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RESEARCH ARTICLE

Contribution of inorganic arsenic sources to population exposure risk on a regional scale

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Abstract Chronic exposure to inorganic arsenic (iAs) in the human population is associated with various internal cancers and other adverse outcomes. The purpose of this study was to estimate a population-scale exposure risk attributable to iAs consumptions by linking a stochastic physiological-based pharmacokinetic (PBPK) model and biomonitoring data of iAs in urine. The urinary As concentrations were obtained from a total of 1,043 subjects living in an industrial area of Taiwan. The results showed that the study subjects had an iAs exposure risk of 27 % (the daily iAs intake for 27 % study subjects exceeded the WHO-recommended value, 2.1 μg iAs day^{-1} kg^{-1} body weight). Moreover, drinking water and cooked rice contributed to the iAs exposure risk by 10 and 41 %, respectively. The predicted risks in the current study were 4.82, 27.21, 34.69, and 64.17 %, respectively, among the mid-range of Mexico, Taiwan (this study), Korea, and Bangladesh reported in the literature. In conclusion, we developed a population-scale-based risk model that covered the broad range of iAS exposure by integrating stochastic PBPK modeling and reverse dosimetry to generate probabilistic distribution of As intake corresponding to urinary As measured from the cohort study. The model can also be updated as new urinary As information becomes available.

Keywords Arsenic · PBPK modeling · Biomonitoring · Reverse dosimetry · Probabilistic risk assessment

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Introduction

The adverse effects of long-term exposure to arsenic (As) in humans are well studied and widely recognized. There are increasing concerns about As as everyone has some exposure via water, food, soil, and air, causing measurable population increases in a variety of health problems. When investigating As exposure from drinking water or foods, the inorganic forms of As [inorganic arsenic (iAs), the sum of arsenite (As^{3+}) and arsenate (As^{5+})], which are considered to be highly toxic and readily bioavailable to humans, are the most serious human health threat (El-Masri et al. 2002).

The biomonitoring evidence, considered as a whole, should reflect variability in the population. Indeed, urinary As levels have been used as the best biomonitoring data of As exposure (Marchiset-Ferlay et al. 2012). The As species in urine include As^{5+}, As^{3+}, monomethylarsenic acid (MMA), and dimethylarsenic acid (DMA), reflecting exposures to iAs. Several studies reported that the average background levels from populations in European countries and in the USA have been 10 μg L^{-1} (Buchet et al. 1996; Jensen et al. 1991). Results for the US population from the National Health and Nutrition Examination Survey (NHANES) suggest that the median of urinary As species combined (the sum of iAs, MMA, and DMA) is approximately 6 μg L^{-1} (Caldwell et al. 2009).

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Exposure to elevated levels of As in drinking water in Taiwan and Argentina has resulted in 5- to 50-fold higher concentrations of these compounds in urine (Chiou et al. 2001; Concha et al. 2006; Kavanagh et al. 1998; Smith et al. 1977; Trepka et al. 1996). Although biomonitoring data of As in urine provide a demonstration of human exposure to iAs, it is difficult to know how best to interpret and apply biomonitoring data in a risk assessment context.

Physiologically based pharmacokinetic (PBPK) models are potentially powerful tools in quantitative risk assessments for target tissue dose estimates, allowing the estimation of target tissue doses through linkage of information on the external metal exposure, the physiological parameters of humans, and the biochemical properties of metals. Yu (1998) have extended the PBPK model to fit the As distribution in the human body, considering both reductive metabolism and methylation. An age-specific PBPK model coupling a Weibull-based dose–response function has been used to predict urinary As metabolites from seafood-As intake and potential cancer risks (Chen et al. 2010).

In addition to the work of predicting the internal metal dose, a population-based exposure reconstruction using PBPK modeling has appeared in Tan et al. (2007) and Lyons et al. (2008). Tan et al. (2006) incorporated variability into the population-scale exposure reconstruction of chloroform using a combined PBPK model and Monte Carlo sampling techniques, with external exposure calculated using an exposure conversion factor (ECF) distribution. Lyons et al. (2008) used a computational framework that integrated PBPK modeling, Bayesian inference, and Markov chain Monte Carlo simulation to obtain a population estimate of environmental chloroform source concentrations consistent with human biomonitoring data. These procedures for reconstructing an estimate of external exposure were consistent with biomonitoring data measured in a population, referred to as reverse dosimetry.

A population-based estimate of exposure should take into account the intrinsic variability in the population, both in the modeling of the distribution and metabolism of the chemical in the human body and in the description of the exposure conditions. Therefore, the quantification of the between-person variability in a population is an important issue in risk assessment for building a robust statistical linkage between urinary concentrations and the intake of a chemical. In this study, Taiwanese populations were examined to determine the sources and extent of exposure to total As (tAs) and iAs.

