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Assessing the cancer risk associated with arsenic-contaminated seafood

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ABSTRACT

Tens of millions of people worldwide ingest excessive amounts of arsenic (As) through drinking water and food. The dietary intake of seafood is the major As exposure route in humans and can cause As-related adverse health effects including cancers. The aim of this study was to quantify potential cancer risks of As exposure for children and adults through seafood consumption. By coupling the age-specific physiologically based pharmacokinetic (PBPK) model and a Weibull-based dose–response function, a more accurate estimate of urinary arsenic metabolites could be achieved to better characterize potential cancer risks. The simulation results show that the proportion of inorganic As, monomethylarsonic acid (MMA), and dimethylarsinic acid (DMA) in human urine are estimated to total 6.7, 26.9, and 66.4% for children, and 6.2, 27.4, and 66.4% for adults, respectively. The estimated median cumulative cancer incidence ratios were respectively 2.67×10^{-6} and 3.83×10^{-6} for children and adults, indicating a low cancer risk for local residents exposed to As through the consumption of seafood. However, it is necessary to incorporate other exposure routes into the model to make it more realistic. The methodology proposed here can not only be applied to calculate the concentrations of As metabolites in urine, but also to provide a direct estimation of adverse health effects caused by the calculated internal concentrations.

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1. Introduction

Arsenic (As) is ubiquitous in the environment due to both anthropogenic and natural processes [1,2]. Tens of millions of people worldwide ingest excessive amounts of As through drinking water and food. In recent years, the adverse effects of long-term chronic exposure to As from contaminated seafood and groundwater have become a major topic and received increasing attention in many countries [3–5].

The toxicity of As in humans varies with its chemical form. It has been generally recognized that inorganic As is more toxic than its organic forms [3]. Several studies have also indicated that inorganic As is a potent human carcinogen of the skin, lung, bladder, and kidney [6,7]. Inorganic trivalent arsenical (arsenite (As^{III})), which reacts directly with protein-bound sulfhydryls, is considered more toxic than the inorganic pentavalent form (arsenate (As^{V})) [8]. Inorganic As is proposed to be metabolized to monomethylarsonic acid (MMA^{V}) and dimethylarsinic acid (DMA^{V}), of lower toxicity [9,10]. The metabolic process of inorganic As in humans is thus generally considered to be a detoxification mechanism. Therefore, to better characterize the hazardous effects associated with human exposure, it is necessary to entirely delineate the kinetics of As and its metabolites in the human body under various exposure scenarios.

The major sources of human exposure to As may be through food, water, air and soil in that dietary intake is the major exposure route [11]. Arsenic species from drinking water are mainly found in the form of inorganic arsenicals, whereas organoarsenic compounds (e.g., arsenobetaine and arsenosugars) predominate in seafood [3,4]. The United States and the World Health Organization lowered the Maximum Contamination Level (MCL) for As in drinking water from 0.05 to 0.01 mg L^{-1} [12]. On the other hand, dietary exposure to organic arsenicals was formerly neglected due to their relatively nontoxic nature. However, more and more studies have focused on As exposure through seafood rather than drinking water because some seafood contains high As concentrations [8,9].

The U.S. Food and Drug Administration [13] indicated that fish and other seafood account for 90% of total As exposure. In our previous study, the As concentrations found in various tissues of tilapia in southwestern Taiwan were relatively higher than the background levels [14]. A probabilistic risk assessment further indicated that the consumption of cultured tilapia from these areas poses a potential risk to human health [15]. Consequently, a determination of the relationship between toxic effects associated with As exposure and seafood consumption is important for assessing potential human health risks.

Arsenic concentrations in hair, nails, and urine have widely served as biomarkers to reflect recent As exposure [3,16]. Based on

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Table 1
The seafood market share of Top 11 species in Taiwan.

Species	% of Market[a]	Total arsenic ($\mu g\,g^{-1}$)[b]	Source
Hairtail	0.63	0.75 ± 0.03	[42]
Tuna fish	6.69	2.38 ± 0.08	[42]
Milkfish	8.57	1.78 ± 0.02	[30]
Tilapia	11.61	1.29 ± 0.80	[43]
Cephalopod	8.94	1.13 ± 0.04	[28]
Shrimp	0.69	0.64 ± 0.03	[28]
Crab	0.69	3.38 ± 1.09	[28]
Oyster	2.02	3.71 ± 0.87	[28]
Hard clam	2.15	4.95 ± 0.95	[28]
Seaweed	0.004	4.40 ± 1.01	[28]
Abalone	0.06	2.82 ± 1.10	[28]

[a] Data adopted from the ROC Fisheries Agency, Council of Agricultural, Executive Yuan.
[b] Mean ± standard deviation.

its ease of collection, non-invasive characteristics, and direct relation to As excretion, urinary As concentration is generally regarded as the most important biomarker not only for reconstruction of the recent intake of As, but also for evaluation of the target tissue dose that actually causes adverse health effects [8,16]. For biomonitoring purposes, therefore, human metabolites of As in urine should be accurately measured. Considering the variations in dilution, creatinine-adjusted analyte concentration in urine is a widely used surrogate for urinary analyte concentration. In practice, creatinine adjustment of urinary As concentrations has been proven to be a good predictor of environmental exposure to As in different populations [4,17].

Physiologically based pharmacokinetic (PBPK) models are potentially powerful tools in quantitative risk assessments for target tissue dose estimates. These models can be useful for human health risk assessments because PBPK modeling permits the calculation of target tissue doses through the integration of information on the external dose, human physiological structure, and the biochemical properties of metals [18]. Most human PBPK models for arsenic have a number of similarities [19–21]. The simplest came from Yu [20], who extended the simplest PBPK model to fit the human child. In relation to this modeling approach, it is of particular concern to delineate the metabolic scheme of the target chemical in different target tissues after oral exposure to this chemical. The metabolic pathways of As in human tissues, including consecutive reduction and oxidative methylation reactions in blood, liver, and urine, are complicated and have been made clearer only for a short period of time [6,22]. Consequently, studies regarding the application of the PBPK model to multiple metabolic pathways for As exposure in humans are limited.

In human health risk assessment schemes, it is also important to establish an appropriate profile to illustrate the dose–response relationship after exposure. Conventionally, the relationship can be interpreted by three empirical models: the log-logit model, the log-probit model, and the Weibull model. The Weibull model, which uses the Weibull distribution as a tolerance distribution, was recommended by a number of studies to precisely describe the dose–response relationship of lifetime cancer risk estimation and a long-term low-dose exposure scenario [23–25].

