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Emerging data indicate that rice consumption may lead to potentially harmful arsenic exposure. However, few human data are available, and virtually none exist for vulnerable periods such as pregnancy. Here we document a positive association between rice consumption and urinary arsenic excretion, a biomarker of recent arsenic exposure, in 229 pregnant women. At a 6-mo prenatal visit, we collected a urine sample and 3-d dietary record for water, fish/seafood, and rice. We also tested women's home tap water for arsenic, which we combined with tap water consumption to estimate arsenic exposure through water. Women who reported rice intake (n = 73) consumed a median of 28.3 g/d, which is ~0.5 cup of cooked rice each day. In general linear models adjusted for age and urinary dilution, both rice consumption (g, dry mass/d) and arsenic exposure through water (μg/d) were significantly associated with natural log-transformed total urinary arsenic ($\hat{\beta}_{rice}$= 0.009, $\hat{\beta}_{water}$ = 0.028, both P < 0.0001), as well as inorganic arsenic, monomethylarsonic acid, and dimethylarsinic acid (each P < 0.005). Based on total arsenic, consumption of 0.56 cup/d of cooked rice was comparable to drinking 1 L/d of 10 μg As/L water, the current US maximum contaminant limit. US rice consumption varies, averaging ~0.5 cup/d, with Asian Americans consuming an average of >2 cups/d. Rice arsenic content and speciation also vary, with some strains predominated by dimethylarsinic acid, particularly those grown in the United States. Our findings along with others indicate that rice consumption should be considered when designing arsenic reduction strategies in the United States.

Arsenic, ubiquitous in the environment, has been linked to multiple adverse health outcomes, including skin lesions (1, 2), cancers (3, 4), and cardiovascular disease (5, 6), and there is increasing concern about the effects of low-dose exposures (7, 8). Arsenic exposure during pregnancy is a particular public health concern due to the additional health risks imposed on the fetus. In epidemiological studies, maternal urinary arsenic (a biomarker of recent exposure) has been related to infant mortality (9) and low birth weight (10). Moreover, in utero arsenic exposure has been linked to hampered immune function (11) and increased mortality from lung cancer later in life (12). Given that fetal development is generally a period of heightened vulnerability to environmental toxicants (13), it is especially crucial to characterize the sources and extent of arsenic exposure in pregnant women.

Whereas arsenic exposure through contaminated drinking water is well-documented, emerging data indicate that dietary intake of arsenic also may be substantial (14, 15). Rice in particular has been implicated as a major potential route for exposure (16–18), in that paddy field biogeochemistry and rice physiology combine to give elevated grain arsenic (19, 20). However, there is large variability in the concentration and speciation of arsenic in different rice cultivars (16–18, 21), which makes exposure assessment difficult. Rice consumption in the United States is much lower than in Asian countries, but is increasing rapidly. Americans consume more than three times as much rice now as during the

1930s (22), averaging about 0.5 cup of cooked rice/d (22). Still, there is great variability by ethnic group, with Asian Americans consuming an average of more than 2 cups/d (23). Rice consumption may be of particular concern in the United States, because rice grown in some regions of the United States has been reported to have higher average total arsenic concentrations than rice grown in other geographic regions (16, 21). However, US rice typically contains a higher proportion of dimethylarsinic acid (16, 21, 24), a form of organic arsenic generally considered less toxic. It is essential to understand the extent of arsenic exposure through this staple food.

Here we report our findings on urinary arsenic excretion in relation to recent rice consumption in 229 pregnant women in a region of the United States with elevated well water arsenic concentrations (25). We quantified the contribution of rice and home tap water to arsenic exposure, measured via urinary arsenic concentration, in the women.

Results and Discussion

Women in this initial sample experienced a range of arsenic exposures via their home tap water (Table 1). Home water arsenic concentration ranged from the detection limit (≤0.07 μg/L) to nearly 100 μg/L and was highly right-skewed. Thirty-two women (14%) consumed home drinking water above the current US Environmental Protection Agency (US EPA) standard and World Health Organization drinking water guideline (10 μg/L). The median consumption of home tap water was 0.7 L/d [interquartile range (IQR) 0.1–1.2] through drinking and cooking. By multiplying each individual's reported home tap water intake by the arsenic concentration in her well water, we estimated that the women consumed a median of 0.27 μg of arsenic/d through home tap water (IQR 0.01–2.23; range 0–133.34).

