Inorganic Arsenic in Rice Bran and Its Products Are an Order of Magnitude Higher than in Bulk Grain

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Received May 5, 2008. Revised manuscript received July 7, 2008. Accepted July 24, 2008.

Rice is more elevated in arsenic than all other grain crops tested to date, with whole grain (brown) rice having higher arsenic levels than polished (white). It is reported here that rice bran, both commercially purchased and specifically milled for this study, have levels of inorganic arsenic, a nonthreshold, class 1 carcinogen, reaching concentrations of ~1 mg/kg dry weight, around 10−20 fold higher than concentrations found in bulk grain. Although pure rice bran is used as a health food supplement, perhaps of more concern is rice bran solubles, which are marketed as a superfood and as a supplement to malnourished children in international aid programs. Five rice bran solubles products were tested, sourced from the United States and Japan, and were found to have 0.61−1.9 mg/kg inorganic arsenic. Manufactures recommend ~20 g servings of the rice bran solubles per day, which equates to a 0.012−0.038 mg intake of inorganic arsenic. There are no maximum concentration levels (MCLs) set for arsenic or its species in food stuffs. EU and U.S. water regulations, set at 0.01 mg/L total or inorganic arsenic, respectively, are based on the assumption that 1 L of water per day is consumed, i.e., 0.01 mg of arsenic/day. At the manufacturers recommended rice bran solubles consumption rate, inorganic arsenic intake exceeds 0.01 mg/day, remembering that rice bran solubles are targeted at malnourished children and that actual risk is based on mg kg^{-1} day^{-1} intake.

Introduction

For regions of the world not suffering elevated arsenic in their drinking water supplies, rice is the primary source of inorganic arsenic, a nonthreshold, class 1 (i.e., proven human) human carcinogen (*1, 2*), into the human diet (*3*−*6*). This is in part due to the anaerobic culture of rice that leads to mobilization of arsenic into soil solution in paddies, coupled with efficient uptake of arsenic from that soil solution (*7*). The situation is further exacerbated in certain rice growing regions of the world where anthropogenic contamination of paddies with arsenic (through application of arsenical pesticides, irrigation with contaminated groundwater or through pollution from base and precious mining activities) has led to further elevation in the grain (*4, 5*).

Studies have shown that total arsenic levels were much higher in bran than in endosperm (white rice) obtained from the same whole grain rice (*10, 11*). Rice grain arsenic speciation is dominated by inorganic arsenic and dimethylarsinic acid (DMA) (*6*−*8*). Meharg et al. (*9*) showed that whole grain (brown) rice had a higher inorganic arsenic and total arsenic content than polished (white) rice. In that study, arsenic was shown to concentrate as arsenite in the layers removed on milling, specifically the aleurone, imaged using μ-X-ray absorption near edge spectroscopy (μ-XANES).

Rice bran is a byproduct of polishing whole grain rice, comprising the pericarp, aleurone layer, embryo, and some endosperm (*9*). It is used as a traditional ingredient in Japanese cooking such as rice bran pickling. It can be added to products such as rice crackers to increase fiber content. Stabilized rice bran extract, known as rice bran solubles, is sold as a “natural superfood” and “premier heath food product”, as it is high in antioxidants, vitamins, mineral nutrients, and soluble fiber (*12, 13*). A number of companies producing this product also supply food aid programs where malnourished children are given a daily ration of the product (*12, 13*). The supplement has already been used in Malawi, Guatemala, and El Salvador, with plans to expand further into Latin America, India, and the Caribbean.

This study set out to characterize if rice bran contained elevated eves of inorganic arsenic as suggested by μ-XANES imaging conducted on whole grain rice (*9*). High-performance liquid chromatography−inductively coupled plasma−mass spectrometry (ICP-MS) was used to characterize whole grain, bran, and endosperm. Then commercial rice bran and rice bran solubles were characterized. Finally, the risk posed by inorganic arsenic in these products was considered.

