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Evaluation of a Physiologically Based Pharmacokinetic (PBPK) Model for Inorganic Arsenic Exposure Using Data from Two Diverse Human Populations

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Background: Multiple epidemiological studies exist for some of the well-studied health endpoints associated with inorganic arsenic (iAs) exposure; however, results are usually expressed in terms of different exposure/dose metrics. Physiologically based pharmacokinetic (PBPK) models may be used to obtain a common exposure metric for application in dose–response meta-analysis.

Objective: A previously published PBPK model for inorganic arsenic (iAs) was evaluated using data sets for arsenic-exposed populations from Bangladesh and the United States.

Methods: The first data set was provided by the Health Effects of Arsenic Longitudinal Study cohort in Bangladesh. The second data set was provided by a study conducted in Churchill County, Nevada, USA. The PBPK model consisted of submodels describing the absorption, distribution, metabolism and excretion (ADME) of iAs and its metabolites monomethylarsenic (MMA) and dimethylarsenic (DMA) acids. The model was used to estimate total arsenic levels in urine in response to oral ingestion of iAs. To compare predictions of the PBPK model against observations, urinary arsenic concentration and creatinine-adjusted urinary arsenic concentration were simulated. As part of the evaluation, both water and dietary intakes of arsenic were estimated and used to generate the associated urine concentrations of the chemical in exposed populations.

Results: When arsenic intake from water alone was considered, the results of the PBPK model underpredicted urinary arsenic concentrations for individuals with low levels of arsenic in drinking water and slightly overpredicted urinary arsenic concentrations in individuals with higher levels of arsenic in drinking water. When population-specific estimates of dietary intakes of iAs were included in exposures, the predictive value of the PBPK model was markedly improved, particularly at lower levels of arsenic intake.

Conclusions: Evaluations of this PBPK model illustrate its adequacy and usefulness for oral exposure reconstructions in human health risk assessment, particularly in individuals who are exposed to relatively low levels of arsenic in water or food. https://doi.org/10.1289/EHP3096

Introduction

Inorganic arsenic (iAs) is widely distributed throughout the Earth's crust (Zhu et al. 2014). Human exposure occurs through ingestion and inhalation of iAs released by agricultural and industrial activities or by use of groundwater supplies which contain iAs derived from soils and sediments (Hughes et al. 2011). Depending on local conditions, these natural or anthropogenic sources of arsenic may make different relative contributions of total arsenic exposure. For example, in the United States where drinking water arsenic levels are typically quite low, for most individuals the primary route of environmental exposure to iAs is through consumption of foodstuffs that contain arsenic (Kurzius-Spencer et al. 2014). However, in some cases, the major source of iAs exposure worldwide is through use of water supplies that contain elevated levels of this metalloid. For these populations, significant exposure occurs through use of a contaminated water supply for drinking water and in food processing and preparation (Khan et al. 2010; Xue et al. 2010). Chronic use of arsenic-containing water has been associated with a range of adverse health effects. Studies in U.S. populations in which arsenic concentrations in the water supply are only modestly elevated (<100 μg of arsenic per liter) have found associations between exposure and increased incidences of cardiovascular disease and mortality (Moon et al. 2013), diabetes (Gribble et al. 2012; James et al. 2013; Kim et al. 2013), and neurodevelopmental toxicity (Wasserman et al. 2014).

To elucidate dose–response relationships for adverse health effects of chronic iAs exposure, the magnitude, pattern, and duration of exposure to iAs must be determined. Many epidemiological studies have used iAs concentrations in water supplies and consumption histories to estimate exposure (Ahsan et al. 2006; Calderon et al. 2013). However, reconstruction of long-term exposure to iAs from these data can be complicated by temporal changes in iAs concentrations in water and food supplies and changes in patterns of water and food consumption (Greschonig and Irgolic, 1997). Because information on arsenic exposure may be obtained from different populations with different sources and different temporal patterns of exposure, a common exposure metric is needed to allow comparisons across studies (NRC 2013).

Urinary arsenic levels are widely used as biomarkers that reflect primarily recent intake of arsenic (Xue et al. 2010). In contrast, some studies used levels of arsenic in nails as a biomarker that reflects aggregate exposure to arsenic over a longer time scale (Wade et al. 2015). Although nail or hair arsenic levels do integrate exposure over a longer timeframe, it is not clear to what extent they represent aggregate exposure to arsenicals from all sources, including food, which contains inorganic, methylated, and other organic arsenicals, and from drinking water in which iAs is the predominant arsenical (Kile et al. 2007).

PBPK models are computational frameworks that quantitatively describe relevant physiological and biochemical processes

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related to ADME of xenobiotics. Rodent PBPK models can be calibrated or validated against data for chemical levels in tissues that are generated experimentally. Human PBPK models are usually calibrated using *in vitro* data and are usually evaluated using data from chemicals in blood or excreted in biological media (e.g., hair, nail, urine, or feces). PBPK models may be used to reconcile exposure, intake, and excretion metrics using human biomonitoring data to inform risk assessment (Georgopoulos et al. 2008). For example, a PBPK model can be used to associate exposure levels with biomarkers of body burden commonly reported in iAs studies, particularly urinary arsenic level (Kenyon et al. 2008). In the current analysis, a published human PBPK model for iAs oral intake by El-Masri and Kenyon (2008) was evaluated using data from two diverse populations. Simulations were conducted using the PBPK model to estimate total iAs levels in urine in comparison with data obtained from two large population studies in Bangladesh and the United States (Ahsan et al. 2006; Calderon et al. 2013; Hudgens et al. 2016). In both comparisons, intake of iAs was examined using data on consumption of iAs-contaminated water alone or in combination with data on consumption of arsenic in food. Results of the evaluation of the PBPK model illustrate the model's utility for exposure reconstruction, especially when combining arsenic exposures from water and food.

