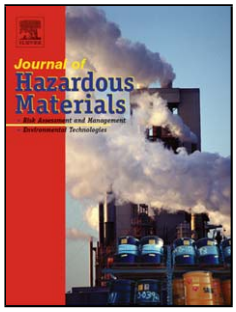
Accepted Manuscript



Title: Assessing the arsenic-contaminated rice (*Oryza sativa*) associated children skin lesions

Authors: Chung-Min Liao, Tzu-Ling Lin, Nan-Hung Hsieh, Wei-Yu Chen

PII: S0304-3894(09)01803-2
DOI: doi:10.1016/j.jhazmat.2009.11.019
Reference: HAZMAT 10887

To appear in: *Journal of Hazardous Materials*

Received date: 7-6-2009
Revised date: 19-9-2009
Accepted date: 3-11-2009

Please cite this article as: C.-M. Liao, T.-L. Lin, N.-H. Hsieh, W.-Y. Chen, Assessing the arsenic-contaminated rice (*Oryza sativa*) associated children skin lesions, *Journal of Hazardous Materials* (2008), doi:10.1016/j.jhazmat.2009.11.019

Assessing the arsenic-contaminated rice (*Oryza sativa*) associated children skin lesions

Chung-Min Liao*, Tzu-Ling Lin, Nan-Hung Hsieh, Wei-Yu Chen
Department of Bioenvironmental Systems Engineering, National Taiwan University, Taipei, Taiwan 10617 Republic of China
*Corresponding author. *E-mail address*: cmliao@ntu.edu.tw

Abstract

The purpose of this study was to assess the potential risk of children skin lesions from arsenic-contaminated rice (*Oryza sativa*) consumption in West Bengal (India). Published age- and gender-specific skin lesions data in West Bengal were reanalyzed and incorporated into a Weibull dose-response model to predict children skin lesion prevalence. Monomethylarsonous acid (MMA(III)) levels in urine was used as a biomarker that could be predicted from a human physiologically based pharmacokinetic (PBPK) model. This study integrated arsenic contents in irrigation water, bioaccumulation factors of paddy soil, cooking methods, and arsenic bioavailability of cooked rice in gastrointestinal tract into a probabilistic risk model. Results indicated that children aged between 13 – 18 years might pose a relative higher potential risk of skin lesions to arsenic-contaminated cooked rice (odds ratios (ORs) = 1.18 (95% CI 1.12 – 2.15)) than those of 1 – 6 years children (ORs = 0.98 (0.85 – 1.40)). This study revealed the need to consider the relationships between cooking method and arsenic in cooked rice when assessing the risk associated with children skin lesions from rice consumption. This study suggested that arsenic-associated skin lesions risk from arsenic-contaminated rice consumption would be reduced significantly by adopting traditional rice cooking method (wash until clean; rice: water = 1:6; discard excess water) as followed in West Bengal (India) and using water containing lower arsenic (e.g., < 10 μg L^{-1}) for cooking.

Keywords: Arsenic; Skin lesions; Cooked rice; Risk assessment; Children

1. Introduction

Recently, one of the most pressing issues in facing with dietary arsenic exposure in Bangladesh and West Bengal (India) is human health risk potential from arsenic-contaminated rice consumption [1-5]. The magnitude of groundwater contaminated with naturally occurring arsenic of alluvial aquifers is particularly severe in Bangladesh and West Bengal (India) where arsenic contaminated groundwater is not only used for drinking water but is also widely used for irrigation of crops [6,7]. Particularly, nearly 30 – 50% of the areas of Bangladesh and West Bengal (India) are irrigated with arsenic-contaminated groundwater to grow dry season rice crops [8-10].

Arsenic-contaminated groundwater for crops irrigation had resulted in elevated arsenic concentration in agricultural soils in Bangladesh, West Bengal (India), and elsewhere [8-15]. Paddy rice (*Oryza sativa*) is the main agricultural crop grown in the arsenic-affected areas of Bangladesh and West Bengal (India) [11]. In the long term this may lead to the accumulation of arsenic in paddy soils and potentially have adverse effects on rice yield and quality, creating a potential risk for future food production and human health effects.

The mechanisms of arsenic transfer from arsenic-contaminated irrigation water to paddy soil and transfer from arsenic-contaminated paddy soil to rice are largely unknown. However, a parsimonious bioaccumulation model may provide a surrogate method to estimate the kinetic constants for the biotransformation processes. The toxic effect of arsenic in any foodstuff is highly dependent on its chemical speciation. Inorganic arsenic compounds are generally thought to be more toxic than organic forms. Meharg et al. [8] indicated that rice grain grown in the arsenic-affected soils had relative high arsenic levels in rice grain of greater than 1.7 $\mu g\ g^{-1}$. Williams et al

[10] indicated that nearly 81% of recovered arsenic was found to be inorganic in Bangladeshi and Indian rice based on the pot experiments.

Laparra et al. [16] indicated that arsenate bioavailability in cooked rice was estimated to be 63 – 99% from a gastrointestinal digestion simulation study. Juhasz et al. [17] indicated that arsenic bioavailability in rice is highly dependent on arsenic speciation varied with rice cultivar, arsenic in irrigation water, and arsenic speciation in cooking water. Juhasz et al. [17] suggested that in assessing arsenic dietary exposure from cooked rice, arsenic speciation and bioavailability are crucial parameters that are needed to be considered. Pal et al. [4] and Sengupta et al. [18] revealed that arsenic content in cooked rice was strong dependent on the cooking methods, indicating that the total arsenic in cooked rice is less than that of in raw rice at rice washing water arsenic concentration of 10 μg L^{-1}, whereas an average 35 – 40% increased in cooked rice at 50 μg L^{-1} of washing water. After cooking, inorganic arsenic contents increase significantly, suggesting that the cooking method together with rice washing water should be considered in arsenic-associated health risk assessment [5,16,18-22].

Some evidence suggests that arsenic-induced skin lesions are early biomarkers of other outcomes such as nonmelanoma skin cancer and cancer of the internal organs [23]. Chronic arsenic exposure and skin lesions (keratosis and hyperpigmentation) are inextricably linked [21,24-27]. There is, however, no effective therapy for skin lesions nowadays [28]. Recently, health effects for arsenic exposure in young children have become a regulatory focus [29,30]. Data used to assess the impact of arsenic exposure on the children arsenic-associated skin lesions are limited but indicate consistently that they have been posed the potential risks [21,23]. Arsenic methylation of urinary arsenic species is strongly associated with skin lesions [23,27,31]. In light of this

relationship between arsenic methylation capacity and children skin lesions together with its effect on manifestation of skin cancer, arsenic-induced skin lesions as a model system was selected to assess children health effects in arseniasis-endemic areas.

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 the PBPK modeling permits the calculation of target tissue doses through integration of information on the external dose, the physiological structure of the human, and biochemical properties of metals. The most human PBPK models for arsenic have a number of similarities [32-35]. The simplest PBPK model for arsenic came from Yu [34]. Yu [34] extended the simplest PBPK model to fit the human child including arsenite (As(III)), arsenate (As(V)), monomethly arsenic (MMA), and dimethylarsinic acid (DMA), and considering both reductive metabolism and methylation. Yu [34] noted that reduction of As(V) to As(III) is a second-order process, dependent on the concentration of both As(V) and glutathione (GSH), suggesting the potential use of a GSH synthesis/depletion submodel linked to the primary kinetic model through the process of arsenic reduction. Yu [35] further refined the model to fit the human adult, indicating that the input parameters that most significantly affected the output of the model were the maximum methylation reaction rate, the level of GSH for determination of the reaction rate of As(V) to As(III), and the urinary excretion constants.

The purpose of this study was to provide a probabilistic risk model for predicting and assessing the arsenic-associated children skin lesions risk from rice *O. sativa* consumption in West Bengal (India). A human PBPK model was linked with a Weibull dose-response model to formulate a probabilistic risk model. The likelihood

of risk was predicted based on the proposed PBPK-Weibull framework followed the published gender/age-specific epidemiological data on arsenic exposure, skin lesions prevalence, and at-risk population from studies conducted in West Bengal (India). Therefore, a risk-based predictive model for arsenic exposure associated children skin lesions from arsenic-contaminated rice consumption was presented. It hoped that this paper can demonstrate the concepts that can be applied generally to the risk assessment in the face of arsenic-associated human health effects in children.

2. Materials and methods

2.1. Quantitative arsenic epidemiological data

Epidemiological data on the arsenic-associated children skin lesions are limited and scarcely. Yet, a remarkable dataset (Appendix A) covers arsenic epidemiology of gander-specific and age-adjusted prevalence of arsenic-induced skin lesions of keratosis and hyperpigmentation in West Bengal (India) [24] gave us the opportunity to test all theoretical considerations of arsenic exposure effects and quantify its strength. A major strength of their study is that it is the first large population-based study with individual exposure data, providing critical information to characterize the exposure-response relationships. The dataset was reanalyzed from the cross-sectional survey conducted between April 1995 and March 1996 to reconstruct quantitatively the pooled arsenic epidemiological data of gender- age-, and skin lesion-specific cumulative prevalence ratios. A total of 7818 individuals were participated in the drinking water study. Water-arsenic levels were obtained from 7683 of the participants (4093 females and 3590 males).

Guha Mazumder and co-workers [24] used a standardized questionnaire to collect information including sources of drinking water, current diet and water intake,

medical symptoms, and height and weight. A detailed description of the recruitment procedure for cross-sectional survey and skin lesions cases ascertainment of keratosis and hyperpigmentation has been reported previously [24]. Guha Mazumder et al. [24] indicated that the age-adjusted prevalence of keratosis was associated strongly to water arsenic levels, rising from zero in the lowest exposure level (< 50 μg L^{-1}) to 8.3×10^{-2} for female based on drinking water arsenic level > 800 μg L^{-1}, and increasing from 0.2×10^{-2} in lowest exposure category to 10.7×10^{-2} for male in the highest exposure level (> 800 μg L^{-1}). Their finding indicated that the steepest exposure-response relationships were found for males. This is due in part to the fact that males have greater water consumption. Their study demonstrated that men had roughly 2 – 3 times the prevalence of both keratosis and hypergigmentation compared to women based on the calculation by dose per body weight. Those with poor nutritional status had an age-adjusted prevalence keratosis that was 1.6 times greater than those considered to be adequately nourished. This suggested that malnutrition may play a role in increasing susceptibility.

Furthermore, the larger number of study participants, 1-year follow-up with more skin lesions cases, and a wider range of arsenic exposure levels (< 50 – > 800 μg L^{-1}) together with gender specific age groups (< 9 – > 60 years) gives us a unique opportunity to investigate the dose-response relationships between ingested arsenic exposure and skin lesions risks.

2.2. Weibull dose-response function and bioaccumulation of rice

A the Weibull probability density function was used to account for the age-specific prevalence ratio for human long-term exposure to low doses of arsenic,

$$g(t,\varepsilon(C)) = \varepsilon(C)k_2 t^{k_2-1}\exp(-\varepsilon(C)t^{k_2}), \quad (1)$$

with

$$\varepsilon(C) = k_0 C^{k_1} + k_3, \quad (2)$$

where $g(t, \varepsilon(C))$ represents the skin lesion-specific prevalence ratio for human exposed to arsenic concentration C (μg L^{-1}) at age t (yr), $\varepsilon(C)$ is the concentration-dependent shape parameter, and k_0, k_1, k_2, and k_3 are the skin lesion-specific best-fitted parameters. The cumulative prevalence ratio for human exposed to arsenic concentration C at age t can then be obtained by integral of Eq. (1) as,

$$P(t, C) = \int_0^t g(t, \varepsilon(C))dt = 1 - \exp(-\varepsilon(C)t^{k_2}) = 1 - \exp(-(k_0 C^{k_1} + k_3)t^{k_2}). \quad (3)$$

A simple bioaccumulation model was used to describe the arsenic accumulate in paddy soil from irrigation water and then from paddy soil bioconcentrate in paddy rice,

$$C_R = \frac{C_S}{C_W} \times \frac{C_R}{C_S} \times C_w = K_{S-W} \times K_{R-S} \times C_W = K_{R-W} \times C_W, \quad (4)$$

where C_R is the arsenic concentration in rice (μg g^{-1}), C_W is the dissolved arsenic concentration in irrigation water (μg mL^{-1}), C_S is the arsenic concentration in paddy soil (μg g^{-1}), $K_{S\text{-}W}$ (mL g^{-1}), $K_{R\text{-}S}$ (g g^{-1}), and $K_{R\text{-}W}$ (mL g^{-1}) are the bioaccumulation constants for soil-water, rice-soil, and rice-water interfaces, respectively.

2.3. Human PBPK model for arsenic

A prototypical human PBPK model for arsenic included compartments for the lung, liver kidney, muscle, fat tissue, skin, and GI tract (Fig. 1A) [32-35]. In this study, the speciation of arsenic considered included As(III), As(V), dimethylarsinous acid (MMA(III)), monomethylarsonic acid (MMA(V)), dimethylarsinous acid (DMA(III)), and dimethylarsinic acid (DMA(V)). The reduction and oxidation processes between

MMA(III) and MMA(V) and between DMA(III) and DMA(V) were incorporated into the kidney and liver compartments (Fig. 1B). The uptake of bioavailable arsenic was considered in the GI tract compartment characterizing by Caco-2 cells [16] (Fig. 1A). In Caco-2 cells, average arsenic retention, transport, and total uptake (retention + transport) from cooked rice can be estimated to be 2.3% (95% CI 0.36 – 8.43 %), 6.70% (2.67 – 15.45%), and 9.33% (3.31 – 22.87%), respectively, based on Laparra et al. [16].