Rice intake ranged from 0 to 112.5 g/d (measured as a dry mass), with a mean of 11.3 g/d. The distribution was highly right-skewed, with 156 out of the 229 women consuming no rice in the 2 d before urine collection and the remaining 73 women consuming a median of 28.3 g/d (IQR 27.5–55.8), which is ~0.5 cup of cooked rice or 1 cup of rice cereal.

Similarly, urinary arsenic concentrations varied among women. The median total urinary arsenic concentration, calculated by

Table 1. Selected characteristics of 229 pregnant women from a New Hampshire pregnancy cohort

Variable	
Maternal age (y)	30.8 (4.5)
Weeks of gestation at urine collection	26.0 (3.1)
Prepregnancy BMI (kg/m^2)	24.8 (4.8)
Parity	1.1 (1.1)
Smoking status	
Never	184 [80.3]
Ever	16 [7.0]
Current	10 [4.4]
Unknown	19 [8.3]
Education level	
Less than 11th grade	3 [1.3]
High school graduate or equivalent	18 [7.9]
Junior college graduate or some college or technical school	51 [22.3]
College graduate	89 [38.9]
Postgraduate schooling	49 [21.4]
Unknown	19 [8.3]
Home water arsenic concentration (µg/L)	1.0 {0.2–4.8}
Home tap water consumption (L/d)	0.7 {0.1–1.2}
Drinking (L/d)	0.7 {0.0–1.2}
Cooking (L/d)	0.0 {0.0–0.1}
Rice consumption (g, dry mass/d)	0.0 {0.0–27.5}

Maternal age, weeks gestation, prepregnancy BMI, parity, smoking status, and education level were from self-reports by subjects. Home water arsenic concentrations were measured from home water samples using inductively coupled plasma mass spectrometry at the Trace Element Analysis facility at Dartmouth College. Consumption of rice and household tap water was measured from a food diary of the 2 d before urine collection. Data are presented as mean (SD), number [%], and median {interquartile range}.

summing the concentrations of inorganic arsenic (iAs), monomethylarsonic acid (MMA), and dimethylarsinic acid (DMA), was 3.78 µg/L (IQR 1.80–6.10), which was within the range of the US population as a whole (26). Total arsenic concentrations were unrelated to gestational week ($r_s = -0.03$, $P = 0.66$). Although other studies found that arsenic methylation increased with gestational week (27, 28), methylation efficiency measured as the ratios of MMA to iAS, and DMA to MMA, was not associated with gestational week in our sample ($r_s = -0.002$, $P = 0.98$ and $r_s = 0.01$, $P = 0.86$, respectively), possibly due to the narrow gestational window under observation (IQR 23.9–28.0 wk). Among the 180

subjects who reported using their tap water for drinking or cooking, home water arsenic concentration was associated with total urinary arsenic concentration ($r_s = 0.43$, $P < 0.0001$).

The median total urinary arsenic concentration was 1.89 µg/L higher among women who reported rice consumption during the 2 d before urine collection compared with those who did not ($P < 0.001$) (Table 2). In examining the median concentrations of the various urinary arsenic species separately, rice consumers had 0.07 µg/L higher iAs ($P = 0.03$), 0.18 µg/L higher MMA ($P < 0.01$), and 1.25 µg/L higher DMA ($P < 0.001$) than nonconsumers. The large difference in urinary DMA concentrations may reflect the consumption of rice that is particularly high in DMA [as found for some US-grown rice (16, 21, 24)], together with the excretion of consumed iAs that was methylated in the body.

Ln-transformed total urinary arsenic concentration increased with increased rice consumption and exposure to arsenic via tap water, controlling for age and urinary creatinine (Table 3 and Fig. 1). Based on our model, each µg of As exposure from water was associated with a 3% increase in total urinary arsenic ($P < 0.0001$), and each g of rice consumed was associated with a 1% increase in total urinary arsenic ($P < 0.0001$) (Table 3). Consuming 0.56 cup (32 g) of cooked rice/d resulted in a predicted total urinary arsenic concentration that was comparable to that predicted from consuming 1 L/d of water at the US EPA Maximum Contaminant Level (MCL) (10 µg/L) (Table 3 and Fig. 1). In our model, arsenic exposure derived from household tap water intake and concentrations explained 12% of the variability of total urinary arsenic. Rice consumption alone, without accounting for the arsenic concentration of the specific rice, was able to explain 4% of the variability of total urinary arsenic. The associations between rice consumption and urinary iAs, MMA, and DMA were similar to those for total urinary arsenic (Table 3 and Fig. S1); no statistically significant associations were observed between rice consumption and arsenobetaine, iAs/MMA, or MMA/DMA (Table S1). Results were robust to outliers.