Materials and Methods

Sample Sourcing and Preparation. Whole grain rice samples were obtained from arsenic elevated regions of China and Bangladesh. A subsample of whole grain was milled using a rice polisher purchased from China. Each sample was polished and weighed at 15 s intervals until 7% of its mass had been removed, the fraction of a commercially milled bran layer that comprises whole grain rice (*14*). Whole grain and endosperm (white or polished rice) samples were then milled to a fine powder using a Moulinex Optiblend blender. The bran, whole grain, and endosperm samples were oven-dried at 80 °C for 24 h. Bran products purchased from Internet suppliers were dried in an oven overnight at 80 °C until constant weight. Whole bran was homogenized in the blender, whereas rice bran solubles were already powdered. NIST 1568a rice flour was used as the certified standard reference material (CRM). All samples were analyzed in duplicate.

Chemicals. All chemicals used were of trace element analysis grade. Aristar nitric acid, Aristar acetic acid, and arsenic 1000 ppb standard solution were obtained from VWR International Ltd. (UK). Trifluoracetic acid (TFA) and ammonia solution were obtained from Thermo Fisher Scientific Inc. (UK). Arsenate and arsenite were prepared from mono-

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10.1021/es801238p CCC: $40.75
Published on Web 08/21/2008

TABLE 1. Comparison of As Species Quantification in NIST 1568a Rice Flour in the Microwave-Assisted Extraction Method Developed Here Compared to Other Extraction Procedures Reported in the Literature[a]

extraction	DMA (mg/kg)	MMA (mg/kg)	arsenite + arsenate (mg/kg)	Σ of species (mg/kg)	extraction efficiency (%)	column recovery (%)	total recovery (%)	ref
2 M TFA	0.174	0.008	0.092	0.274	112.0	84.4	94.5	*8*
2 M TFA	0.168	0.012	0.087	0.267	95.0	96.0	92.0	*27*
2 M TFA	0.160	0.002	0.080	0.240			80.0	*6*
enzymatic digest, pepsin, and pancreatin	0.148	0.011	0.101	0.260			89.7	*27*
methanol:water with sonication	0.165	0.015	0.109	0.288	99.0			*28*
enzymatic hydrolysis, α-amylase	0.158	0.013	0.106	0.277			95.5	*29*
ultrasonic & enzymatic hydrolysis, protease & α-amylase	0.135	0.008	0.088	0.231	98.6	80.8	79.7	*30*
1 M H_3PO_4 with sonication	0.155	0.009	0.102	0.267			92.0	*31*
1% HNO_3	0.162	0.005	0.099	0.266	101	91.1	91.6	this study

[a] Extraction efficiency is the quantity of arsenic removed by the extraction divided by the total arsenic in the sample, multiplied by 100. Column recovery is the sum of species detected postcolumn divided by the quantity in the extract solution, multiplied by 100.

sodium arsenate and sodium arsenite, respectively, obtained from Sigma Aldrich Chemicals (UK). DMA and monomethylarsonic acid (MMA) were also purchased from Sigma Aldrich. Indium was diluted from a preprepared stock solution made from indium chloride (Sigma Aldrich). Metal standard solutions for Co, Zn, Cu, Se, Pb, and Mn were obtained from Thermo Fisher Scientific. Ammonium hydrophosphate and ammonium dihydrogen orthophosphate, used to prepare the HPLC mobile phase, were obtained from BDH Chemicals Ltd. (UK) and the ICP carrier gas, Argon, was purchased for BOC Gases Ltd. (UK).

Total Arsenic. For each grain fraction sample, duplicate sub samples of 0.2 g were weighed into separate 50 mL polyethylene centrifuge tubes and concentrated nitric acid (2 mL) added and left to stand overnight at room temperature. For quality control, 3 CRM samples were digested along with 3 spikes of 10 μg As/L and 3 reagent blanks. Samples were microwave digested (MARS, Matthew Inc., USA) on a 3 stage temperature ramping program. Each stage ramped to temperature over a 5 min period: stage 1 maintained samples at 55 °C for 10 min, stage 2 at 75 °C for 10 min, and stage 3 at 95 °C for 30 min. Samples were cooled and 0.5 mL of 10 μg indium/L in 1% HNO_3 was added as an internal standard. Each subsample was then diluted to 50 mL with Millipore ultrapure water. The samples were then analyzed for total arsenic content using an ICP-MS 7500 (Agilent Technologies). As well as As^{75} and indium isotopes, selenium isotopes Se^{77}, Se^{78}, and Se^{82} were measured to monitor polyatomic argon chloride interferences; no polyatomic interference occurred.

