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Estimating Inorganic Arsenic Exposure from U.S. Rice and Total Water Intakes

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Background: Among nonoccupationally exposed U.S. residents, drinking water and diet are considered primary exposure pathways for inorganic arsenic (iAs). In drinking water, iAs is the primary form of arsenic (As), while dietary As speciation techniques are used to differentiate iAs from less toxic arsenicals in food matrices.

Objectives: Our goal was to estimate the distribution of iAs exposure rates from drinking water intakes and rice consumption in the U.S. population and ethnic- and age-based subpopulations.

Methods: The distribution of iAs in drinking water was estimated by population, weighting the iAs concentrations for each drinking water utility in the Second Six-Year Review data set. To estimate the distribution of iAs concentrations in rice ingested by U.S. consumers, 54 grain-specific, production-weighted composites of rice obtained from U.S. mills were extracted and speciated using both a quantitative dilute nitric acid extraction and speciation (DNAS) and an *in vitro* gastrointestinal assay to provide an upper bound and bioaccessible estimates, respectively. Daily drinking water intake and rice consumption rate distributions were developed using data from the *What We Eat in America* (WWEIA) study.

Results: Using these data sets, the Stochastic Human Exposure and Dose Simulation (SHEDS) model estimated mean iAs exposures from drinking water and rice were 4.2 μg/day and 1.4 μg/day, respectively, for the entire U.S. population. The Tribal, Asian, and Pacific population exhibited the highest mean daily exposure of iAs from cooked rice (2.8 μg/day); the mean exposure rate for children between ages 1 and 2 years in this population is 0.104 μg/kg body weight (BW)/day.

Conclusions: An average consumer drinking 1.5 L of water daily that contains between 2 and 3 ng iAs/mL is exposed to approximately the same amount of iAs as a mean Tribal, Asian, and Pacific consumer is exposed to from rice. https://doi.org/10.1289/EHP418

Introduction

The International Agency for Research on Cancer characterizes inorganic arsenic (iAs) as a Class 1 carcinogen (IARC 2004). Minimizing human iAs exposures has motivated guidance issued by the World Health Organization (WHO 1993) and the U.S. Environmental Protection Agency (EPA 2001). Among nonoccupationally exposed U.S. residents, drinking water and diet are considered primary exposure pathways for iAs. In drinking water, iAs is the primary form of arsenic (As), while in food matrices dietary As speciation techniques are used to differentiate iAs from less toxic arsenicals.

Table S1 summarizes published probabilistic models that estimate U.S. iAs exposures (Meacher et al. 2002; Schoof et al. 1999a; Tsuji et al. 2007; Xue et al. 2010; Yost et al. 1998; Yost et al. 2004). Predicted iAs exposures from drinking water intakes range from 1.75 to 2.5 μg/day, while dietary iAs estimates range from 3.1 to 3.6 μg/day. Each of these assessments uses iAs drinking water concentration data collected between 1980 and 1998. The age of these data, given changes in treatment and water sources, and the relatively small sample size [$n = 500$] utilities in one study (Meacher et al. 2002)] limit their usefulness for estimating current exposures.

In each of these previous iAs intake assessments, information regarding the As concentrations and species present in foods was based on samples collected from two U.S. cities in 1997 (Schoof et al. 1999b). Xue et al. (2010) and Yost et al. (2004) estimated that rice consumption contributes approximately 20% of the total estimated iAs dietary intake in the United States, while Yost et al. (2004) estimated that, for children at the 95th percentile, rice consumption contributes 50% of the total iAs exposure. A study of adult Michigan residents also underscored the importance of rice consumption to total iAs exposures (Meliker et al. 2006).

Because rice consumption contributes to total dietary iAs exposure in the U.S. population, the authors of the studies in Table S1 highlighted the need for collecting speciated As data from dietary samples to address this source of uncertainty. In response, the U.S. Food and Drug Administration (FDA) measured speciated As levels in 1,300 samples of rice and rice-containing products (FDA 2013). Less stratified literature surveys of iAs species in rice suggest the ranges are 0.01–0.379 μg/g for iAs and 0.004-0.9 μg/g for dimethylarsenic acid (DMA) (Ackerman et al. 2005; Heitkemper et al. 2009; Heitkemper et al. 2001; Lamont 2003; Laparra et al. 2005; Meharg et al. 2009; Torres-Escribano et al. 2008; Trenary et al. 2012; Williams et al. 2005; Zavala et al. 2008; Zhu et al. 2008), with some reports of monomethylarsonic acid near the detection limit. The European Food Safety Authority (EFSA 2014) recently developed an As exposure assessment based on 353 rice samples; the mean and standard deviation of the iAs concentration in brown, white, and parboiled rice were 0.152 ± 0.05, 0.089 ± 0.03, and 0.105 ± 0.06 μg/g, respectively.

The bioavailability of ingested As species in rice also contributes to uncertainty in exposure assessments. While bioavailability studies have been conducted in swine (Brattin and Casteel 2013; Juhasz et al. 2006, 2008; Rodriguez et al. 1999) and mice

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(Bradham et al. 2011), the high cost of these studies has led to development of *in vitro* enzymatic gastrointestinal extraction (Ackerman et al. 2005; Alava et al. 2012; He et al. 2012; Laparra et al. 2005; Sun et al. 2012; Trenary et al. 2012) and human *in vivo* bioaccessibility (solubilized in the gastrointestinal tract but not necessarily absorbed) approaches (He and Zheng 2010) to estimate the physiological relevance of iAs intakes.

In this study, we used the Stochastic Human Exposure and Dose Simulation (SHEDS) model (Xue et al. 2012) to estimate iAs exposures from drinking water and rice consumption in the United States, addressing concerns identified previously (Meacher et al. 2002; Schoof et al. 1999a; Tsuji et al. 2007; Xue et al. 2010; Yost et al. 2004). To improve drinking water iAs exposure estimates, we incorporated the Second Six-Year Review drinking water database (U.S. EPA 2010), which sampled approximately five times more U.S. drinking water utilities than any previous study and provides iAs estimates in 20 states not represented in previous studies (see Table S1).

To address concerns identified in previous studies regarding the levels of As species in U.S. rice, a collaboration with the USA Rice Federation was established to generate a grain- and mill-specific, production-weighted sampling protocol for developing rice composites that reflect the sources and types of rice eaten by U.S. consumers. We measured the iAs concentrations in production-weighted rice composites and incorporated the iAs from the drinking water used to cook the rice based on the Second Six-year Review data set. These data were used to estimate the distribution of iAs concentrations in cooked rice available to the U.S. consumer.