Methods

Epidemiological Studies of Human iAs Urine Levels

Two data sets were used to evaluate the selected PBPK model. The first data set was provided by the Health Effects of Arsenic Longitudinal Study (HEALS), a multidisciplinary and large prospective cohort study on the health consequences of chronic use of iAs-contaminated groundwater as the source of drinking water in Araihazar, Bangladesh, conducted between October 2000 and May 2002 (Ahsan et al. 2006). Approximately 12,000 men and women between 18 and 75 y of age participated in the study. The second data set was provided by a U.S. Environmental Protection Agency (U.S. EPA) study that investigated the effects of biological and behavioral factors on arsenic exposure in Churchill County, Nevada, USA, between August and September 2002 (Churchill County study) (Calderon et al. 2013; Hudgens et al. 2016). The Churchill County study participants were 904 adult residents whose home tap water supplies contained various concentrations of iAs (Table 1).

Details of urine and water samples processing for both studies are given in Hudgens et al. (2016) and Ahsan et al. (2006). For Churchill County participants, urinary arsenic concentrations used in modeling were the summed concentrations of iAs, MMA, and DMA in urine. Samples from Churchill County participants with the concentration of an analyte below the LOD were designated as nondetect samples and concentrations of analyte in nondetect samples were estimated by imputation. Details of the imputation process have been reported (Hudgens et al., 2016). For HEALS participants, total arsenic concentrations in urine were used for modeling.

PBPK Model Selection and Modification

El-Masri and Kenyon (2008) developed the PBPK model selected for evaluation against human data. The model predicts levels of arsenic and its metabolites in human tissues and urine after oral exposure. Arsenic intake can include four different arsenic species: arsenate (As^V), arsenite (As^{III}), monomethylarsenic (MMA) and dimethylarsenic acid (DMA). The model accounts for the fate and transport of two iAs species (As^{III}, As^V) and mono- and dimethylated arsenical metabolites in humans. The full model, coded in acslX Libero™ software (version 3.0.2.1; The AEgis Technologies Group, Inc.) for this study, is described in El-Masri and Kenyon (2008).

To compare predictions of the PBPK model against observations, two output variables were simulated: urinary arsenic concentration and creatinine-adjusted urinary arsenic concentration. The latter value is the ratio between urinary arsenic concentration and amount of excreted urinary creatinine.

To account for variability within and across the study populations, the following model inputs and outputs were adjusted for each modeled individual (based on bodyweights) during the simulation: arsenic intake rate, the volume of the tissue compartments (gastrointestinal lumen, skin, brain, etc.), the urinary flow rate, and urinary creatinine excretion rate based on subject-specific body weight.

The arsenic water intake rate was set as the product of the reported arsenic water concentration and the reported daily water intake, both of which were provided for each individual in both datasets, calculated from the equation:

$$\text{Water As intake} = \text{Water As concentration} \times \text{Water intake} \quad (1)$$

Ingested arsenic was modeled as either As^V, or As^{III}. The model converts 90% of the ingested As^V mass to As^{III}. The ingested As^{III} mass is kept as is (El-Masri and Kenyon 2008).

Table 1. Summary of HEALS and Churchill County data sets.

Parameter	HEALS	Churchill County
Number of observations	Total: 11,438	Total: 904
	Male: 4,876	Male: 368
	Female: 6,562	Female: 536
Age (years)	Range:17–75	Range: 45–92
	Median: 36	Median: 61
Height (m)	Range: 1.30–1.85	Range: 1.45–1.95
	Median: 1.54	Median: 1.66
Weight (kg)	Range: 24.50–100.00	Range: 44.90–165.80
	Median: 46.00	Median: 79.70
Smoking status	Non-smokers: 7,405	Non-smokers: 755
	Past-smokers: 755	Smokers: 149
	Current smokers ≤10 cigarettes/day: 1953	
	Current smokers >10 cigarettes/day: 1314	
As water conc. (μg/L)	Range: 0.1–864.0	Range: 0.86–1850.00
	Median: 61.0	Median: 61.00
Total daily water consumption (mL)	Range: 175.0–10,240.0	Range: 0.00–25,260.00
	Median: 2,850.0	Median: 1,893.00
Urinary As conc. (μg/L)	Range: 1.0–2,273.0	Range: 0.50–856.30
	Median: 87.0	Median: 39.00
Creatinine adjusted urinary As conc. (μg/g)	Range: 6.64–5,000.00	Range: 2.84–5,186.00
	Median: 198.40	Median: 85.44

The model assumes default tissue compartment volumes (L) based on the relative proportions in a 70-kg male. To adjust the volumes for males and females in the study populations, the assumption was made that the relative proportions were similar across populations, but the standard body weight (BW) can differ. Thus, a variable BWMULT (Body weight divided by 70 kg) was added to the model to adjust the 70 kg value for the population-average for either a male or female, depending on the subject being modeled.

The original PBPK model returns the rate of arsenic excretion in moles per minute . To convert this value to an arsenic urinary concentration for comparison with the urinary metric in the datasets, the urinary flow rate for ages 20 to 59 y (Hays et al. (2015) was adjusted using the BWMULT variable to estimate the urinary flow rate ($V_{urinary}$ in milliliters per hour) for the individual

$$V_{urinary} = 0.65\ (\mathrm{ml/hr})/\mathrm{kg} \times \mathrm{BW} \times \mathrm{BWMULT} \tag{2}$$

where average urine flow rate was 0.65 ml/kg/h.