Therefore, the main purpose of this study was to develop a thorough methodology that can greatly improve our ability to estimate lifetime cancer risk through seafood consumption. The analysis in this paper was based on a variety of survey data and prior analyses. Epidemiological data for various As-induced cancers, as well as data on urinary As metabolites provided by previous studies, were used to implement the proposed methodology. The results of the present study may be helpful in generating and/or refining the reference dose (RfD) of As in seafood from the human health perspective.

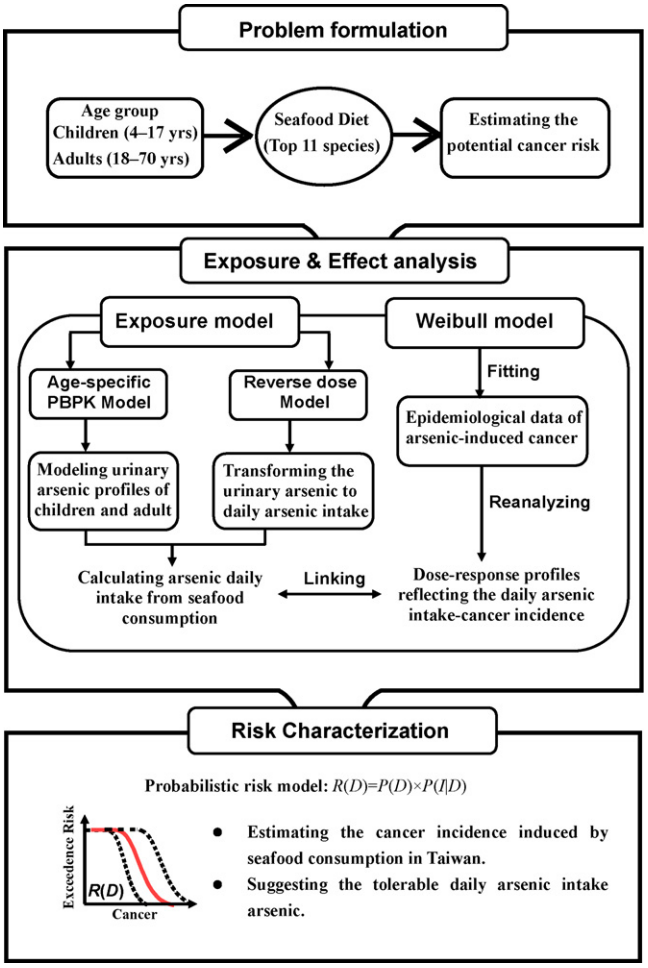

Fig. 1. Schematic showing the proposed risk analysis framework for estimating the arsenic tolerable daily intake by seafood consumption. The methodology was modified from USEPA [26].

2. Materials and methods

2.1. General framework

Based on the USEPA risk assessment paradigm [26], the proposed approach for estimating lifetime cancer risk through seafood consumption is depicted in Fig. 1. The overall paradigm was divided into four phases: problem formulation, exposure analysis, effect analysis, and risk characterization. In the present study, As exposure was limited to seafood consumption. Eleven different types of seafood, which were very popular foodstuffs in the indigenous market, were investigated for their total As contents (Table 1). An age-specific PBPK model was developed to calculate urinary As metabolites after seafood consumption. Model validation was achieved by comparing the simulation results to the measured DMA concentration from a previous study. Effect analysis was performed by fitting the Weibull model to As epidemiological data to obtain reconstructed dose–response profiles. The cancer risk from the seafood consumption of residents in Taiwan was then estimated by coupling the analytical results obtained from exposure analysis and effect analysis.

2.2. PBPK modeling

The PBPK model developed in the present work consisted of three absorption compartments and three tissue compartments,

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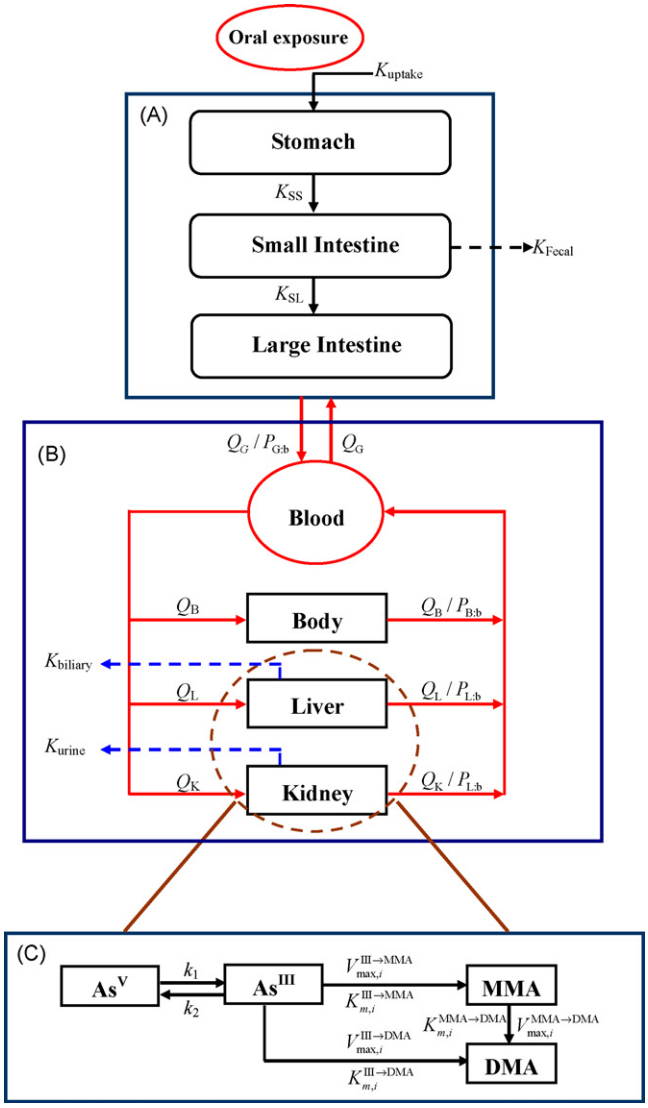

Fig. 2. Schematic of the proposed PBPK-metabolism model showing (A) absorption tissue compartments of stomach, small intestine, and large intestine, (B) target tissue compartments of body, liver, and kidney interconnected by blood flow, and (C) biotransformation of arsenic showing oxidation/reduction of inorganic arsenic and methylation of As^{III} in kidney and liver.

which were interconnected by the blood circulatory system (Fig. 2). Equations describing the model's structure and symbols used in the present study are given in the Appendix A. The compartments were chosen according to their physiochemical properties and affinity to As and its metabolites. For the absorption process, only the oral exposure route was considered in the model. As ingested via seafood consumption was diluted and absorbed in the stomach, small intestine, and large intestine. For the excretion processes, it was assumed that the excretion of As mainly occurred through urine and feces, and was described using first-order kinetics. Arsenic absorbed in these compartments was then transferred into the other compartments via blood circulation.