Our findings suggest that many people in the United States may be exposed to potentially harmful levels of arsenic through rice consumption. The average daily rice consumption in the United States is about 0.5 cup of cooked rice (22), just below our estimated threshold based on the drinking water MCL urinary equivalent. Importantly, there is high variability in rice consumption (23), such that some groups may have considerably higher arsenic exposure through rice. In two national surveys, non-Hispanic blacks, Hispanics, and those of "other race" (including Asian, Pacific Islander, American Indian, and Alaskan Native) were more likely to consume rice than non-Hispanic whites; members of the "other race"

Table 2. Median {interquartile range} of creatinine and urinary arsenic metabolites for all subjects, then rice eaters and non-rice eaters separately

Variable	Total ($n = 229$)	Rice eaters* ($n = 73$)	Non-rice eaters ($n = 156$)	$P^†$
Creatinine‡ (mg/dL)	54.85 {27.69–101.05}	51.81 {29.02–89.73}	57.65 {26.68–107.10}	0.69
Arsenobetaine (µg/L)	0.67 {0.07–5.47}	0.57 {0.07–3.66}	0.69 {0.09–7.74}	0.33
iAS (µg/L)	0.24 {0.13–0.40}	0.28 {0.13–0.51}	0.21 {0.13–0.36}	0.03
MMA (µg/L)	0.30 {0.14–0.50}	0.41 {0.18–0.63}	0.23 {0.13–0.43}	<0.01
DMA (µg/L)	3.25 {1.51–5.53}	4.09 {2.42–7.20}	2.84 {1.34–4.40}	<0.001
Total arsenic (µg/L)	3.78 {1.80–6.10}	5.27 {2.86–8.72}	3.38 {1.64–5.39}	<0.001
MMA/iAs (µg/L)	1.07 {0.70–1.52}	1.16 {0.76–1.70}	1.01 {0.68–1.41}	0.11
DMA/MMA (µg/L)	9.86 {8.05–13.14}	9.86 {7.89–15.21}	9.83 {8.17–12.65}	0.63

Urinary creatinine was measured using Cayman's Creatinine Assay, and urinary arsenic metabolites were measured via HPLC. Total urinary arsenic is the sum of inorganic arsenic, monomethylarsonic acid, and dimethylarsinic acid; arsenobetaine was not included in this total.

*Women who reported any rice consumption during the 2 d before urine collection were categorized as "rice eaters."

†P from the Wilcoxon rank-sum test comparing the median urinary concentration of different variables in rice eaters and non-rice eaters.

‡Sample sizes for creatinine measurements are 64 for rice eaters and 134 for non-rice eaters, respectively.

Table 3. Parameter estimates (95% confidence interval) for the increase in natural log-transformed total urinary arsenic (sum of iAs, MMA, and DMA) with increased rice consumption and arsenic exposure from water, with and without urinary creatinine in the model

	$\hat{\beta}$, without creatinine	$\hat{\beta}$, creatinine included
Age (y)	0.028 (0.004, 0.053)	0.012 (−0.005, 0.030)
Urinary creatinine (mg/dL)		0.011 (0.009, 0.012)
Rice consumption (dry g/d)	0.008 (0.002, 0.013)	0.009 (0.005, 0.013)
As exposure from water (μg/d)	0.021 (0.013, 0.029)	0.028 (0.021, 0.036)

All analyses are adjusted for maternal age (n = 198).

category consumed the largest average amount of rice (2.2 cups/d) (23). In a 2009 study of a US Korean community, the mean cooked rice intake was 2.9 cups/d (29), and the median total urinary arsenic concentration (iAs + MMA + DMA) was more than three times the national median (21.6 μg/L vs. 6.0 μg/L) (26). Additionally, ~3 million Americans (30) with celiac disease, an autoimmune disease triggered by gluten ingestion, may also have high levels of arsenic exposure via rice. Consuming a gluten-free diet is the only medically accepted treatment for celiac disease, and affected individuals often substitute rice for the gluten-containing grains of wheat, barley, and rye (30).