Next, utilizing an *in vitro* extraction procedure that simulates the human gastrointestinal tract, we estimated the bioaccessible iAs in rice and provided an upper-bound assessment available through a quantitative (complete speciation of all arsenicals in a solid rice sample) As speciation-based analysis using ion chromatography inductively coupled plasma-mass spectrometry (IC-ICP-MS). Finally, using the rice ingestion rates from the 2001–2006 *What We Eat in America* (WWEIA) database (53,522 person-day) (CDC 2012), we compared iAs exposure estimates through rice consumption among various ethnicity- and age-based U.S. subpopulations.

Methods

Implications of Domestic/Import Statistics on Rice Sampling Design

The "Sampling" section of Figure 1 illustrates how data from the 2007 – 2008 USA Rice Federation's *U.S. Rice Domestic Usage Report* (USA Rice Federation 2008) were combined with import statistics from the U.S. Department of Agriculture (USDA 2015) to formulate our rice sampling protocol. Broadly, 81% of the rice intended for consumption in the U.S. is grown domestically, while the remaining rice is imported, mainly from Thailand. Figure 1 further delineates rice production based on grain type, with domestic white long grain representing a little less than one-half of U.S. rice usage. Because rice mills are the distribution sources of all wholesale and retail domestic rice in the U.S., their relative production reflects the consumer's grain selection within the U.S. marketplace after correction for exports and usage in pet foods. In 2009, 21 rice mills sent samples and provided their grain-specific annual production records (see Supplemental Material, "Rice Sampling Protocol"). The cumulative production from these 21 mills represented 108% of the production reported by the USA Rice Federation between August 2007 and July 2008 (USA Rice Federation 2008), indicating a broad-based participation in the sampling. The production-weighted, grain-specific composites were formulated by dividing the grain-type-specific production for a mill by the total production for all participating mills and then multiplying by 100 to obtain a percentage. Summation of these grain specific percentages for all mills is the basis for the pie chart in Figure 1. The individual mill- and grain-specific weighting factors were then used to create the domestic production-weighted composites for that grain type. For example, in the case of white long grain rice (WLG), 13 mills supplied samples, but several of the small production mills were added together to make one composite, while the eight weekly samples from a larger mill were split into two sets of four samples each to make two composites. When mills were combined, the relative weighting factors were summed for that composite. If a larger mill was split into two separate composites, the mill-specific relative weighting factor was halved. When multiple weekly samples were received from a relatively small mill, it was often necessary to equally weight these weekly samples into one sample before adding it to the grain-specific composites that were analyzed. These production-weighted composites (weighting factors are reported in Tables S3 and S5 and used in the SHEDS model) reflect the contributions of these larger mills to the mean levels of iAs in rice available to U.S. consumers. Rice production is assumed to provide a reasonable surrogate for consumed rice. If different grain types are disproportionately not consumed (e.g., wasted), then this would be a source of uncertainty associated with this sampling approach. Import rice samples were collected in seven different U.S. cities (Figure 1) and the 14 composites were weighted based on the USDA import data (USDA 2015). Seven city-specific composites were made from the two Thailand samples collected from each city, and the India basmati samples were analyzed without compositing.

Cooking, Subsampling, and Speciation of the 54 Rice Composites

The "Analysis" section in Figure 1 provides a block diagram summarizing the analysis of the composite rice samples. A 50-g rice composite was cooked in 18-MΩ water using a rice-to-water ratio (v/v) of approximately 1 : 2, which produced no residual water after cooking. Each of the 54 whole-grain, cooked, rice composites were then subsampled into nine 1.5-g portions for the *in vitro* gastrointestinal assay (Glahn et al. 2002; Glahn et al. 1998; Trenary et al. 2012), and each sample was then oven dried and ground prior to sampling for a microwave total digestion and a dilute nitric acid extraction and speciation (DNAS, quantitative speciation) (Huang et al. 2010). The iAs method detection limits (MDL) in the enzymatic and dilute nitric acid extracts were 0.2 and 0.09 ng/g, respectively, as determined by seven replicate analyses of a fortified blank (Glaser et al. 1981). The final weight of the gastrointestinal and the DNAS extracts were 17 g and 25 g, respectively. The microwave total digestion of the oven dried rice composites was completed as described by Heitkemper et al. (2001). The average digested solution-based detection limit was 0.029 ng As/g determined by analyzing 30 method blank preparations. All data were collected using a mass balance approach (with ICP-MS detection) to facilitate the comparison of extraction efficiencies and chromatographic recoveries associated with each rice composite. The data associated with the mass balance and a summary of the quality control results (laboratory reagent blanks, laboratory fortified blanks, laboratory fortified matrices, and the analysis of rice flour SRM 1568a) associated with these analytical procedures can be found in the Tables S2 and S3 for DNAS and Tables S4 and S5 for gastrointestinal. The DNAS procedure liberates all the As from the rice and thus provided a species-specific upper limit to iAs in rice associated with this