The biotransformation mechanism of arsenic in the body consists of an oxidation/reduction and two methylation reactions in that MMA and DMA also subject to oxidation/reduction [36] (Fig. 1B). Gong et al. [36] indicated that MMA(III) in urine at 25°C was oxidized completely to MMA(V) within 14 d (i.e., $K_4 = 5.95 \times 10^{-3}$ h^{-1}), whereas the conversion of DMA(III) to DMA(V) was completely in 17 h (i.e., $K_6 = 5.88 \times 10^{-2}$ h^{-1}) (Fig. 1B). No information was available for reduction of MMA and DMA. It assumed reasonably that reduction rates of K_3 and K_5 can be estimated from the proportionality of K_1/K_2. The oxidation/reduction of inorganic arsenic takes place in the plasma and in the kidney and liver, whereas the methylation of As(III) takes place mainly in the liver and kidney followed by Michaelis-Menten kinetics [34,35]. Mann et al. [32,33] suggested that the reduction of As(V) to As(III) can be modeled as a first-order oxidation/reduction reaction. It assumed kidney and urine having the same levels of arsenic species.

The age-specific distribution of secondary methylation ratio (DMA/MMA) was used to adjust the age-dependent arsenic methylation rate constants based on a study focused on the excretion of arsenic species in children urine from an arsenic exposed area in Bangladesh [37]. A fitted normal distribution of $y = 1.32 + 2.56\exp(-0.5((x-0.54)/1.0)^2)$ ($r^2 = 0.80$, $p < 0.05$) can be obtained (Fig.

1C). The dynamic behavior of PBPK and metabolic processes in the PBPK model can be described by a set of first-order differential equations (Appendix B). The physiological parameters, age-adjusted metabolic constants, tissue/blood partition coefficients, and biochemical parameters are listed in Tables C1, C2, and C3, respectively (Appendix C).

2.4. Arsenic distributions in irrigation water, paddy soil, and rice

Data sources were derived from published relevant literature where available. The recently published data were analyzed to obtain the arsenic distributions in irrigation water, paddy soil, and paddy rice in West Bengal (India) based on Eq. (4). Arsenic concentration profiles in arsenic-contaminated irrigation water were estimated from Rhaman et al. [7]. Rhaman et al. [7] carried out an in-depth research to determine arsenic contamination in groundwater in an arsenic-affected village of Rajapur in Murshidabad district, West Bengal (India), where the agricultural system was mostly groundwater dependent. The result indicated that 91% and 63% of hand-pump tube-wells contained arsenic concentrations of > 10 and > 50 $\mu g\ L^{-1}$, respectively. The distributions of arsenic in paddy soil in West Bengal (India) were based on Norra et al. [9]. Norra et al. [9] carried out a study in an intensively cultivated agricultural area of the Bengal delta Plain in West Bengal (India) to determine the arsenic contamination degrees in paddy soil. Norra et al. [9] indicated that arsenic concentration in the uppermost paddy soil was found to be 38 $\mu g\ g^{-1}$.

On the other hand, the published data regarding arsenic levels in raw rice were adopted from Roychowdhury et al. [38]. Roychowdhury et al. [38] carried out an investigation for determining the arsenic levels in food composites collected from the villagers in arsenic-affected areas of the Murshidabad district, West Bengal (India).

The result indicated that the highest mean arsenic levels in rice ranged from 226.18 – 245.39 ng g^{-1}. To determine the percentage of arsenic retained in cooked rice varied by different cooking methods, three major cooking methods (designed as cooking methods A, B, and C) used in West Bengal (India) were adopted to estimate arsenic levels in cooked rice [18]. Cooking method A is a traditional method used in West Bengal by which raw rice is washed 5 – 6 times with a ratio of boiled water: weight of rice = 5 – 6:1. In method B, raw rice is washed as method A, yet the boiled water: weight of rice = 1.5 – 2:1. On the other hand, in method C, the raw rice is unwashed with boiled water: weight of rice = 1.5 – 2:1.

2.5. Risk estimation

Odds ratio (OR) was estimated to assess relative magnitude of the effect of arsenic exposure on likelihood of prevalence of children skin lesions at a particular setting. OR can be calculated as: OR $= P_{\exp}(C_{\text{U-MMA(III)}}, t) / P_{\text{con}}(C_{\text{U-MMA(III)}}, t)$ where $P_{\exp}(C_{\text{U-MMA(III)}}, t)$ is the exposed prevalence ratio as a function of urine MMA(III) level and age t, $P_{\text{con}}(C_{\text{U-MMA(III)}}, t)$ is the control prevalence ratio in that prevalence ratio can be predicted by Weibull model and urine MMA(III) level can be predicted from PBPK model.

To assess risk contribution from cooked rice to total arsenic intake, a parsimonious model [3, 8], 100 × (As in cooked rice × 0.575 kg^{-1}/(As in cooked rice × 0.575 kg^{-1} + As in drinking water × 2.0 L)), was adopted to estimate the dietary arsenic exposure including contaminated drinking water calculated from the proposed PBPK model. Here rice consumption rate of 0.575 kg d^{-1} and drinking water consumption of 2.0 L d^{-1} for 13-18 yr children were used to calculate the percentage daily arsenic intake.

The TableCurve 3D (Version 4, AISN Software Inc., Mapleton, OR, USA) was used to perform model fitting to pooled published arsenic epidemiological data to reflect the reasonable trend of dose-response relationships. The Berkeley Madonna: Modeling and Analysis of Dynamic Systems (Version 8.3.9, http://www.berkeleymadonna.com) was used to perform the PBPK simulations. To explicitly quantify the uncertainty/variability of data, a Monte Carlo simulation was performed with 10000 iterations (stability condition) to obtain the 95% confidence interval (CI). The Monte Carlo simulation was implemented by using the Crystal Ball software (Version 2000.2, Decisioneering Inc., Denver, CO, USA). The χ^2 and Kolmogorov-Smirnov (K-S) statistics were used to optimize the goodness-of-fit of the distribution.

3. Results

3.1. Fitting Weibull model to arsenic epidemiological data

Table 1 shows the gender-specific best-fitted parameters k_0, k_1, k_2, and k_3 in Weibull dose-response model for hyperpigmentation and keratosis obtained by fitting Eq. (3) to gender- and skin lesion-specific cumulative prevalence ratios in West Bengal (India) (Tables A1 and A2). The results indicate that male skin lesions have the highest r^2 values (0.94 – 0.96) than female skin lesions (r^2 = 0.91) (Table 1). Specifically, arsenic exposure has notably influence than age (k_1 = 0.61 – 0.70, k_2 = 0.12 – 0.18) for all gender skin lesions, indicating that arsenic exposure is attributable mainly to skin lesion prevalence for residents in West Bengal (India) (Table 1). A similar trend was revealed for arsenic-specific cumulative prevalence ratios for gender- and age-specific skin lesions in the ages of the 6th, 12th, and 18th yr (Fig. 2A, B). This indicated that cumulative prevalence ratios of skin lesions increased with

increasing of arsenic exposure concentration and age.

3.2. Arsenic distributions in water, soil, rice, and cooked rice

The distributions of arsenic in paddy rice, paddy soil, and irrigation water can be best described by the lognormal model (Fig. 3A). Median arsenic level in paddy rice was estimated to be 0.24 μg g^{-1} dry wt (95% CI 0.12 – 0.48) with a geometric standard deviation (gsd) of 1.41, whereas the estimates of arsenic in paddy soil and irrigation water were 15.66 μg g^{-1} (95% CI 5.42 – 43.71) (gsd = 1.70) and 0.06 μg mL^{-1} (95% CI 0.01 – 0.58) (gsd = 2.93), respectively (Fig. 3A). The factors describing the accumulation of arsenic concentration from irrigation water to paddy water ($K_{S\text{-}W}$) and from paddy soil to rice ($K_{R\text{-}S}$) were estimated to be 248 mL g^{-1} (95%CI 24.54 – 2943.15) (gsd = 3.33) and 15.13×10^{-3} g g^{-1} (95%CI 4.51×10^{-3} – 53.73×10^{-3}) (gsd = 1.88), respectively (Fig. 3B). Given that $K_{S\text{-}W}$ and $K_{R\text{-}S}$, bioaccumulation factor between irrigation water and paddy rice $K_{R\text{-}W}$ can be estimated to be 3.84 mL g^{-1} (95%CI 0.38 – 36.53) (gsd = 3.13) (Fig. 3B).

A baseline relationship between arsenic in cooking water and arsenic in cooked rice can be determined by fitting a linear model ($y = 35.14 + 1.44x$, $r^2 = 0.99$) to the published data (Fig. 4A). Given the best-fitted model in Fig. 4A and cooking method-specific estimated percentage of arsenic retained in cooked rice in Fig. 4B, cooking method-specific cooked rice arsenic contents can then be calculated. Fig. 4 C – E shows the profiles describing the relations of cooking method-specific arsenic contents in cooked rice varied with arsenic in cooking water.

3.3. Risk estimates

In estimating OR, two bioavailabilities of α = 22.87% (95% upper limit) and

100% were used to represent the fraction of absorbed arsenic from cooked rice in GI tract. The results show that male average ORs (0.84 – 1.49 for α = 100% and 0.91 – 1.28 for α = 22.87%) were greater than those of female (0.83 – 1.26 for α = 100% and 0.87 – 1.14 for α = 22.87%) among three children age groups (Table 2). ORs of hyperpigmentation (0.83 – 1.49 for α = 100% and 0.87 – 1.28 for α = 22.87%) were greater than that of keratosis (0.97 – 1.12 for α = 100% and 0.97 – 1.05 for α = 22.87%) and increased with increasing of ages in West Bengal (India) (Table 2). Further analysis also revealed that cooking Method C gave higher ORs (1.01 – 1.49) than those of Methods A and B (ORs = 0.84 – 1.24 for Method A and ORs = 1.01 – 1.43 for Method B). The result indicates that among the three cooking methods, Method A had the lowest risk estimate.

Overall predicted OR distributions of children skin lesions gave the mean estimates of 0.98 (95% CI 0.85 – 1.40), 1.09 (1.03 – 1.92) and 1.18 (1.12 – 2.51) for three age groups of 1 – 6, 7 – 12, and 13 – 18 yr, respectively (Fig. 5). The findings indicated that children aged between 7 – 18 years may pose a relative higher potential risk (overall ORs = 1.09 – 1.18) of skin lesions exposed to chronic arsenic from arsenic-contaminated cooked rice consumption compared to 1 – 6 yr-old children (OR = 0.98). The result also showed that arsenic intake from cooked rice accounts for 20.6% and 34.1% of arsenic consumption if cooked rice contained 0.1 and 0.2 $\mu g\ g^{-1}$ of arsenic, respectively, with 100 $\mu g\ L^{-1}$ arsenic in water at a 575 $g\ d^{-1}$ rice consumption rate and a 2 $L\ d^{-1}$ of drinking water intake for 13 – 18 year of age (Fig. 6).

In the present case in West Bengal (India), with a nearly 1 $\mu g\ g^{-1}$ arsenic (upper limit of 95% CI) in cooked rice based on median 0.23 $\mu g\ g^{-1}$ arsenic in paddy rice grown on paddy soils with median 15.6 $\mu g\ g^{-1}$ arsenic (Fig. 5), the present model

estimates 81.2% contribution by cooked rice to dietary arsenic exposure if the 13 – 18 yr children were drinking 2 L of 60 μg L^{-1} arsenic-contaminated water (median arsenic in groundwater). At lower concentrations of arsenic in groundwater (e.g., 10 μg L^{-1}), cooked rice contained arsenic becomes the dominant source of dietary arsenic exposure (Fig. 6). These findings suggested that consumption of arsenic-contaminated cooked rice is a major source of arsenic exposure in West Bengal (India).

4. Discussion

The use of PBPK models in risk assessment has grown substantially in the last decade and should only increase in the future [39]. These types of approaches are necessary to allow more reliable low-dose predictions since they can take into account not only low-dose exposure regimens but also the effects of species differences and nonlinear kinetics for biotransformation. Although building these models may be time-consuming and has to be done for each chemical independently, the knowledge generated is essential to perform risk and safety assessment on low-dose metal exposure regimens with higher levels of confidence.

The Weibull dose-response model based on the published arsenic epidemiological data should provide better estimates of skin lesions prevalence for areas where arsenic concentrations are relative high (e.g., Bangladesh and Taiwan) and for areas where incidence/prevalence rates must be extrapolates to low arsenic concentrations (e.g., USA) [10]. It anticipated that this Weibull model-based arsenic epidemiology and human PBPK approach, which accounts to arsenic-associated children skin lesions risk estimates, might provide the basis of a future population-based risk management strategy.