The large variability in arsenic in different rice strains leads to considerable uncertainty in estimated exposures for a given mass of consumed rice. Both the concentration and speciation of arsenic in rice vary with rice cultivar and the arsenic content of the agricultural soil (16, 17). For example, Williams et al. (17) found that rice grown in the south-central United States had a substantially higher average total arsenic concentration than rice grown in California (0.30 vs. 0.17 μg As/g rice). The percentage of arsenic in rice that is in inorganic forms also has been shown to vary substantially (21); one study reported rice samples that ranged from 27 to 86% inorganic arsenic, with the remainder largely composed of DMA (16). This same study found that the arsenic in rice grown in the United States was predominantly DMA, with 42% of the arsenic in inorganic forms (16). Although inorganic arsenic is thought to be more harmful than DMA (31), further epidemiological studies are needed to better understand the health risks of DMA, which is a demonstrated carcinogen in rats (32). More detailed information regarding the types and

sources of rice consumed, combined with further characterization of arsenic concentrations and speciation in rice and rice products, would allow future epidemiological studies to better assess arsenic exposure through this grain.

Fetal development represents a particularly vulnerable window of arsenic exposure, with both immediate and long-term health risks (10–12). At present, the health consequences of low levels of arsenic exposure to the developing fetus are not well-understood, as epidemiological studies of arsenic and fetal development have been done almost exclusively in populations with high levels of exposure. Knowing whether the health risks of arsenic exposure extend to low levels for developmental outcomes, as they do with cancer outcomes (33), would allow for better consultation with pregnant women about arsenic-related risks and ways to limit those risks during pregnancy.

The large and statistically significant association we observed between rice consumption and urinary arsenic, in addition to earlier reports of elevated arsenic concentrations in rice (16, 17), highlights the need to regulate arsenic in food (34, 35). There are no statutory limits for the arsenic content of food sold in the United States and European Union, in stark contrast to China, where the maximum safe level of inorganic arsenic in rice is 0.15 μg/g (36). Setting such limits would protect consumers from unknowingly purchasing rice or rice products with high levels of arsenic. In addition, limits would encourage cultivation of rice strains that do not incorporate as much arsenic and reduce the use of arsenic-contaminated land for agriculture. Given the potentially adverse health consequences of arsenic at low levels of exposure, it is imperative that the health impact of arsenic exposure through rice consumption be characterized.

Methods

Pregnancy Cohort. In January 2009, we began enlisting pregnant women (ages 18–45) who reported using a private, unregulated water system (e.g., private well) at their home, through prenatal clinics in New Hampshire. A spot urine sample was requested at the prenatal visit at ~24–28 wk of gestation. Women were provided with a prelabeled, acid-washed, screw-top, 120-mL urine specimen container that contained 30 μL of 10 mM diammonium diethyldithiocarbamate to stabilize arsenic species. Samples were stored upright, maintained at 4 °C, and sent via courier in a styrofoam box to the Pathology Department at Dartmouth Hitchcock Medical Center for processing within 24 h. Samples were aliquoted and stored at −80 °C. One aliquot was shipped on dry ice to the University of Arizona Hazard Identification Core for analysis, with every tenth sample replicated as part of quality control. We determined urinary creatinine in a second aliquot using Cayman's Creatinine Assay Kit and protocol.

Women were asked to record their intake of water, rice, rice products, and fish/seafood in each of the 3 d before the urine sample. We asked the source of intake (home tap water, work tap water, restaurant tap water, bottled water, or other) for water used in both beverages (e.g., tea and coffee) and food (e.g., soups and jello). Rice products included rice and hot rice cereals prepared with or without home tap water, premade rice, and cold dry rice cereals.