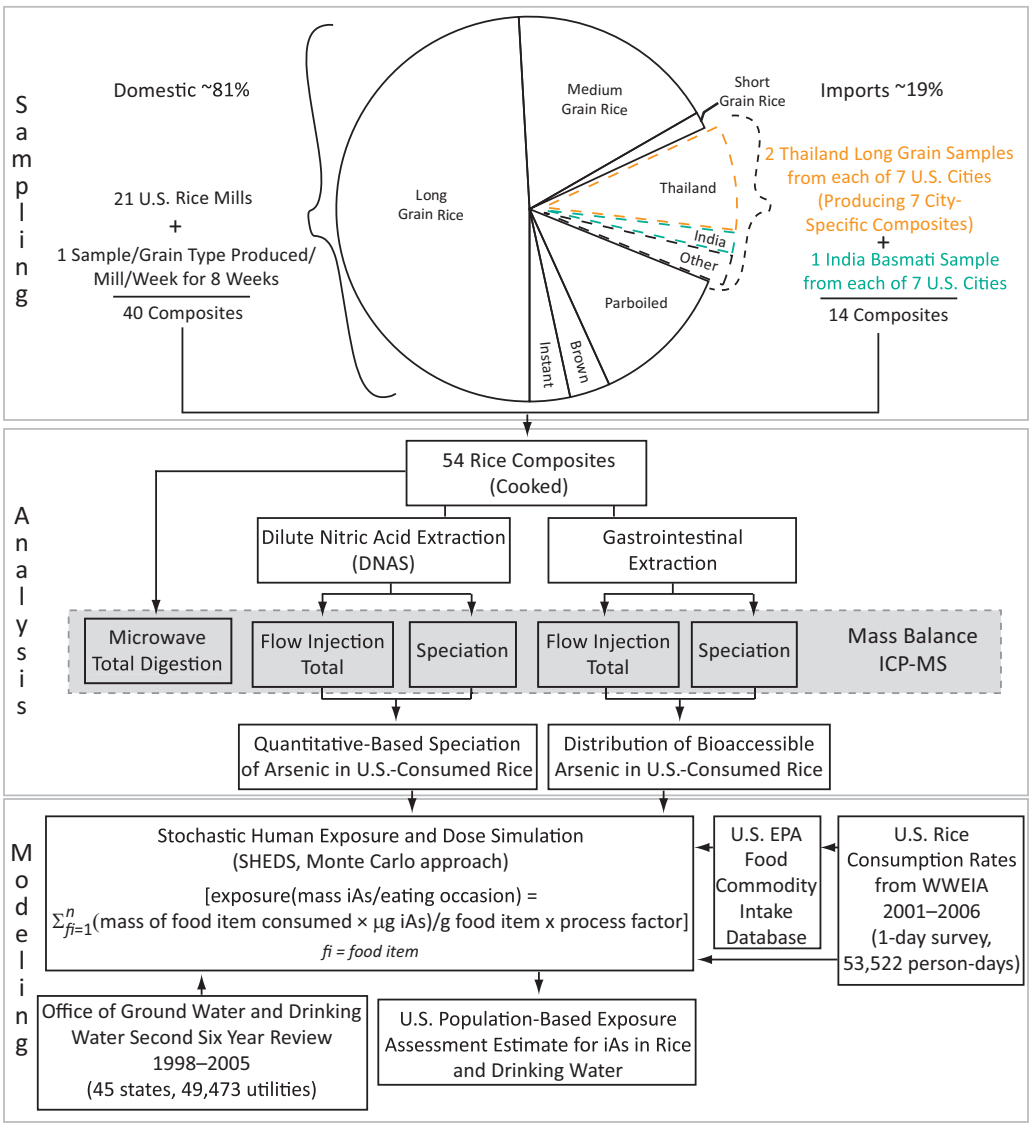

Figure 1. Overview of Sampling, Analysis, and Modeling of iAs Exposure from Rice and Drinking Water for the U.S. Population and Subpopulations. Notes: DNAS, dilute nitric acid extraction and speciation; iAs, inorganic arsenic; ICP-MS, inductively coupled plasma mass spectrometry; SHEDS, Stochastic Human Exposure and Dose Simulation; WWEIA, *What We Eat in America*.

exposure. The *in vitro* gastrointestinal assay was used to estimate the bioaccessible component of iAs in rice.

The flow injection total As concentration was compared to the sum of the chromatographic species to verify column recovery. The flow injected total was determined using standard addition and is determined in the chromatographic autosampler vial by using a chained sequence in combination with the column switching valve on the Agilent 1100 LC. A drift standard was also injected with each flow injection and chromatographic analysis using a postcolumn Rheodyne injection valve. This provided a means to correct for instrumental drift during the 18 hr of chromatographic analysis associated with an analysis batch. An Agilent 7700 ICP-MS was used for As detection at *m/z* 75, while *m/z* 77 was used to monitor the less abundant $^{40}Ar^{37}Cl$ and *m/z* 82 was used to evaluate the possibility of co-eluting Se on *m/z* 77. The use of HCl in the *in vitro* gastrointestinal assay dictated the use of the helium collision cell for the flow injection determination. On a daily basis, a 0.5% weight/weight (w/w) HCl solution was used to evaluate the performance of the cell and no more than a 100-pg/g interference $^{40}Ar^{35}Cl$ on ^{75}As was observed using a typical helium flow of 2.6 mL/min. The ion chromatography (IC) system used in both gastrointestinal and DNAS speciation was an Agilent 1100, and the isocratic elution was accomplished using 10 mM $NH_4NO_3/NH_4H_2PO_4$, pH-adjusted to 8.2 with concentrated ammonium hydroxide (NH_4OH). The ammonium nitrate (NH_4NO_3) and NH_4OH were purchased from Fisher Scientific while the ammonium dihydrogenphosphate ($NH_4H_2PO_4$), was purchased from Sigma-Aldrich. The chromatographic column was a Hamilton PRP-X100. The pH of 8.2 was chosen because it provided baseline resolution of As^{III} (4.0-min retention time, SPEX CertiPrep), As^{V} (13.9-min retention time, SPEX CertiPrep), dimethylarsinic acid (DMA, 4.9-min retention time, ChemServices), monomethylarsonic acid (MMA, 7.0-min retention time, ChemServices), $^{40}Ar^{35}Cl$ (10.2-min retention time), and dimethylmonothioarsinic acid (DMMTA (Fricke et al. 2007), 15.2-min retention time). The stability of DMMTA within the DNAS approach was evaluated and the dilute nitric acid was shown to convert DMMTA to DMA (data not shown). The detection of DMMTA in the gastrointestinal extract has not been evaluated, but the detection in the extract indicates at least a partial preservation throughout this analysis procedure. Chromatographic peaks were integrated using vendor-based software, and integrated areas were used to calculate concentrations. The peak areas for As^{III} and As^{V} were

combined to produce iAs in order to compensate for the potential for interconversion of As^{III} and As^{V} in the matrix. All arsenic standards were verified against NIST 1640 Trace Elements in Water based on total As. Finally, all autosampler vials were cleaned by soaking overnight in 10% HNO_3 then rinsing them three times with 18 MΩ water.

SHEDS Modeling: WWEIA and Drinking Water As Concentrations from the Second Six-year Review

The "Modeling" section of Figure 1 identifies the databases used to estimate the intake rate parameters for the exposure equations in the SHEDS model. WWEIA data were used to estimate daily U.S. rice and total drinking water consumption rate distributions (CDC 2012). Total water consumption included direct and indirect (e.g., water used in food preparation) ingestion of tap water and other fluids, including bottled waters and beverages. The model assumed that for any individual, all drinking water was from a single source. The EPA's Second Six-year Review data (U.S. EPA 2010) were used to estimate the As concentration in the water used for both rice preparation and total water consumption by the U.S. population. These data were collected between 1998 and 2005 from 49,473 public water utilities in 45 states serving approximately 230 million people. Details regarding database censoring (0.7% of 224,035 records) and estimating the best iAs concentration for each utility (e.g., no detect equals one-half MDL) are provided in the Supplemental Material, "Censoring of the Second Six-year Review Database for Arsenic in Drinking Water." All exposure estimates are calculated using the best estimate of drinking water iAs concentration except where noted. In addition, all As reported in water samples is assumed to be iAs that is 100% bioavailable.