Furthermore, this approach should have certain advantages over methods for

dose response profile selection that are dependent on the use of arsenic epidemiological data to characterize particular aspects of risk analysis. The main potential application envisaged for Weibull-PBPK approach is with respect to human health, and there is clearly a need for further development and to investigate how well the approach can be transferred from West Bengal (India) to Bangladesh or Taiwan populations to account for plausible greater chronic arsenic exposure and environmental variations.

Williams et al. [12] suggested that the maximum tolerable daily intake (MTDI) of arsenic by rice consumption must not exceed 2 $\mu g\ kg^{-1}$ body mass recommended by World Health Organization (WHO). From a conservative point of view, if a 25 kg 10 yr of age child in West Bengal (India) consumes 0.4 kg d^{-1} of cooked rice [40] with the present estimated average cooked rice of 500 $\mu g\ kg^{-1}$ arsenic; cooked rice will contribute 8 $\mu g\ kg^{-1}$ body weight per day. When added to the water consumption (2 L $d^{-1} \times 60\ \mu g\ L^{-1}$ / 25 kg = 4.8 $\mu g\ kg^{-1}\ d^{-1}$), total consumption is nearly 6.5 times the WHO's arsenic MTDI. The present estimated arsenic daily intake from water and cooked rice (8 + 4.8 = 12.8 $\mu g\ kg^{-1}\ d^{-1}$) is consistent with the estimated provisional tolerable daily intake value of 12.9 $\mu g\ kg^{-1}\ d^{-1}$ for high arsenic-affected families in West Bengal, India by Uchino et al. [40].

The proposed PBPK modeling and Weibull model-based epidemiological framework provides a template for integrating the irrigation water arsenic data, bioaccumulation of paddy soil and rice, epidemiological data, and risk modeling to estimate the children arsenic-associated skin lesions risk from rice consumption. The results revealed that arsenic-rich groundwater in tube-wells in West Bengal would lead to high accumulation of arsenic in paddy soils and potential arsenic transfer into rice. Inevitably, adverse health effect from rice consumption will increase in the most

pronounced arsenic-affected areas. Although the present findings pointed out that consumption of arsenic-contaminated cooked rice in West Bengal (India) are unlikely to pose substantial children skin lesions risk (overall mean ORs = 1.09 – 1.18). Yet, the consequences for arsenic consumption from arsenic-contaminated cooked rice are considerable to the regions where arsenic levels in rice increased from cultivation on arsenic contaminated paddy soils [8,10,14,41].

In conclusion, rice can contain a relatively high amount of arsenic. Human arsenic intake from rice consumption can be substantial because rice is particularly efficient in assimilating arsenic from paddy soils, although the mechanism has not been elucidated. This study revealed that the bioavailability (i.e., the fraction of absorbed arsenic that reaches the GI tract) of inorganic arsenic from cooked rice play an important role in risk assessment. As to our knowledge, very little research has been done in this area. This study implicated the need to consider the relationships between cooking method and arsenic in cooked rice when assessing the risk associated with children skin lesions from arsenic-contaminated rice consumption. This study also indicated that arsenic-associated skin lesions risk from arsenic-contaminated rice consumption would be reduced substantially by adopting traditional rice cooking method A (wash until clean; rice: water = 1:6; discard excess water) as followed in West Bengal (India) and using water containing lower arsenic (e.g., < 10 $\mu g\ L^{-1}$) for cooking.

References

[1] Y.G. Zhu, P.N. Williams, A.A. Meharg. Exposure to inorganic arsenic from rice: A global health issue? Environ. Poll. 154 (2008) 169-171.

[2] Y.J. Zavala, J.M. Duxbury. Arsenic in rice: I. Estimating normal levels of total arsenic in rice grain. Environ. Sci. Technol. 42 (2008) 3856-3860.

[3] J.F. Ma, N. Yamaji, N. Mitani, X.Y. Xu, Y.H. Su, S.P. McGrath, F.J. Zhao. Transpoters of arsenic in rice and their role in arsenic accumulation in rice grain. Proc. Nat. Acad. Sci. USA 105 (2008) 9931-9935.

[4] A. Pal, U. K.U. Chowdhury, D. Mondal, B, Das, B. Nayak, A. Ghosh, S. Maity, D. Chakraborti. Arsenic burden from cooked rice in the populations of arsenic affected and nonaffected areas and Kolkata city in West-Bengal, India. Environ. Sci. Technol 43 (2009) 3349-3355.

[5] G.I. Norton, M.R. Islam, C.M. Deacon, F.J. Zhao, J.L. Stroud, S.P. McGrath, S. Islam, M. Jahiruddin, J. Feldmann, A.H. Price, A.A. Meharg. Identification of low inorganic and total grain arsenic rice cultivars from Bangladesh. Environ. Sci. Technol. 43 (2009) 6070-6075.

[6] T.R. Chowdhury, G.K. Basu, B.K. Mandal, B.K. Biswas, G. Samanta, U.K. Chowdhury, Arsenic poisoning in the Ganges delta. Nature 401 (1999) 545–546.

[7] M.M. Rahman, M.K. Sengupta, S. Ahmad, U.K. Chowdhury, D. Lodh, A. Hossain, Arsenic contamination of groundwater and its health impact on residents in a village in West Bengal, India. Bull. World Health Organ. 83 (2005) 49–57.

[8] A.A. Meharg, M.M. Rahamn, Arsenic contamination of Bangladesh paddy field soils: implications for rice contribution to arsenic consumption. Environ. Sci. Technol. 37 (2003) 229–234.

[9] S. Norra, Z.A. Berner, P. Agarwala, F. Wagner, D. Chandrasekharam, D. Stuben,

Impact of irrigation with As rich groundwater on soil and crops: a geochemical case study in West Bengal delta plain, India. Appl. Geochem. 20 (2005) 18901–18906.

[10] P.N. Williams, A.H. Price, A. Raab, S.A. Hossain, J. Feldmann, A.A. Meharg, Variation in arsenic speciation and concentration in paddy rice related to dietary exposure. Environ. Sci. Technol. 39 (2005) 5531–5540.

[11] T. Roychowdhury, H. Tokunaga, T. Uchino, M. Ando, Effect of arsenic-contaminated irrigation water on agricultural land soil and plants in West Bengal, India. Chemosphere 58 (2005) 799–810.

[12] J. Dittmar, A. Voegelin, L.C. Roberts, S. Hug, G.C. Saha, M.A. Ali, Spatial distribution and temporal variability of arsenic irrigated rice fields in Bangladesh. 2 Paddy soil. Environ. Sci. Technol. 41 (2007) 5967–5972.

[13] L.C. Roberts, S.J. Hug, J. Dittmar, A. Voegelin, G.C. Saha, M.A. Ali, Spatial distribution and temporal variability of arsenic irrigated rice fields in Bangladesh. 1. Irrigation water. Environ. Sci. Technol. 41 (2007) 5960–5966.

[14] G.C. Saha, M.A. Ali, Dynamics of arsenic in agricultural soils irrigated with arsenic contaminated groundwater in Bangladesh. Sci. Total Environ. 379 (2007) 180–189.

[15] M.L. Polizzotto, B.D. Kocar, S.G. Benner, M. Sampson, S. Fendorf. Near-surface wetland sediments as a source of arsenic release to ground water in Asia. Nature 454 (2008) 505-508.

[16] L.M. Laparra, D. Velez, R. Barbera, R. Farre, R. Montoro, Bioavailability of inorganic in cooked rice: practical aspects for human health risk assessments. J. Agric. Food Chem. 53 (2005) 8829–8833.

[17] A. Juhasz, E. Smith, J. Weber, M. Rees, A. Rofe, T. Kuchel, In vivo assessment of

arsenic bioavailability in rice and its significance for human risk assessment. Environ. Health Perspect. 114 (2006) 1826–1831.

[18] M.K. Sengupta, M.A. Hossain, A. Mukherjee, S. Ahamed, B. Das, B. Nayak, Arsenic burden of cooked rice: traditional and modern methods. Food Chem. Toxicol. 44 (2006) 1823–1829.

[19] M. Bae, C. Watanabe, T. Inaoka, M. Sekiyama, N. Sudo, M.H. Bokul, Arsenic in cooked rice in Bangladesh. Lancet 360 (2002) 1839–1840.

[20] A.H. Ackerman, P.A. Creed, A.N. Parks, M.W. Fricke, C.A. Schwegel, J.T. Creed, Comparison of a chemical and enzymatic extraction of arsenic from rice and an assessment of the arsenic absorption from contamination water by cooked rice. Environ. Sci. Technol. 239 (2005) 5241–5246.

[21] M. Rahman, M. Vahter, N. Sohel, M. Yunus, M.A. Wahed, P.K. Streatifeld, Arsenic exposure and age- and sex-specific risk for skin lesions: A population-based case-referent study in Bangladesh. Environ. Health Perspect. 114 (2006) 1847–1852.

[22] V.G.. Mihucz, E. Tatar, I. Virag, C. Zang, Y. Jao, G. Zaray, Arsenic removal from rice by washing and cooking with water. Food Chem. Toxicol.105 (2007) 1718–1725.

[23] G.S. Sun, Y. Xu, X. Li, Y. Jin, B. Li, X. Sun, Urinary arsenic metabolites in children and adults exposed to arsenic in drinking water in Inner Mongolia, China. Environ. Health Perspect. 115 (2007) 648–652.

[24] D.N. Guha Mazumder, R. Haque, N. Ghosh, B.K. De, A. Santra, D. Chakraborty, Arsenic levels in drinking water and the prevalence of skin lesions in West Bengal, India. Int. J. Epidemiol. 27 (1998) 871–877.

[25] B.K. Caldwell, W.T. Smith, K. Lokuge, G. Ramnuthugala, K. Dear, A.H. Milton,

Access to drinking-water and arsenicosis in Bangladesh. J. Heatlh Popul. Nutr. 224 (2006) 336–345.

[26] C. McDonald, R. Hoque, N. Huda, N. Cherry, Prevalence of arsenic-related skin lesions in 53 Widely-scattered villages of Bangladesh: an ecological survey. J. Heatlh Popul. Nutr. 24 (2006) 228–235.

[27] K.M. McCarty, Y.C. Chen, Q. Quamruzzaman, M. Rahman, G. Mahiuddin, Y.M. Hsueh, Arsenic methylation, GSTT1, GSTM1, GSTM1, GSTP1 polymorphisms, and skin lesions. Environ. Health Perspect. 115 (2007) 341−345.

[28] Y. Bhattacharjee, Toxicology - A sluggish response to humanity's biggest mass poisoning. Science 315 (2007) 1659–1661.

[29] ATSDR, Toxicological profile for arsenic (uptake). U.S. Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA. (2000)

[30] US EPA, Arsenic in Drinking Water. US Environmental Protection Agency. Washington DC. (2002)

[31] O.L. Valenzuela, V.H. Borja-Aburto, G.G..Garcia-Vargas, M.B. Cruz-Gonzalez, E.A. Garcia-Montalvo, E.S. Calderon-Aranda, Urinary trivalent methylated arsenic species in a population chronically exposed to inorganic arsenic. Environ. Health Perspect. 113 (2005) 250−254.

[32] S. Mann, P.O. Droz, M. Vahter, A physiologically based pharmacokinetic model for arsenic exposure. I. Development in hamsters and rabbits. Toxicol. Appl. Pharmacol. 137 (1996) 8–22.

[33] S. Mann, P.O. Droz, M. Vahter, A physiologically based pharmacokinetic model for arsenic exposure. II. Validation and application in humans. Toxicol. Appl. Pharmacol. 140 (1996) 471–486.

[34] D. Yu, Uncertainties in a pharmacokinetic modeling for inorganic arsenic. J

Environ Sci Health A 33 (1998) 1369−1390.

[35] D. Yu, A physiologically based pharmacokinetic model of inorganic arsenic. Regul. Toxicol. Pharmacol. 29 (1999) 128−141.

[36] Z. Gong, X. Lu, W.R. Cullen, X.C. Le, Unstable trivalent arsenic metabolites, monomethylarsonous acid and dimethylarsinous acid. J. Anal. At. Spectrom. 16 (2001) 1409−1413.

[37] U.K. Chowdhury, M.M. Rahman, M.K. Sengupta, D. Lodh, C.R. Chanda, S. Roy, Pattern of excretion of arsenic compounds [arsenite, arsenate, MMA(V), DMA(V)] in urine of children compared to adults from an arsenic exposed area in Bangladesh. J. Environ. Sci. Health A 38 (2003) 87−113.

[38] T. Roychowdhury, T. Uchino, H. Tokunaga, M. Ando, Survey of arsenic in food composites from an arsenic-affected area of West Bengal, India. Food Chem Toxicol. 40 (2002) 1611−1621.

[39] M.B. Reddy, R.S.H. Yang, H.J. Clewell III, M.E. Andersen. Physiologically based pharmacokinetic modeling: Science and Application. 2005. John Wiley & Sons, New York, NY.

[40] T. Uchino, T. Roychodhury, M. Ando, H. Tokunaga, Intake of arsenic from water, food composites and excretion through urine, hair from a studied population in West Bengal, India. Food Chem. Toxicol. 44 (2006) 455−461.