Additionally, we instructed women on the collection of water samples from their household (i.e., kitchen) tap. Women were given containers with prepaid mailing materials to return the samples to the study office. Samples were collected in commercially washed (mineral-free) high-density polyethylene bottles that meet EPA standards for water collection (I-Chem).
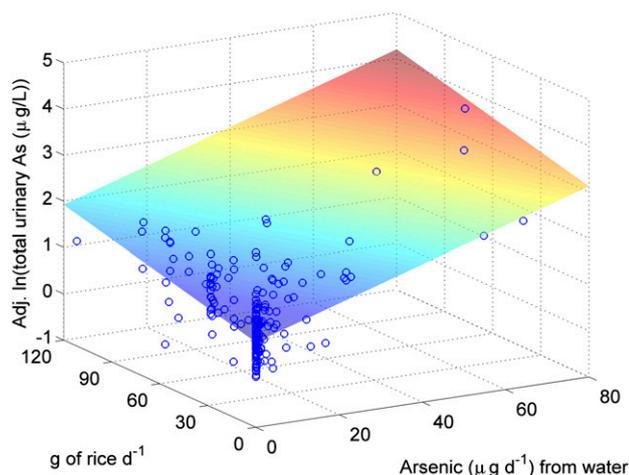
Fig. 1. Circles show age- and creatinine-adjusted ln-transformed total urinary arsenic (sum of inorganic As, MMA, and DMA) versus arsenic exposure via tap water (μg/d) and rice consumption (dry g/d). The plane represents the predicted urinary arsenic concentrations from our multiple regression model, given the cohort's mean age of 30.9 y and median urinary creatinine concentration of 58.3 mg/dL.

Bottles were kept in clean, sealed plastic bags to prevent contamination. Instructions stated to collect the sample using the provided gloves after running the tap for 2–3 min and to transfer the sample into a provided, sealed plastic bag to avoid contamination. Two water samples were requested if tap water filters were used—one before and one after filtration. All samples were labeled with preprinted labels with the subject's ID number. Water samples were frozen at −20 °C upon arrival at the study office and then sent frozen to the Dartmouth Trace Element Analysis Core for analysis. Every tenth sample was sent in duplicate as part of quality control.

Arsenic Analysis: Water. Drinking water samples were analyzed for arsenic concentration by inductively coupled plasma mass spectrometry (ICP-MS) at the Trace Element Analysis Core at Dartmouth using a quadrupole collision cell 7500c Octopole Reaction System ICP mass spectrometer (Agilent) and He as a collision gas to remove polyatomic interferences. All sample preparations and analyses were carried out in a trace metal-clean HEPA-filtered-air environment. Analytical blanks and potential instrumental drifts were carefully monitored, and instrument standardization and reproducibility were performed with National Institute of Standards and Technology traceable standards and certified standard reference materials.

Samples (3-mL) were transferred to a polypropylene vial and 20 μL of concentrated trace metal-grade nitric acid was added before analysis. The analytical uncertainty of ICP-MS analyses using a weighted linear regression calibration method is typically ±3–5%. The detection limit ranged from 0.009 to 0.074 μg/L (mean = 0.014 μg/L), with detectable levels in over 96% of the samples tested to date.

Arsenic Analysis: Urine. Upon arrival at the University of Arizona, urine samples were transferred to 15-mL tubes and frozen at −20 °C until analysis (within 1 mo of collection). Samples were analyzed for individual species of urinary arsenic using a high-performance liquid chromatography (HPLC) ICP-MS system (37–39). This system uses an HPLC pump (Dionex GP50 pump) and an HPLC column (Hamilton PRP100X) connected to a collision cell ICP mass spectrometer. The arsenic speciation method is capable of quantitatively determining five arsenic species in urine: As^{III}, As^V, DMA^V, MMA^V, and arsenobetaine. Before injection into the chromatographic system, the urine sample was filtered through a 0.45-μm membrane filter under pressure from a disposable syringe and diluted fivefold with the mobile phase [30 mM $(NH_4)_2HPO_4$, pH 8]. The sample volume was 100 μL and the column flow rate was 1 mL/min. The separated arsenic species were detected by ICP-MS using time-resolved analysis at m/z 75. The detection limits ranged from 0.10 to 0.15 μg/L for the individual arsenic species.

We calculated total urinary arsenic concentrations by summing inorganic arsenic (As^{III} and As^V) and the metabolic products MMA^V and DMA^V. Arsenobetaine was excluded from this calculation, as it is thought to be nontoxic and pass through the body without being metabolized (40).