In the PBPK scheme, an equilibrium constant (i.e., partition coefficient) was used to represent the ratio of As concentration in the blood leaving an organ to the As concentration in the organ [27]. The liver and kidney were the major metabolizing organs for As in the model. Metabolism of As consisted of a series of reductions and oxidation with methylation reactions. The oxidation and reduction reactions were modeled by a first-order process, whereas the oxidative methylation was followed by Michaelis–Menten kinetics, as suggested by previous studies [12,20]. In addition, the body compartment was used to represent the remaining tissues such as lung, muscle, skin, bone, etc. Physiological parameters, metabolic rate constants, partition coefficients, blood flow fractions, and tissue densities for the children and adults used in the model were scaled to body weight and obtained from the available literature (Tables 2 and 3).

2.3. Validation of PBPK model

For the present study, validation of the PBPK model was achieved with published data from the available literature. Initially, age-related changes in body weight were derived from body weight data released by the Department of Health, Taiwan (http://www.doh.gov.tw). Measurement data retrieved from Hata et al. [4] were used in a curve-fitting exercise to yield an age-specific equation of urinary DMA/MMA ratios. The data source used for model validation was obtained from a study by Yao [28]. DMA concentrations in the urine samples for 16 volunteers after consumption of 4 seafood types (seaweed, clam, oyster, and shrimp) were analyzed in the above-mentioned study. Exposure inputs used for model simulation were captured from the data for daily ingestion of seafood provided by the study. Simulation results were then compared with the measurement data from Yao [28] to validate the derived PBPK model.

2.4. Weibull dose–response function

The Weibull dose–response function proposed was employed to estimate the cumulative cancer incidence ratio, $F(X)$, which can be expressed as [24]

$$F(X) = 1 - \exp(-\alpha X^{\beta}) \quad (1)$$

where X represents daily As intake ($\mu g\,kg^{-1}\,d^{-1}$), and α and β are the cancer-specific best-fitted parameters.

One of the major challenges in constructing the proposed model is the lack of epidemiological data that can relate the cancer incidence ratio to the dietary exposure of a population. As an alternative, the reconstructed Weibull model was fitted to pooled As epidemiological data, including liver, lung, and bladder cancers, on drinking water intake in arseniasis-endemic areas in Taiwan, provided by the Blackfoot Disease Study Group in Taiwan (cjchen@ha.mc.ntu.edu.tw), to reflect a reasonable trend of dose–response relationship. Model fitting was performed using TableCurve 3D (Version 4, AISN Software Inc., Mapleton, OR, USA).

2.5. Risk characterization

In the present study, the conservative seafood consumption rates of $39.15\,g\,d^{-1}$ for children and $49.34\,g\,d^{-1}$ for adults recommended by Lu et al. [29] were adopted for exposure analysis. To quantify the variability of As exposure from seafood consumption, the lognormal distribution model was fit to the total As contents in the 11 most popular seafoods in indigenous markets. The χ^2 and Kolmogorov–Smirnov (K–S) statistics were used to optimize the goodness-of-fit of the lognormal distribution. The exposure inputs were then incorporated into the Weibull dose–response function to evaluate the lifetime cancer risk via seafood consumption of residents in Taiwan. To explicitly quantify the uncertainty/variability of the data, a Monte Carlo simulation was performed with 10,000 iterations (stability condition) to obtain the 95% confidence interval. The Monte Carlo simulation was implemented using Crystall

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Table 2
Input physiological parameters for children and adults groups in the PBPK model.

Parameter	Children (4–17 yrs)	Adults (18–70 yrs)	Source/reference
Physiologic values			
BH (cm)	143.63 ± 22.19	167.23 ± 3.47	[40]
BW (kg)	38.91 ± 15.48	62.98 ± 2.08	[40]
Q_T[a] ($L\,h^{-1}$)	225.29	321.74	[44]
Blood volume[b] (L)	3.68	4.98	[45]
Tissue volume (L)[c]			
V_G	0.74	1.20	
V_L	1.12	1.81	
V_K	0.19	0.31	
V_B	32.26	52.21	
Blood flow ($L\,h^{-1}$)[d]			
Q_G	33.79	48.26	
Q_L	14.64	20.91	
Q_K	42.80	61.13	
Q_B	134.05	191.43	
Daily drinking water ($L\,d^{-1}$)			
IW	2.27	3.67	[24]
Seafood consumption ($g\,d^{-1}$)			
IR	39.15	49.34	[29]
Personal daily urinary creatinine-excretion rate ($mg\,kg^{-1}\,d^{-1}$)[e]			
CE	36.94	24.65	[46]
Elimination constants (h^{-1})			
K^{III}_{fecal}	2.86×10^{-3}	4.64×10^{-3}	[20]
K^{V}_{fecal}	2.86×10^{-3}	4.64×10^{-3}	[20]
K^{III}	0.04	0.07	[20]
K^{V}	0.04	0.07	[20]
K^{III}	0.12	0.19	[20]
K^{V}	0.18	0.29	[20]
K^{MMA}	0.17	0.27	[20]
K^{DMA}	0.01	0.15	[20]

Abbreviations and parameters symbols: BH is the body height, BW is the body weight, Q_T is the cardiac output fraction, V_G is the GI tract tissue volume (including large, small intestine and stomach), V_L is the liver tissue volume, V_K is the kidney tissue volume, Q_G is GI tract blood flow, Q_L is liver blood flow, Q_K is kidney blood flow, Q_B is body blood flow, and K_i^j is elimination rate of arsenic species *j* in organ/tissue *i*.