The purpose of this study was to estimate a population-scale exposure risk attributable to iAs consumptions by linking a stochastic PBPK model and biomonitoring data of iAs in urine. The estimation of the sources of contribution to iAs exposure risk and comparison of the iAs exposure risk of diverse populations corresponding to a predefined urinary As concentration from published studies in different countries were also included.

Materials and methods

Sample populations

To represent a group with chronic low-to-moderate-dose exposure for Taiwanese people, we assembled a sample population of 1,043 residents from 16 townships of Changhua County in Taiwan. These townships are in an area where environmental As contamination has occurred (Wang et al. 2007). Urinary As concentrations in Changhua residents have been reported previously (Chen et al. 2011a). Prior to data collection, informed consent was obtained from each participant. The study protocol and informed consent form were reviewed and approved by the Human Subjects Review Board of National Health Research Institutes in Taiwan.

Exposure assessment

Urinary As concentrations were measured by an ELAN 6100 inductively coupled plasma mass spectrometer (ICP-MS, Perkin Elmer, Shelton, CT). Generally, ICP-MS has better sensitivity with lower limits of detection than atomic absorption spectrometry (McLean et al. 1998). Quality assurance and control were conducted with simultaneous analysis of samples of the reference urine which contained reference material (SRM 2670). Urine samples with As concentrations $<0.05\ \mu g\ L^{-1}$ limit of detection (LOD) were assigned the LOD divided by $\sqrt{2}$.

Estimates of dietary As exposures

For oral-route exposure, cooked rice and drinking water were selected to assess the source of ingested As. We collected water from the present drinking water source of each family and from a container in a house. Water samples were transported to the laboratory and then 1 % *v*/*v* nitric acid was added to the samples, which were kept in a dark container at 4 °C until analyzed. On the other hand, we collected rice samples by the duplicated portion sampling method (Pal et al. 2009). We randomly selected 106 families from the study cohort as the respondents who submitted their cooked rice for one day. Cooked rice was collected in a separate plastic bag and weighed. Furthermore, the individual average consumption rate for drinking water and cooked rice in the study cohort was calculated based on the answers to questionnaires. To determine the direct water and cooked rice intake, subjects were asked to report how many cups of water or bowls of cooked rice they consumed in a day. At the first visit, the cup/bowl used for drinking water/cooked rice was identified and the capacity of the cup and bowl was measured. These results are presented in ESM Table S2.

Dietary chronic exposure to iAs was assessed at the population level by multiplying the distribution of daily consumption of cooked rice and drinking water with the corresponding distribution of estimated iAs, summing up the population intakes through the diet. By dividing the total iAs exposure predicted from the biomonitoring data, the contributions to iAs intake of cooked rice, drinking water, and others (the rest of the foods, except rice and water) were estimated.

Computerized simulation model of population As exposure

As shown in Fig. 1a, a stochastic PBPK model was used to simulate the population iAs exposure based on a modified version of the seven-compartment PBPK model from our previous paper (Chen et al. 2010). Briefly, the structure of the existing PBPK model for arsenic was taken as a generic model framework used in conjunction with Monte Carlo analysis to incorporate the variability of physiological parameters and human pharmacokinetics (Fig. 1b). Among the physiological and pharmacokinetic parameters, cardiac output, tissue volume, and blood flow to tissues were assigned normal distributions; partition coefficients and metabolic parameters were assigned log-normal distributions (Delic et al. 2000).

All physiological parameter distributions were fitted from the epidemiological data in the Taiwan cohort study and tested by the statistical method (Kolmogorov–Smirnov test). These parameters used in PBPK should be reliable because of the random sampling from measurement data. All distributions were truncated at 1.96 times the standard deviation (SD) above and below the mean to exclude physiologically irrational values. The incorporation of variability permitted stochastic characterization of the population distribution of arsenic concentrations in urine (Fig. 1c). Equations and most of the parameter values describing the model's structure and symbols are given in ESM Tables S3, S4, and S5.

The PBPK model was validated with data from the NHANES data on the general US population exposure to As, as detailed elsewhere by Caldwell et al. (2009). To compare the modeled and observed results, the best fit was evaluated using root mean squared error (RMSE), calculated from $\mathrm{RMSE} = \sqrt{\sum_{n=1}^{N}\left(C_{m,n}-C_{s,n}\right)^{2}}/N$, where N denotes the number of measurements, $C_{\mathrm{m},n}$ is the measurement data, and $C_{\mathrm{s},n}$ is the simulation result corresponding to data point n.