The National Health and Nutrition Examination Surveys 2001 – 2006 (Food and Nutrient Database for Dietary Studies 1.0 – 3.0) data based on 53,522 person-days of dietary consumption were used to estimate daily rice intake rates. Food codes in the Food and Nutrient Database for Dietary Studies (USDA 2014) were used to identify dietary sources of rice. In some cases, rice was a component in a food code of the Food and Nutrient Database for Dietary Studies, and recipe files associated with EPA's Food Commodity Intake Database (University of Maryland/FDA 2015) were used to estimate the fraction of that food code comprised of rice. Experimental details (a process flowchart, exposure equations, and examples of Food Commodity Intake Database conversions to raw agricultural commodity) for the SHEDS modeling can be found in the Figure S2. Xue et al. (2012) describes the SHEDS modeling of dietary data. In addition, the National Health and Nutrition Examination Survey 2003 – 2006 two 24-hr recalls were treated as independent survey events. The survey sample size provides a robust distribution of single day rice consumption rates in the United States. Finally, the use of the word Tribal as a subpopulation designation encompasses both Native Americans and Native Alaskans (Eskimo) (Hightower et al. 2006).

Results and Discussion

As Concentrations in Drinking Water and Water Consumption Rates

Arsenic concentrations in U.S. drinking water were estimated using the Second Six-year Review (1998 – 2005), the most current and comprehensive data set for both utility and geographic coverage. Figure 2 presents the population-weighted distribution of drinking water iAs concentrations associated with the 49,473 utilities by partitioning the x-axis based on discrete ($0 < x \leq 1$ ng/mL, $1 < x \leq 2$ ng/mL, etc.) iAs concentration intervals and listing the sizes of the populations corresponding to these concentrations below each interval. Approximately 196 million of the estimated 230 million people included in the Second Six-year Review are serviced by utilities with water containing estimated As concentrations of ≤ 3 ng/mL ("best estimate," see Supplemental Material, "Censoring of the Second Six-year Review Database for Arsenic in Drinking Water"). Approximately 4.5 million people are served by utilities with drinking water iAs concentrations between 10 and 40 ng/mL. Roughly 0.1 million people receive drinking water with concentrations of iAs above 40 ng/mL. For the 49,473 utilities, the utility mean and standard deviation of the iAs concentrations are $3.0\,\text{ng/mL} \pm 5.6$, and 67% (33,191) of these utilities serve fewer than 500 people each. Finally, Figure 2 also compares raw rice (DNAS) and total water as exposure sources to iAs which will be discussed in a later section entitled "*Comparing iAs Intakes from Drinking Water and Rice Exposures*."

Figure S1 presents total (direct + indirect) daily drinking water consumption rates from the WWEIA survey for the whole U.S. population and for 1- to 2-year-old children. Drinking water iAs concentrations were randomly assigned, weighting each utility by the population served. In this study, the mean total drinking water consumption rate (1.54 L of water/day) was about 20% higher than the rates used in previous studies (Meacher et al. 2002; Tsuji et al. 2007) (see Table S1) and slightly higher than those reported in the *Exposure Factors Handbook* (U.S. EPA 2011). Finally, since water used in commercial processing (e.g., canned foods) is not captured in the Food Commodity Intake Database, iAs exposures from indirect water intakes are potentially underestimated.

Speciation of As: Comparing DNAS and in vitro *Gastrointestinal Procedures*

Measurement of total As determined after a hot mineral acid dissolution does not differentiate among forms of As and is a poor basis upon which to estimate potential risks, because of differential toxicity. Speciation improves this measure, but the type of extraction prior to speciation analysis should inform the exposure assessment. For instance, quantitative speciation provides an upper-bound (conservative) exposure assessment by extracting and speciating all the arsenicals in a matrix, but these types of extractions provide limited insight into the biological relevance of the exposure, which is essential to improved exposure characterization. *In vitro* gastrointestinal assays represent a step towards biological relevance.

Using a mass balance approach, Figure 3A compares the speciation-based techniques (quantitative DNAS and *in vitro* gastrointestinal assay) and the total As concentration for the 54 composite rice samples. The slope of 1.00 for the DNAS procedure indicates all the arsenicals (mainly iAs and DMA) were removed from the rice matrix, while the correlation coefficient (R^2) of 0.96 indicates little variability across grain types, providing assurance that all the arsenicals present in each grain-specific composite have been removed and speciated. These species-specific concentrations are used to estimate the distribution of iAs in rice in the exposure model, based on the production-weighted approach for preparing the rice composites; these represent the iAs distribution in rice available to the U.S. consumer. The maximum sum of species reported in Figure 3A is approximately 300 ng/g, which is lower than the single-sample maxima reported previously (FDA 2013; Zhao et al. 2013) and is likely due to production-weighted compositing. Alternatively, the iAs distribution in U.S.-consumed rice can be estimated using the *in vitro* gastrointestinal assay data, which produces a slope of 0.63 and a R^2 of 0.83 relative to the total digest. This slope indicates that the simulated *in vitro* gastrointestinal extraction liberates less As