Estimation of Rice Consumption. For the 73 women who consumed rice and rice products, we estimated their total rice consumption by converting the information in the dietary record using the US Department of Agriculture (USDA) National Nutrient Database (41). For cooked rice, participants reported the number of 8-oz cups of cooked rice eaten; we calculated the dry mass of rice consumed (g) by dividing the number of kcal in a cooked cup of rice by the kcal/g in dry rice of that type. We repeated this calculation for each of the nine types of rice listed in the database and obtained an average of 55.1 g dry rice in 1 cup of cooked white rice and 59.3 g dry rice in 1 cup of cooked brown rice. Relative consumption of white and brown rice from a postpartum questionnaire was then used to weight the values for white and brown rice, producing a single estimate of 56.7 g of dry rice in each cup of cooked rice. The USDA database also was used to obtain the mass of dry rice in 1 cup of hot rice cereal using the Cream of Rice entry (34.3 g) and for 1 cup of cold rice cereal using the Rice Krispies and Rice Chex entries (average = 27.5 g). We then multiplied the cups consumed for each category of rice item by the average mass per cup and summed across all categories of rice.

Estimation of Arsenic Exposure via Water. Each woman's consumption of home tap water was also determined. For the women who consumed rice prepared with home tap water, we added 0.52 cup of water per cup of cooked rice consumed to this total. We made this correction because women who ate rice prepared with home tap water did not report using water for cooking rice as they did for other foods (e.g., soups, juices, etc.). The correction factor was determined using the USDA database for moisture in dry and cooked rice for all nine types of rice in the database, paralleling our estimates for grams of rice consumed. Including this water for cooking did not change the estimated associations or level of significance between rice and water intake and urinary arsenic concentrations. We converted the number of 8-oz cups of home water consumed via drinking or food preparation during each of the 2 d before the urine sample to liters.

Finally, we estimated arsenic exposure via water (μg) by multiplying water consumption (L) in the 2 d before the urine sample by the measured arsenic concentration in that water (μg/L). At this stage, we excluded one woman from further analysis because she reported using water from two wells with very different arsenic concentrations, but not the number of cups of water consumed from each well.

Data Analysis. We categorized women who reported any rice or rice product consumption in the 2 d before urine collection as "rice eaters," and all others as "non-rice eaters," and then compared median urinary creatinine, arsenic metabolites, MMA/iAs, DMA/MMA, and total arsenic (sum of iAs, MMA, and DMA) between groups using the nonparametric Wilcoxon rank-sum test (SAS version 9.2; SAS Institute).

We evaluated the relationship between ln-transformed urinary arsenic and estimated arsenic exposure via water and intake of rice in grams for the 2 d before the urine sample using general linear models (SAS version 9.2). A 2-d window was used based on arsenic excretion studies by Buchet et al. (42) and Tam et al. (43); results were not sensitive to the use of 1-, 2-, or 3-d intake windows.

We adjusted for age (y) based on an established relationship between age and urinary arsenic (40, 44, 45) and for urinary dilution by including urinary creatinine in the model (46). Time of pregnancy at urine collection (gestational week), prepregnancy body mass index (BMI), parity, smoking, and education level were not included in the adjustment model because they were not related to urinary arsenic concentrations and rice or water consumption in bivariate analyses.

Given our multiple regression model for ln-transformed urinary arsenic concentration as a function of age, urinary creatinine, rice consumption, and water exposure (μg arsenic/d), we predicted the urinary arsenic concentration for a woman at the mean age in our cohort (30.9 y) and median urinary creatinine concentration (54.9 mg/dL) for different rice consumptions and arsenic exposures through water. For rice, we back-converted the grams of dry rice/d consumed into cups/d of cooked rice for easy interpretation, assuming that the rice was cooked in arsenic-free water; this assumption should result in a more conservative estimate of the impact of rice consumption on urinary arsenic.