Reverse dosimetry

To estimate the population As exposure based on the measured biomonitoring data of As in urine, the stochastic PBPK model for As was used to predict the distribution of As concentrations in urine given 1 unit of iAs intake. The output distribution was then inverted to obtain a distribution of an ECF in a unit of (μg iAs intake)/(μg L^{-1} tAs in urine), where the product of the ECF distribution with an observed urinary As concentration provided probabilistic distribution of As intake corresponding to urinary tAs (the sum of As^{3+}, As^{5+}, MMA, and DMA) measured from the cohort study. A detailed description of the ECF approach and the validation of ECF are described in the ESM Fig. S1 and S2.

Risk characterization

The probabilistic exposure modeling offers a complete description of the exposure in the human population taking the variation between individuals into account. The probabilistic risk assessment allows two routes. One is to compare the (probabilistic) limit value with the probabilistic exposure estimate. The other is to estimate the possible health effects in the human population at a given level of exposure (Woodruff et al. 2007; NRC 2009). In this study, we used PBPK modeling and Monte Carlo simulation to reconstruct the iAs exposure distribution in the Taiwanese population based on the human biomonitoring data.

As shown in Fig. 1c, we used the ECF and urinary tAs concentration distributions to estimate the iAs exposure risk of the population group. In this study, the ECF was used as the conditional probability. Therefore, the relationship between 1-unit iAs intake and urinary tAs concentrations can be expressed as $P(\mathrm{iAs}_{\mathrm{intake}}|\mathrm{tAs}_{urine})$. The tAs concentrations in urine measured from our cohort study can be expressed as the probabilistic distribution. The population-scale iAs exposure can be calculated as the probability density functions of $|\mathrm{tAs}_{urine}$ multiplied by the conditional probabilities of ECF. To assess the iAs exposure risk, the population-scale iAs exposure distribution was used for comparison to the tolerable daily intake (TDI), 2.1 μg iAs day^{-1} kg^{-1}, recommended by the World Health Organization (WHO) in 1989 (WHO 1989).

$$P(\mathrm{iAs}_{intake}) = P(\mathrm{tAs}_{urine}) \times P(\mathrm{iAs}_{intake}|\mathrm{tAs}_{urine}) \quad (1)$$

$$P(R_{iAs}) = P(\mathrm{iAs}_{intake} > \mathrm{TDI}), \quad (2)$$

where $P(R_{iAs})$ represents the human As exposure risk estimated as the probability that the daily intake estimated from this study exceeds the TDI.

Results

Validation of the PBPK model

The evaluated PBPK models were performed in conjunction with Monte Carlo simulation to incorporate variability regarding the physiological parameters, pharmacokinetics, and exposure patterns (ESM Tables S2 and S3) to predict the