[41] A.A. Meharg, G. Sun, P.N. Williams, E. Adomako, C. Deacon, Y.G. Zhu, J. Feldmann, A. Raab. Inorganic arsenic levels in baby rice are of concern. Environ. Poll. 152 (2008) 746-749.

[42] K. Price, S. Haddad, K. Krishnan, Physiological modeling of age-specific changes in the pharmacokinetics of organic chemicals in children. J. Toxicol. Environ. Health A 66 (2003) 417−433.

[43] S. Haddad, C. Restieri, K. Krishnan, Characterization of age-related changes in body weights and organ weights from birth to adolescence in humans. J. Toxicol. Environ. Health Part A 64 (2001) 453–464.

[44] A.M. Hissink, L.W. Wormhoudt, P.J. Sherratt, J.D. Hayes, J.N.M. Commandeur, N.P.E. Vermeulen, A physiologically-based pharmacokinetic (PB-PK) model for ethylene dibromide: relevance of extrahepatic metabolism. Food Chem. Toxicol. 38 (2000) 707–716.

[45] D. Yu, J.K. Kim, A physiologically based assessment of human exposure to radon released from groundwater. Chemosphere 54 (2004) 639–645.

[46] Y.C. Huang, Introduction to anatomy and physiology. Taipei, Taiwan: Hweihua Publishing Company; Chap 14, pp. (2000) 589–609.

Appendix A: Study Data

Table A1

Epidemiological data of gender– and age–specific hyperpigmentation prevalence ratio varied with arsenic exposure concentrations in West Bengal (India)[a]

Age group	Arsenic concentration (μg L^{-1})								
	<50	50–99	100–149	150–199	200–349	350–499	500–799	≥800	Total
					Male				
≤9	0.0 (0)[b]	0.0 (0)	4.6 (3)	3.7 (1)	3.9 (3)	0.0 (0)	7.1 (2)	7.19 (2)	2.0 (12)
10–19	0.0 (0)	2.7 (2)	2.0 (1)	3.6 (2)	9.4 (9)	11.8 (6)	3.1 (2)	13.8 (4)	3.5 (26)
20–29	0.8 (3)	1.3 (1)	12.5 (7)	11.5 (6)	17.7 (14)	14.0 (6)	13.6 (8)	30.69 (9)	7.5 (54)
30–39	0.4 (1)	3.2 (2)	15.8 (6)	12.5 (5)	13.3 (10)	22.7 (10)	22.6 (12)	33.3 (6)	9.0 (52)
40–49	0.0 (0)	11.6 (5)	10.3 (3)	8.3 (2)	13.2 (7)	40.9 (9)	16.0 (4)	25.0 (3)	9.0 (53)
50–59	2.5 (3)	6.9 (2)	5.9 (1)	6.7 (1)	28.6 (10)	15.8 (3)	39.1 (9)	45.5 (5)	12.6 (34)
≥60	0.0 (0)	2.9 (1)	45.0 (9)	9.5 (2)	18.5 (5)	6.3 (1)	33.3 (5)	0.0 (0)	8.7 (23)
All age	0.5 (7)	3.4 (13)	11.0 (30)	8.1 (19)	13.2 (58)	15.5 (38)	12.5 (40)	22.5 (29)	6.5 (254)
Age–adjusted	0.4	3.2	11.0	7.8	13.1	15.7	13.8	22.7	6.4
					Female				
≤9	0.0 (0)	0.0 (0)	1.9 (1)	0.0 (0)	2.4 (2)	12.0 (6)	0.0 (0)	0.0 (0)	1.7 (9)
10–19	0.0 (0)	0.0 (0)	1.7 (1)	5.6 (3)	7.7 (9)	1.8 (1)	3.1 (2)	11.5 (3)	2.2 (19)
20–29	0.0 (0)	0.0 (0)	1.0 (1)	4.0 (3)	4.4 (6)	11.1 (7)	6.0 (5)	8.3 (2)	2.1 (24)
30–39	0.0 (0)	1.3 (1)	12.5 (6)	6.5 (3)	8.9 (7)	12.5 (5)	0.0 (0)	6.7 (1)	3.5 (23)
40–49	1.4 (2)	0.0 (0)	13.0 (3)	37.0 (1)	16.7 (6)	14.3 (3)	17.9 (5)	20.0 (2)	6.2 (22)
50–59	1.9 (3)	2.6 (1)	13.0 (3)	11.1 (2)	0.0 (0)	5.6 (1)	16.7 (5)	27.3 (3)	5.6 (12)
≥60	0.0 (0)	6.9 (2)	11.1 (1)	11.8 (2)	7.4 (2)	15.0 (3)	0.0 (0)	33.3 (2)	5.6 (12)
All age	0.3 (5)	1.0 (4)	5.1 (16)	5.4 (14)	6.3 (32)	9.7 (26)	5.1 (17)	11.0 (13)	3.1 (127)
age–adjusted	0.3	0.8	5.7	5.1	6.5	9.5	5.3	11.5	31

[a] Adopted from Guha mazumder et al. [24].

[b] Observed number.

Table A2
Epidemiological data of gender– and age–specific keratosis ratio varied with arsenic exposure concentrations in West Bengal (India)[a]

Age group	Arsenic concentration (μg L^{-1})								
	<50	50–99	100–149	150–199	200–349	350–499	500–799	≥800	Total
					Male				
≤9	0.0 (0)[b]	0.0 (0)	0.0 (0)	3.7 (1)	1.3 (1)	2.0 (1)	0.0 (0)	0.0 (0)	0.5 (3)
10–19	0.3 (1)	0.0 (0)	0.0 (0)	1.8 (1)	5.2 (5)	3.9 (2)	3.1 (2)	6.9 (2)	1.7 (13)
20–29	0.0 (0)	0.0 (0)	1.8 (1)	3.8 (2)	5.1 (4)	7.0 (3)	10.2 (6)	20.0 (5)	2.8 (21)
30–39	0.4 (1)	3.7 (2)	2.6 (1)	7.5 (3)	6.7 (5)	15.9 (7)	18.9 (10)	22.2 (4)	5.7 (33)
40–49	0.0 (0)	4.7 (2)	0.0 (0)	8.3 (2)	5.7 (3)	27.3 (6)	12.0 (3)	8.3 (1)	4.6 (17)
50–59	0.8 (1)	6.9 (2)	59 (1)	6.7 (1)	8.6 (3)	15.8 (3)	13.0 (3)	9.1 (1)	5.6 (15)
≥60	0.8 (1)	0.0 (0)	5.0 (1)	4.8 (1)	3.7 (1)	0.0 (0)	13.3 (2)	0.0 (0)	2.3 (6)
All age	0.3 (4)	1.6 (6)	1.5 (4)	4.7 (11)	5.0 (22)	8.9 (22)	8.1 (26)	10.1 (13)	3.0 (108)
Age–adjusted	0.2	1.5	1.6	4.7	4.9	9.0	8.9	10.7	3.0
					Female				
≤9	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	2.0 (1)	0.0 (0)	0.0 (0)	0.2 (1)
10–19	0.0 (0)	0.0 (0)	0.0 (0)	1.9 (1)	2.6 (3)	0.0 (0)	3.1 (2)	11.5 (3)	1.0 (9)
20–29	0.0 (0)	0.0 (0)	1.0 (1)	1.4 (1)	1.5 (2)	3.2 (2)	0.0 (0)	4.2 (1)	0.6 (7)
30–39	0.0 (0)	2.5 (2)	0.0 (0)	2.2 (1)	2.5 (2)	2.5 (1)	4.6 (1)	0.0 (0)	1.2 (8)
40–49	0.0 (0)	0.0 (0)	0.0 (0)	0.0 (0)	5.6 (2)	9.5 (2)	10.7 (3)	10.0 (1)	2.3 (8)
50–59	0.0 (0)	0.0 (0)	4.4 (1)	11.1 (2)	0.0 (0)	0.0 (0)	10.0 (3)	27.3 (3)	2.8 (8)
≥60	0.0 (0)	0.0 (0)	11.1 (1)	5.9 (1)	3.7 (1)	5.0 (1)	0.0 (0)	33.3 (2)	2.8 (9)
All age	0.0 (0)	0.5 (2)	1.0 (3)	2.3 (6)	2.0 (10)	2.6 (7)	3.0 (10)	8.5 (10)	1.2 (6)
age–adjusted	0.0	0.4	1.2	2.3	2.0	2.7	3.1	8.3	1.2

[a] Adopted from Guha mazumder et al. [24].

[b] Observed number.

Appendix B: Equations used for the proposed human arsenic PBPK model

Lung

As^{3+}

$$\frac{dA_{Lung}^{3+}}{dt} = Q_{Lung} \times (C_a^{As^{3+}} - \frac{C_{Lung}^{As^{3+}}}{\mathrm{P}_{\mathrm{Lung}}^{3+}}) + (\mathrm{K}_1 \times C_{Lung}^{As^{5+}} - \mathrm{K}_2 \times C_{Lung}^{As^{3+}}) \times V_{Lung}$$

As^{5+}

$$\frac{dA_{Lung}^{As^{5+}}}{dt} = Q_{Lung} \times (C_a^{As^{5+}} - \frac{C_{Lung}^{As^{5+}}}{\mathrm{P}_{\mathrm{Lung}}^{5+}}) - (\mathrm{K}_1 \times C_{Lung}^{As^{5+}} - \mathrm{K}_2 \times C_{Lung}^{As^{5+}}) \times V_{Lung}$$

MMA^{5+}

$$\frac{dA_{Lung}^{MMA^{5+}}}{dt} = Q_{Lung} \times (C_a^{MMA^{5+}} - \frac{C_{Lung}^{MMA^{5+}}}{P_{Lung}^{MMA^{5+}}})$$

MMA^{3+}

$$\frac{dA_{Lung}^{MMA^{3+}}}{dt} = Q_{Lung} \times (C_a^{MMA^{3+}} - \frac{C_{Lung}^{MMA^{3+}}}{P_{Lung}^{MMA^{3+}}})$$

DMA^{5+}

$$\frac{dA_{Lung}^{DMA^{5+}}}{dt} = Q_{Lung} \times (C_a^{DMA^{5+}} - \frac{C_{Lung}^{DMA^{5+}}}{P_{Lung}^{DMA^{5+}}})$$

DMA^{3+}

$$\frac{dA_{Lung}^{DMA^{3+}}}{dt} = Q_{Lung} \times (C_a^{DMA^{3+}} - \frac{C_{Lung}^{DMA^{3+}}}{P_{Lung}^{DMA^{3+}}})$$

Kidney (urine)

As^{3+}

$$\frac{dA_{Kid}^{As^{3+}}}{dt} = Q_{Kid} \times (C_a^{As^{3+}} - \frac{C_{Kid}^{As^{3+}}}{\mathrm{P}_{\mathrm{Kid}}^{\mathrm{As}^{3+}}}) + (\mathrm{K}_1 \times C_{Kid}^{As^{5+}} - \mathrm{K}_2 \times C_{Kid}^{As^{3+}}) \times V_{Kid} - \frac{\mathrm{V}_{\mathrm{max,Kid}}^{\mathrm{As}^{3+} \to \mathrm{MMA}^{5+}} \times C_{Kid}^{As^{3+}}}{\mathrm{K}_{\mathrm{m,Kid}}^{\mathrm{As}^{3+} \to \mathrm{MMA}^{5+}} + C_{Kid}^{As^{3+}}}$$

$$- \frac{\mathrm{V}_{\mathrm{max,Kid}}^{\mathrm{As}^{3+} \to \mathrm{DMA}^{5+}} \times C_{Kid}^{As^{3+}}}{\mathrm{K}_{\mathrm{m,Kid}}^{\mathrm{As}^{3+} \to \mathrm{DMA}^{5+}} + C_{Kid}^{As^{3+}}} - W_{day} \times \mathrm{K}_{\mathrm{urine}} \times \frac{C_{Kid}^{As^{3+}}}{\mathrm{P}_{\mathrm{Kid}}^{As^{3+}}}$$

As^{5+}

$$\frac{dA_{Kid}^{As^{5+}}}{dt} = Q_{Kid} \times (C_a^{As^{5+}} - \frac{C_{Kid}^{As^{5+}}}{\mathrm{P}_{\mathrm{Kid}}^{\mathrm{As}^{5+}}}) - (\mathrm{K}_1 \times C_{Kid}^{As^{5+}} - \mathrm{K}_2 \times C_{Kid}^{As^{3+}}) \times V_{Kid} - W_{day} \times \mathrm{K}_{\mathrm{urine}} \times \frac{C_{Kid}^{As^{5+}}}{\mathrm{P}_{\mathrm{Kid}}^{\mathrm{As}^{5+}}}$$

MMA^{5+}

$$\frac{dA_{Kid}^{MMA^{5+}}}{dt} = Q_{Kid} \times (C_a^{MMA^{5+}} - \frac{C_{Kid}^{MMA^{5+}}}{P_{Kid}^{MMA^{5+}}}) + \frac{V_{\mathrm{max,Kid}}^{As^{3+} \to MMA^{5+}} \times C_{Kid}^{As^{3+}}}{K_{m,Kid}^{As^{3+} \to MMA^{5+}} + C_{Kid}^{As^{3+}}} - K_3 \times C_{Kid}^{MMA^{5+}} + K_4 \times C_{Kid}^{MMA^{3+}}$$

$$W_{day} \times K_{Urine} \times \frac{C_{Kid}^{MMA^{5+}}}{P_{Kid}^{MMA^{5+}}}$$