[a] $Q_T\,(L\,h^{-1}) = 15(L\,kg^{-1}\,h^{-1}) \times BW^{0.74}$.

[b] Blood volume = $(13.1 \times BH + 18.05 \times BW - 480) \times 0.001/0.5723$.

[c] $V_i = BW \times W_i/D_i$ [24].

[d] $Q_i = F_i \times W_i$ [24].

[e] $CE = (-12.63 \times age + 15.12 \times BW + 7.39 \times BH - 79.90)/BW$ [46].

Ball software (Version 2000.2, Decisioneering Inc., Denver, CO, USA).

3. Results

3.1. Validation of PBPK model

The optimal fits of body weight and DMA/MMA ratio as a function of age are shown in Fig. 3A and 3B, with r^2 values of 0.97 and 0.84, respectively. The physiological parameters for children and adults derived from these curves are presented in Tables 2 and 3. Fig. 4 shows the results of the model comparisons with the measured data of DMA concentrations in the urine samples for 16 volunteers after consumption of the 4 seafood types proposed by Yao [28]. The PBPK predictions were considered to agree with experimentally determined values if they were within one standard deviation (SD) of the mean.

The goodness-of-fit was evaluated using root-mean-squared-error (RMSE), computed from $RMSE = \sqrt{\sum_{n=1}^{N}(C_{m,n} - C_{s,n})^2/N}$, where N denotes the number of measurements, $C_{m,n}$ is the measurement data, and $C_{s,n}$ is the simulation result corresponding to data point n. Each RMSE value was less than 1SD from the experimental data, as shown in Fig. 4, indicating that the PBPK model simulated values were in good agreement with the experimentally determined concentration–time profiles of DMA in urine after seafood exposure.

3.2. Fitting Weibull model to As epidemiology data

Fig. 5 shows the optimal fit of the Weibull dose–response function (Eq. (1)) to the pooled As epidemiological data, including liver, lung, and bladder cancers, through drinking water intake in arseniasis-endemic areas in Taiwan. The cancer-specific best-fitted parameter was 1.36×10^{-4} for α and 0.77 for β, respectively. The β parameter is usually referred to as the shape factor. In the present study, a value of less than one indicates that the cancer prevalence ratio is occurring less frequently with an increasing exposure concentration of As. In addition, the higher r^2 value (0.89) indicated that the relationship between cumulative cancer incidence ratio and daily inorganic As intake can be fitted reasonably well by the Weibull model.

3.3. Estimating lifetime cancer risks through seafood consumption

Fig. 6 demonstrates the best-fitted lognormal models of total arsenic concentration in the top 11 seafood species in the indigenous market ($r^2 = 0.89$). The fitted distribution was then incorporated into the PBPK model as exposure input to evaluate As species in urine. The estimated daily As intake, as well as the creatinine-adjusted concentration of urinary As species for children and adults, are given in Table 4. In addition, the excess lifetime cancer risks through seafood consumption were also calculated by incorporating the estimated As burden data into the

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Table 3
Metabolic rate constants, partition coefficient, blood flow fraction and tissue density parameters used in the PBPK model.

Metabolic rate constants for arsenic in human					
Oxidation/reduction[a]	First order				
Reduction, k_1 (h^{-1})	1.37				
Oxidation, k_2 (h^{-1})	1.83				
Methylation[b]					
	As^{III}→MMA	As^{III}→DMA	MMA→DMA		
			Population (children)	Population (adults)	
Liver					
V_{max} (μmol h^{-1})	11.25	22.25	16.02	56	
K_m (μmol h^{-1})	100	100			
Kidney					
V_{max} (μmol h^{-1})	7.5	10.02	5.00	17.48	
K_m (μmol h^{-1})	100	100			

Partition coefficients, blood flow fraction, and tissue density

Tissue	F_i[c] (%)	W_i[c] (%)	D_i[c] (kg L^{-1})	E_i[c,d] (%)	Species-specific tissue/blood partition coefficient, P_i[b]			
					As^{III}	As^{V}	MMA	DMA
GI tract	15	1.98	1.04	8	2.80	2.80	1.20	1.40
Liver	6.5	2.99	1.04		5.30	5.30	2.35	2.65
Kidney	19	0.52	1.05	60	4.15	4.15	1.80	2.08
Body	59.5	94.51	1.14	32	2.39	2.39	1.29	1.61
Total				100				

[a] Adopted from Mann et al. [19].
[b] Adopted from Yu [20].
[c] F_i is the blood flow fraction, W_i is the percentage of body weight, D_i is the density and E_i is the percentage of total water elimination amount, which are adopted from Yu and Kim [21].
[d] Adopted from Mai et al. [47].

Table 4
As-related variables for human urine and estimated daily intake of As from seafood consumption.

	Urinary creatinine, C_r (g L^{-1})[a]	Urinary creatinine-adjusted As, ME (μg g^{-1})[b]	Ratio of urinary excretion to total elimination, f (%)[c]	Arsenic daily intake (μg kg^{-1} d^{-1})[d]
Children (4–17 yrs)				
InAs	1.17	1.76 ± 0.51[e]	45.72	0.01 (0.002–0.01)[f]
MMA	1.43	7.09 ± 1.48	25.60	0.04 (0.023–0.06)
DMA	1.45	17.49 ± 3.36	14.63	0.17 (0.106–0.23)
Total As	1.20	26.35 ± 1.78	0.85	0.21 (0.187–0.24)
Adults (18–70 yrs)				
InAs	1.13	3.61 ± 1.04	45.72	0.01 (0.006–0.02)
MMA	1.25	15.98 ± 3.35	25.60	0.11 (0.062–0.15)
DMA	1.29	38.72 ± 7.44	14.63	0.45 (0.278–0.61)
Total As	1.15	58.31 ± 3.94	0.85	0.56 (0.492–0.64)

[a] Medium value calculated from Hata et al. [4].
[b] ME = C_{urine}/C_r where C_{urine} is the urinary As concentration (μg L^{-1}) calculated from the PBPK model.
[c] $f = K_{urine}/K_{total}$ where K_{urine} is the urinary excretion constant and K_{total} is the elimination constant.
[d] Arsenic daily intake = (ME × CE)/f calculated from Itoh et al. [46] where CE is the personal daily urinary creatinine-excretion rate (mg kg^{-1} d^{-1}).
[e] Mean ± standard deviation.
[f] Mean with 95% confidence interval.