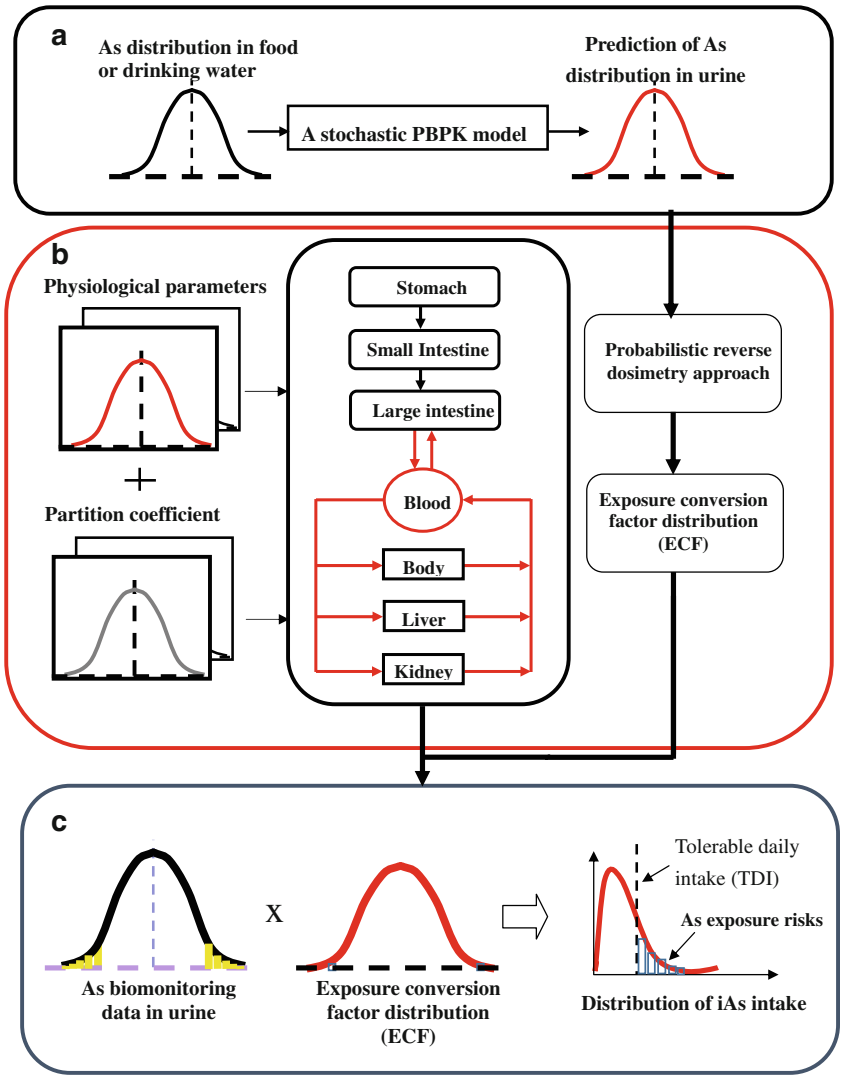

Fig. 1 Schematic showing the framework of the proposed population-based PBPK model and reverse dosimetry for arsenic exposure risk assessment

distributions of As^{3+}, As^{5+}, MMA, and DMA concentrations in urine. From the Monte Carlo analysis, 10,000 predictions were obtained for each tAs exposure pattern from the NHANES data. The tAs concentration in urine from the PBPK prediction had a geometric mean (gm) of 17.57 μg L^{-1} (95 % confidence interval (CI), 14.84–20.60) for the entire simulated population (Table 1). On the other hand, the urinary DMA concentration had a gm of 5.4 (4.68–6.50).

Overall, the predicted distributions of tAs and DMA concentrations in urine by the simulation of the general US population from a PBPK model agreed well with the measured distributions from the NHANES data ($r^2 = 0.86$ and 0.89, respectively). Each RMSE value was less than 1 SD from the experimental data (Table 1), indicating that the PBPK model simulation values were in good agreement with the experimentally determined concentration profiles of tAs and DMA in urine after As exposure.

Risk characterization

Figure 2 shows the resulting curves of the mean and the 95 % CI for predicted arsenic species (As^{3+}, As^{5+}, MMA, and DMA) concentrations in urine. The wide 95 % CI bounds in Fig. 2 result from combined variability of the parameters describing the physiological, exposure scenario, and pharmacokinetics in the population. We applied the predictions of arsenic species using a PBPK model incorporating Monte Carlo simulation (Fig. 2a–d) to establish the probability density function (PDF) for As^{3+}, As^{5+}, MMA, and DMA (*e–h* in Fig. 2).

We inverted these PDFs of the arsenic species in urine predicted from model prediction to generate the iAs ECF distribution, a reference value for iAs exposure, and to reconstruct the exposure to populations with measured urinary tAs concentrations (Fig. 3). In constructing the iAs ECF distribution based on these PDFs of the arsenic species, we assumed that the arsenic species concentrations in urine represented the exposure to iAs. Therefore, we reconstructed the exposure

Table 1 Measured and predicted arsenic concentrations in urine (in micrograms per liter)

	Geometric mean (95 % CI)	Selected percentile (95 % CI)						
		5th	10th	25th	50th	75th	90th	95th	RMSE[c]
Measured arsenic concentrations (NHANES data)[a]									
tAs	8.30 (7.19–9.57)	–	2.10	4.10	7.70	16.00	37.40	65.40	
DMA	3.71 (3.33–4.14)	–	–	2.00	3.90	6.00	11.00	16.00	
Predicted arsenic concentrations (PBPK model)[b]									
As^{3+}	0.6 (0.02–0.10)	0.08	0.09	0.13	0.50	0.75	1.05	1.12	–
As^{5+}	0.7 (0.06–0.15)	0.07	0.06	0.15	0.18	1.13	1.72	1.83	–
MMA	1.50 (1.27–1.76)	0.30	0.49	0.18	0.45	3.42	3.06	4.75	–
DMA	5.54 (4.68–6.50)	1.66	2.12	3.02	4.43	11.42	13.40	17.23	2.74
tAs	17.57 (14.84–20.60)	2.11	2.76	3.48	5.56	16.72	19.23	24.93	17.95

[a] Data adopted from Caldwell et al. (2009)

[b] Value estimated from the PBPK model

[c] Root mean squared error computed from $\mathrm{RMSE} = \sqrt{\sum_{n=1}^{N}\left(C_{m,n}-C_{s,n}\right)^2}/N$

distribution of the whole population exposed to tAs corresponding to that urine level by estimating the product of tAs ECF distribution with an observed urinary tAs concentration (b in Fig. 3).