Speciation of Arsenic. A microwave method for extracting arsenic species was developed and performance was developed to enhance the speed of sample processing. The method was checked using the well-characterized NIST rice flour CRM 1568a (see Table 1). Though this CRM is certified only for total arsenic, not arsenic species, it has been characterized in a wide number of speciation studies (Table 1), enabling cross referencing of studies. The CRM (0.2 g) was weighed into 3 × 50 mL polyethylene centrifuge tubes and 10 mL of 1% nitric acid added. Centrifuge tubes were left to stand overnight then microwaved on the same temperature program used for total arsenic determination (see above). Each tube was then made back up to weight with extractant and centrifuged in a Coolspin centrifuge at 3500 rpm for 50 min. The supernatant was pipetted into 5 mL polyethylene centrifuge tubes and vortexed before dispensing into HPLC vials for analysis.

An aliquot of each speciation extract was then analyzed for total As by ICP-MS, following the addition of 10 μg/L indium. For speciation analysis, matrix matched standards were prepared. Extracts were analyzed using HPLC (HP1100, Agilent Technologies), coupled to the ICP-MS. The mobile phase was of 6.66 mM NH_4NO_3 and 6.66 mM NH_4HPO_4, adjusted to pH 6.2 using ammonia solution. Samples were placed in a cooled autosampler. A precolumn connected to a PRP-X100 10 μm anion-exchange column (Hamilton, UK) was used. Injection volume was 100 μL and flow rate set at 1 mL/min. Indium (10 μg/L in 1% HNO_3) was added online postcolumn as the internal standard. Pure arsenate, arsenite, DMA, and MMA were run to obtain retention times. Matrix-matched DMA standards were used to calibrate the instrument.

Recovery of total As in NIST rice flour CRM was 0.29 ± 0.1 mg/kg (Table 2), which is 100% recovery of its certified value of 0.29 mg/kg. No rice CRM with certified speciation is available. The NIST rice flour CRM has been speciated in 8 previous studies using a range of extraction techniques, tabulated in Table 1, with the results of this current study included for comparison, showing our analysis is in agreement with previous investigations. This method was used in all subsequent analysis.

TABLE 2. Arsenic Speciation in Whole Grain, Polished Grain, and Bran for Freshly Milled Samples[a]

rice source	grain fraction	DMA (mg/kg)	MMA (mg/kg)	Arsenite + arsenate (mg/kg)	species sum (mg/kg)	total digest As (mg/kg)	organic As %	inorganic As %	extraction efficiency %
	endosperm	0.08	<L.O.D.	0.17	0.26	0.31	29	54	75
China (CH1A)	whole grain	0.07	<L.O.D.	0.25	0.33	0.46	17	55	79
	bran	0.08	0.04	1.56	1.68	2.65	5	59	82
	endosperm	0.10	<L.O.D.	0.33	0.44	0.71	14	47	72
China (CH2G)	whole grain	0.12	<L.O.D.	0.76	0.89	1.18	11	64	83
	bran	0.11	0.03	3.47	3.61	6.24	2	55	81
	Endosperm	0.19	<L.O.D.	0.17	0.37	0.54	36	32	79
Bangladesh (BR6)	whole grain	0.20	<L.O.D.	0.31	0.52	0.70	30	45	83
	bran	0.15	0.02	1.67	1.85	3.07	6	54	88
	endosperm	0.35	<L.O.D.	0.18	0.53	0.75	47	24	88
Bangladesh (BR 17)	whole grain	0.43	0.01	0.39	0.82	0.98	44	39	81
	bran	0.25	0.02	1.64	1.91	3.23	9	51	80
	endosperm	0.27	<L.O.D.	0.22	0.50	0.70	39	32	85
Bangladesh (BR 19)	whole grain	0.26	<L.O.D.	0.32	0.59	0.85	32	38	85
	bran	0.25	0.02	1.75	2.01	3.00	9	59	81
	endosperm	0.09	<L.O.D.	0.19	0.28	0.32	28	60	86
Bangladesh (BR 35)	whole grain	0.05	<L.O.D.	0.23	0.28	0.41	14	57	79
	bran	0.07	0.01	1.09	1.17	1.63	5	67	77

[a] L.O.D. for MMA is 0.008 mg/kg. Extraction efficiency is the quantity of arsenic removed by the extraction divided by the total arsenic in the sample, multiplied by 100. Percentage inorganic and organic arsenic are expressed with respect to total arsenic in the sample.

