Arsenic in your food: potential health hazards from arsenic found in rice

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Abstract: Rice is a staple food for over half of the world population, but there is some concern about the occurrence of arsenic (As) in this cereal and the possible overexposure to this metalloid. Recently, the Codex Alimentarius Commission established a maximum limit of 200 µg kg⁻¹ for inorganic arsenic (iAs) in rice. Because the maximum content of As in water has been reduced to 10 µg L⁻¹, intoxication through rice and rice-based products can be considered an important source of As poisoning. The chronic effects of this iAs exposure can be lung and bladder cancer, skin lesions, or other noncarcinogenic diseases. There is clear evidence of high levels of iAs in rice and rice-based products. Different solutions for the reduction of As intake are proposed at different levels: 1) during the plant-growing process through agronomic practices, 2) pretreatment of rice before its use in the food industry, 3) optimization of the conditions of unit operations during processing, and 4) by cooking.

Keywords: arsenic speciation, food safety, dietary exposure, Oryza sativa

Introduction

It is very well known that rice (Oryza sativa) is a staple food for over half of the world population. It is also the second cereal crop after maize, with an estimated production in 2013 of 745 million tons (497 million tons of rice milled for human consumption).¹

The main reason for the well-established relationship between rice and arsenic (As) is the peculiar growing conditions (flooded soils) of rice. In the past, many fertilizers containing organic As (oAs) were used as pesticides or defoliants. Now, although its use is prohibited or has been minimized, the presence of As in soils and groundwater persists to this day. Therefore, flooded soils offer a unique environment for growth and nutrition of rice, but at the same time, they are the perfect scenarios for the highest possible availability of As for rice plants.²

There are four elements, iron (Fe), phosphorus (P), sulfur (S), and silicon (Si), that interact strongly with As during its route from the soil to the plants. Plants take up arsenate [As(V)] through the phosphate transporters, and arsenite [As(III)] and undissociated methylated As species through the nodulin 26-like intrinsic aquaporin channels. Arsenate is readily reduced to arsenite in the plant, which is later detoxified by complexation with thiol-rich peptides such as phytochelatins and/or vacuolar sequestration.³

While the maximum limit of As in water is highly regulated worldwide (10 mg L⁻¹), the maximum level of As residues in highly consumed foods, such as rice, is still a pending matter; the main reason is political because none of the governmental organizations want to set up a maximum threshold for iAs, which can
jeopardize their rice production. Although there is serious concern about the presence of As in this cereal and the possible overexposure, no international agency dealing with food safety, such as the European Food Safety Authority (EFSA), the Food and Drug Administration of the United States, and the Food and Agriculture Organization of the United Nations (FAO), have yet established maximum limits for this pollutant in rice or rice-based products; however, all of them are intensively working on this topic, as of 2014. People’s Republic of China is the country with the strictest regulation, with a maximum threshold of 150 μg iAs kg⁻¹. Very recently, toward the end of July 2014, the Codex Alimentarius Commission has established a maximum limit of 200 μg iAs kg⁻¹, which is more permissible than that of People’s Republic of China. In addition, all previously cited organizations are compiling global data on total As (tAs) and iAs in polished rice and rice-based products, in order to establish an appropriate maximum residue level that reflects the actual content of this metalloid and that does not jeopardize the international rice market. If an exceedingly low maximum residue limit is established for iAs in rice, a global crisis can be created and the safe supply of rice worldwide could be threatened; this situation could generate a significant international crisis, especially affecting the poor segments of countries that highly depend on rice as the staple food.

As for the maximum safe intake of this toxic substance, in 1988, The Joint FAO/WHO (World Health Organization) Expert Committee on Food Additives proposed a provisional tolerable weekly intake of 15 mg kg⁻¹ body weight (bw). But in 2011, this value was discarded because the EFSA concluded in 2009 that a single value was not appropriate because intakes between 0.3 μg kg⁻¹ bw and 8.0 μg kg⁻¹ bw are within the benchmark dose lower confidence limit (BMDL₉₀) for certain types of cancer. At the moment, there is no maximum safe intake value set up by any international food safety authority.¹⁰

### Potential health hazards and risks resulting from dietary As

Considered a metalloid, As possesses properties intermediate between metals and nonmetals, because it can form metal alloys, but also covalent bonds with carbon, hydrogen, and oxygen. It originates naturally in the environment and occupies an important place in the list of the most abundant elements: the 20th place in the earth’s crust, 14th in seawater, and 12th place in the human body; moreover, it is a component of more than 245 minerals.¹⁶

Usually, the organic compounds of metals are more toxic than the inorganic forms, eg, mercury. However, this is not the case for As; for this particular element, the organic forms are significantly less toxic than the inorganic ones. The toxicity of As decreases from inorganic compounds containing As in the trivalent form (arsenic trioxide, sodium arsenite, arsenic trichloride, etc), to inorganic compounds of pentavalent As (arsenic pentoxide, arsenic acid, lead arsenate, calcium arsenate, etc), and finally the organic compounds (oAs), which are the least toxic ones (dimethylarsinate [DMA] and monomethylarsonate [MMA]).⁹

The main routes of As exposure to humans are air, water, food, and soil. In general, when As is introduced into the body through the diet, the level of absorption in the gastrointestinal tract depends on the chemical species, oxidation state, water solubility, and complexity of the food matrix. For instance, about 95% of arsenite and arsenate from drinking water is rapidly absorbed after ingestion.¹⁰