We probabilistically estimated the population As exposure risk based on the respective TDIs and the prediction of iAs exposure distribution (Fig. 3, inset b). The results showed that this study cohort had an iAs exposure risk of 20 % (the daily

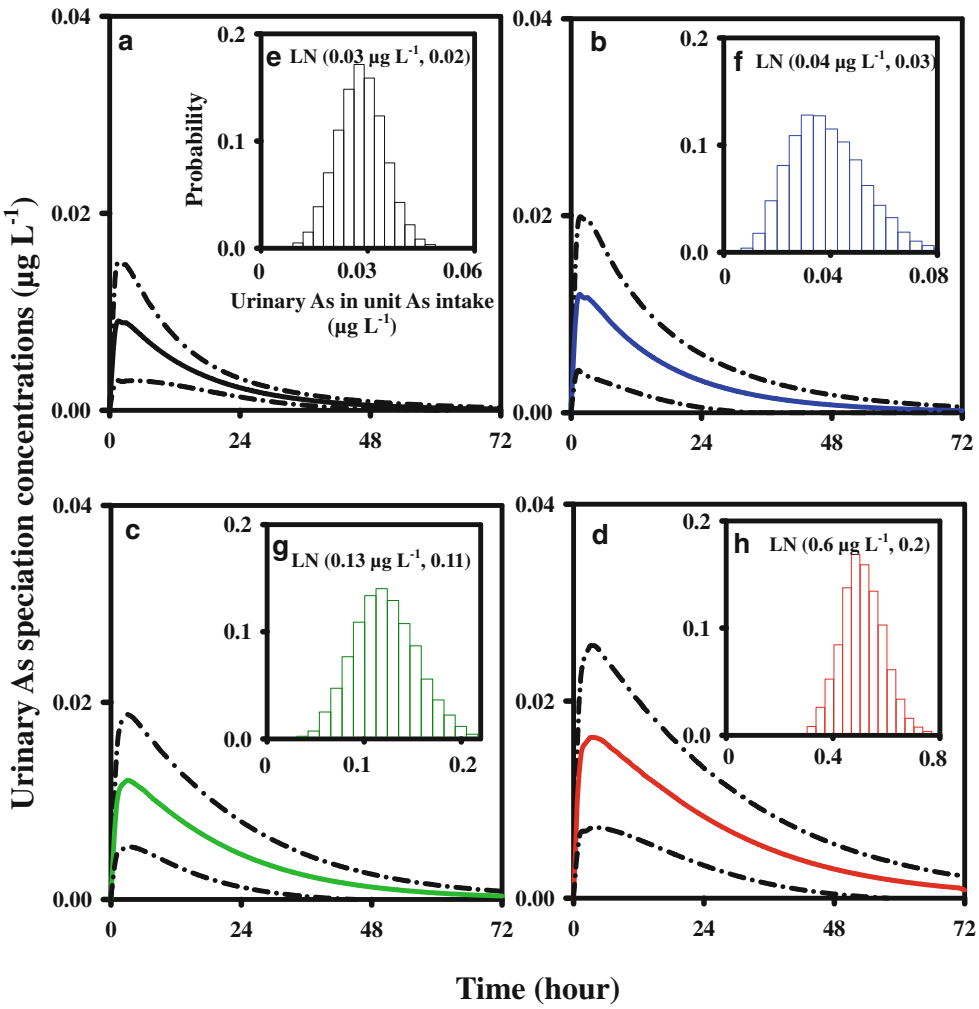

Fig. 2 Predictions of urinary concentrations for As^{3+} (**a**), As^{5+} (**b**), MMA (**c**), and DMA (**d**) in one-unit iAs intake from 10,000 simulations. The simulated data are represented as geometric means (*solid line*), 95 % prediction interval (*dotted line*), and the probability of distributions of urinary As species (*insets e*, *f*, *g*, and *h*)

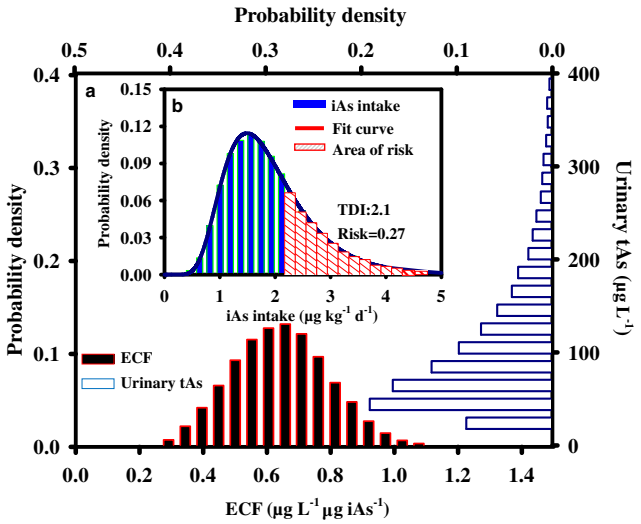

Fig. 3 *a* Estimated exposure conversion factor (*ECF*) of iAs (*lower*) that are consistent with 10,000 hypothetical urine concentrations in one-unit iAs intake. Insert *b* shows the probabilistic distribution of iAs intake generated from the measured urinary tAs (*right*) concentration multiplied by ECF