Moles of arsenic were converted to mass using the species-specific molar weight of arsenic. The urinary concentration was then estimated as

$$C_{urinary}\ \mathrm{in}\ \mu\mathrm{g/L} = \frac{RA_{urine}}{V_{urinary}} \times \mathrm{molar\ mass} \times 10^6\ \mu\mathrm{g/g} \tag{3}$$

where RA_{urine} is given in mmole/h. To obtain the urinary concentration in units of μg/g creatinine, an empirical equation was used to estimate each individual's urinary creatinine excretion (mass of creatinine or MCR in μmol/kg/d). The empirical equation takes into account the individual's sex, body mass index (BMI), and age.

$$\mathrm{MCR} = \beta_0 + \beta_1 * \mathrm{sex} + \beta_2 * \mathrm{BMI} + \beta_3 * \mathrm{age} + \beta_4 * \mathrm{age}^2 \tag{4}$$

where β_0, β_1, β_2, β_3, and β_4 were set at 266.16, −47.71 (women), −22.33, 0.66, and −0.017; respectively (Forni Ogna et al. 2015)

The urinary creatinine concentration $C_{urinary\text{-}cr}$ was calculated as

$$C_{urinary\text{-}cr}\ (\mu\mathrm{g/g}) = \frac{RA_{urine}\left(\frac{\mathrm{mol}}{\mathrm{min}}\right)}{\mathrm{MCR}\ (\mathrm{g/d})} \times \mathrm{As\ molar\ mass} \times 1440\ \mathrm{min/d} \times 1\mathrm{e}\,6 \tag{5}$$

Estimation of dietary arsenic intake. Because arsenic in urine can be derived from multiple exposure routes, we also considered population-specific estimates of dietary intake of arsenic as a complement to arsenic exposure through ingestion of iAs-contaminated drinking water.

HEALS iAs in food consumption data. A 39-item semiquantitative food frequency questionnaire and two 7-d food diaries undertaken as part of the HEALS study indicated that rice and vegetables compose as much as 80% of the food consumed by Bangladeshis (Chen et al. 2004; Khan et al. 2009).

In the current study, the primary dietary sources of arsenic intake among Bangladeshis were rice and vegetables. Several studies provided estimates for consumption rates of rice and vegetables and levels of the chemical in these food items as reported in Table 2. Watanabe et al. (2004) evaluated arsenic consumption from tube wells for 19 male and 19 female individuals from 2 rural Bangladesh communities using 24-h self-reports and interviews (Watanabe et al. 2004). Khan et al. (2009) implemented an interviewer-administered Food Frequency Questionnaire (FFQ) to determine age- and gender-specific dietary intake of arsenic. In their study, information on dietary intake of food and water was collected from 1,023 individuals, composed of 386 adult males, 397 adult females, and 240 children from 18 villages in Bangladesh (Khan et al. 2009). Rahman et al. (2009) measured levels of arsenic in rice grain samples that were collected between December 2003 and March 2004 from 214 households in 25 Bangladeshi villages (Rahman et al. 2009). Rahman et al. (2011) reported exposure of adults to iAs from drinking water and rice in two adjacent rural villages of Bangladesh. Samples were collected from 14 families for uncooked and cooked rice, drinking water, and cooking water to determine total arsenic concentrations (Rahman et al. 2011). Khan et al. (2010) measured arsenic and cadmium in foods from the agriculture-based community of Matlab, a rural area in Bangladesh. They sampled both raw and cooked food items from village homes (households, $n = 13$) and analyzed them to quantify concentrations of arsenic and cadmium using atomic absorption spectrophotometry (Khan et al. 2010). Khan et al. (2012) used a Food Frequency Questionnaire (FFQ) to estimate householders' dietary intake of food and water in 60 households from 6 villages located in the Sirajdikhan upazila of the Munshiganj district in Bangladesh. In this study, dietary information was collected from 345 householders including adult males ($n = 125$), adult females ($n = 139$) and children ($n = 81$) (Khan et al. 2012).

Table 2. Estimated arsenic dietary intake for Bangladesh and U.S. populations.

Variable	Mean (range)	Source
Food consumption (Bangladesh)		
Rice (g/d)	Male: 523[a]	
Female: 300[a]	Watanabe et al. (2004)	
Vegetables (g/d)	Male: 153.0[a]	
Female: 146.9[a]	Khan et al. (2009)	
Arsenic levels in food (Bangladesh)		
Rice (μg/kg)		
	173[a]	Watanabe et al. (2004)
	150 (10–500)	Rahman et al. (2009)
	153 (74–301)	Rahman et al. (2011)
Vegetables (μg/kg)		
	12.1 (1.3–22.8)	Khan et al. (2010)
	15 (0–136)	Khan et al. (2012)
Arsenic dietary intake rate (U.S.)		
Rate (μg/d)	5.8–8.0[b]	Kurzius-Spencer et al. (2014)
Rate(μg/min)	0.04 (0.03–0.05)	Tao and Bolger (1999)

[a]Range not available.
[b]Values are reported for total inorganic arsenic rates.

Based on available data, daily rice consumption for the HEALS study was set in the PBPK model to 410 g, using average of the reported values for men and women (Table 2). Rice arsenic concentration was taken as 150 μg/kg consistent with an estimate by Khan et al. (2012). Therefore, arsenic intake rate by rice consumption was calculated as product of rice intake rate and arsenic concentration in rice to be $4.3 \times 10^{-2}\,\mu\mathrm{g\ min^{-1}}$. Daily vegetable consumption was set to 150 g, and the arsenic level in vegetables was set to 15 μg/kg (Khan et al. 2012). Therefore, the intake rate of arsenic through vegetable consumption was calculated as the product of 15 μg/kg and 0.150 kg/day and is set at $1.56 \times 10^{-3}\,\mu\mathrm{g\ min^{-1}}$.