Weibull dose–response function for children and adults (Fig. 7). The results showed that the estimated median cumulative cancer incidence ratio was 2.67×10^{-6} and 3.83×10^{-6}, with the upper 97.5th percentile of 5.98×10^{-6} and 9.92×10^{-6} for children and adults, respectively; these were all well below the acceptable value of 10^{-4} (Fig. 7B). These findings demonstrate that the lifetime cancer risk for local residents exposed to As through consumption of seafood is acceptable.

4. Discussion

Arsenic cancer risks to the health of subpopulations such as children, adolescents, and adults that occur through dietary exposure have received increasing attention in many countries in recent years. Several studies highlight the need to assess health risks on a dose-per-body-weight basis during childhood for risk management decisions [11,30–32]. It is generally recognized that older age groups would reflect more cumulative exposure than children because of increasing exposure duration. The predicted results in the present study showed that children had lower accumulated levels of all As species than those in older age groups on a per-unit-body-weight basis (Table 4); thus, a lower cumulative cancer incidence ratio was observed for children (Fig. 7). This result was in good agreement with the finding of a previous study regarding an age-dependent difference in the concentration of As in urine in Taiwan [9]. Therefore, coupling of a body-weight based PBPK model and a Weibull-based PD model could accurately delineate the exposure profile and corresponding effects for reliable risk assessment.

In the PBPK model scheme, it is crucial to appropriately determine the input parameters for the model simulation. Generally,

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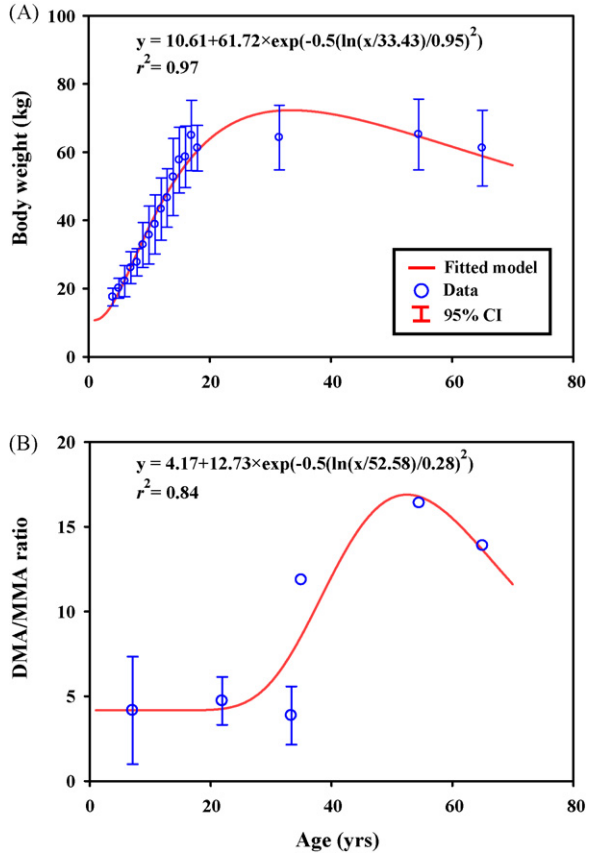

Fig. 3. Age-specific (A) body weight and (B) secondary methylation ratio (DMA/MMA) distributions adopted from D.O.H. [40] and Hata et al. [4].

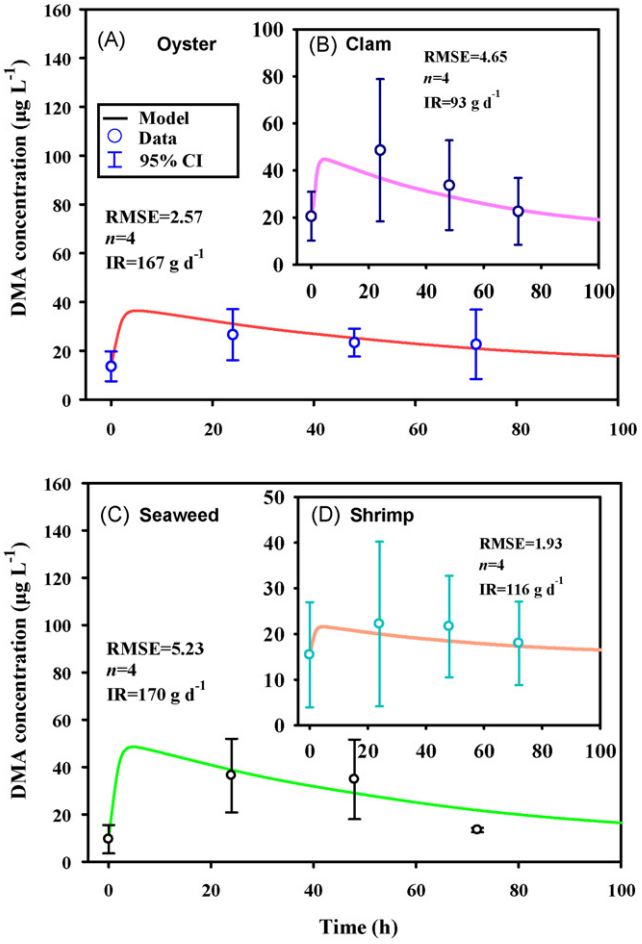

Fig. 4. Comparing the PBPK model simulations to experimentally measured DMA concentrations in urine from 4 specific group who intake (a) oyster, (b) clam, (c) seaweed, and (d) shrimp seafood, respectively (IR: seafood intake frequency) [28].

the PBPK model is composed of four types of parameters: exposure, physiological, partitioning, and metabolic parameters [18]. It is especially difficult to estimate the metabolic parameters for the model because there are few studies associated with the mechanisms of metabolism for chemicals within the human body. In the present study, the initial set of physiological and partitioning parameters used in the proposed model were adopted from literature and calculated based on the body weights of adults and children. The metabolic parameters, which were adopted from Mann et al. [19] and Yu [20] regarding the metabolism of inorganic As in humans, were carefully used to estimate the amount of different As species after seafood consumption. In addition, the proposed model was validated using the data on DMA concentration in urine after seafood exposure proposed by Yao [28]. Thus, the PBPK model developed in the present study was capable of predicting the time course of the As concentration and its metabolites in human organs after dietary exposure with a known ingestion rate.