MMA^{3+}

$$\frac{dA_{Kid}^{MMA^{3+}}}{dt} = Q_{Kid} \times (C_a^{MMA^{3+}} - \frac{C_{Kid}^{MMA^{3+}}}{P_{Kid}^{MMA^{3+}}}) + K_3 \times C_{Kid}^{MMA^{5+}} - K_4 \times C_{Kid}^{MMA^{3+}} - \frac{V_{\mathrm{max,Kid}}^{MMA^{3+} \to DMA^{5+}} \times C_{Kid}^{MMA^{3+}}}{K_{m,Kid}^{MMA^{3+} \to DMA^{5+}} + C_{Kid}^{MMA^{3+}}}$$

$$W_{day} \times K_{Urine} \times \frac{C_{Kid}^{MMA^{3+}}}{P_{Kid}^{MMA^{3+}}}$$

DMA^{5+}

$$\frac{dA_{Kid}^{DMA^{5+}}}{dt} = Q_{Kid} \times (C_a^{DMA^{5+}} - \frac{C_{Kid}^{DMA^{5+}}}{P_{Kid}^{DMA^{5+}}}) + \frac{V_{\max,Kid}^{MMA^{3+}\to DMA^{5+}} \times C_{Kid}^{DMA^{3+}}}{K_{m,Kid}^{MMA^{3+}\to DMA^{5+}} + C_{Kid}^{DMA^{3+}}} - K_5 \times C_{Kid}^{DMA^{5+}} + K_6 \times C_{Kid}^{DMA^{3+}}$$

DMA^{3+}

$$+ \frac{V_{\max,Kid}^{As^{3+}\to DMA^{5+}} \times C_{Kid}^{As^{3+}}}{K_{m,Kid}^{As^{3+}\to DMA^{5+}} + C_{Kid}^{As^{3+}}} - W_{day} \times K_{Urine} \times \frac{C_{Kid}^{DMA^{5+}}}{P_{Kid}^{DMA^{5+}}}$$

$$\frac{dA_{Kid}^{DMA^{3+}}}{dt} = Q_{Kid} \times (C_a^{DMA^{3+}} - \frac{C_{Kid}^{DMA^{3+}}}{P_{Kid}^{DMA^{3+}}}) + K_5 \times C_{Kid}^{DMA^{5+}} - K_6 \times C_{Kid}^{DMA^{3+}} - W_{day} \times K_{Urine} \times \frac{C_{Kid}^{DMA^{3+}}}{P_{Kid}^{DMA^{3+}}}$$

Skin

As^{3+}

$$\frac{dA_{Skin}^{As^{3+}}}{dt} = Q_{Skin} \times (C_a^{As^{3+}} - \frac{C_{Skin}^{As^{3+}}}{\mathrm{P}_{\mathrm{Skin}}^{\mathrm{As}^{3+}}}) + (\mathrm{K}_1 \times C_{Skin}^{As^{5+}} - \mathrm{K}_2 \times C_{Skin}^{As^{3+}}) \times V_{Skin} - W_{day} \times \mathrm{K}_{\mathrm{Skin}} \times C_{Skin}^{As^{3+}}$$

As^{5+}

$$\frac{dA_{Skin}^{As^{5+}}}{dt} = Q_{Skin} \times (C_a^{As^{5+}} - \frac{C_{Skin}^{As^{5+}}}{\mathrm{P}_{\mathrm{Skin}}^{\mathrm{As}^{5+}}}) - (\mathrm{K}_1 \times C_{Skin}^{As^{5+}} - \mathrm{K}_2 \times C_{Skin}^{As^{3+}}) \times V_{Skin} - W_{day} \times \mathrm{K}_{\mathrm{Skin}} \times C_{Skin}^{As^{5+}}$$

MMA^{5+}

$$\frac{dMMA_{Skin}^{MMA^{5+}}}{dt} = Q_{Skin} \times (C_a^{MMA^{5+}} - \frac{C_{Skin}^{MMA^{5+}}}{P_{Skin}^{MMA^{5+}}}) - W_{day} \times K_{Skin} \times C_{Skin}^{MMA^{5+}}$$

MMA^{3+}

$$\frac{dMMA_{Skin}^{MMA^{3+}}}{dt} = Q_{Skin} \times (C_a^{MMA^{3+}} - \frac{C_{Skin}^{MMA^{3+}}}{P_{Skin}^{MMA^{3+}}}) - W_{day} \times K_{Skin} \times C_{Skin}^{MMA^{3+}}$$

DMA^{5+}

$$\frac{dMMA_{Skin}^{DMA^{5+}}}{dt} = Q_{Skin} \times (C_a^{DMA^{5+}} - \frac{C_{Skin}^{DMA^{5+}}}{P_{Skin}^{DMA^{5+}}}) - W_{day} \times K_{Skin} \times C_{Skin}^{DMA^{5+}}$$

DMA^{3+}

$$\frac{dMMA_{Skin}^{DMA^{3+}}}{dt} = Q_{Skin} \times (C_a^{DMA^{3+}} - \frac{C_{Skin}^{DMA^{3+}}}{P_{Skin}^{DMA^{3+}}}) - W_{day} \times K_{Skin} \times C_{Skin}^{DMA^{3+}}$$

G.I. tract

As^{3+}

$$\frac{dA_{GI}^{As^{3+}}}{dt} = Q_{GI} \times (C_a^{As^{3+}} - \frac{C_{GI}^{As^{3+}}}{\mathrm{P}_{\mathrm{GI}}^{\mathrm{As}^{3+}}}) - Q_{GI} \times (\frac{C_{GI}^{As^{3+}}}{\mathrm{P}_{\mathrm{GI}}^{\mathrm{As}^{3+}}} - \frac{C_{Liver}^{As^{3+}}}{\mathrm{P}_{\mathrm{Liver}}^{\mathrm{As}^{3+}}}) + (\mathrm{K}_1 \times C_{GI}^{As^{5+}} - \mathrm{K}_2 \times C_{GI}^{As^{3+}}) \times V_{GI} - W_{day} \times \mathrm{K}_{\mathrm{GI}} \times C_{GI}^{As^{3+}} + \mathrm{K}_{\mathrm{uptake}}^{\mathrm{As}^{3+}}$$

As^{5+}

$$\frac{dA_{GI}^{As^{5+}}}{dt} = Q_{GI} \times (C_a^{As^{5+}} - \frac{C_{GI}^{As^{5+}}}{\mathrm{P}_{\mathrm{GI}}^{\mathrm{As}^{5+}}}) - Q_{GI} \times (\frac{C_{GI}^{As^{5+}}}{\mathrm{P}_{\mathrm{GI}}^{\mathrm{As}^{5+}}} - \frac{C_{Liver}^{As^{5+}}}{\mathrm{P}_{\mathrm{Liver}}^{\mathrm{As}^{5+}}}) - (\mathrm{K}_1 \times C_{GI}^{As^{5+}} - \mathrm{K}_2 \times C_{GI}^{As^{3+}}) \times V_{GI} - W_{day} \times \mathrm{K}_{\mathrm{GI}} \times C_{GI}^{As^{3+}} + \mathrm{K}_{\mathrm{uptake}}^{\mathrm{As}^{5+}}$$

MMA^{5+}

$$\frac{dMMA_{GI}^{5+}}{dt} = Q_{GI} \times (C_a^{MMA^{5+}} - \frac{C_{GI}^{MMA^{5+}}}{P_{GI}^{MMA^{5+}}}) - Q_{GI} \times (\frac{C_{GI}^{MMA^{5+}}}{P_{GI}^{MMA^{5+}}} - \frac{C_{Liver}^{MMA^{5+}}}{P_{Liver}^{MMA^{5+}}}) - W_{day} \times K_{GI} \times C_{GI}^{MMA^{5+}}$$

MMA^{3+}

$$\frac{dMMA_{GI}^{3+}}{dt} = Q_{GI} \times (C_a^{MMA^{3+}} - \frac{C_{GI}^{MMA^{3+}}}{P_{GI}^{MMA^{3+}}}) - Q_{GI} \times (\frac{C_{GI}^{MMA^{3+}}}{P_{GI}^{MMA^{3+}}} - \frac{C_{Liver}^{MMA^{3+}}}{P_{Liver}^{MMA^{3+}}}) - W_{day} \times K_{GI} \times C_{GI}^{MMA^{3+}}$$

DMA^{5+}

$$\frac{dDMA_{GI}^{5+}}{dt} = Q_{GI} \times (C_a^{DMA^{5+}} - \frac{C_{GI}^{DMA^{5+}}}{P_{GI}^{DMA^{5+}}}) - Q_{GI} \times (\frac{C_{GI}^{DMA^{5+}}}{P_{GI}^{DMA^{5+}}} - \frac{C_{Liver}^{DMA^{5+}}}{P_{Liver}^{DMA^{5+}}}) - W_{day} \times K_{GI} \times C_{GI}^{DMA^{5+}}$$

DMA^{3+}

$$\frac{dDMA_{GI}^{3+}}{dt} = Q_{GI} \times (C_a^{DMA^{3+}} - \frac{C_{GI}^{DMA^{3+}}}{P_{GI}^{DMA^{3+}}}) - Q_{GI} \times (\frac{C_{GI}^{DMA^{3+}}}{P_{GI}^{DMA^{3+}}} - \frac{C_{Liver}^{DMA^{3+}}}{P_{Liver}^{DMA^{3+}}}) - W_{day} \times K_{GI} \times C_{GI}^{DMA^{3+}}$$

Liver

As^{3+}

$$\frac{dA_{Liver}^{As^{3+}}}{dt} = Q_{Liver} \times (C_a^{As^{3+}} - \frac{C_{Liver}^{As^{3+}}}{\mathrm{P}_{\mathrm{Liver}}^{\mathrm{As}^{3+}}}) + Q_{GI} \times (\frac{C_{GI}^{As^{3+}}}{\mathrm{P}_{\mathrm{GI}}^{\mathrm{As}^{3+}}} - \frac{C_{Liver}^{As^{3+}}}{\mathrm{P}_{\mathrm{Liver}}^{\mathrm{As}^{3+}}}) + (\mathrm{K}_1 \times C_{Liver}^{As^{5+}} - \mathrm{K}_2 \times C_{Liver}^{As^{3+}}) \times V_{Liver} - \mathrm{W}_{\mathrm{Biliary}} \times C_{Liver}^{As^{3+}}$$
$$- \frac{\mathrm{V}_{\mathrm{max,Liver}}^{3+\to \mathrm{MMA}^{5+}} \times C_{Liver}^{3+}}{\mathrm{K}_{\mathrm{m,Liver}}^{3+\to \mathrm{MMA}^{5+}} + C_{Liver}^{3+}} - \frac{\mathrm{V}_{\mathrm{max,Liver}}^{3+\to \mathrm{DMA}^{5+}} \times C_{Liver}^{III}}{\mathrm{K}_{\mathrm{m,Liver}}^{3+\to \mathrm{DMA}^{5+}} + C_{Liver}^{III}}$$

As^{5+}

$$\frac{dA_{Liver}^{As^{5+}}}{dt} = Q_{Liver} \times (C_a^{As^{5+}} - \frac{C_{Liver}^{As^{5+}}}{P_{Liver}^{As^{5+}}}) + Q_{GI} \times (\frac{C_{GI}^{As^{5+}}}{P_{GI}^{As^{5+}}} - \frac{C_{Liver}^{As^{5+}}}{P_{Liver}^{As^{5+}}}) - (K_1 \times C_{Liver}^{As^{5+}} - K_2 \times C_{Liver}^{As^{3+}}) \times V_{Liver} - W_{Biliary} \times C_{Liver}^{As^{5+}}$$

MMA^{5+}

$$\frac{dMMA^{5+}}{dt} = Q_{Liver} \times (C_a^{MMA^{5+}} - \frac{C_{Liver}^{MMA^{5+}}}{P_{Liver}^{MMA^{5+}}}) + Q_{GI} \times (\frac{C_{GI}^{MMA^{5+}}}{P_{GI}^{MMA^{5+}}} - \frac{C_{Liver}^{MMA^{5+}}}{P_{Liver}^{MMA^{5+}}}) + \frac{V_{\max,Liver}^{As^{3+} \to MMA^{5+}} \times C_{Liver}^{As^{3+}}}{K_{m,Liver}^{As^{3+} \to MMA^{5+}} + C_{Liver}^{As^{3+}}}$$

MMA^{3+}

$$- K_3 \times C_{Liver}^{MMA^{5+}} + K_4 \times C_{Liver}^{MMA^{3+}} - W_{Biliary} \times C_{Liver}^{MMA^{5+}}$$

$$\frac{dMMA^{3+}}{dt} = Q_{Liver} \times (C_a^{MMA^{3+}} - \frac{C_{Liver}^{MMA^{3+}}}{P_{Liver}^{MMA^{3+}}}) + Q_{GI} \times (\frac{C_{GI}^{MMA^{3+}}}{P_{GI}^{MMA^{3+}}} - \frac{C_{Liver}^{MMA^{3+}}}{P_{Liver}^{MMA^{3+}}}) + K_3 \times C_{Liver}^{MMA^{5+}} - K_4 \times C_{Liver}^{MMA^{3+}}$$

$$- \frac{V_{\max,Liver}^{MMA^{3+} \to DMA^{5+}} \times C_{Liver}^{MMA^{3+}}}{K_{m,Liver}^{MMA^{3+} \to DMA^{5+}} + C_{Liver}^{MMA^{3+}}} - W_{Biliary} \times C_{Liver}^{MMA^{3+}}$$