Results and Discussion

Arsenic Speciation in Milled Grain. The mean ($n = 6$) arsenic concentration for the endosperm, whole grain, and bran was 0.56 ± 0.08, 0.76 ± 0.12, and 3.3 ± 0.6 mg/kg arsenic, respectively. The pattern of total arsenic concentration in grain fractions was thus endosperm < whole grain < bran. There was a significant correlation between the arsenic concentration of the wholegrain and that of the endosperm ($r = 0.929$, $p = 0.007$, data not shown). Whole grain and bran fractions also displayed a significant positive correlation ($r = 0.854$, $p = 0.030$). There was no significant correlation between the endosperm and bran fraction ($r = 0.614$, $p = 0.194$). Ren et al. (*10*) determined the total concentration of arsenic in Chinese whole grain rice and corresponding bran and polished rice and found that As concentrations were the highest in bran (in the range of 0.55−1.20 mg/kg), followed by wholegrain (0.14−0.80 mg/kg) and polished rice (0.07−0.4 mg/kg). Rahman et al. (*11*) conducted a similar, though less extensive, study on Bangladesh rice samples. Here they found that bran (0.9−1.2 mg/kg arsenic) was higher than wholegrain (0.8 mg/kg arsenic) and polished rice (0.4 mg/kg arsenic), still showing the same trend as for Table 2 and the study of Ren et al. (*10*), but with less difference between whole grain and bran samples. The total As level in rice products reported here are in the range of arsenic concentration in rice bran, whole grain rice, and polished rice reported by Ren et al. 2006. In Rahman et al.'s (*15*) more extensive study of arsenic levels in rice grain, but where they did not analyze bran, whole grain rice was also found to have more total arsenic than the polished rice obtained from it.

The results of the arsenic speciation analysis for rice grain fractions are tabulated in Table 2. All arsenic species were above limits of detection (LO.D.) (0.01 mg/kg) except for MMA in whole grain and polished rice. The concentration of the organic species detected (DMA plus MMA) was fairly uniform throughout the grain being 0.18 ± 0.05, 0.20 ± 0.06, and 0.18 ± 0.03 mg/kg arsenic for polished, whole grain, and bran, respectively. The mean concentration of inorganic arsenic varied greatly in different grain fractions, being 0.21 ± 0.03, 0.40 ± 0.08, and 1.9 ± 0.3 mg/kg arsenic for polished grain, whole grain, and bran, respectively. There were no significant correlations between total and inorganic arsenic concentrations in the endosperm and the whole grain. However, the levels of inorganic arsenic and total arsenic in the bran were positively correlated ($r = 0.982$, $p = 0.001$, data not shown). The percentage of organic arsenic was significantly greater in the polished grain (14−47%) than in whole grain (11−44%) and bran (2−10%) ($p = 0.011$ and $p < 0.001$, respectively), whereas the wholegrain fraction had a significantly greater percentage of detected organic arsenic than the bran ($p < 0.001$). Percentage inorganic arsenic content ranged from 24−67% for all samples analyzed. There was no significant difference between the percentage inorganic arsenic (one-way analysis of variance, $P = 0.058$), though the trend was polished grain < whole grain < bran. There appears to be greater variance in inorganic arsenic content compared to organic arsenic content.

Meharg et al. (*9*) had found that percentage inorganic arsenic was higher in wholegrain rice than in polished rice, but where the polished rice was not directly prepared from the whole grain, rather both whole grain was obtained from market and field surveys and polished rice solely obtained from market surveys. In that study, percentage inorganic arsenic decreased as total grain arsenic levels increased. This concentration dependence of percentage arsenic species with total grain arsenic must be considered when interpreting arsenic speciation in grain, along with whether the rice is polished or not. For example, Zavala et al. (*16*) classified rice into "DMA type" and "inorganic type" without considering that speciation changes with increasing total grain arsenic, and without differentiating between whole grain and polished rice.