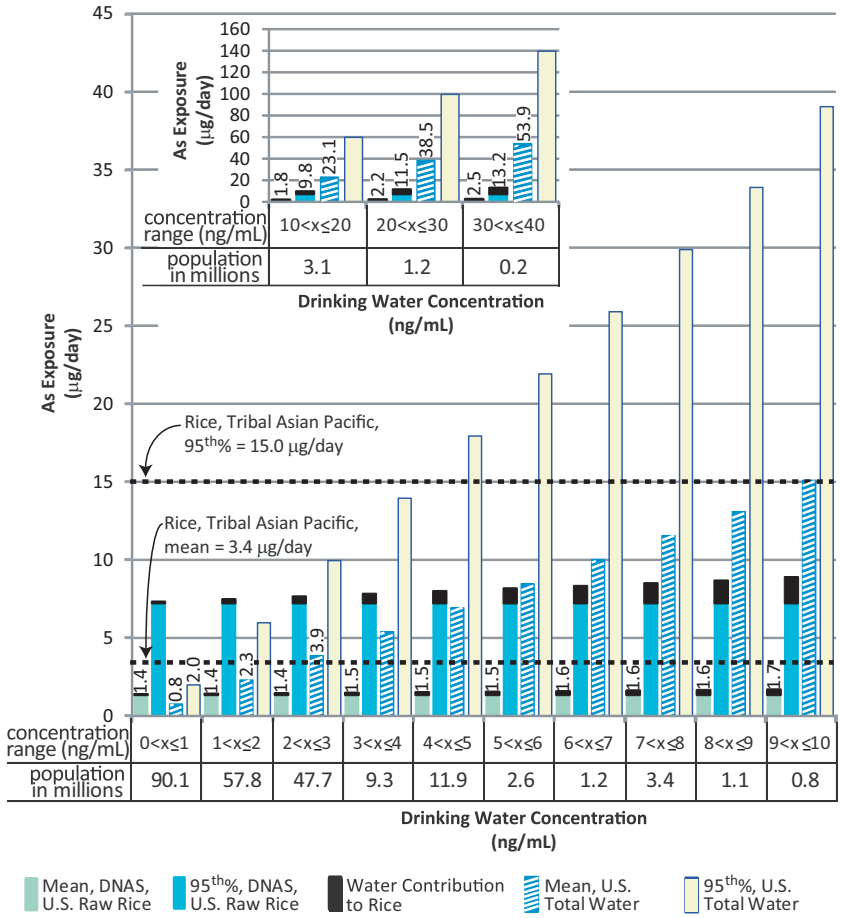

Figure 2. Exposure Comparisons between Drinking Water and Rice after Stratifying the Population Based on the iAs Concentration for Each DW Utility. Notes: As, arsenic; DNAS, dilute nitric acid extraction and speciation; iAs, inorganic arsenic. The midpoint of each x-axis concentration range is used to estimate the iAs concentration in the drinking water associated with that discrete population (i.e., 0.5 ng/mL is used for the $0 < x \leq 1$ ng/mL concentration range which has 90.1 million people from across the U.S. associated with it).

from the rice samples than the DNAS procedure, while the R^2 indicates an increased grain-dependent extraction efficiency. The slopes in Figure 3A reflect the across-matrix average for the extraction efficiency reported in Tables S2–S5 for U.S.-produced and imported rice using both DNAS and *in vitro* gastrointestinal assay.

Figure 3B and Figure S3 provide species-specific comparisons between the two extraction protocols for iAs (slope = 1.37 and $R^2 = 0.80$) and DMA (slope = 1.89 and $R^2 = 0.87$), respectively. Figure 3B summarizes the grain-specific mean and standard deviations associated with the iAs; these means are consistent with the 2013 FDA rice survey (FDA 2013), while the maximum iAs (DNAS) concentration (~ 140 ng/g) is consistent with previous U.S. rice studies (FDA 2013; Zhao et al. 2013). These grain-specific means compare well with the means reported by the European Food Safety Authority (EFSA 2014), with a similar decreasing trend from brown through white long grain rice. The DMA concentrations (see Figure S3) are lower than in previous studies (FDA 2013; Zhao et al. 2013), which report concentrations above 180 ng/g, the highest observed concentration in our study. Again, the production-weighted sampling is likely responsible for this DMA difference.

Collectively, these figures and tables indicate that the DNAS procedure liberates and speciates all the arsenicals, while the *in vitro* gastrointestinal assay less efficiently removes the arsenicals from the rice matrix; on average, less DMA is extracted relative to iAs. This partial extraction is consistent with previous *in vitro* results (He et al. 2012), and reduces the iAs concentration estimate in rice used to formulate the iAs distribution within the model. The grain-specific iAs concentrations plotted in Figure 3B were statistically evaluated using a Holms test for both the DNAS and the *in vitro* gastrointestinal assay procedures. The comparison brackets next to the legend indicate grain types that are not statistically different ($\alpha = 0.01$). Such grain-specific differences have been reported (Meharg et al. 2008), and if the WWEIA survey provided grain-specific details, then that information was used by the model. Otherwise, the production-weighted (see Figure 1), grain-specific distributions of iAs concentrations in rice (both DNAS and gastrointestinal; see Tables S2–S5) was used to estimate iAs exposure from rice in the U.S. population. In this context, the fixed iAs concentrations in rice used by previous models (see Table S1) are replaced by the grain-specific, production-weighted iAs distributions (summarized in Figure 3B, both DNAS and gastrointestinal). These distributions allow the model to simulate the inherent variability of the iAs in rice available to the U.S. consumer, while providing a physiologically relevant estimate through the inclusion of the *in vitro* gastrointestinal assay data set.

Rice Consumption: Total Population, Ethnic- and Age-Based Subpopulations

Based on the WWEIA data, approximately one-half of the U.S. population did not consume rice on the day surveyed (see Figure S4). Tribal, Asian, and Pacific ($\bar{X} = 41.6$ g/day), and Other Hispanic ($\bar{X} = 31.9$ g/day) subpopulations exhibit elevated rice