DMA^{5+}

$$\frac{dDMA^{5+}}{dt} = Q_{Liver} \times (C_a^{DMA^{5+}} - \frac{C_{Liver}^{DMA^{5+}}}{P_{Liver}^{DMA^{5+}}}) + Q_{GI} \times (\frac{C_{GI}^{DMA^{5+}}}{P_{GI}^{DMA^{5+}}} - \frac{C_{Liver}^{DMA^{5+}}}{P_{Liver}^{DMA^{5+}}}) + \frac{V_{\max,Liver}^{As^{3+} \to DMA^{5+}} \times C_{Liver}^{As^{3+}}}{K_{m,Liver}^{As^{3+} \to DMA^{5+}} + C_{Liver}^{As^{3+}}}$$

DMA^{3+}

$$+ \frac{V_{\max,Liver}^{MMA^{3+} \to DMA^{5+}} \times C_{Liver}^{MMA^{3+}}}{K_{m,Liver}^{MMA^{3+} \to DMA^{5+}} + C_{Liver}^{MMA^{3+}}} - K_5 \times C_{Liver}^{DMA^{5+}} + K_6 \times C_{Liver}^{DMA^{3+}} - W_{Biliary} \times C_{Liver}^{MMA^{5+}}$$

$$\frac{dDMA^{3+}}{dt} = Q_{Liver} \times (C_a^{DMA^{3+}} - \frac{C_{Liver}^{DMA^{3+}}}{P_{Liver}^{DMA^{3+}}}) + Q_{GI} \times (\frac{C_{GI}^{DMA^{3+}}}{P_{GI}^{DMA^{3+}}} - \frac{C_{Liver}^{DMA^{3+}}}{P_{Liver}^{DMA^{3+}}}) + K_5 \times C_{Liver}^{DMA^{5+}} - K_6 \times C_{Liver}^{DMA^{3+}}$$

$$- W_{Biliary} \times C_{Liver}^{MMA^{3+}}$$

Muscle

As^{3+}

$$\frac{dA_{Muscle}^{As^{3+}}}{dt} = Q_{Muscle} \times (C_a^{As^{3+}} - \frac{C_{Muscle}^{As^{3+}}}{P_{Muscle}^{As^{3+}}}) + (K_1 \times C_{Muscle}^{As^{5+}} - K_2 \times C_{Muscle}^{As^{3+}}) \times V_{Muscle}$$

As^{5+}

$$\frac{dA_{Muscle}^{As^{5+}}}{dt} = Q_{Muscle} \times (C_a^{As^{5+}} - \frac{C_{Muscle}^{As^{5+}}}{P_{Muscle}^{As^{5+}}}) - (K_1 \times C_{Muscle}^{As^{5+}} - K_2 \times C_{Muscle}^{As^{3+}}) \times V_{Muscle}$$

MMA^{5+}

$$\frac{dMMA_{Muscle}^{MMA^{5+}}}{dt} = Q_{Muscle} \times (C_a^{MMA^{5+}} - \frac{C_{Muscle}^{MMA^{5+}}}{P_{Muscle}^{MMA^{5+}}})$$

MMA^{3+}

$$\frac{dMMA_{Muscle}^{MMA^{3+}}}{dt} = Q_{Muscle} \times (C_a^{MMA^{3+}} - \frac{C_{Muscle}^{MMA^{3+}}}{P_{Muscle}^{MMA^{3+}}})$$

DMA^{5+}

$$\frac{dMMA_{Muscle}^{DMA^{5+}}}{dt} = Q_{Muscle} \times (C_a^{DMA^{5+}} - \frac{C_{Muscle}^{DMA^{5+}}}{P_{Muscle}^{DMA^{5+}}})$$

DMA^{3+}

$$\frac{dMMA_{Muscle}^{DMA^{3+}}}{dt} = Q_{Muscle} \times (C_a^{DMA^{3+}} - \frac{C_{Muscle}^{DMA^{3+}}}{P_{Muscle}^{DMA^{3+}}})$$

Fat tissue

As^{3+}

$$\frac{dA_{Fat}^{As^{3+}}}{dt} = Q_{Fat} \times (C_a^{As^{3+}} - \frac{C_{Fat}^{As^{3+}}}{P_{Fat}^{As^{3+}}}) + (K_1 \times C_{Fat}^{As^{5+}} - K_2 \times C_{Fat}^{As^{3+}}) \times V_{Fat}$$

As^{5+} $$\frac{dA_{Fat}^{As^{5+}}}{dt} = Q_{Fat} \times (C_a^{As^{5+}} - \frac{C_{Fat}^{As^{5+}}}{P_{Fat}^{As^{5+}}}) - (K_1 \times C_{Fat}^{As^{5+}} - K_2 \times C_{Fat}^{As^{3+}}) \times V_{Fat}$$

MMA^{5+} $$\frac{dMMA_{Fat}^{MMA^{5+}}}{dt} = Q_{Fat} \times (C_a^{MMA^{5+}} - \frac{C_{Fat}^{MMA^{5+}}}{P_{Fat}^{MMA^{5+}}})$$

MMA^{3+} $$\frac{dMMA_{Fat}^{MMA^{3+}}}{dt} = Q_{Fat} \times (C_a^{MMA^{3+}} - \frac{C_{Fat}^{MMA^{3+}}}{P_{Fat}^{MMA^{3+}}})$$

DMA^{5+} $$\frac{dMMA_{Fat}^{DMA^{5+}}}{dt} = Q_{Fat} \times (C_a^{DMA^{5+}} - \frac{C_{Fat}^{DMA^{5+}}}{P_{Fat}^{DMA^{5+}}})$$

DMA^{3+} $$\frac{dMMA_{Fat}^{DMA^{3+}}}{dt} = Q_{Fat} \times (C_a^{DMA^{3+}} - \frac{C_{Fat}^{DMA^{3+}}}{P_{Fat}^{DMA^{3+}}})$$

Blood

As^{3+} $$\frac{dA_a^{As^{3+}}}{dt} = (\sum_{i=1}^{8} Q_i \times \frac{C_i^{As^{3+}}}{\mathrm{P_i}^{As^{3+}}} - \sum_{i=1}^{8} Q_i \times C_a^{As^{3+}}) + (\mathrm{K_1} \times C_a^{As^{3+}} - \mathrm{K_2} \times C_a^{As^{3+}}) \times V_a$$

As^{5+} $$\frac{dA_a^{As^{5+}}}{dt} = (\sum_{i=1}^{8} Q_i \times \frac{C_i^{As^{5+}}}{\mathrm{P_i}^{As^{5+}}} - \sum_{i=1}^{8} Q_i \times C_a^{As^{5+}}) - (\mathrm{K_1} \times C_a^{As^{5+}} - \mathrm{K_2} \times C_a^{As^{3+}}) \times V_a$$

MMA^{5+} $$\frac{dMMA^{5+}}{dt} = (\sum_{i=1}^{8} Q_i \times \frac{C_i^{MMA^{5+}}}{P_i^{MMA^{5+}}} - \sum_{i=1}^{8} Q_i \times C_a^{MMA^{5+}})$$

MMA^{3+} $$\frac{dMMA^{3+}}{dt} = (\sum_{i=1}^{8} Q_i \times \frac{C_i^{MMA^{3+}}}{P_i^{MMA^{3+}}} - \sum_{i=1}^{8} Q_i \times C_a^{MMA^{3+}})$$

DMA^{5+} $$\frac{dDMA^{5+}}{dt} = (\sum_{i=1}^{8} Q_i \times \frac{C_i^{DMA^{5+}}}{P_i^{DMA^{5+}}} - \sum_{i=1}^{8} Q_i \times C_a^{DMA^{5+}})$$

DMA^{3+} $$\frac{dDMA^{3+}}{dt} = (\sum_{i=1}^{8} Q_i \times \frac{C_i^{DMA^{3+}}}{P_i^{DMA^{3+}}} - \sum_{i=1}^{8} Q_i \times C_a^{DMA^{3+}})$$

Abbreviations and parameter symbols: A_i^j is the dose of arsenic species j in organ/tissue i (μmol), C_i^j is the concentration of arsenic species j in organ/tissue i (μmol L^{-1}), $K_{m,i}^{j \to k}$ is the Michaelis-Menten constant for arsenic species j methylated to k in organ/tissue i (μmol L^{-1}), P_i^j is the tissue/blood partition coefficient of arsenic species j in tissue, Q_i is the blood flow in organ/tissue i (L h^{-1}), V_i is the volume of organ/tissue i (L), $V_{\max i}^{j \to k}$ is the maximum reaction rate for arsenic species j methylated to k in organ/tissue i (μmol h^{-1}), $W_{Biliary}$ is the bile elimination amount (L), W_{day} is the human daily drinking water amount (L h^{-1}), and W_i is the percentage of the mass of organ i in body weight (%).

Appendix C: Relevant parameter values used in the human arsenic PBPK model

Table C1

PBPK input parameters used for four age groups

	Parameters	Age groups (yr)		
		1-6	7-12	13-18
1.Lung	Q_{Lung} [a] (L h^{-1})	5.17	7.65	10.84
	V_{Lung} [b] (L)	0.257	0.507	0.888
2.Kidney	Q_{Kid} (L h^{-1})	39.3	58.1	82.4
	V_{Kid} (L)	0.0669	0.132	0.231
3. Skin	Q_{Skin} (L h^{-1})	10.3	15.3	21.7
	V_{Skin} (L)	3.45	6.80	11.9
4. G.I. tract	Q_{GI} (L h^{-1})	41.3	61.2	86.7
	V_{GI} (L)	0.305	0.602	1.06
	K_{uptake}^{3+} [c] (μmol h^{-1})	0.0144	0.0192	0.0244
	K_{uptake}^{5+} (μmol h^{-1})	0.0216	0.0288	0.0367
5. Liver	Q_{Liver} (L h^{-1})	10.3	15.3	21.7
	V_{Liver} (L)	0.392	0.773	1.36
	$W_{Biliary}$ [d] (L d^{-1})	0.136	0.268	0.470
6. Muscle	Q_{Muscle} (L h^{-1})	35.1	52.0	73.7
	V_{Muscle} (L)	6.10	12.0	21.1
7. Fat	Q_{Fat} (L h^{-1})	10.3	15.3	21.7
	V_{Fat} (L)	3.19	6.30	11.0
8. Blood	V_a [e] (L)	1.20	2.37	4.16

[a] $Q_i = F_i \times Q_T$ (F_i: Blood flow fraction; Q_T: Cardiac output rate) [42]. [b] V_i (L) = BW (kg) × W_i/D_i (kg L^{-1}) (V_i: Volume of organ i; BW: Body weight; W_i: Percentage of body weight; D_i: Density of organ i). [c] K_{uptake} (μmol h^{-1}) = As in drinking water (μg L^{-1}) × Daily drinking water (L d^{-1}) / 74.9216 (As = 74.9216). [d] It assumed that $W_{Biliary\text{-}Children} = W_{Biliary\text{-}Adult} \times BW_{Children} / BW_{Adult}$. [e] $V_a = BW_{Children} \times 0.08/D_a$ [43].

Table C2

Metabolic rate constants for arsenic in children

Reduction/oxidation	As	MMA [b]	DMA
Reduction (h^{-1})	K_1 = 1.37	$K_3 = 4.47\times 10^{-3}$	$K_5 = 4.40\times 10^{-2}$
Oxidation (h^{-1})	K_2 = 1.83	$K_4 = 5.95\times 10^{-3}$	$K_6 = 5.88\times 10^{-2}$

Methylation [c]					
Age group			1-6 yr	7-12 yr	13-18 yr
	$As^{3+}\rightarrow MMA^{5+}$	$As^{3+}\rightarrow DMA^{5+}$		$MMA^{3+}\rightarrow DMA^{5+}$	
Liver					
V_{max} (μmol h^{-1})	11.25	22.25	1.86693×10^{-5} (1.52×10^{-5}-2.28×10^{-5})[d]	2.08569×10^{-5} (2.04×10^{-5}-2.24×10^{-5})	4.84044×10^{-5} (4.13×10^{-5}-5.22×10^{-5})
K_m (μmol L^{-1})	100	100		3.04×10^{-6}	
Kidney					
V_{max} (μmol h^{-1})	7.5	10.02	1.93251×10^{-5} (1.61×10^{-5}-2.34×10^{-5})	1.93880×10^{-5} (1.94×10^{-5}-2.04×10^{-5})	4.01268×10^{-5} (3.31×10^{-5}-4.39×10^{-5})
K_m (μmol L^{-1})	100	100		3.04×10^{-6}	

[a] Adapted from Yu [34]. [b] Adapted from Gong et al. [36]. [c] Adapted from Mann [32]. [d] 95% CI.

