tendency of the relationship between exposure and urinary concentration (ECR) was derived from the simulation of four different exposure characteristics. The application of biomonitoring data in exposure assessment requires the assumption that the rate of absorption and excretion from the body reaches equilibrium with repeated exposure. From a pharmacokinetic point of view, this assumption can be generally achieved when the biomarker level at the time point reaches 95% of the level at steady state (Boroujerdi, 2001; Gibaldi and Perrier, 1982). This assumption was achieved in this study for oral exposure when the exposure period was approximately four to five times the HL of the substance in the body. The total amount of dose for 5 days of total exposure period was set uniformly so that external dose was distributed proportionally to τ.

The relative changes in ECR slope were larger as HL increased, which can be explained by the accumulation of substances in the body (Rappaport and Kupper, 2008). The initial value of ECR slope was largest when the HL was 20 hours. Also, the relative changes increased drastically by 10-20% when the exposure interval exceeded 24 hours (Figure 3). Aylward et al. (2012) proposed to estimate daily intake with TK model simulation by the function of HL relative to τ, suggest the degree of over- or under-estimation in predicted spot urine concentrations from underlying dose distribution. The present study focused on demonstrating how dose estimates can vary between each τ for chemicals with HL less than a day.

However, the sources of variability in the TK model should be discussed as well. Intra-individual and inter-individual variation in elimination half-life and physiological factors, including daily urinary excretion volume and body weight, were not considered for both methods in this study. It has been reported that variation of elimination half-life is predominant between individual, and is relatively lower for chemicals with short half-lives less than a week (Spaan et al., 2010). Also, urinary volume can change due to different hydration status, gender, and age, which result in further inter- and intra-individual variation (Van Haarst et al., 2004). These inter- and intra-individual variability can be simulated using Monte Carlo analysis for TK parameters (Clewell et al., 2008). In addition, spot urine concentration data used in back calculations only captures a single time point without any information on the time of last exposure. The complementary information on the time of sample collection can be simulated with the simple compartment model, which will help reduce uncertainty (Aylward et al., 2014; Aylward et al., 2017; Brown et al., 2015).

Nevertheless, TK model simulation can explain different exposure scenarios that can be used to elaborate on the external exposure of biomonitoring data. To overcome the knowledge gap, the TK model should be performed with sufficient information on the possible exposure frequency of the chemical of interest collected from questionnaires (Andersen, 2003; Tan et al., 2018).

4. Conclusions

In conclusion, the conventional reverse dosimetry method using F_{ue} was evaluated by comparing the results from the TK model simulation based on the authentic biomonitoring data of BPS and DEHP. Also, the impact of exposure events on the uncertainties that may occur in exposure assessment based on urinary biomarkers was characterized by simulating various combinations of exposure intervals and elimination half-lives. The simulation results presented here suggest that the back calculation of chemical intake should consider elimination half-life and possible exposure intervals. Furthermore, the simple reverse dosimetry approach with TK modeling used in this study can be applied for various environmental chemicals regarding hypotheses on compartment model structures.

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6. Supplementary material

Uncertainty on conventional methods for reverse dosimetry from urinary biomarkers of environmental chemicals

Table S1. Physiological variables of representative age groups used in this study

Figure S1. Model fitting for total BPS in urine using predicted (lines) and observed (scatters) cumulative excreted amount (in nmol)

Figure S2. Model fitting for urinary DEHP metabolites using predicted (lines) and observed (scatters) cumulative excreted amount (in μmol)

Table S1. Physiological variables of representative age groups used in this study

Population		Body weight (kg)	Daily urinary excretion (L/day)	References
Children	Male	40	0.7	Valentin (2002); Yoon et al. (2020)
	Female	35	0.7	Valentin (2002); Yoon et al. (2020)
Adolescents	Male	60	1.2	Valentin (2002); Yoon et al. (2020)
	Female	55	1.2	Jang et al. (2014); Valentin (2002)
Adults	Male	70	1.6	Jang et al. (2014); Valentin (2002)
	Female	60	1.2	Jang et al. (2014); Valentin (2002)