iAs intake for 20 % study subjects exceeded the WHO-recommended value, 2.1 μg iAs day^{-1} kg^{-1} body weight). Moreover, we used the measured distributions of urinary tAs to convert them into the daily iAs intake levels by reverse dosimetry (Table 2). The values of iAs intake were 0.08–0.62, 0.26–2.10, 0.47–3.52, 0.72–5.34, 1.57–12.40, and 2.1–16.38 μg day^{-1} kg^{-1} corresponding to the 2.5th, 25th, 50th, 75th, 95th, and 97.5th percentiles, respectively (Table 2). Based on the TDI that was employed as the benchmark of the health risk of iAs exposure, the iAs exposure risk was lower than the safe levels as long as the urinary tAs concentrations were not higher than 18.79 μg L^{-1} in this study cohort.

Estimates of dietary iAs exposure

Figure 4 (part a) shows the distribution of iAs daily intake in this study cohort, which had an iAs exposure risk of 20 % based on the TDI recommended by WHO. In the iAs exposure risk, the probabilistic estimation for iAs exposure from rice, drinking water, and others is presented in Fig. 4 (part b). The major contributors to iAs exposure risks by dietary iAs intake were others (49 %), rice (41 %), and water (10 %), respectively (c in Fig. 4).

iAs exposure risk assessment in diverse population

To estimate the As exposure risk from various populations of different countries, we applied reverse dosimetry approach to estimate the cumulative distribution functions of iAs daily intakes corresponding to average urinary tAs concentrations of 50 μg L^{-1} (standard), 65.4 μg L^{-1} (Mexico), 106 μg L^{-1} (this study), 127.3 μg L^{-1} (Korea), and 263.7 μg L^{-1} (Bangladesh; Fig. 5). The curves show that the dietary iAs intakes exceeding the TDIs recommend by WHO were from the populations from this study, Korea, and Bangladesh, whereas the calculated iAs intakes corresponding to urinary tAs concentrations of standard and Mexico were in the safe level (a in Fig. 5). The predicted exceedance risks (the percentage of exceeding TDI) showed 0.04, 4.82, 27.21, 34.69, and 64.17 % for a standard level with four study cohorts in Mexico, Taiwan (this study), Korea, and Bangladesh, respectively (b in Fig. 5).

Discussion

Linkage of biomonitoring data and iAs exposure risk

Human biomonitoring data represent a measurement of internal dose from all exposure routes (inhalation, dermal, and oral) and sources of exposure, providing an effective tool for assessing population exposure. It is increasingly being collected in the USA, Bangladesh, and other countries in large-scale field studies. These studies found that many chemicals are detected in the human body at very low levels; it is interesting to estimate the health effects of these chemicals by a dose-per-body-weight basis in a population and ask what we can do about these exposures. Based on the actual human exposure data and parameter values reported in the literature, our stochastic PBPK model generated a range of results that include human biomonitoring data of urinary As from a Taiwanese population. The application of PBPK modeling and reverse

Table 2 Inorganic arsenic intake distribution and estimated risk from the measured concentration of total arsenic in human urine

Percentile	tAs concentration (μg L^{-1})	iAs intake (μg kg^{-1} day^{-1})	Risk
2.5th	14.91	0.08–0.62	NR[a]
25th	18.79	0.26–2.10	NR[a]
50th	42.46	0.47–3.52	0.21
75th	74.12	0.72–5.34	0.62
95th	130.03	1.57–12.40	0.99
97.5th	212.78	2.10–16.38	1

[a] NR represents no risk (inorganic arsenic intake is within the safe arsenic intake value of 2.1 μg kg^{-1} day^{-1})

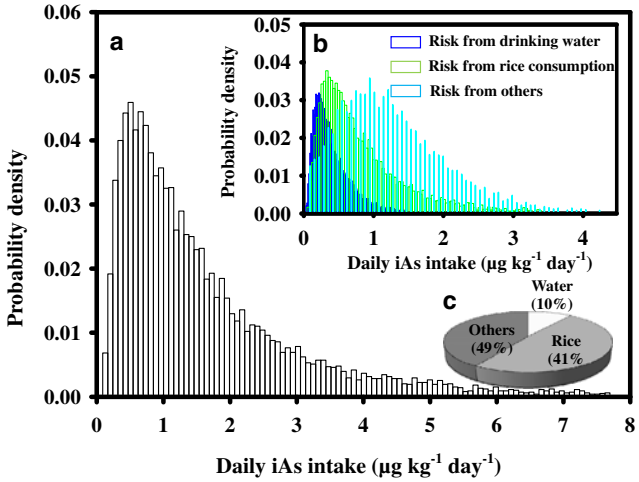

Fig. 4 Predictions of estimated probabilistic distribution of iAs intake for all (*a*) and dietary (*b*) exposure contributions and percentage contribution to the mean iAs population exposure risks (*c*)

dosimetry in the present study offers a linkage between biomonitoring data and As exposure risks in human populations.