It is worth noting that low but detectable traces of MMA were detected in all freshly milled bran samples. MMA has been detected in trace quantities in Taiwanese (*17*) and Indian basmati (*6*) milled rice. The levels of MMA found in bran (0.014−0.04 mg/kg arsenic) were lower than the maximum found in Taiwanese milled rice (0.05 mg/kg arsenic). Like DMA, for which MMA is an intermediate plant and microbial metabolite (*18*), it is not known if the MMA was synthesized *in planta*, or assimilated directly from the soil.

To the best of our knowledge, no previous study has extracted and speciated arsenic in rice bran. Meharg et al. (*9*) used μXANES to locate and speciate arsenic in polished and wholegrain rice. They found that arsenic was concentrated in the aleurone layer where it is primarily speciated as arsenite. The aleurone lies adjacent to the bran and is removed during milling. The aleurone is the protein and

TABLE 3. Arsenic Speciation in Commercial Rice Bran Products[a]

rice product	total As (mg/kg)	sum speciation (mg/kg)	extraction efficiency (%)	organic As (mg/kg)	inorganic As (mg/kg)	inorganic As (%)	origin and/or distributors
bran solubles	1.08 ± 0.02	0.75 ± 0.04	69	0.04 ± 0.001	0.71 ± 0.04	66	Pure Planet Products, Long Beach, CA, USA
bran solubles	1.19 ± 0.03	0.89 ± 0.01	75	0.03 ± 0.001	0.86 ± 0.01	72	Holistic Enterprised LLC, Santa, Ana, USA
bran solubles	0.82 ± 0.01	0.65 ± 0.03	79	0.04 ± 0.001	0.61 ± 0.03	74	Integris, RiSoTriene, USA
bran solubles	1.16 ± 0.02	0.87 ± 0.00	75	0.04 ± 0.003	0.82 ± 0.01	71	Nutracea, USA
defatted bran	1.60 ± 0.02	1.20 ± 0.05	75	0.03 ± 0.001	1.16 ± 0.05	73	Tsuno Rice Fine Chemicals Co. Ltd., Japan
riceo-ex	1.98 ± 0.04	1.94 ± 0.02	98	0.06 ± 0.001	1.88 ± 0.02	95	Tsuno Rice Fine Chemicals Co. Ltd., Japan
bran	1.89 ± 0.05	1.71 ± 0.10	90	0.06 ± 0.001	1.65 ± 0.10	87	Tsuno Rice Fine Chemicals Co. Ltd., Japan
bran	0.71 ± 0.01	0.52 ± 0.02	73	0.04 ± 0.001	0.48 ± 0.02	68	General Dietary Ltd.; UK & Eire
bran	1.07 ± 0.002	0.79 ± 0.03	73	0.15 ± 0.001	0.64 ± 0.03	60	The Barry Farm, Ohio, USA
rice flour	0.29 ± 0.01	0.29 ± 0.01	98	0.18 ± 0.003	0.11 ± 0.01	38	NIST CRM 1568a, USA

[a] Standard error of the mean is also reported. Percentage inorganic and organic arsenic are expressed with respect to total arsenic in the sample.

nutrient rich part of the grain. The results of Meharg et al. (*9*), using a very different analytical approach (μXANES) was in agreement with extraction and HPLC-ICP-MS speciation of bran, both showing high arsenic concentration in the bran associated layers, and that speciation of that arsenic is primarily in its inorganic form.

Rice Bran Products. Total arsenic content of bran products reported here ranged from 0.71−1.98 mg/kg arsenic, with inorganic arsenic ranging from 0.61−1.88 mg/kg arsenic and the percentage of inorganic arsenic ranging from 60−95% (Table 3). Rice bran solubles had similar total and inorganic arsenic contents as untreated bran. All MMA in bran products were below limits of detection, and DMA was much lower in bran products than for freshly milled bran (Table 2). The Japanese bran and products were higher in total and inorganic arsenic than U.S.-derived materials, although the Japanese products all came from one supplier, whereas the U.S. products came from a range of suppliers (Table 3).