Churchill County iAs in Food Consumption Data

Two studies reported dietary intake levels of arsenic in the U.S. population that are given in Table 2. Kurzius-Spencer et al. (2014) used data from three different population studies, the National Human Exposure Assessment Survey (NHEXAS), the Binational Arsenic Exposures Study (BAsES), and the 2003-04 National Health and Nutrition Examination Survey (NHANES), to model exposure to inorganic and total arsenic among nonseafood eaters using subject-specific data. Tao and Bolger (1999)

estimated levels of iAs in food in a Total Dietary Study (TDS), a yearly market-basket program designed to monitor the levels of toxic chemical contaminants (pesticide residues, industrial and elemental contaminants) and essential nutrients in the U.S. food supply. The analysis using TDS included foods that are collected from retail stores once a year from each of four geographic areas of the United States and are analyzed either after preparation/cooking or as ready-to-eat (Tao and Bolger 1999). Unlike in the HEALS study, where modeled arsenic dietary intake was broken down by food items (vegetables and rice), dietary intake of arsenic in Churchill County was directly set to 6.9 μg/d (average of the reported 5.8 μg/d to 8 μg/d) as reported by Kurzius-Spencer et al. (2014).

Comparing PBPK Model Simulations to Data

A numerical index to evaluate PBPK model simulations in comparison with experimental data (PBPK index) was described by Krishnan et al. (1995). A discrepancy measure between model simulations and data is calculated as the ratio of the root mean square of the simulation error to the root mean square of the experimental values. The root mean square error is the difference between the individual simulated and experimental values. If several data sets were obtained in a single experiment, the resulting numerical values of discrepancy measures for all the data can be combined on the basis of a weighting proportional to the number of data points contained in each data set. A PBPK index is then calculated when consolidated discrepancy measures obtained from several experiments (e.g., exposure scenarios, doses, routes, species) are averaged. The higher the value for PBPK index, the greater the agreement between model predictions and experimentally derived data.

Results

Summary Statistics for HEALS and Churchill County Data Sets

A comparison of the HEALS and Churchill County data sets (Table 1) found that (1) the sample size for HEALS was larger than for Churchill County; (2) participants in HEALS were younger, shorter, and weighed less than Churchill County participants; (3) most participants in both studies were females and nonsmokers; (4) although reported arsenic levels in water supplies in Churchill County had a wider range than levels found in the HEALS study, the median arsenic level in water supplies was the same for both data sets; (5) HEALS participants drank more water (based on median consumption rate) than did Churchill County participants whose water consumption varied more widely; and (7) urinary arsenic levels (both creatinine-unadjusted and -adjusted) were higher in HEALS than in Churchill County study participants.

Figure 1 shows relationship between arsenic water levels and creatinine-adjusted urinary arsenic concentrations for HEALS and Churchill County data. For the HEALS data, a moderate positive correlation was identified between these two variables (Spearman's correlation coefficient = 0.69). A similar relationship between this pair of variables was also found for the Churchill County data set (Spearman's correlation coefficient = 0.52).

PBPK Model Simulation Results for HEALS Data

The relationship between arsenic exposure from water alone or from both water and food and urinary arsenic level was examined for HEALS participants. Figure 2 shows the relationship between arsenic levels in water and observed or model-predicted creatinine-adjusted urinary arsenic for both exposure scenarios. Overall, there was a strong correlation (Spearman's correlation coefficient = 0.95) between model-predicted creatinine-adjusted urinary arsenic concentration and water arsenic concentration when arsenic intake was derived only from water. However, for this exposure scenario, the model underestimated urinary arsenic levels at lower levels of arsenic in water and slightly overestimated urinary arsenic concentration at higher levels of arsenic in water. Underestimation of urinary arsenic levels at low levels of arsenic in water might reflect existence of other sources of arsenic intake. To evaluate the contribution of food arsenic to exposure, a simulation was performed that included arsenic intake from water calculated from arsenic concentration and water intake data along with population-specific arsenic intake from food. With the inclusion of food arsenic intake, better