In pharmacodynamic theory, the dose–response relationship after exposure is typically expressed by a sigmoid model, such as the Hill model, with the effect approaching maximum value [27,33]. Weibull distribution, traditionally used to represent processes of the time to complete a task, is considered more flexible for representing non-negative physical quantities [34]. Kodell et al. [23] used the Weibull distribution as the pharmacodynamic model in dose–response assessment; they indicated that the Weibull model is more accurate in reflecting the curvature of extreme data. Liao et al. [24] also employed the Weibull model to assess the risk of arsenic-induced skin lesions in children. In the present study, the Weibull model is successfully fitted to pooled published As epidemiological data to reflect the cancer prevalence ratio for humans chronically exposed to a low dose of As. Therefore, by coupling of an appropriate PBPK model and a Weibull-based PD model, a complete profile of risk assessment can be depicted for human exposed to As.

In the present study, the total concentration of As in urine from seafood consumption was estimated to be 26.35 and 58.31 $\mu g\, g^{-1}$ creatinine for children and adults, respectively. This result agreed

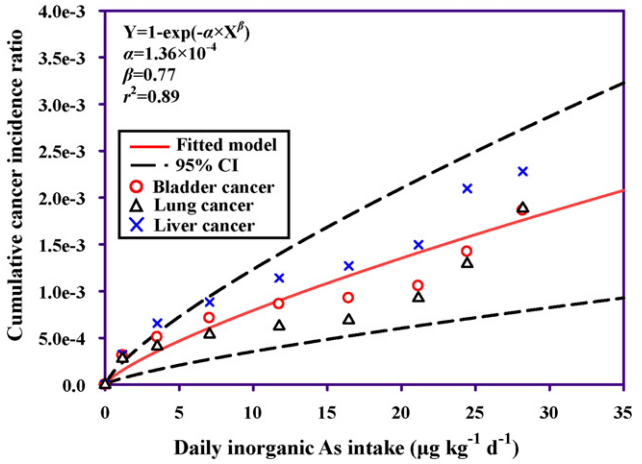

Fig. 5. Reconstructed Weibull model-based dose–response profiles for daily arsenic intake-induced lifetime cancer incidence ratio from 3 cancer-specific groups, bladder, lung, and liver (data adopted from Morales et al. [41]).

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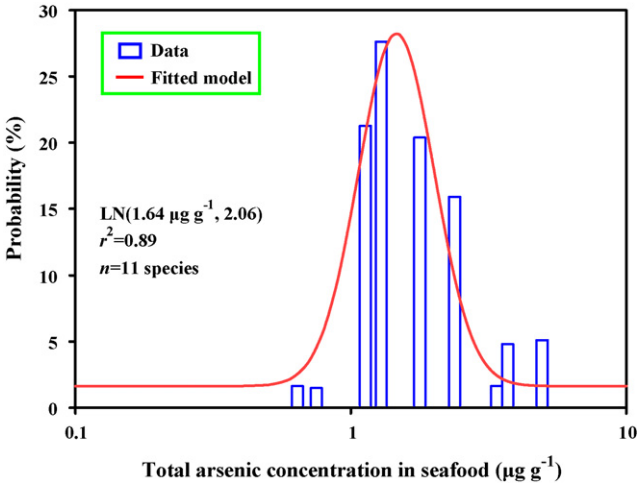

Fig. 6. Goodness-of-fit lognormal distribution of total arsenic concentration in 11 seafood species.

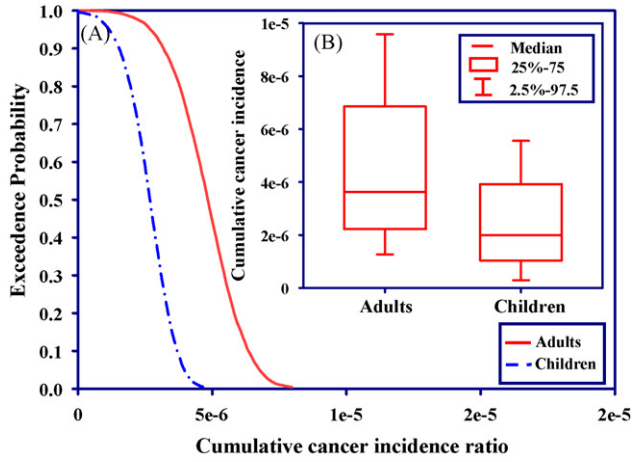

Fig. 7. Estimated (A) exceedence risk curves for children (4–17 yrs) and for adults (18–70 yrs) by seafood consumption, and (B) box and whisker plots showing the predicted cumulative cancer incidence distributions from seafood consumption in Taiwan with different age groups.

well with the investigation of urinary As metabolites for adults in Taiwan (range: 45.53–91.70 $\mu g\,g^{-1}$ creatinine) proposed by Hsueh et al. [9], yet remarkably lower than that for Japanese adults (range: 101.0–193.7 $\mu g\,g^{-1}$ creatinine) reported by Hata et al. [4]. Recently, Brima et al. [3] measured As levels in urine samples from healthy populations and indicated that the total concentration of As in urine for the Asian population is 20.6 $\mu g\,g^{-1}$ creatinine. Therefore, the discrepancy in the total concentration of As in urine may mainly result from differences in food habits.

An age-specific PBPK model has been developed in the present study. The proposed model was shown to predict not only total As levels, but also As metabolite distribution in human urine after the consumption of seafood. By linking the proposed PBPK model and a Weibull-based PD model, the cancer risk of As exposure through seafood can be assessed for different populations. From the simulation results of this study, the lifetime cancer risk for local residents exposed to As through the consumption of seafood is acceptable. The main contribution of the current methodology is that it provides a direct estimation of adverse health effects caused by internal concentrations of As metabolites in urine, instead of external As concentrations in the diet.