1. Ahsan H, et al. (2000) Associations between drinking water and urinary arsenic levels and skin lesions in Bangladesh. *J Occup Environ Med* 42:1195–1201.
2. Karim M (2000) Arsenic in groundwater and health problems in Bangladesh. *Water Res* 34:304–310.
3. Karagas MR, et al. (1998) Design of an epidemiologic study of drinking water arsenic exposure and skin and bladder cancer risk in a U.S. population. *Environ Health Perspect* 106(Suppl 4):1047–1050.
4. Hopenhayn-Rich C, Biggs ML, Smith AH (1998) Lung and kidney cancer mortality associated with arsenic in drinking water in Córdoba, Argentina. *Int J Epidemiol* 27:561–569.
5. Chen CJ, Chiou HY, Chiang MH, Lin LJ, Tai TY (1996) Dose-response relationship between ischemic heart disease mortality and long-term arsenic exposure. *Arterioscler Thromb Vasc Biol* 16:504–510.
6. Tseng CH, et al. (2003) Long-term arsenic exposure and ischemic heart disease in arseniasis-hyperendemic villages in Taiwan. *Toxicol Lett* 137(1-2):15–21.
7. Ahsan H, et al. (2006) Arsenic exposure from drinking water and risk of premalignant skin lesions in Bangladesh: Baseline results from the Health Effects of Arsenic Longitudinal Study. *Am J Epidemiol* 163:1138–1148.
8. Karagas MR, et al. (2004) Incidence of transitional cell carcinoma of the bladder and arsenic exposure in New Hampshire. *Cancer Causes Control* 15:465–472.

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9. Rahman A, et al. (2010) Arsenic exposure and risk of spontaneous abortion, stillbirth, and infant mortality. *Epidemiology* 21:797–804.

10. Rahman A, et al. (2009) Arsenic exposure during pregnancy and size at birth: A prospective cohort study in Bangladesh. *Am J Epidemiol* 169:304–312.

11. Raqib R, et al. (2009) Effects of in utero arsenic exposure on child immunity and morbidity in rural Bangladesh. *Toxicol Lett* 185(3):197–202.

12. Smith AH, et al. (2006) Increased mortality from lung cancer and bronchiectasis in young adults after exposure to arsenic in utero and in early childhood. *Environ Health Perspect* 114:1293–1296.

13. Brent RL, Tanski S, Weitzman M (2004) A pediatric perspective on the unique vulnerability and resilience of the embryo and the child to environmental toxicants: The importance of rigorous research concerning age and agent. *Pediatrics* 113(4 Suppl): 935–944.

14. European Food Safety Authority (2009) EFSA Panel on Contaminants in the Food Chain (CONTAM): Scientific opinion on arsenic in food. *EFSA Journal* 7:1351.

15. Xue J, Zartarian V, Wang SW, Liu SV, Georgopoulos P (2010) Probabilistic modeling of dietary arsenic exposure and dose and evaluation with 2003–2004 NHANES data. *Environ Health Perspect* 118:345–350.

16. Williams PN, et al. (2005) Variation in arsenic speciation and concentration in paddy rice related to dietary exposure. *Environ Sci Technol* 39:5531–5540.

17. Williams PN, Raab A, Feldmann J, Meharg AA (2007) Market basket survey shows elevated levels of As in South Central U.S. processed rice compared to California: Consequences for human dietary exposure. *Environ Sci Technol* 41:2178–2183.

18. Nriagu JO, Lin T-S (1995) Trace metals in wild rice sold in the United States. *Sci Total Environ* 172:223–228.

19. Ma JF, et al. (2008) Transporters of arsenite in rice and their role in arsenic accumulation in rice grain. *Proc Natl Acad Sci USA* 105:9931–9935.

20. Carey AM, et al. (2011) Phloem transport of arsenic species from flag leaf to grain during grain filling. *New Phytol* 192(1):87–98.

21. Meharg AA, et al. (2009) Geographical variation in total and inorganic arsenic content of polished (white) rice. *Environ Sci Technol* 43:1612–1617.

22. US Department of Agriculture (2008) *Food Availability (per Capita) Data System/Food Availability* (Econ Res Serv, Washington, DC).

23. Batres-Marquez SP, Jensen HH, Upton J (2009) Rice consumption in the United States: Recent evidence from food consumption surveys. *J Am Diet Assoc* 109:1719–1727.

24. Zavala YJ, Gerads R, Gorleyok H, Duxbury JM (2008) Arsenic in rice: II. Arsenic speciation in USA grain and implications for human health. *Environ Sci Technol* 42: 3861–3866.