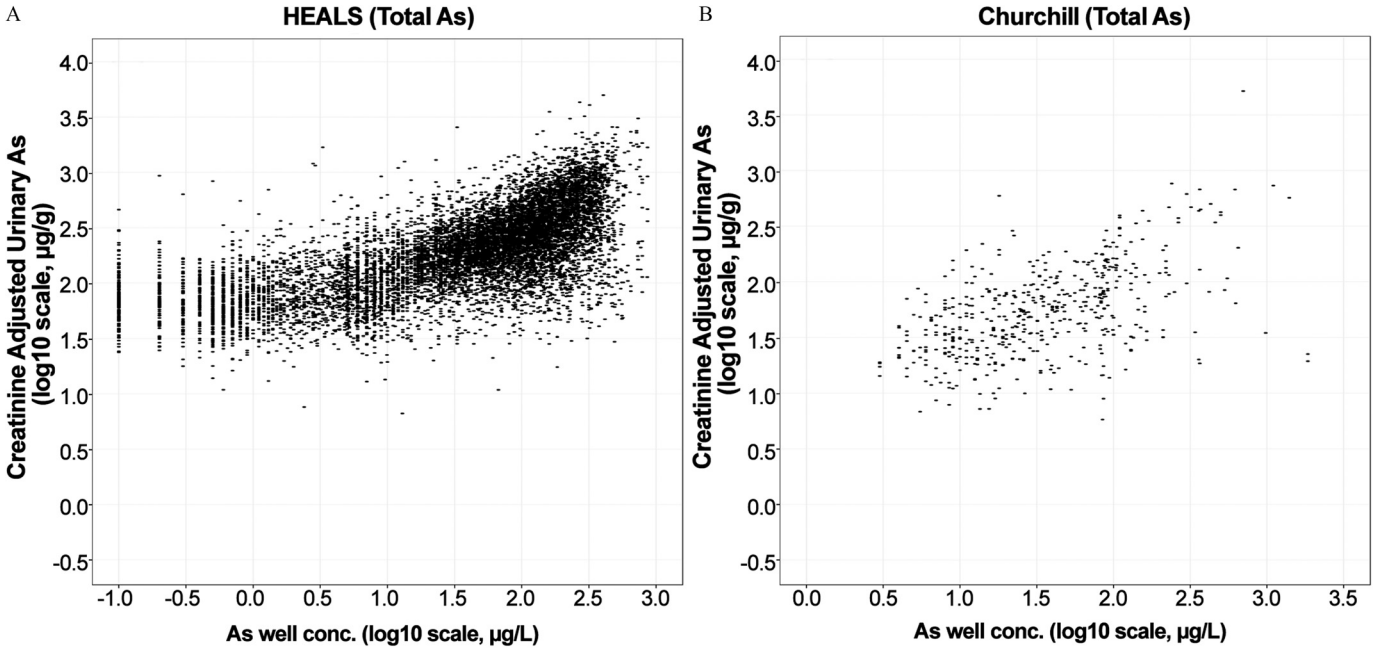

Figure 1. Relationship between arsenic water concentrations and reported creatinine-adjusted total urinary arsenic concentrations from the HEALS (Panel A) and Churchill County data (Panel B).

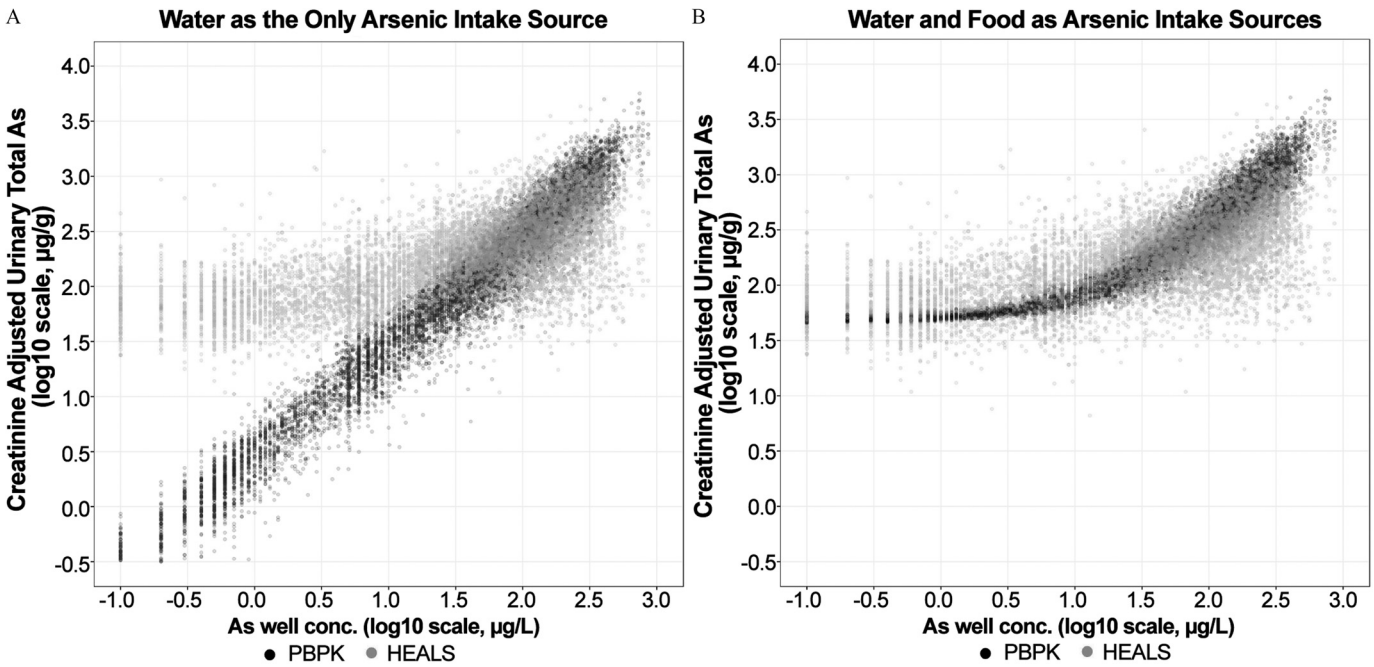

Figure 2. Relationship between arsenic water levels and PBPK model-predicted creatinine-adjusted urinary arsenic concentrations for the HEALS data set. Light and dark dots are measured and predicted total arsenic concentrations in urine; respectively. Panel A: well water as the only arsenic intake source. Panel B: well water and dietary exposure as the arsenic intake source.

agreement was found between observed and model-predicted urinary arsenic levels, particularly for lower arsenic water concentrations. In this situation, the PBPK index increased from 0.87 for the model that used only water arsenic levels to 0.96 for the model that used both water and food estimates. Although inclusion of arsenic intake from food improved model fit for lower water arsenic levels, it did not noticeably improve model fit to observations for participants who used highly contaminated water supplies (Figure 2).