Table C3

Partition coefficients, blood flow fraction, and tissue density used in the PBPK model

Tissue	Blood flow fraction (F_i) (%)[a]	% of body weight (W_i) (%)[a]	Density (D_i) (kg L^{-1})[a]	% of total water elimination amount (%)[b]	Species-specific tissue/blood partition coefficient[c]			
					As(III)	As(V)	MMA(V)	DMA(V)
Lung	2.5	1.7	1.05	12	4.15	4.15	1.8	2.075
Kidneys	19	4.4	1.05	60	4.15	4.15	1.8	2.075
Skin	5	20	1.05	20	2.5	2.5	1.25	1.25
GI tract	20	2	1.04	8	2.8	2.8	1.2	1.4
Liver	6.5	2.57	1.05		5.3	5.3	2.35	2.65
Muscle	17	40	1.04		2.6	2.6	1.8	2.8
Fat	27.5	21	0.92		0.3	0.3	0.3	0.3
Total				100				

[a] Adapted from Hissink et al. [44] and Yu et al. [45].

[b] Adapted from Huang [46].

[c] Adapted from Hissink et al. [44] and Yu et al. [45].

Figure captions

Fig. 1. Schematic of the proposed human PBPK-metabolism model for arsenic exposure. (A) Target tissue compartments of lung, skin, fat, muscle, kidney, liver and GI tract interconnected by blood flow in that GI tract is represented as Caco-2 cells showing arsenic retention, transport, and total uptake. (B) Biotransformation of arsenic showing oxidation/reduction of inorganic and organic arsenic as well as methylation of As(III) in the kidney and liver. (C) Best-fitted model of age-specific secondary methylation ratio (DMA/MMA).

Fig. 2. Weibull model predicted gender- and age-specific skin lesions cumulative prevalence ratios varied with arsenic exposure concentrations for (A) hyperpigmentation and (B) keratosis.

Fig. 3. Box and whisker plots showing (A) arsenic concentration distributions for irrigation water, paddy soil and paddy rice and (B) bioaccumulation factor distributions for irrigation water to paddy soil ($K_{W\text{-}S}$), paddy soil to paddy rice ($K_{S\text{-}R}$) and irrigation water to paddy rice ($K_{W\text{-}R}$).

Fig. 4. (A) Best-fitted model describing arsenic contents in the cooked rice varied with different arsenic concentrations in cooking water. Error bar represents standard deviation from mean. (B) Box and whisker plots showing the percentage of arsenic retained in cooked rice for different cooking methods. (C, D, E) Predicted arsenic concentration in cooked rice varied with different arsenic contents in cooking water for three cooking methods.

Fig. 5. Schematic representation of a descriptive model showing the interactions among bioaccumulation factors of $K_{W\text{-}S}$ and $K_{S\text{-}R}$, arsenic content in cooked rice with three cooking methods, PBPK mode-predicted age group-specific urinary MMA(III) levels, and Weibull model-predicted average odds ratios.

Fig. 6. The PBPK model predicted percentage contributions of cooked rice to daily arsenic intake varied with arsenic contents in drinking water of 10, 100, and 1000 μg L^{-1}.

Table 1

Weibull model fitting parameters (mean with 95%CI) for male and female of hyperpigmentation and keratosis

	Hyperpigmentation		Keratosis	
	Male	Female	Male	Female
k_0	5.41×10^{-4}	2.95×10^{-4}	1.44×10^{-4}	8.79×10^{-5}
	(0-1.3×10^{-3})	(0-8.15×10^{-4})	(0-3.02×10^{-4})	(0-2.55×10^{-4})
k_1	0.62	0.61	0.70	0.65
	(0.43-0.82)	(0.37-0.85)	(0.55-0.85)	(0.39-0.91)
k_2	0.18	0.17	0.18	0.12
	(0.12-0.24)	(0.10-0.24)	(0.13-0.23)	(0.047-0.19)
k_3	1.00×10^{-4}	1.00×10^{-4}	1.00×10^{-4}	1.00×10^{-4}
	(0-4.98×10^{-3})	(0-3.21×10^{-3})	(0-1.51×10^{-3})	(0-1.30×10^{-3})
r^2	0.94	0.91	0.96	0.91

Table 2

Predicted age-, gender-, and skin lesion-specific odds ratio (OR) (mean with 95% CI) varied with % of GI tract uptake (α) and cooking methods

Cooking method	Age group	OR							
		Hyperpigmentation				Keratosis			
		Male		Female		Male		Female	
		α=22.87%	α=100%	α=22.87%	α=100%	α=22.87%	α=100%	α=22.87%	α=100%
A	1-6	0.91 (0.84-1.00)	0.84 (0.79-1.07)	0.87 (0.80-0.94)	0.83 (0.76-0.96)	0.99 (0.98-1.00)	0.98 (0.95-1.03)	0.97 (0.96-0.98)	0.97 (0.94-1.01)
	7-12	1.06 (0.96-1.44)	1.08 (0.82-1.92)	0.97 (0.87-1.18)	0.97 (0.80-1.52	1.03 (0.98-1.10)	1.02 (1.02-1.21)	1.01 (1.01-1.07)	1.01 (0.96-1.17)
	13-18	1.16 (1.04-1.72)	1.24 (0.82-2.47)	1.04 (0.90-1.36)	1.07 (0.85-1.85)	1.02 (1.03-1.13)	1.05 (1.01-1.32)	1.00 (1.02-1.12)	1.03 (1.01-1.28)
B	1-6	1.07 (0.92-1.54)	1.06 (0.76-2.05)	1.00 (0.87-1.27)	1.01 (0.79-1.62)	1.00 (0.96-1.10)	1.02 (0.96-1.25)	0.98 (0.96-1.09)	1.00 (0.93-1.22)
	7-12	1.17 (0.93-1.94)	1.27 (0.80-2.78)	1.05 (0.87-1.49)	1.13 (0.82-2.08)	1.02 (1.02-1.17)	1.05 (0.97-1.44)	1.02 (1.06-1.15)	1.03 (1.01-1.28)
	13-18	1.23 (1.08-2.21)	1.43 (0.82-3.37)	1.10 (0.91-1.69)	1.24 (0.83-2.48)	1.04 (1.01-1.23)	1.10 (1.06-1.59)	1.02 (1.04-1.21)	1.07 (1.05-1.52)
C	1-6	1.08 (0.88-1.63)	1.06 (0.74-2.17)	1.01 (0.88-1.32)	1.01 (0.75-1.74)	1.03 (0.98-1.12)	1.01 (0.95-1.31)	1.01 (0.96-1.11)	1.00 (0.93-1.28)
	7-12	1.18 (0.89-2.04)	1.28 (0.76-2.99)	1.08 (0.89-1.59)	1.13 (0.78-2.27)	1.03 (1.02-1.21)	1.07 (1.01-1.54)	1.03 (1.04-1.17)	1.06 (1.06-1.47)
	13-18	1.28 (0.96-2.39)	1.49 (1.04-3.69)	1.14 (1.07-1.82)	1.26 (1.01-2.71)	1.05 (1.02-1.28)	1.12 (1.09-1.72)	1.04 (1.05-1.25)	1.10 (1.18-1.64)

Fig. 1.

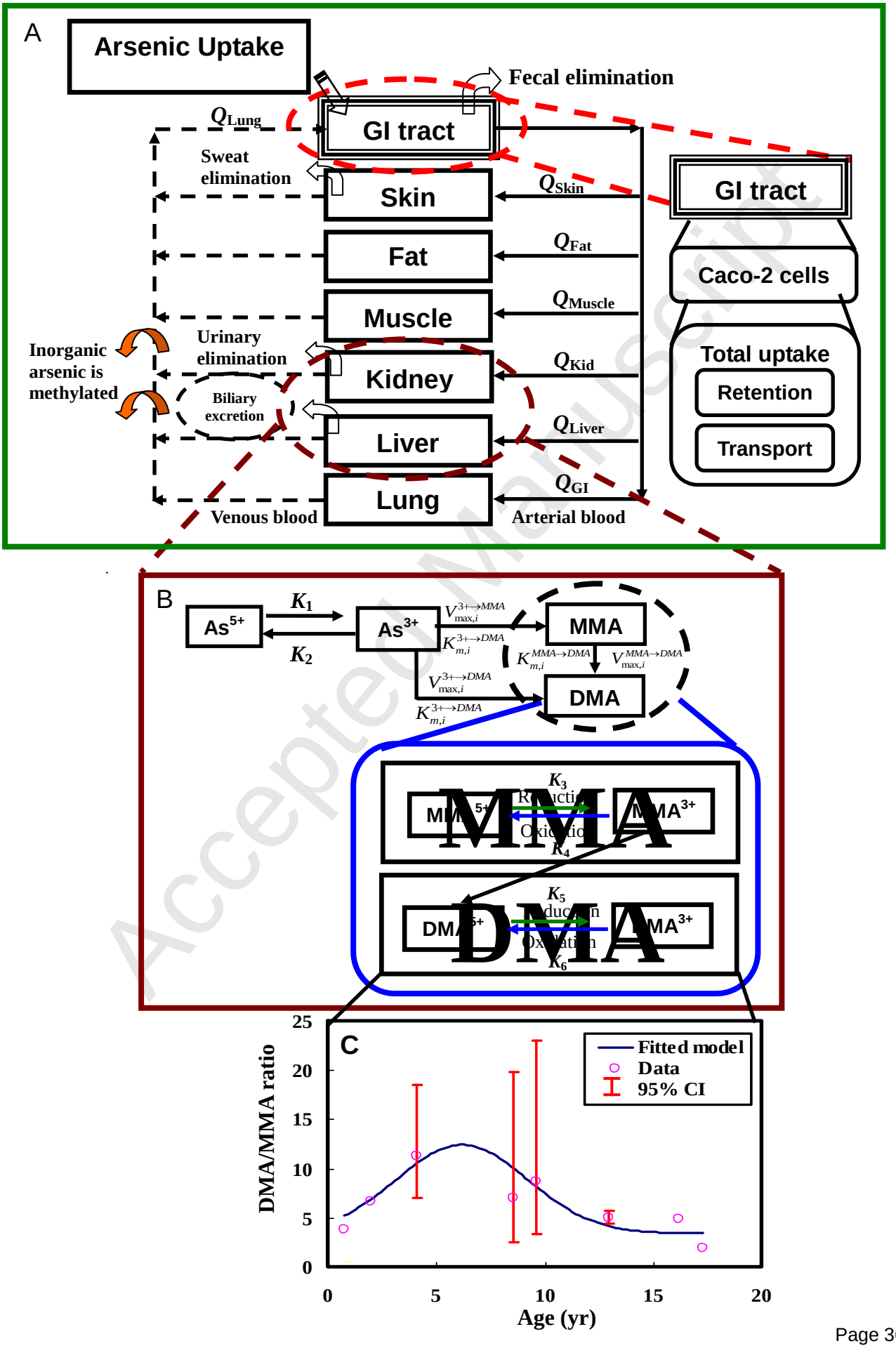


Fig. 2.

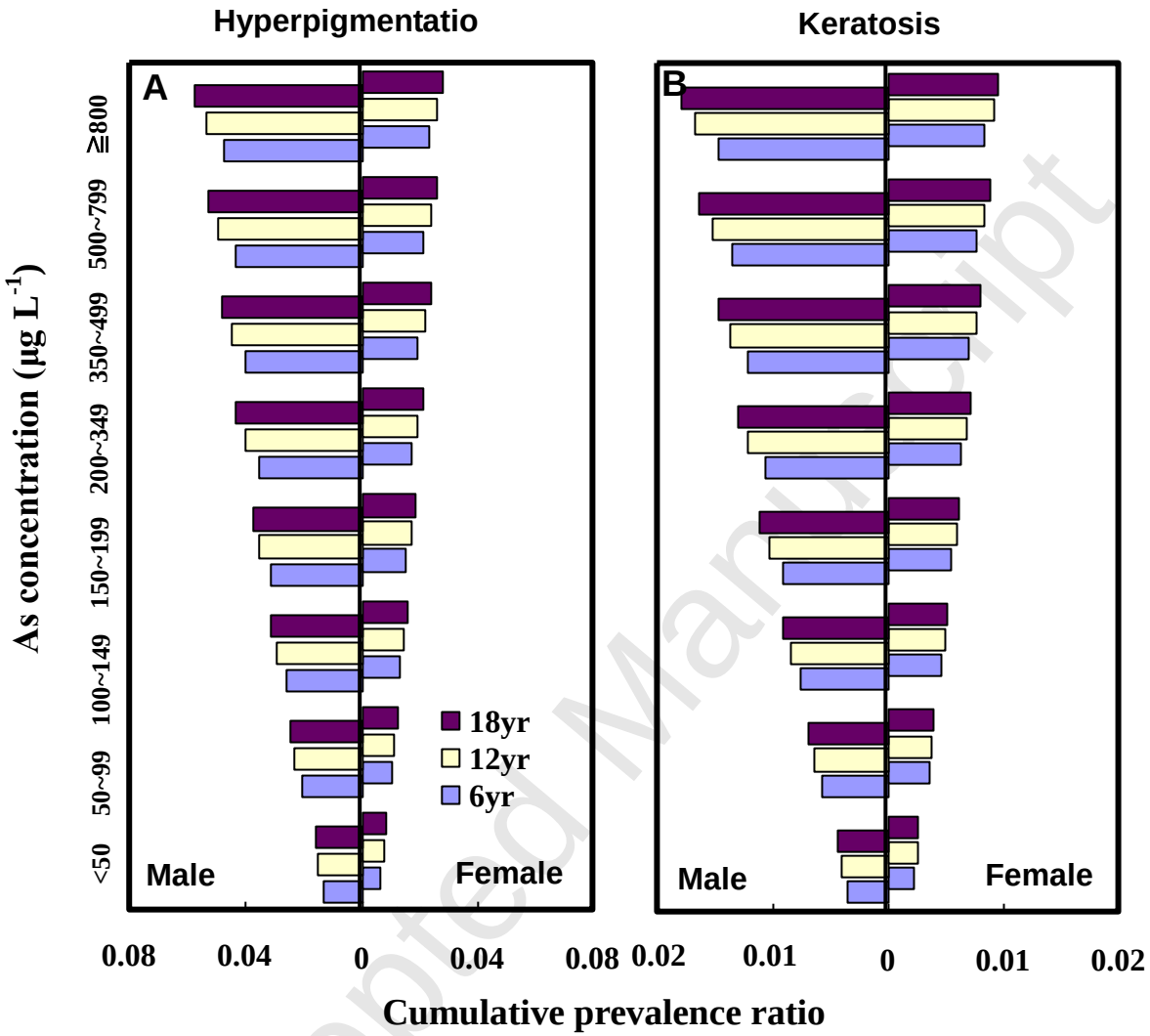


Fig. 3.