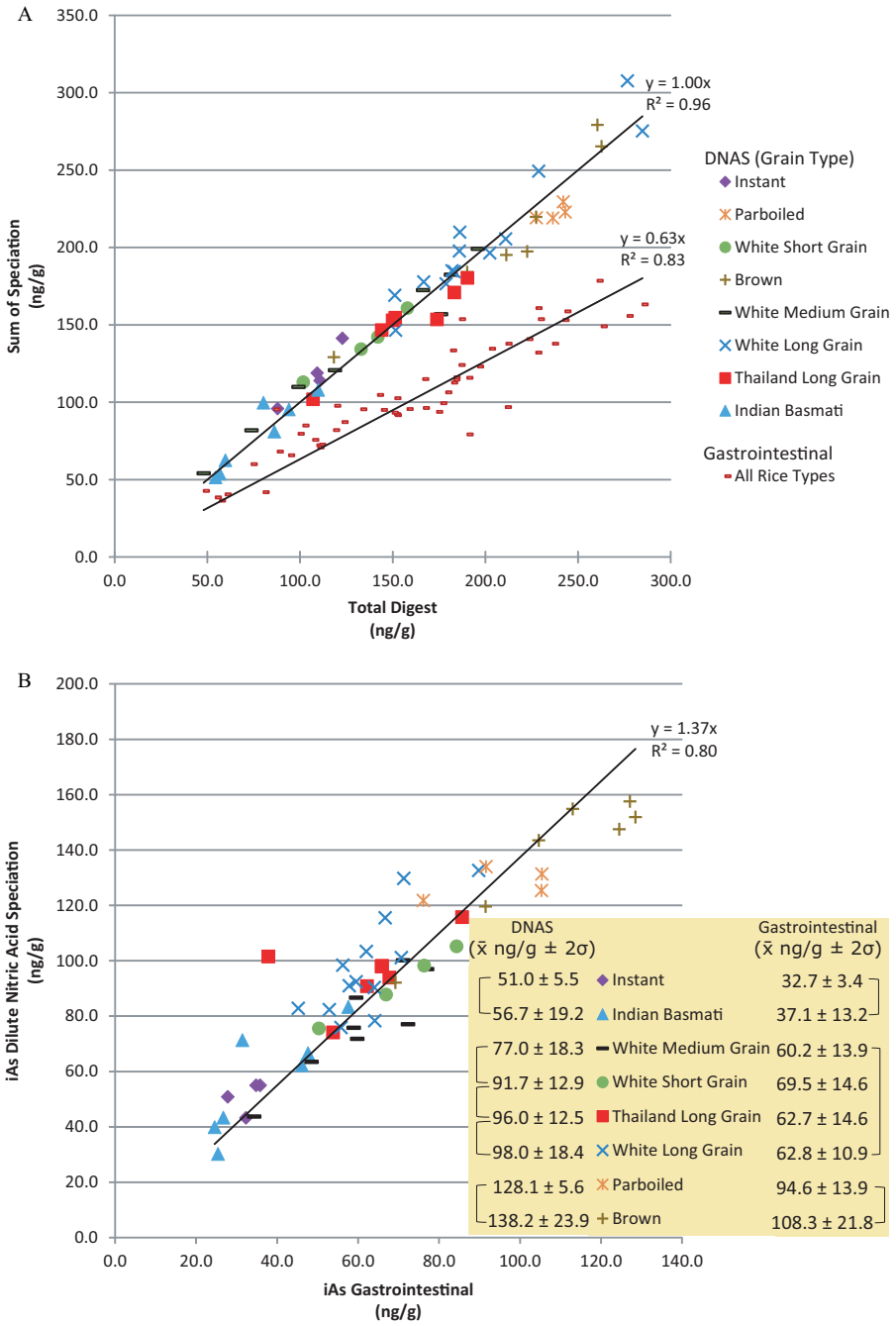

Figure 3. (*A*) Scatter Plot Showing Correlation of the Sum of the Arsenic Species with the Total Digest Concentration in U.S.-Consumed Rice after a DNAS and Gastrointestinal-Based Extraction. Notes: DNAS, dilute nitric acid extraction and speciation. (*B*) Scatter Plot Showing Correlation of Grain-Specific iAs Concentrations in U.S.-Consumed Rice Determined after DNAS and Gastrointestinal-Based Extractions. Abbreviations: DNAS, dilute nitric acid extraction and speciation; iAs, inorganic arsenic. The comparison brackets next to the legend indicate grain types that are not statistically different ($\alpha = 0.01$).

consumption rates relative to the overall U.S. population ($\bar{X} = 15.7$ g/day). Table S6 summarizes the rice-consumption rate estimates in both g/day and g/kg body weight (BW)/day for each subpopulation ($\bar{X} = 12.7$–41.6 g/day) and for the children 1 – 2 years ears old in these subpopulations ($\bar{X} = 4.8$–19.7 g/day). If these consumption rates are normalized using BW, the 1- to 2-year-old children's exposures are roughly double those of the corresponding adults. Normalizing to BW also assists in identifying subpopulations likely to have higher iAs exposures. For example, the mean rice consumption rate for the 1- to 2-year-old Tribal, Asian, and Pacific subpopulation (1.55 g/kg BW/day) is about six times higher than that of the all U.S. general population (0.27 g/kg BW/day). The above discussion has focused on the more reliable mean consumption estimates, but Figure S4 and Table S6 also report the model's 1-day rice intake rate estimates for the 90th and 95th percentile. The European Food Safety Authority (EFSA 2014) estimates the 95th percentile consumption rate for rice for an adult-only subpopulation at 175 g/day, which is comparable to the 169.3 g/day associated with the 95th percentile for the Tribal, Asian, and Pacific subpopulation. The upper percentile 1-day estimates in Figure S4 and Table S6 are also less statistically robust than the general population estimates although they were estimated using the largest available U.S. data set. Further, the short-term recall approach of WWEIA