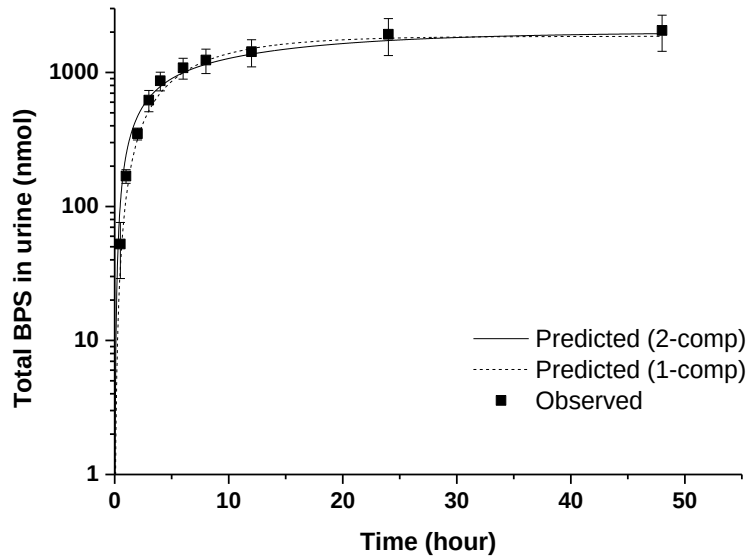

Figure S1. Model fitting for total BPS in urine using predicted (lines) and observed (scatters) cumulative excreted amount (in nmol). Dashed and solid lines are from 1-compartment and 2-compartment model prediction, respectively. Measured data is taken from Oh et al., 2018 (N = 7). Each point and error bar represent mean and standard deviation of participants.

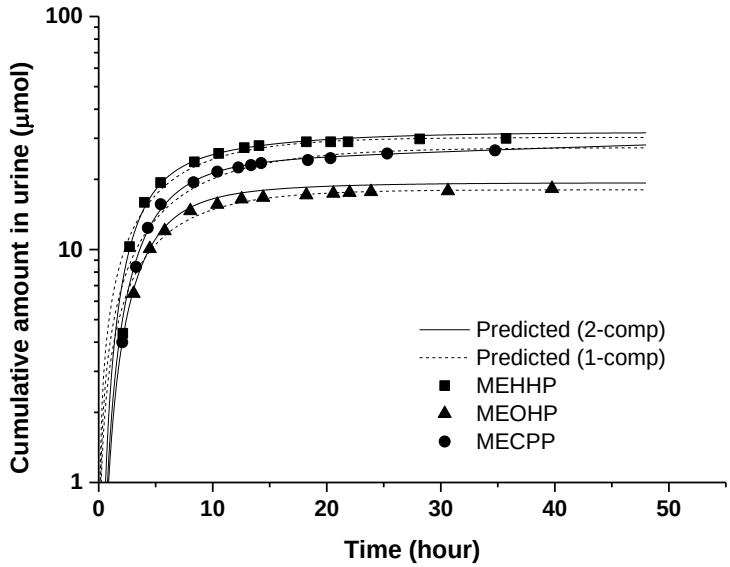

Figure S2. Model fitting for urinary DEHP metabolites using predicted (lines) and observed (scatters) cumulative excreted amount (in μmol). Dashed and solid lines lines are from 1-compartment and 2-compartment model prediction, respectively. Measured data is taken from Koch et al., 2004 and Koch et al., 2005 (N = 1).

국문초록

소변 바이오마커를 이용한 노출량 역산법의 불확실성

서울대학교 보건대학원
환경보건학과 환경보건전공
권 진 현

바이오모니터링 연구는 인구집단의 내적 노출량을 보여주는 지표로서 노출평가에 널리 쓰이고 있다. 유해 화학물질의 노출을 관리할 때에는 일평균 노출량 같은 인체 노출 안전 기준을 도출해 이뤄지기 때문에 바이오마커 농도를 노출량으로 역추정하는 다양한 방법이 개발되어 왔다. 노출량을 역추정할 때에는 대표적으로 소변 배설 분율(F_{ue}) 또는 독성동태학 모델(TK)를 이용할 수 있다. 이러한 방법은 생체 시료 중 바이오마커의 농도가 외적 노출이 지속적으로 일어나는 상황에서 평균적인 노출을 반영한다는 가정한다. 하지만 체내 반감기가 짧은 물질은 실제로 물질에 노출되는 간격에 따라서 바이오마커의 농도가

달라질 수 있으므로 바이오모니터링 기반 노출 평가 시에는 노출 특성을 고려하는 것이 중요하다.

본 연구에서는 인체 노출 실험 결과가 존재하며, 체내 대사가 빠르게 일어나 국가 바이오모니터링 연구에서 소변 중 바이오마커를 측정하는 BPS와 DEHP를 대상 물질로 선정하였다. 1-구획과 2-구획 TK 모델을 각각의 바이오마커에 대해 최적화해 경구 등가 노출량을 역산한 값을 토대로 Fue 값을 활용해 산출한 결과를 평가하였다. 그 결과 F_{ue} 값을 활용한 경우에는 TK 모델로 현실적인 8시간 간격 노출을 시뮬레이션한 경우와 비교했을 때 노출량이 약 2배 이상 달라지는 것으로 나타났다. 또한, 1-구획 TK 모델을 활용해 체내 반감기가 짧은 물질에 대해 물질이 다양한 시간 간격으로 노출될 때 노출량 추정에 미치는 영향을 살펴보았다. 그 결과, 노출 평가를 할 때에는 역산 방법의 불확실성을 줄이기 위해서 물질의 노출 특성을 파악하는 것이 중요하다는 것을 확인하였다.

주요어: 바이오모니터링, 위해성 평가, 불확실성, 독성동태학 모형, 소변 중 배설 분율

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