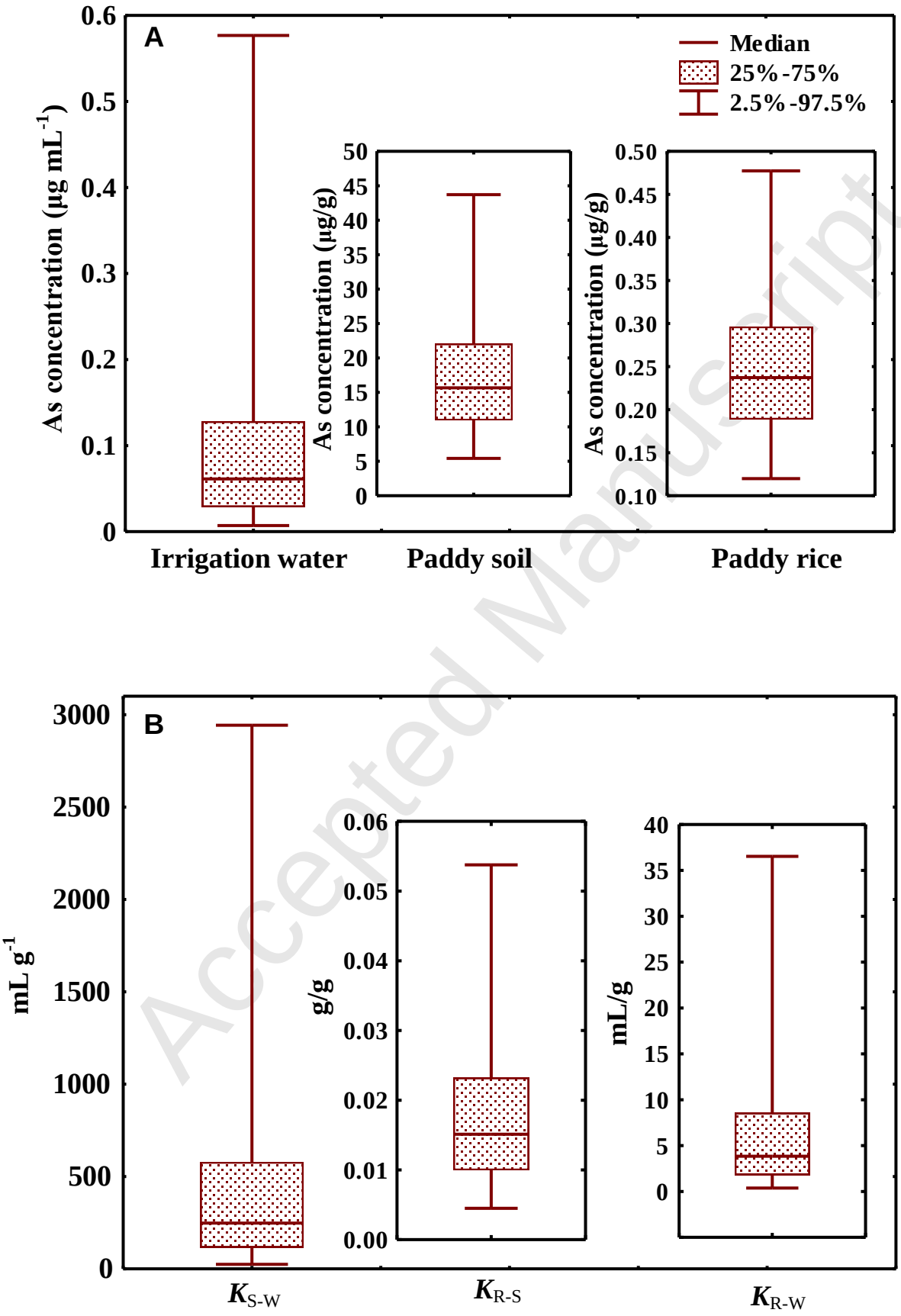


Fig. 4.

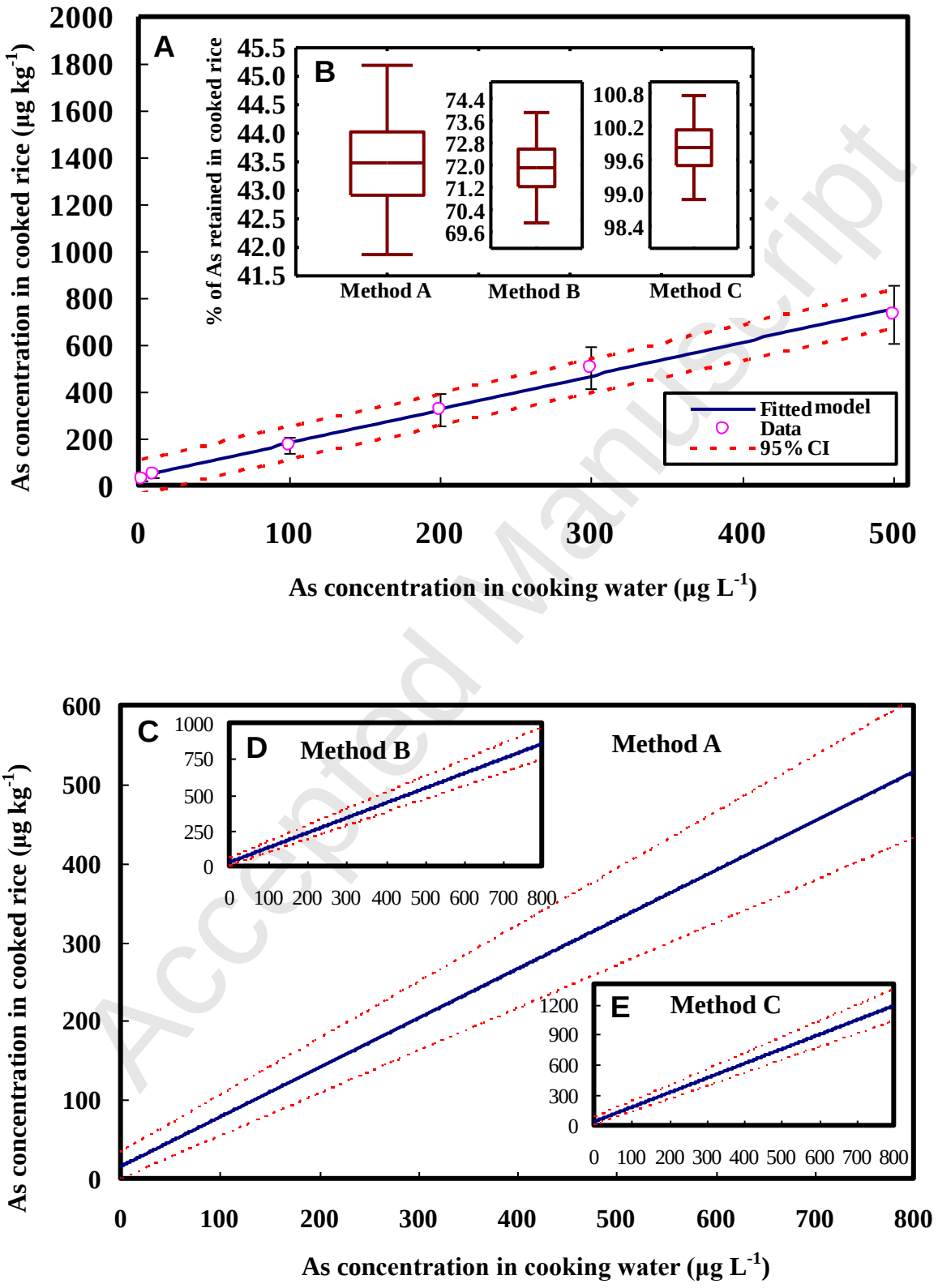


Fig. 5.

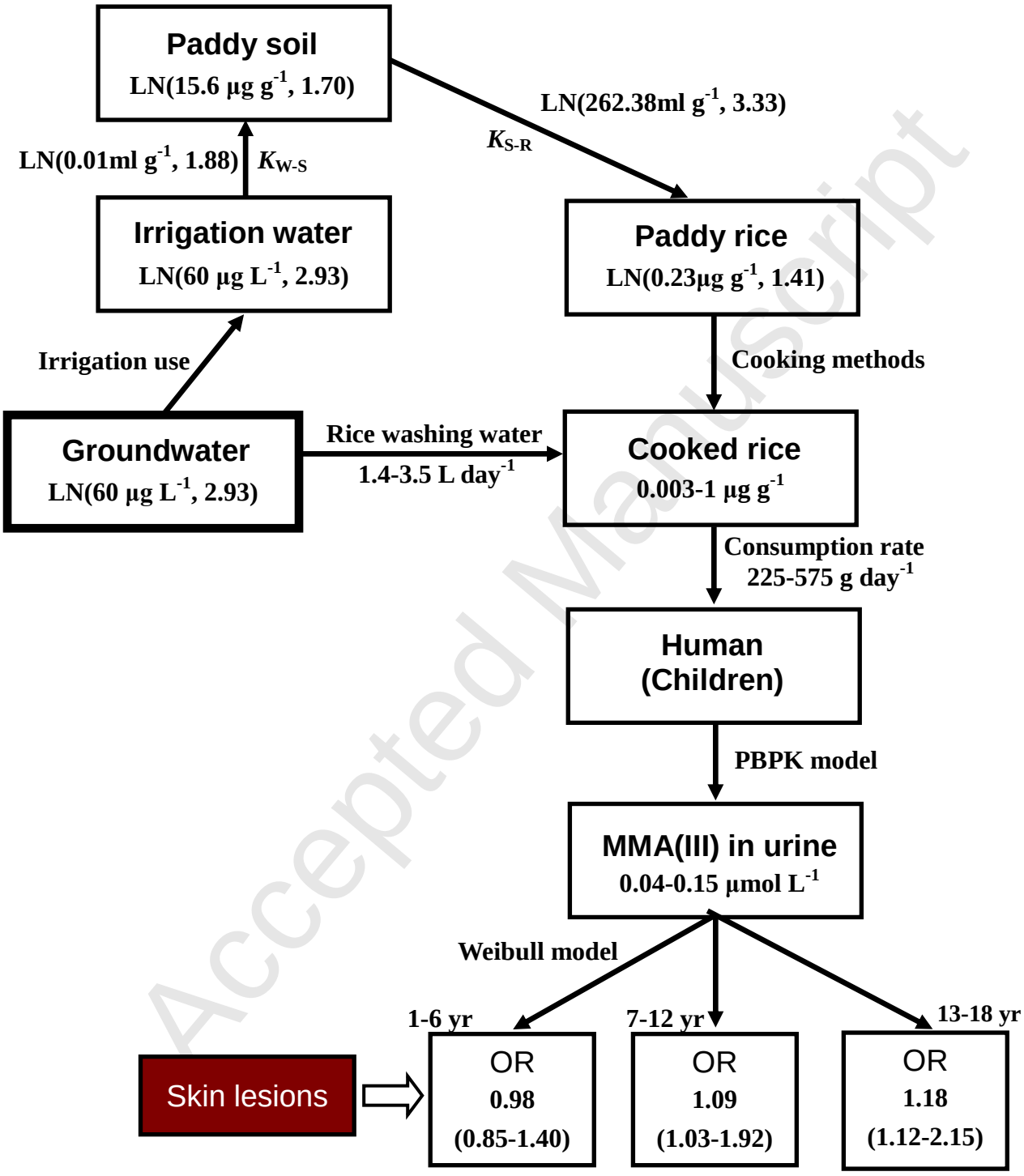


Fig. 6.