To further characterize the performance of the PBPK model, creatinine-adjusted urinary arsenic concentrations were categorized by deciles of arsenic water concentrations (Figure 3). This presentation of data showed that the PBPK model consistently

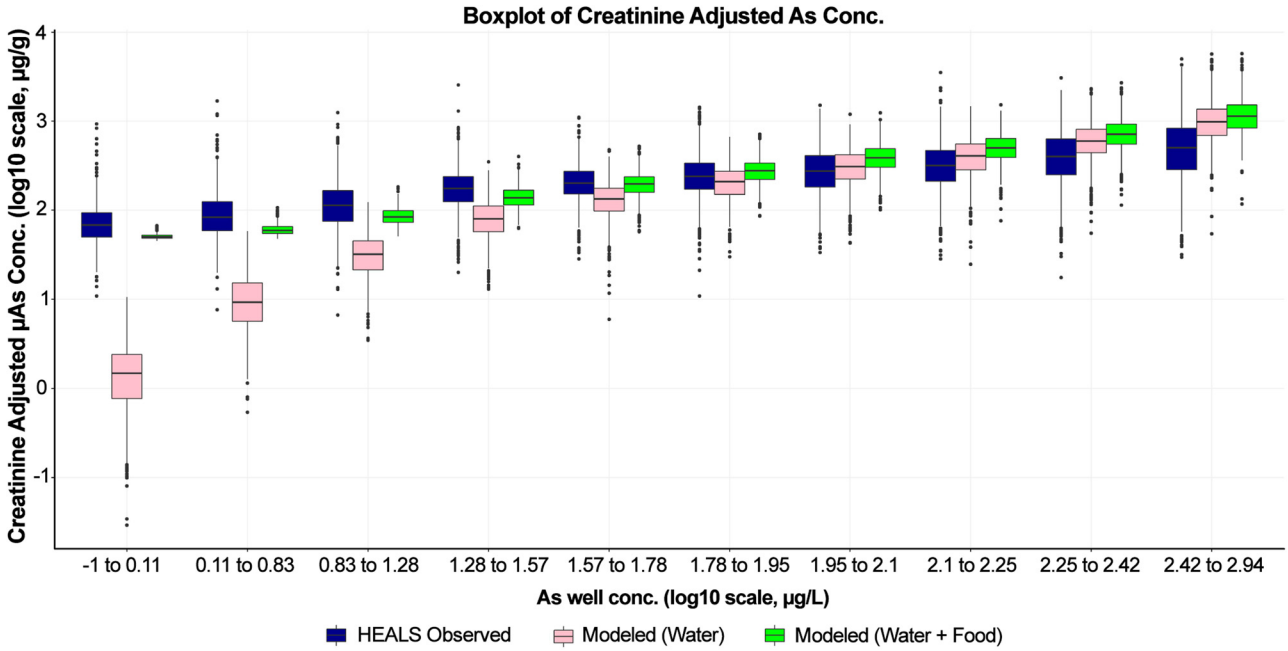

Figure 3. Creatinine-adjusted urinary arsenic concentrations, by decile of arsenic water levels. For each decile, the left box (blue) shows HEALS observed values, the center box (pink) shows predicted values with water only as a source, and the right box (green) shows predicted values for both water and food as exposure sources. The boxplots are a convenient graphical method to depict all data. The top of each box is the upper quartile (25% of data is greater than this value), and the bottom end is the lower quartile (25% of data is less than this value). Horizontal line in the middle of each box is the median value. Top and bottom ends of the whiskers for each box are the maximum value, and minimum values for the data; respectively. Dots for each box depict the outliers where the top ones are measures for data where values exceed 3/2 times the upper quantile limit, and lower dots are outliers where data is less than 3/2 times of lower quartile limit.

underpredicted urinary arsenic concentration at lower arsenic water levels when water was assumed to be the only source of arsenic intake. As shown in Figure 2, including dietary arsenic in the exposure scenario markedly improved agreement between observations and model predictions. For the higher deciles of arsenic water concentration, model predictions based on intake of arsenic from water or water and food consistently exceeded observed levels of arsenic in urine. Notably, for higher exposure scenarios, the boxplots for model predictions were narrower than for observations, suggesting that the PBPK model did not adequately reflect sources of interindividual variability that are present in the population.

PBPK Model Simulation Results for Churchill County Data

A similar analytical approach was taken to evaluate PBPK model performance using Churchill County data. In Figure 4, observed and model-predicted arsenic levels are shown using exposures based on intake of arsenic from water and intake from water and food. When only water arsenic exposure was modeled, observed and model-predicted urinary arsenic levels were congruent with a moderate-to-strong Spearman's correlation coefficient (0.58). Overlapping observed and model predicted values suggested that, for either exposure scenario, the PBPK model adequately captured interindividual variation. Figure 5 shows the results for the creatinine-adjusted urinary arsenic concentrations when categorized by deciles of arsenic water levels. For the lowest decile, use of drinking water as the sole source of arsenic led to underestimation of urinary arsenic level, and inclusion of food as an arsenic source improved agreement between observed values and model predictions. Notably, inclusion of food as an arsenic source, improved the PBPK prediction index slightly (from 2.74 to 2.80) in comparison with the previous HEALS study analysis. Improved fit with the inclusion of food for the lowest decile of arsenic water levels is consistent with a recent analysis showing that only among individuals consuming drinking water containing zero to 1 μg of arsenic per liter does the mean daily intake of iAs from rice exceed arsenic intake from water (Mantha et al. 2017).

Discussion

Human exposures to arsenic are linked to a range of sources and exposure pathways, with individual intakes varying widely by location, employment, gender, age, and other characteristics that differ across individuals and populations (Chi et al. 2018; Minatel et al. 2018; Shakoor et al. 2017). Recognizing this potential variation, some generalizations can be made regarding the environmental media and exposure routes most relevant for arsenic. In general, oral ingestion is the primary route of exposure to environmental iAs in most populations, typically occurring through dietary intake of contaminated food or drinking water (Kurzius-Spencer et al. 2014; Wilson 2015).