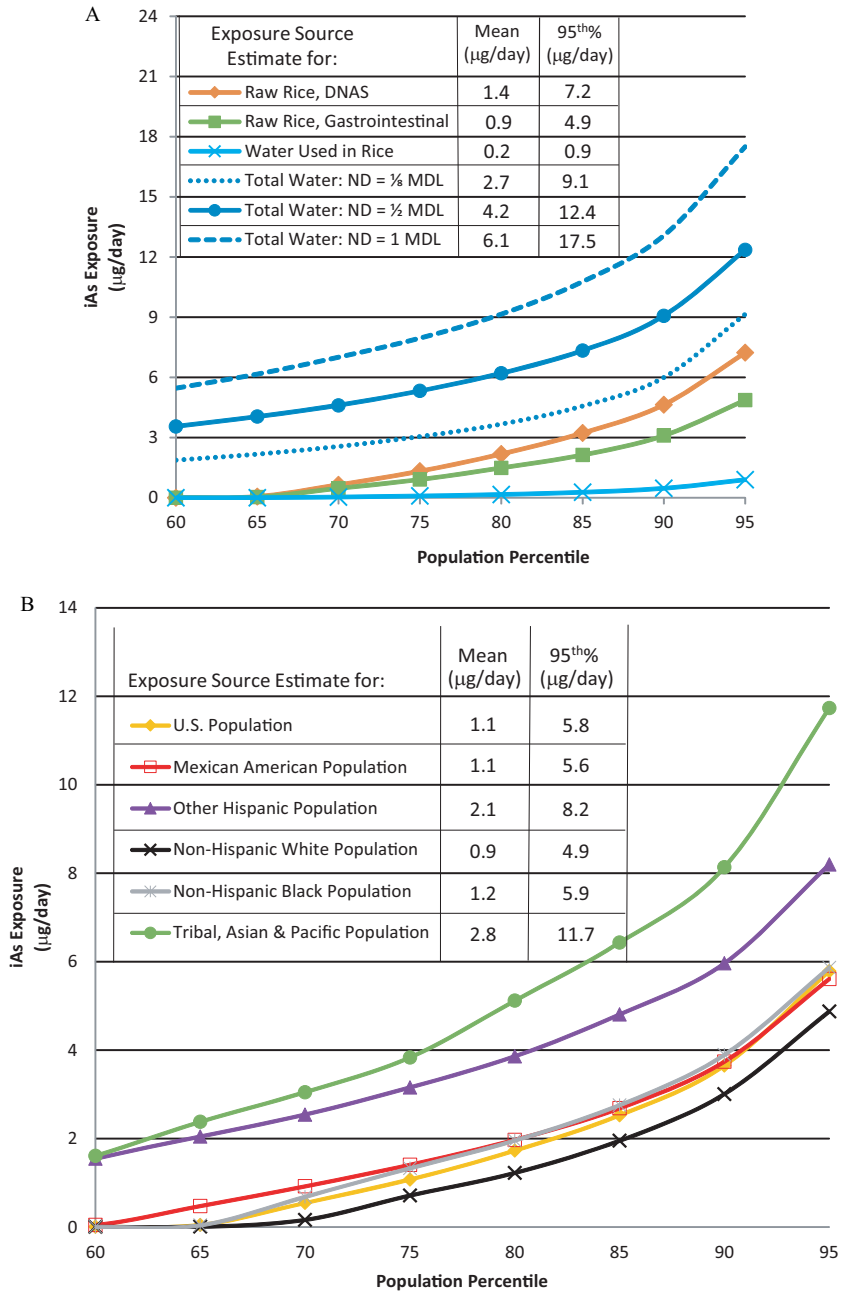

Figure 4. (*A*) Cumulative Density Function Plots of iAs Exposures (µg/day) from Rice, Water Used to Cook Rice, and from Total Water Consumption for the Whole U.S. Population. Abbreviations: DNAS, dilute nitric acid extraction and speciation; iAs, inorganic arsenic; MDL, method detection limits; ND, no detect. Total water comes from three sources which include direct + indirect (food prep) + other fluids (bottled water, etc.). There is uncertainty in estimating the iAs exposure associated with the upper percentiles of exposure in the population due to the use of the single 24-hr dietary recall. (*B*) Cumulative Density Function Plots of iAs Exposures (µg/day) from Cooked Rice for Different Ethnic Subpopulations Using a Gastrointestinal-Based Extraction Procedure. Abbreviations: iAs, inorganic arsenic. There is uncertainty in estimating the exposures associated with the "Other Hispanic Population" and "Tribal, Asian, and Pacific Population" due to the small sample size and added uncertainty from estimating the iAs exposure associated with the upper percentiles of exposure in the population due to the use of the single 24-hr dietary recall.

would likely overestimate the long-term consumption rates associated with the upper percentile consumers (i.e., infrequent rice consumers would have a higher estimated rate if they happened to consume rice on a survey day) and likely underestimate the total percentage of consumers (i.e., infrequent rice consumers are less likely to have consumed rice during the survey period, therefore their consumption may have been missed). While this manuscript does not estimate long-term rice consumption rate data, Table S7 compares single-day (direct + indirect) rice consumption estimates for age, gender- and ethnicity-specific subpopulations reported in the WWEIA to longer term daily (direct) rice consumption rates estimates based on long term oriented questionnaires used in the Nurses' Health Study, the Nurses' Health Study II and the Health Professional Follow-Up Study.

Estimating U.S. iAs Intakes from Rice and Water

The SHEDS model conducts a Monte Carlo–based exposure simulation integrating the iAs distribution in rice (determined by DNAS or *in vitro* gastrointestinal assay), the distribution of iAs in drinking water (Second Six-year Review database), and the

distribution of U.S. rice consumption and total (direct + indirect) drinking water intake rates (WWEIA). These inputs are allowed to vary independently within the boundary conditions of each distribution to estimate iAs exposure. Figure 4A compares daily iAs intake rates (μg/day) from rice and total water for the entire U.S. population. The rice component of the exposure is estimated independently using the iAs distributions developed from the DNAS (upper-bound estimate) and the *in vitro* gastrointestinal assay. The estimated mean iAs rice-exposure rate for the U.S. population using the DNAS extraction protocol (1.4 μg/day) is higher than the mean estimates of both Tsuji et al. (2007) (1 μg/day, estimated from graph) and Xue et al. (2010) (0.6 μg/day, derived from reported 0.05 μg/kg BW/day, assuming an individual weighing 70 kg and that rice is 17% of total iAs in their diet). Using the distribution of iAs in rice based on the *in vitro* gastrointestinal assay, the mean exposure estimate for iAs was 0.9 μg/day for the U.S. population. Again the upper percentiles are reported, but water used to cook the rice is less important in the aggregate exposure from these sources ($\bar{X} = 0.2$ μg/day), while the mean exposure from total water (4.2 μg/day) is about a factor of 3 higher than rice using the mean estimated by the DNAS procedure. The mean iAs exposure from water is considerably higher than the $1.75 - 2.5$ μg iAs means used previously (see Table S1). Part of this difference can be explained by the lower consumption rates (about 1.26 L/day) used by Tsuji et al. (2007) and Meacher et al. (2002), while the population-weighted geometric mean and standard deviation associated with the Second Six-year Review (1.76 ng iAs/mL ± 2.52) and the National Resource Defense Council (1.03 ng iAs/mL ± 4.06) (Xue et al. 2010) data sets contribute to the higher mean exposure for water. Both data sets calculate the best estimate by replacing all "no detects" with a value of one-half the method detection limit (one-half MDL). To estimate the effect of a growing number of utilities complying with the Arsenic Rule, Tsuji et al. (2007) compared a truncated (all utilities >10 ppb were set equal to 10 ppb) to an untruncated data set and reported a marginal change in the mean exposure from drinking water, with a more pronounced difference associated with the exposure estimates for the 95th percentile. Similar reductions would be predicted in the exposure estimates in Figure 4A as an increasing percentage of smaller utilities comply with the Arsenic Rule. Finally, the majority of this discussion of Figure 4A has focused on the mean estimates, while the upper percentiles reported should be considered less certain.

A sensitivity analysis was conducted to evaluate the effect of replacing no detects in the drinking water database with ⅛, ¼, ½, ¾, and 1 MDL. This resulted in population weighted geometric means and standard deviations of 0.7 ng iAs/mL ± 3.9, 1.1 ng iAs/mL ± 3.1, 1.8 ng iAs/mL ± 2.5, 2.3 ng iAs/mL ± 2.3, and 2.9 ng iAs/mL ± 2.2, respectively. The cumulative density function plots for the ⅛, ½, and 1 MDL have been included in Figure 4A for the U.S. population and in Figure S5 for the 1- to 2-year-old U.S. subpopulation to illustrate the impact of this assumption on the total water exposure assessment.

Considering these potentially higher drinking water iAs concentrations, Figure 4A shows that the largest exposure source for the whole U.S. population is from total water. The total water exposure exceeds the DNAS rice exposure for the U.S. population when the no detects are replaced with as little as ⅛ MDL (see sensitivity analysis in Figure 4A). Only for individuals with rice consumption rates above the 90th percentile does rice (DNAS) exceed the mean exposure estimate (4.2 μg/day) associated with total water (no detects = ½ MDL). A similar trend is observed for the children between 1 and 2 years of age, but the difference between the mean exposures from water and rice is reduced by a factor of about 2 (see Figure S5). The sensitivity analysis for the 1- to 2-year- old subpopulations indicates that the upper percentiles do experience a higher exposure from rice relative to water when the no detects are replaced with the ⅛ MDL. The mean exposure from rice (0.63 μg/day, DNAS) for the 1- to 2-year-olds is similar to the 0.63 μg/day reported by Yost et al. (2004) for 1- to 6-year-olds. In addition, the mean water exposure (1.2 μg/day) for 1- to 2-year -olds is slightly higher than the 1.0 μg/day estimate reported by Tsuji et al. (2007) for 1- to 6-year-old children using untruncated drinking water databases. Neither of these comparisons are corrected for BW differences across these age groups, and the small sample size of 1- to 2-year-olds increases the uncertainty of these estimates.