In this model, we addressed uncertainties and variability in our PBPK model for simulating population-scale As exposures by introducing such inter-individual differences as the inputs in the model using Monte Carlo sampling, leading to a robust probability distribution for the population PBPK modeling. Our results showed that iAs intakes in the Taiwanese population varied from 0.08 to 16.39 μg kg^{-1} day^{-1}. From a conservative point of view, it shows that 27 % of this population had intakes higher than the TDI recommend by WHO (2.1 μg iAs day^{-1} kg^{-1} body weight). Indeed, previous studies have indicated high As levels measured by an agriculture soil survey (Chang et al. 1999) and the thousands of metal-related industries (http://www.moeaidb.gov.tw/Fidbweb/index.jsp) in our study area. In this way, natural As exposures occur through various routes and sources. Several studies have

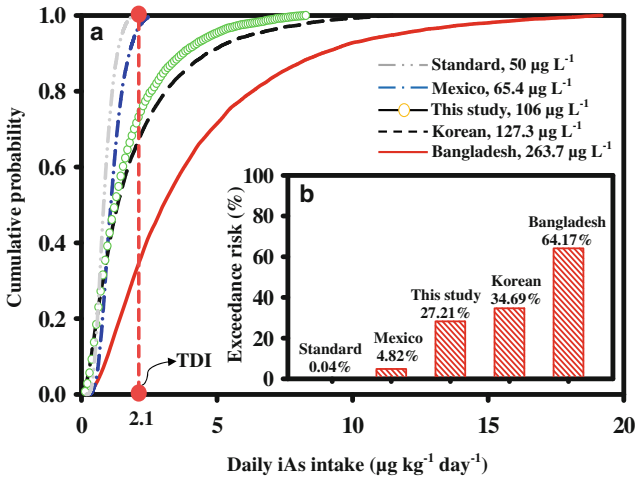

Fig. 5 *a* Cumulative probability of iAs intake in diverse populations from model simulations. *b* Predictions of percentage of iAs exposure risks among populations

reported the association of iAs exposure and an increased risk of metabolic syndrome (Wang et al. 2007) and renal dysfunction (Chen et al. 2011a) in this population. Our model successfully describes the probabilistic distribution for population As exposure, providing an example of the utility of human biomonitoring data to predict population-scale risk characterization.

As daily intake from dietary route

The issue of the impact of body burden versus oral intake on the concentrations of iAs in foods needs to be discussed. As is a naturally occurring element in soil and water and all plants take up As. It has been found in most of the 65 rice products, particularly iAs (Tao and Bolger 1999), in the USA. Rice absorbs As from soil or water much more effectively than other plants because it is one of the only major crops grown in water-flooded conditions. Under such conditions, it allows As to be more easily taken up by its roots and stored in the grains. According to a study in a US population, rice contributes 17 % of dietary exposure to iAs behind fruits and fruit juices at 18 %, and vegetables at 24 % (Xue et al. 2010). In Asia, cooking rice is a major source of iAs exposure owing to the dietary habits. A recent study of more than 18,000 people in Bangladesh established a link between rice consumption and arsenic exposure and toxicity, pointing out that steamed rice consumption was positively associated with urinary total arsenic and skin lesion prevalence (Melkonian et al. 2013).

In the present study, the iAs exposure risk from rice consumption was 41 %, whereas that from drinking water was only 10 %. Not surprisingly, the daily intake of As via cooking rice (ranging from 9.7 to 31.4 μg day^{-1}) was higher than that of drinking water (ranging from 4.3 to 20.8 μg day^{-1}) in the study population. In addition, the subjects lived in a non-arsenic-endemic area in Taiwan that is supplied with arsenic-safe water (<10 μg L^{-1}). Therefore, the iAs exposure risks may primarily be through cooking rice or other routes. Our results were consistent with the report in West Bengal supplied with arsenic-safe water (<50 μg L^{-1}) by Mazumder et al. (2014). They found that daily As intake from diet was found to be significantly positively associated with urinary arsenic level, but no significant association was found with arsenic dose from water.

On the other hand, the highest contribution to iAs exposure risks in this Taiwanese population was from others, implicating other sources of iAs exposure aside from cooking rice and drinking water. Seafood consumption has an important role in arsenic exposure, especially in Asian countries, because of the higher seafood intake than in Europe and the USA (Kim and Lee 2011). Several studies have reported overall health risk arising from the ingestion of different types of fish and shellfish (Chen et al. 2010; Liang et al. 2011). Furthermore, our study area was located in the nearby area of a thermal power

plant. Previous studies indicated that average high seasonal concentrations of arsenic were found in $PM_{2.5}$ (Chen et al. 2013) and total suspended particles (Fang et al. 2011). These sources of arsenic exposure possibly provide the high contribution to iAs exposure in our study populations.