The Agency for Toxic Substances and Disease Registry (ATSDR) lists arsenic as the most commonly occurring contaminant found at National Priority Listing (NPL) sites found throughout the United States (ATSDR 2007). Exposure to high levels of arsenic in drinking water has been documented in several regions of the world, including India, Bangladesh, China, Taiwan, and South America (ATSDR 2007; IARC 2012). Arsenic concentrations in drinking water found in the United States are typically lower than the high levels found in non-U.S. regions (ATSDR 2007; IARC 2012). Nevertheless, drinking water can still be an important exposure pathway for some U.S. populations, especially those located in areas near smelting and mining operations and those obtaining drinking water from high-arsenic geological formations (Ayotte et al. 2017; Loh et al. 2016). Dietary intake of foods contaminated with arsenic can also be an important pathway; indeed, for U.S. residents for whom exposures via drinking water are low, most arsenic exposure is likely to come via the diet (at relatively low levels) (Bhattacharya et al. 2012; Halder et al. 2012; Rahman and Hasegawa 2011; Signes et al. 2008; Sofuoglu et al. 2014; Zavala and Duxbury 2008). Foods can be contaminated during production through the accumulation of arsenic from contaminated soil or water or by use of arsenic-contaminated water in food preparations.

Arsenic in ground water used as drinking water and in food production and preparation is mostly present in the inorganic form (Pellizzari and Clayton 2006). Under some conditions, arsenic in foods can be a significant source of oral exposure to the

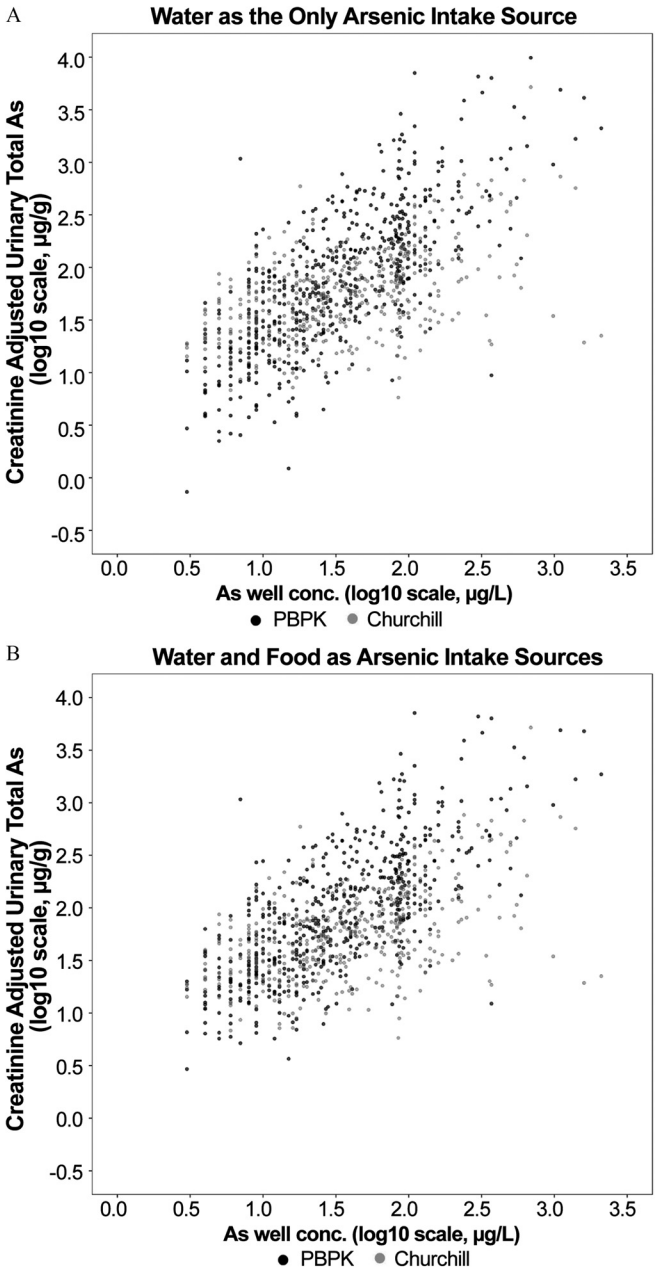

Figure 4. Relationship between arsenic water levels and PBPK model-predicted creatinine-adjusted urinary arsenic concentrations for the Churchill County data set. Light and dark dots are measured and predicted total arsenic concentrations in urine; respectively. Panel A is for well water as the only arsenic intake source; Panel B is for well water and food exposures as arsenic intake sources.