Despite the advantages mentioned above, there are still some limitations while applying the proposed models. First, absorption of As was subject to restriction from oral exposure via seafood in the present study. In exposure assessment, however, people may be exposed to xenobiotics through three major routes: ingestion, inhalation, and dermal absorption. Moreover, the inorganic As level in seafood used in the model is assumed to be 20% of total As, which is lower than the proposed value for milkfish in Taiwan (44.1%) [35]. In light of these reasons, it can be expected that the lifetime cancer risk of residents exposed to As may be underestimated in this study. According to the official data reported by Department of Health [36], the age-adjusted cancer incidence ratios of local residents in Taiwan are estimated to be 3.64×10^{-4}, 3.16×10^{-4}, and 1.03×10^{-4}, for liver, lung, and bladder cancer, respectively. Our estimated cancer incidence ratios of local residents account for nearly 1% of the practical data. However, the proposed model could equally be applied to characterize As accumulation from other foods. More accurate estimates of As intakes could therefore be achieved by combining food consumption data from all dietary sources.

Second, the present methodology should be expanded to elucidate the effects of other factors on As methylation capacity. The proportions of inorganic As, MMA, and DMA in human urine were 6.7, 26.9, and 66.4% for children, and 6.2, 27.4, and 66.4% for adults, respectively (Table 4). The percent of inorganic As found in the present study is a little lower than those proposed by Vahter [37] and Hsueh et al. [9], which ranged from 10 to 30% of total As. However, it is generally recognized that a wide interindividual variability exists in As methylation capacity [38]. In addition, the result showed a very small age difference in the distribution of As species. Several studies, however, pointed out that As methylation capacity is significantly associated with age. Hsueh et al. [9] indicated that the elderly have a poor As methylation capacity. Gamble et al. [38] studied the As metabolism in a subset of 300 adults residing in Bangladesh and found that age is associated with %MMA (positive) and %inorganic As (negative). Recently, Lindberg et al. [5] also demonstrated that the percent inorganic As is positively associated with age for children and adolescents, and negatively associated with age for adults.

Finally, several factors, including smoking, gender, food habits, and socio-economic status might affect As methylation capacity. Hall et al. [16] found that both blood As and urinary As were positively associated with smoking. Gamble et al. [38] indicated that urinary creatinine is greater for males than females, thus a correction factor should be used to adjust the sexual variation. Brima et al. [3] studied urinary As metabolism from three ethnic groups (Asian, White, and Somali group), and attributed the ethnic difference in As metabolism to dietary or genetic factors. A recent study by Brima et al. [39] pointed out that the pattern of urinary As excretion would be influenced by Ramadan fasting. Although more complex models may be developed to consider specific effects of these factors, the simple model presented here can meet the essential needs in risk analysis, and is flexible to include the effects occurring at subpopulation scales if more data regarding the influence of these factors on the capacity of As methylation are available.

5. Conclusion

In the present study, a Weibull-PBPK approach was conducted and applied to estimate the creatinine-adjusted As metabolites in urine from seafood consumption. The estimated result agreed well with a previous investigation of urinary As metabolites for adults in Taiwan, yet remarkably lower than that reported for Japanese adults. The estimated cumulative cancer

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incidence ratio for children and adults exposed to As through consumption of seafood were all well below the value of 10^{-4}, indicating that the life time cancer risk for local residents associated with As-contaminated seafood is acceptable. To apply the model in a more realistic fashion, however, it would necessary to consider additional exposure routes and the influence of particular factors on the capacity of As methylation.