SHEDS Model: Predicted iAs Intake from Rice in Subpopulations

Using the *in vitro* gastrointestinal assay-based iAs distribution, Figure 4B and Figure S6 and Table S8 examine cooked rice as an exposure source for different ethnic subpopulations and different age groups. Figure 4B indicates that exposures in Tribal, Asian, and Pacific ($\bar{X} = 2.8$ μg iAs/day), and Other Hispanic ($\bar{X} = 2.1$ μg iAs/day) populations are elevated relative to the U.S. population as a whole ($\bar{X} = 1.1$ μg iAs/day), due to differences in rice consumption rates. Figure S6 presents a cumulative density function for 1- to 2-year-old children in each ethnic subpopulation, which roughly shows a 2-fold lower iAs exposure from rice relative to the same ethnic subpopulation. However, if these exposures are estimated on a per BW basis (see Table S8), the 1- to 2-year-old children have about two times higher exposure relative to the whole population from that same ethnic subgroup. The *in vitro* gastrointestinal assay-based exposure estimates for cooked rice are slightly lower than the DNAS exposure estimates for the same age- and ethnic-based subpopulations reported in Table S9. Finally, we note that there are fewer than 200 children aged $1 - 2$ years sampled in some of the WWEIA subpopulations, increasing the uncertainty associated with both the mean and upper percentile estimates.

Comparing iAs Intakes from Drinking Water and Rice Exposures

Figure 2 compares the mean and 95th percentile iAs exposures from total water and rice for both the whole U.S. population and the Tribal, Asian, and Pacific subpopulation. The x-axis is partitioned based on iAs concentration range associated with the public water utilities from across the U.S., and the population served is reported below each discrete concentration range on the x-axis (e.g., 90.1 million people are provided water from a public utility with a concentration range of $0 < x \leq 1$ ng/mL). In Figure 2, the mean and the 95th percentile exposure from iAs in raw rice (distribution derived from DNAS) for the whole U.S. population is plotted as a bar above each discrete drinking water concentration range. On top of each rice exposure bar, the contribution from water used to cook the rice has been estimated using the corresponding consumption rate and the midpoint of the corresponding drinking water concentration range (i.e., 0.5 ng/mL for the $0 < x \leq 1$ ng/mL concentration range). In addition, the corresponding mean and the 95th percentile exposure from total water have been added for comparison, again using the midpoint of that concentration range to estimate the exposure for that discrete group. These estimates assume that every consumer will get all water from only one drinking water utility and that the rice and total water consumption rates estimated from WWEIA for the U.S. population as a whole apply to each subpopulation along the x-axis. With these limitations in mind, the lowest discrete drinking water concentration ($0 < x \leq 1$ ng/mL, 90.1 million) is the

only concentration subgroup (representing approximately 40% of the U.S. population) in which the iAs exposure at the mean 1-day rice consumption rate exceeds that of the mean total daily water exposure. For all subgroups above $1 < x \leq 2\,\mathrm{ng/mL}$, the mean and 95th percentile for total water exposure exceed the mean and 95th percentile associated with rice exposures, and total water becomes an increasingly dominant term in estimating the exposure.

Finally, the mean and 95th percentile for raw rice exposures for the Tribal, Asian, and Pacific subpopulation (based on the DNAS distribution) are presented (horizontal dashed lines) in Figure 2. This indicates the mean rice exposure for this subpopulation corresponds to a mean total water exposure for the $2 < x \leq 3\,\mathrm{ng/mL}$ subgroup, and the 95th percentile rice exposure corresponds to a 95th percentile total water exposure for the $3 < x \leq 4\,\mathrm{ng/mL}$ subgroup.

Conclusions

Rice consumption and drinking water intakes are important sources of iAs in the U.S. population. This research generated (DNAS and *in vitro* gastrointestinal assay based) grain-specific, production-weighted distribution of iAs in U.S. consumed rice that allowed the SHEDs model to better simulate the inherent variability of the iAs in rice available to the U.S. consumer while facilitating the inclusion of grain-specific differences into the exposure assessment when grain-specific consumption was reported by WWEIA. All rice composites contained quantifiable iAs concentrations while almost ⅔ of the drinking water data in the Second Six-year Review were below the minimum detection limit requiring data treatment assumptions within the SHEDS model. The mean daily iAs intake from total water for the U.S. population changes from 1.9 times that of raw rice (DNAS) for no detects = ⅛ MDL data treatment to three times if the "no detects" are replaced with ½ MDL. This sensitivity analysis conducted using the Second Six-year Review, indicates a shift in the mean iAs from total water which is greater than the estimate associated with the mean iAs from rice (DNAS) for the U.S. population and points to the inherent benefits of a nationwide drinking water survey using only the most sensitive analytical methods.

Two subpopulations (Tribal, Asian, and Pacific and Other Hispanics) and all 1- to 2-year-olds subpopulations except non-Hispanic white have mean 1-day iAs intake rates from cooked rice (DNAS) which are two to six times the corresponding All U. S. (General Population) based on BW. These differences are further amplified for the 90th percentile consumer within these subpopulations relative to the mean All U.S. (General Population). This rice and water oriented assessment has sources of uncertainty embedded in it with implications across food groups in a more holistic dietary assessment. Therefore, research to develop longer term surveys or mathematical modeling approaches used to estimate longer term consumption rates based on survey data are essential.

Clearly, from an exposure assessment perspective, the elevated rice consumption rates for some ethnic subpopulations are predicted to increase iAs exposures. In this context, the mean daily cooked rice exposure (DNAS) for each ethnic subpopulation is less than 20% of the exposure associated with drinking 2 L of water at the 10-ppb maximum contaminant level while this percentage increases to 60% for the 90th percentile Tribal, Asian, and Pacific (General) rice consumer. In addition, these exposures are increased when this population also has elevated iAs in its drinking water source. In the United States, iAs in drinking water is predominantly a concern in small ground water systems; identifying members of sub-populations who consume such waters and eat high levels of rice is an important research need complicated by the small numbers of Asians residing in rural areas of the United States (U.S. Census Bureau 2012), which are typically served by small ground water systems.

Supporting Information

Detailed experimental results are provided in the Supplemental Material for the censoring of the Second Six-year Review database and for the use of recipes in the Food Commodity Intake Database, Tables S1–S9, and Figures S1–S6. This material is available free of charge via the Internet at http://pubs.acs.org.

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