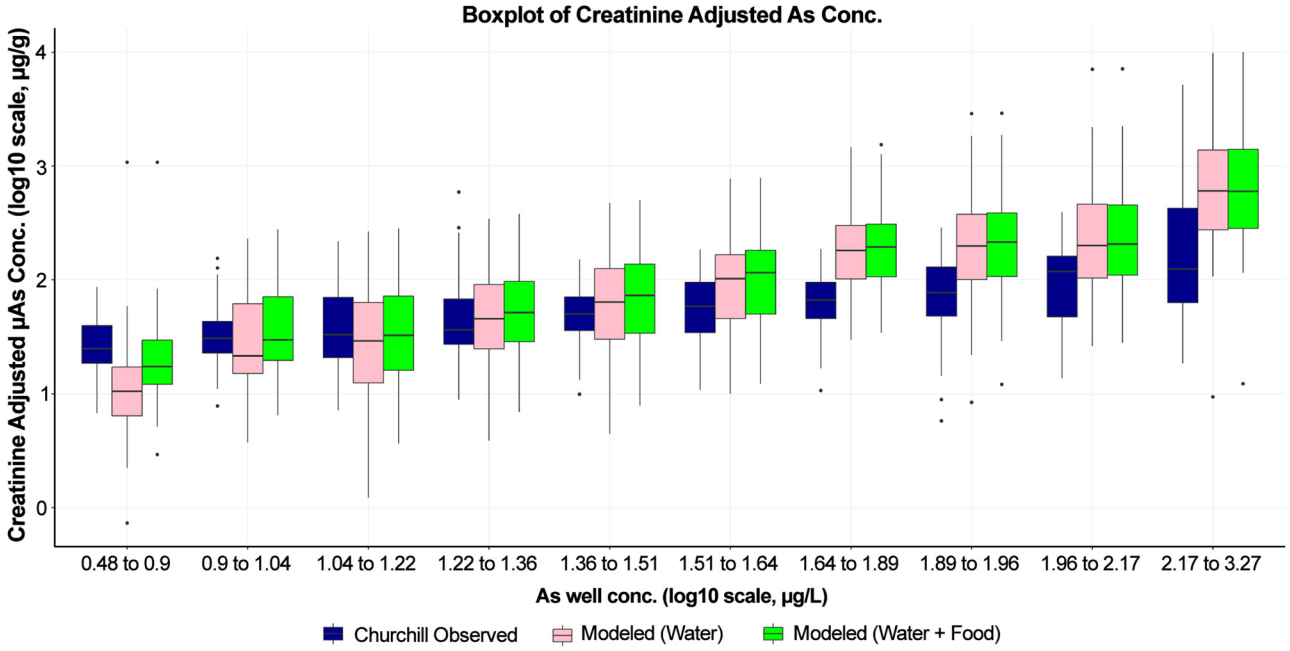

Figure 5. Creatinine-adjusted urinary arsenic concentrations, presented by decile of arsenic water levels. For each decile, the left box (blue) shows Churchill County observed values, the center box (pink) shows predicted values with water only as a source, and the right box (green) shows predicted values for both water and food as exposure sources. The boxplots are a convenient graphical method to depict all data. The top of each box is the upper quartile (25% of data is greater than this value), and the bottom end is the lower quartile (25% of data is less than this value). Horizontal line in the middle of each box is the median value. Top and bottom ends of the whiskers for each box are the maximum value, and minimum values for the data; respectively. Dots for each box depict the outliers where the top ones are measures for data where values exceed 3/2 times the upper quantile limit, and lower dots are outliers where data is less than 3/2 times of lower quartile limit.

chemical. For example, analysis of 2003–2010 NHANES data found that the largest association for adults was between urinary DMA levels and intake of fish (deCastro et al. 2014). Intake of seafood (fish and shellfish) in the U.S. population is influenced by age, gender, and income (Jahns et al. 2014; Tran et al. 2013). Among the older adult (≥45 years old) population examined in the Churchill County study (Calderon et al. 2013; Hudgens et al. 2016), 29% reported seafood consumption during 48 h before urine-sample collection. However, summed urinary concentrations of inorganic, and mono- and dimethylated arsenicals and seafood intake were not associated in a stepwise selection procedure that identified candidate variables for multivariate statistical analysis, suggesting that seafood consumption was not a statistically significant predictor of urinary DMA levels (Hudgens et al. 2016). Thus, consumption of DMA-rich seafood had little, if any, effect on exposure of participants to this arsenical. The arsenic burden of some foods, especially seafoods, is present as complex organic arsenicals (e.g., arsenobetaine, arsenosugars). Although there is evidence that some complex organic arsenicals can be metabolized to release dimethylated arsenicals, it is unlikely that foods rich in this class of arsenicals contribute much to aggregate exposure to iAs (Thomas and Bradham 2016).

For application of the PBPK model to data from the HEALS and Churchill County studies, vegetables and rice were identified as major sources of arsenic exposure. Rice has been identified as a significant source of exposure to both inorganic and dimethylated arsenic (Arslan et al. 2017; Wang et al. 2015; Zhao et al. 2013). Geographic origin affected the relative amounts of iAs and DMA in rice (Halder et al. 2012; Rahman et al. 2011; Williams et al. 2005). Furthermore, iAs and its methylated metabolites have also been identified in vegetables. In west Bengal, India, leafy and root vegetables contained arsenic close to 100% in the iAs form; non-leafy vegetables contained ∼74% of the iAs form (Halder et al. 2013). In raw vegetables, iAs as iAs(V) and iAs(III) accounted for 33 to 100%, MMA for 1 to 11%, and DMA for 3 to 40% of total arsenic (Biswas et al. 2013). Because concentrations of arsenic in rice are typically much higher than arsenic concentrations in vegetables, rice consumption would be expected to the primary determinant of dietary intake of arsenic. Although the bioavailability of arsenic for most foodstuffs has not been well characterized (Yager et al. 2015), there is evidence that the contribution of arsenic in rice to aggregate arsenic intake may be influenced by differences in the bioavailability of arsenic species present in this grain. In the juvenile swine model, oral bioavailability of arsenic in rice with a high percentage DMA (33%) is much lower than for high-iAs rice (89%) (Juhasz et al. 2006). For different rice cultivars from Bangladesh, estimated oral bioavailability of arsenic in juvenile swine has been reported to vary from 25% to 94%, suggesting an important role of rice genotype in bioavailability (Islam et al. 2017).

The National Research Council (NRC) recommended conducting dose–response meta-analyses for available epidemiological studies for iAs. By conducting meta-analyses, studies across the range of exposure can be pooled together to strengthen confidence (NRC 2013). To this purpose, a common exposure metric is needed to integrate information across epidemiologic studies to conduct meta-analyses. Measures of internal doses would be desirable and could be obtained from pharmacokinetic models. Specifically, the application of a human PBPK model in dose–response meta-analyses can improve human health risk assessment for iAs. The application of the published iAs human PBPK model to the data clearly highlighted the need to incorporate food intake, in addition to water consumption, as a significant source for iAs at low environmentally relevant exposure situations. More important, the PBPK model evaluations illustrate its adequacy and usefulness for oral exposure reconstructions in human health risk assessment using available urine data as a biometric for total iAs exposure in humans.

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