The inorganic arsenic and total arsenic contents of bran freshly milled from the whole grain were lower than for bran products. When freshly milled bran was speciated, 51−67% of the arsenic was inorganic, whereas for rice bran products, this percentage ranged from 60 to 95%. This suggests that either storage and/or chemical processing had altered the speciation, or that perhaps that Chinese and Bangladeshi rice has intrinsically different speciation to Japanese and U.S. rice. There does appear to be large differences in speciation between U.S. and Bangladeshi rice but it was found that U.S. rice had a lower inorganic content that Bangladeshi (*6*), opposite to the trend between freshly milled bran and rice bran products presented here.

Implications of High Inorganic Content of Bran Products. Rice bran is sold pure as a human dietary supplement and is present as an ingredient in cooked products such as muffins, breads, breakfast cereals and rice cakes, and the preparation of traditional Japanese foods (such as rice bran pickle). It is also used as an animal feed.

A range of other rice products, besides pure bran and rice bran solubles, have been found to be high in inorganic and total arsenic, but rice bran products have the highest total and inorganic arsenic content of commercially widely available products. Baby rice (precooked and milled rice) has high levels of inorganic arsenic, to such an extent that 35% of samples tested in the UK would be illegal for sale in China (*18*). China has a rice standard of 0.15 mg/kg inorganic arsenic, one of the few countries with modern food standards for arsenic and its species (*18*). UK-purchased rice milk, a health food product (targeted at vegan, macrobiotic, lactose, and hormone avoidance diets) enzymatically extracted from rice (polished or whole grain), has inorganic arsenic levels generally in excess of the U.S. water standards of 0.01 mg/L, and all above the EU water limit of 0.01 mg/L total arsenic (*19*).

There are no modern food standards in the United States and EU for arsenic or its species (*20*). Some countries have older standards for arsenic in food that are invoked because of the absence of a modern standard setting. The UK arsenic standards were set back in 1959 at 1 mg/kg total arsenic in foodstuffs (*21*). Only 2 out of the 9 bran products listed in Table 3 would be deemed safe by this 50 year old standard.

With respect to the threat that rice bran products pose to dietary exposure, dosage needs to be considered. The manufacturers recommended daily serving of rice bran solubles is around 20 g per day, based on either direct weights given on packaging, or using the provided scoops. A 20 g serving equates to 0.014−0.017 mg of inorganic arsenic for the 4 products specifically described as rice bran solubles. Using the WHO and U.S. drinking water standard of 0.01 mg/L, assuming 1 L of water consumption per day (*2*), equates to 0.01 mg/day intake. Therefore, the recommended intake of rice bran solubles leads to a higher daily arsenic intake than assumed under U.S. water regulations and WHO guidelines (*22*). However, cancer risks from inorganic arsenic are governed by daily intake on a body weight basis, i.e., mg kg^{-1} day^{-1} (*3*). The WHO has Provisional Maximum Tolerable Daily Intake (PMTDI) of 2 μg kg^{-1} day^{-1} (*22*). This equates to consumption of 3 L of 0.05 mg/L As for a 75 kg person. This PMTDI is in effect, therefore, 15-fold higher than U.S., WHO, and EU drinking water standards, i.e., 1 L of 0.01 mg/L.

As outlined in the introduction, these rice bran soluble products are specifically marketed to food aid programmes as nutritional supplements to undernourished children, who have low body weights. Children appear to be especially prone to disease resulting from arsenic exposure (*23, 24*), and poor nutrition is thought to increase the severity of arsenical disease (*24, 25*).

All experiential evidence to date suggests that arsenic bioavailability from rice grain is high, particularly for inorganic arsenic where swine studies suggest a gut bioavailability on the order of 90% (*26*). As rice bran solubles are themselves a soluble extract of bran, and are dissolved in water for their main formulated uses, this suggests that inorganic arsenic bioavailability from these products should also be high.

Rice bran solubles are inappropriate for use in food aid programs because of their high inorganic arsenic content. "Health food" conscious consumers are also probably unaware that daily consumption of rice bran solubles is considerably increasing their inorganic arsenic exposure. The findings presented here, along with research into inorganic arsenic in rice milk (*17*) and baby rice (*18*) suggest that food standards should be set for inorganic arsenic.

Acknowledgments

The Royal Society London, Natural Science Foundation of China (20720102042) and the Chinese Academy of Sciences are thanked for financial support.

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ES801238P