Human As exposure risk in diverse population

We used data sets of 2,557 participants in a US population from the National Health and Nutrition Examination Survey during the period 2003–2004 for validation of this model (Table 2). Although there was a similar distribution in the population-based validation data and model predictions, the levels of As in urine were slightly different. This is not wholly unexpected in a population-based study because values are usually mean values and because such a cohort is subject to great inter- and intra-individual differences. Similarly, the mean values and ranges of tAs and DMA in urine in this validation data are of limited use because the diet and physiological attributes differ. However, they are able to validate the ranges and mean values of our simulation.

A good agreement between model prediction and data helps us to further estimate the human As exposure risks in diverse populations. From our model simulation, the Taiwanese participants in this study had 27 % iAs exposure risks, higher than that estimated in Mexico (5 %), but below that in Bangladesh (64 %) and Korea (35 %). As expected, the highest iAs intake was in the Bangladesh population because As contamination of water in tube wells has been well studied and recognized (Chen et al. 2011b; Sohel et al. 2009; Vahter et al. 2006). In the Korean cohort, foodstuffs containing As were consumed on a daily basis, including rice, seaweed, and shellfish. Rice consumption (163 g day^{-1}) may be a significant source of iAs exposure within this community (Cleland et al. 2009). This is probably a reflection that iAs exposure is dependent on a specific population's lifestyle, location, and dietary behaviors. Similar analyses can be made if other parameters are known for a certain population. Additionally, this model can be expanded to places with population-scale biomonitoring information that can be compared to exposure-based quantities such as a reference dose (RfD).

Limitations and implications

A population-based estimate of exposure should be considered in risk assessments, either to help in the determination of the particular adverse effect seen in a specific population or to support the establishment of acceptable levels for population-scale exposures. The characterization and interpretation of uncertainty and variability on the computation model, both in the modeling of deposition of the chemical in the body and in the description of exposure conditions, becomes more important. Here, we presented a systematic framework for population-based measurement of urinary tAs levels on the basis of daily iAs intake from dietary exposure. Our model provides insight on human variability for risk assessment. Moreover, the strengths of our study were using probabilistic distribution of questionnaire-based or literature-based physiological and pharmacokinetic parameters to predict iAs exposure risks from diverse sources of exposure in a population.

The accuracy of the results is limited by the approximate nature of the model and the quality of the experimental data. Our model combined PBPK and the reverse dosimetry approach to consider the population-scale physiological and pharmacokinetic parameters. Uncertainties in these parameters may cause model predictions as wide as or wider than the range of concentrations measured in a population. Additionally, several factors, including smoking, sex, food habits, and socioeconomic status, might affect the predictions of this model. This suggests that the limiting factors in improving the predictions of models lie more on understanding the inputs of the existing parameters than in increasing the complexity of the model by adding tissue compartments.

From a conservative point of view, we assumed that urinary inorganic and organic arsenic metabolites are both transformed from the iAs in drinking water, foods, and others. Therefore, we used urinary total tAs (iAs + MMA + DMA) data to calculate the iAs exposure in a population through the ECF method. Although it is a study limitation, we can estimate a conservative iAs exposure risk in the Taiwanese population based on such assumption.

Although the method presented here is attempted to be a tool to reconstruct iAs exposure from biomonitoring data, there are no corresponding iAs intake data available. For example, we only considered iAs intake in rice and drinking water consumption at the single dietary exposure. Risk assessment of exposure to iAs may be underestimated. Therefore, comparison of the results with such data would greatly assist in raising the accuracy of the model, and such results could be validated with other studies. Further research is needed to estimate other food resources, such as seafood, vegetables, fruits, and meat.

Conclusions

We developed a population-based risk model that covered urinary tAs levels and daily iAs intake exposure by integrating stochastic PBPK modeling and reverse dosimetry information. Four major findings could be concluded from this study: (1) the mean dietary exposure to iAs of Taiwanese people was 0.47–3.52 μg kg^{-1} day^{-1}, with 95th percentile of 1.57–12.40 μg kg^{-1} day^{-1}; (2) the estimated iAs exposure risk was 27 % higher than that estimated in Mexico (5 %), but below that in Bangladesh (64 %) and Korea (35 %); (3) rice, being the staple food of Taiwanese, is estimated as a major

contributor of dietary exposure to iAs (41 %); and (4) the other sources of iAs contributed 49 % of iAs exposure risk, indicating that the other routes of iAs exposure, including seafood, vegetable, and inhalation, may also be important in the Taiwanese population. The specific risk model we developed in the present study can provide superior predictive power for leading causes of mortality of iAs exposure compared with a range of alternative model forms.

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Compliance of ethical standards

Conflict of interest The authors declare that they have no competing interests.

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