Appendix A. Equations used in the proposed PBPK model

Tissue	Mass balance differential equations
Kidney	
As^{III}	$\frac{dA_K^{III}}{dt} = Q_K \times \left(C_b^{III} - \frac{C_K^{III}}{P_K^{III}}\right) + (k_1 \times C_K^V - k_2 \times C_K^{III}) \times V_K - \frac{V_{max,K}^{III\to MMA} \times C_K^{III}}{K_{m,K}^{III\to MMA} + C_K^{III}} - \frac{V_{max,K}^{III\to DMA} \times C_K^{III}}{K_{m,K}^{III\to DMA} + C_K^{III}} - W_{day} \times K^{III} \times \frac{C_K^{III}}{P_K^{III}}$
As^{V}	$\frac{dA_K^{V}}{dt} = Q_K \times \left(C_b^{V} - \frac{C_K^{V}}{P_K^{V}}\right) - (k_1 \times C_K^V - k_2 \times C_K^{III}) \times V_K - W_{day} \times K^{V} \times \frac{C_K^{V}}{P_K^{V}}$
MMA	$\frac{dA_K^{MMA}}{dt} = Q_K \times \left(C_b^{MMA} - \frac{C_K^{MMA}}{P_K^{MMA}}\right) + \frac{V_{max,K}^{III\to MMA} \times C_K^{III}}{K_{m,K}^{III\to MMA} + C_K^{III}} - \frac{V_{max,K}^{MMA\to DMA} \times C_K^{MMA}}{K_{m,K}^{MMA\to DMA} + C_K^{MMA}} - W_{day} \times K^{MMA} \times \frac{C_K^{MMA}}{P_K^{MMA}}$
DMA	$\frac{dA_K^{DMA}}{dt} = Q_K \times \left(C_b^{DMA} - \frac{C_K^{DMA}}{P_K^{DMA}}\right) + \frac{V_{max,K}^{III\to DMA} \times C_K^{III}}{K_{m,K}^{III\to DMA} + C_K^{III}} - \frac{V_{max,K}^{MMA\to DMA} \times C_K^{MMA}}{K_{m,K}^{MMA\to DMA} + C_K^{MMA}} - W_{day} \times K^{DMA} \times \frac{C_K^{DMA}}{P_K^{DMA}}$
G.I. tract	
As^{III}	$\frac{dA_G^{III}}{dt} = Q_G \times \left(C_b^{III} - \frac{C_G^{III}}{P_G^{III}}\right) - Q_G \times \left(\frac{C_{GI}^{III}}{P_{GI}^{III}} - \frac{C_L^{III}}{P_L^{III}}\right) + (k_1 \times C_{GI}^V - k_2 \times C_{GI}^{III}) \times V_{GI} - W_{day} \times K_{fecal}^{III} \times C_{GI}^{III} + W_{uptake}^{III}$
As^{V}	$\frac{dA_G^{V}}{dt} = Q_G \times \left(C_b^{V} - \frac{C_G^{V}}{P_G^{V}}\right) - Q_G \times \left(\frac{C_G^{V}}{P_G^{V}} - \frac{C_L^{V}}{P_L^{V}}\right) + (k_1 \times C_{GI}^V - k_2 \times C_{GI}^{III}) \times V_{GI} - W_{day} \times K_{fecal}^{V} \times C_{GI}^{III} + W_{uptake}^{V}$
MMA	$\frac{dA_G^{MMA}}{dt} = Q_G \times \left(C_b^{MMA} - \frac{C_G^{MMA}}{P_G^{MMA}}\right) - Q_G \times \left(\frac{C_G^{MMA}}{P_G^{MMA}} - \frac{C_L^{MMA}}{P_L^{MMA}}\right) - W_{day} \times K_{fecal}^{MMA} \times C_{GI}^{MMA}$
DMA	$\frac{dA_G^{DMA}}{dt} = Q_G \times \left(C_b^{DMA} - \frac{C_G^{DMA}}{P_G^{DMA}}\right) - Q_G \times \left(\frac{C_G^{DMA}}{P_G^{DMA}} - \frac{C_L^{DMA}}{P_L^{DMA}}\right) - W_{day} \times K_{fecal}^{DMA} \times C_{GI}^{MMA}$
Liver	
As^{III}	$\frac{dA_L^{III}}{dt} = Q_L \times \left(C_b^{III} - \frac{C_L^{III}}{P_L^{III}}\right) + Q_L \times \left(\frac{C_{GI}^{III}}{P_{GI}^{III}} - \frac{C_L^{III}}{P_L^{III}}\right) - (k_1 \times C_L^V - k_2 \times C_L^{III}) \times V_L - K^{III} \times C_L^{III} - \frac{V_{max,L}^{III\to MMA} \times C_L^{III}}{K_{m,L}^{III\to MMA} + C_L^{III}} - \frac{V_{max,L}^{III\to DMA} \times C_L^{III}}{K_{m,L}^{III\to DMA} + C_L^{III}}$
As^{V}	$\frac{dA_L^{V}}{dt} = Q_L \times \left(C_b^{V} - \frac{C_L^{V}}{P_L^{V}}\right) + Q_{GI} \times \left(\frac{C_{GI}^{V}}{P_{GI}^{V}} - \frac{C_L^{V}}{P_L^{V}}\right) - (K_1 \times C_L^V - K_2 \times C_L^{III}) \times V_L - K^V \times C_L^V$
MMA	$\frac{dA_L^{MMA}}{dt} = Q_L \times \left(C_b^{MMA} - \frac{C_L^{MMA}}{P_L^{MMA}}\right) + Q_{GI} \times \left(\frac{C_{GI}^{MMA}}{P_{GI}^{MMA}} - \frac{C_L^{MMA}}{P_L^{MMA}}\right) + \frac{V_{max,L}^{III\to MMA} \times C_L^{III}}{K_{m,L}^{III\to MMA} + C_L^{III}} - \frac{V_{max,L}^{MMA\to DMA} \times C_L^{MMA}}{K_{m,L}^{MMA\to DMA} + C_L^{MMA}} - K^{MMA} \times C_L^{MMA}$
DMA	$\frac{dA_L^{DMA}}{dt} = Q_L \times \left(C_b^{DMA} - \frac{C_L^{DMA}}{P_L^{DMA}}\right) + Q_{GI} \times \left(\frac{C_{GI}^{DMA}}{P_{GI}^{DMA}} - \frac{C_L^{DMA}}{P_L^{DMA}} + \frac{V_{max,L}^{III\to DMA} \times C_L^{III}}{K_{m,L}^{III\to DMA} + C_L^{III}} - \frac{V_{max,L}^{MMA\to DMA} \times C_L^{MMA}}{K_{m,L}^{MMA\to DMA} + C_L^{MMA}}\right) - K^{DMA} \times C_L^{DMA}$
Body	
As^{III}	$\frac{dA_B^{III}}{dt} = Q_B \times \left(C_b^{III} - \frac{C_B^{III}}{P_B^{III}}\right) + (k_1 \times C_B^V - k_2 \times C_B^{III}) \times V_B$
As^{V}	$\frac{dA_B^{V}}{dt} = Q_B \times \left(C_b^{V} - \frac{C_B^{V}}{P_B^{V}}\right) + (k_1 \times C_B^V - k_2 \times C_B^{III}) \times V_B$
MMA	$\frac{dA_B^{MMA}}{dt} = Q_B \times \left(C_b^{MMA} - \frac{C_B^{MMA}}{P_B^{MMA}}\right)$
DMA	$\frac{dA_B^{DMA}}{dt} = Q_B \times \left(C_b^{DMA} - \frac{C_B^{DMA}}{P_B^{DMA}}\right)$
Blood	
As^{III}	$\frac{dA_b^{III}}{dt} = \left(\sum_{i=1}^{4} Q_i \times \frac{C_i^{III}}{P_i^{III}} - \sum_{i=1}^{4} Q_i \times C_b^{III}\right) + (k_1 \times C_F^V - k_2 \times C_F^{III}) \times V_b$
As^{V}	$\frac{dA_b^{V}}{dt} = \left(\sum_{i=1}^{4} Q_i \times \frac{C_i^{V}}{P_i^{V}} - \sum_{i=1}^{4} Q_i \times C_b^{V}\right) - (k_1 \times C_F^V - k_2 \times C_F^{III}) \times V_b$
MMA	$\frac{dA_b^{MMA}}{dt} = \left(\sum_{i=1}^{4} Q_i \times \frac{C_i^{MMA}}{P_i^{MMA}} - \sum_{i=1}^{4} Q_i \times C_b^{MMA}\right)$
DMA	$\frac{dA_b^{DMA}}{dt} = \left(\sum_{i=1}^{4} Q_i \times \frac{C_i^{DMA}}{P_i^{DMA}} - \sum_{i=1}^{4} Q_i \times C_b^{DMA}\right)$

Abbreviations and parameter symbol: A_i^j is dose of arsenic species j in organ/tissue i (μg), C_i^j is concentration of arsenic species j in organ/tissue i (μg L^{-1}), $K_{m,i}^{j\to k}$ is Michaelis–Menten constant for arsenic species j methylated to k in organ/tissue i (μmol L^{-1}), P_i^j is tissue/blood partition coefficient of arsenic species j in tissue i, V_i is volume of organ/tissue i (L), $V_{max,i}^{j\to k}$ is maximum reaction rate for arsenic species j methylated to k in organ/tissue i (μmol h^{-1}), W_{day} is human daily drinking water amount (L d^{-1}), and W_{day}^j is human daily intakes seafood contain arsenic species j concentration (μg d^{-1}).

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