25. Peters SC, Blum JD, Klaue B, Karagas MR (1999) Arsenic occurrence in New Hampshire drinking water. *Environ Sci Technol* 33:1328–1333.

26. Caldwell KL, et al. (2009) Levels of urinary total and speciated arsenic in the US population: National Health and Nutrition Examination Survey 2003–2004. *J Expo Sci Environ Epidemiol* 19(1):59–68.

27. Gardner RM, et al. (2011) Arsenic methylation efficiency increases during the first trimester of pregnancy independent of folate status. *Reprod Toxicol* 31:210–218.

28. Hopenhayn C, et al. (2003) Profile of urinary arsenic metabolites during pregnancy. *Environ Health Perspect* 111:1888–1891.

29. Cleland B, et al. (2009) Arsenic exposure within the Korean community (United States) based on dietary behavior and arsenic levels in hair, urine, air, and water. *Environ Health Perspect* 117:632–638.

30. Ludvigsson JF, Green PH (2011) Clinical management of celiac disease. *J Intern Med* 269:560–571.

31. Cohen SM, Arnold LL, Eldan M, Lewis AS, Beck BD (2006) Methylated arsenicals: The implications of metabolism and carcinogenicity studies in rodents to human risk assessment. *Crit Rev Toxicol* 36:99–133.

32. Wei M, Arnold L, Cano M, Cohen SM (2005) Effects of co-administration of antioxidants and arsenicals on the rat urinary bladder epithelium. *Toxicol Sci* 83:237–245.

33. Karagas MR, et al. (2001) Skin cancer risk in relation to toenail arsenic concentrations in a US population-based case-control study. *Am J Epidemiol* 153:559–565.

34. Meharg AA, et al. (2008) Inorganic arsenic levels in baby rice are of concern. *Environ Pollut* 152:746–749.

35. Francesconi KA (2007) Toxic metal species and food regulations—Making a healthy choice. *Analyst* 132(1):17–20.

36. People's Republic of China (2005) FAIRS product specific maximum levels of contaminants in foods 2006, GAIN Report No. CH6064, trans Butterworth J, Bugang W (United States Department of Agriculture Foreign Agricultural Service, Beijing, China). Available at http://www.fas.usda.gov/gainfiles/200608/146208660.pdf. Accessed May 11, 2011.

37. Larsen EH, Pritzl G, Hansen SH (1993) Speciation of eight arsenic compounds in human urine by high-performance liquid chromatography with inductively coupled plasma mass spectrometric detection using antimonate for internal chromatographic standardization. *J Anal At Spectrom* 8:557–563.

38. Le XC, et al. (2000) Speciation of key arsenic metabolic intermediates in human urine. *Anal Chem* 72:5172–5177.

39. Wei X, et al. (2001) A comparison of urinary arsenic speciation via direct nebulization and on-line photo-oxidation-hydride generation with IC separation and ICPMS detection. *J Anal At Spectrom* 16:12–19.

40. Tseng CH (2009) A review on environmental factors regulating arsenic methylation in humans. *Toxicol Appl Pharmacol* 235:338–350.

41. US Department of Agriculture (2010) *USDA National Nutrient Database for Standard Reference* (Agric Res Serv, Washington, DC), Release 23.

42. Buchet JP, Lauwerys R, Roels H (1981) Comparison of the urinary excretion of arsenic metabolites after a single oral dose of sodium arsenite, monomethylarsonate, or dimethylarsinate in man. *Int Arch Occup Environ Health* 48(1):71–79.

43. Tam GK, Charbonneau SM, Bryce F, Pomroy C, Sandi E (1979) Metabolism of inorganic arsenic (^{74}As) in humans following oral ingestion. *Toxicol Appl Pharmacol* 50:319–322.

44. Karagas MR, et al. (2000) Measurement of low levels of arsenic exposure: A comparison of water and toenail concentrations. *Am J Epidemiol* 152(1):84–90.

45. Lindberg AL, et al. (2008) Gender and age differences in the metabolism of inorganic arsenic in a highly exposed population in Bangladesh. *Environ Res* 106(1):110–120.

46. Barr DB, et al. (2005) Urinary creatinine concentrations in the U.S. population: Implications for urinary biologic monitoring measurements. *Environ Health Perspect* 113:192–200.