Meharg et al¹¹ claim that the bioavailability of As, both oAs and iAs, in the intestine through the consumption of rice is an open question. In the literature, there are in vitro simulations suggesting that only in the intestine, the availability of iAs through cooked rice consumption is in the range between 60% and 100%.¹²⁻¹⁴ The only in vivo study was in animals, and it showed 90% bioavailability in blood monitoring.¹⁵

Generally, once absorbed, iAs enters the bloodstream and is distributed between plasma and erythrocytes. This iAs binds to the globin chains of the hemoglobin molecule. From the bloodstream, iAs can reach several target organs, including liver, kidney, spleen, and lung, and later on, it accumulates and can be found in hair, nails, and skin.¹⁶⁻¹⁷

In the human body, As experiences large biotransformation mediated by enzymes, resulting in sequential methylation. The methylation of As occurs mainly in the liver via arsenite methyltransferase enzyme (As3MT), which has been isolated from the cytosol of hepatocytes.¹⁸ In contrast, fibroblasts and urothelial cells do not express As3MT; thus, As is accumulated in these cells. Toxicity due to As in hepatocytes is confirmed by its accumulation in the nucleus and mitochondria.¹⁹ Other methylation sites are the kidney, testes, and lungs. The most recent method describing As detoxification in the human body is the one elucidated by Hayakawa (Figure 1).²⁰

The major metabolites excreted in human urine are organic As species (oAs), basically DMA and MMA, with a typical ratio of DMA (60%–80%), MMA (10%–20%), and iAs (10%–20%) in individuals who do not eat seafood.
(fish, shellfish, and algae). Fish consumption increases urinary excretion of arsenobetaine and DMA in a few days after consumption because they are rich in arsenobetaine and arsenosugars. Different studies have correlated rice consumption and urinary As excretion, indicating that rice consumption leads to an increased excretion of iAs. Cascio et al carried out a biomonitoring study on the effect of rice consumption on urinary arsenicals in a general population group of UK Bangladeshis and UK Caucasians, because the Bangladeshi population still represents the largest rice consumer group in the UK, with an average rice consumption 30 times higher than that of White Caucasians. The main results showed that even if total urinary As did not significantly differ between the two groups, the sum of medians of DMA, MMA, and iAs for the Bangladeshi group was found to be over threefold higher than that of the Caucasians. Urinary DMA and iAs were significantly higher among the UK Bangladeshis than among White Caucasians. In contrast, cationic compounds were significantly lower in the Bangladeshis as compared to the same in Caucasians. Significant positive correlations were found between the levels of both iAs and DMA and the daily rice consumption. The higher DMA and iAs levels in the Bangladeshis were considered by the authors to be the consequence of higher rice consumption in this community. Rice in fact accumulates both iAs and oAs, and after ingestion, iAs can be metabolized through MMA to DMA by humans.

Furthermore, the presence of other elements affects the bioavailability of As. Zinc intake increases the concentration of metallothioneins, favoring detoxification of As. A higher As intake, as compared with that of Se, encourages competition between the elements, and As can replace Se in the Se-dependent enzymes, thereby inactivating them and increasing As toxicity. Nutritional status also influences the risk of exposure to As. Several studies indicate that high intakes of vitamin C and methionine reduce As toxicity, whereas a deficiency of vitamin A intensifies it.

Arsenic poisoning can be classified as acute or chronic. An oral intake of 100–300 mg (1–5 mg kg\(^{-1}\) bw) of iAs in humans usually leads to death within 1 hour, if untreated. The most relevant and evident signs of As chronic toxicity or arsenicism are associated with daily consumption of contaminated drinking water. But for those who consume As-free water or water with As content <10 µg L\(^{-1}\), intoxication through rice and rice-based products is considered the main source of poisoning.

The toxicity of iAs has been classified by the International Agency for Research on Cancer in group 1 of carcinogens for humans. This classification is based on the induction of primary skin, lung, and bladder cancers. For other cancers, such as cancers of the kidney, liver, and prostate, only a very small number of studies have been conducted and the results are certainly not conclusive. Moreover, skin (dermis) lesions, such as hyperpigmentation and palmar-plantar hyperkeratosis (blackfoot disease), are sensitive indicators of chronic ingestion of iAs. These typically appear after 5–10 years of consuming As-contaminated water and may evolve into carcinogenic forms on the skin (nonmelanoma skin cancer) and in the internal organs.

Along with the carcinogenic properties of iAs, a number of noncarcinogenic effects have been proposed. Exposure to As may result in neurobehavioral and neuropathic effects in adolescence, effects on memory and intellectual function, reproductive effects with increased fetal loss and premature delivery, steatosis, steatosis, steatosis, ischemic heart diseases, carotid atherosclerosis, and respiratory system effects such as chronic cough and chronic bronchitis. Even at concentrations as low as 0.4 µg L\(^{-1}\), iAs has been reported to behave as an endocrine disruptor that is able to alter gene transcription. Despite the number of in vivo and in vitro studies trying to elucidate the role of As in the development of diabetes in humans, the current available evidences are not adequate to establish a causal role.
After adjustment for biomarkers of seafood intake, total urine As was found to be associated with increased prevalence of type 2 diabetes by Navas-Acien et al. These authors reported that their findings support the hypothesis that low levels of chronic exposure to iAs in drinking water, and a widespread exposure worldwide, may play a role in diabetes prevalence. However, more recent studies seem to suggest that there is no such link between As exposure and diabetes.4,5

**Evidence for presence of As in rice and rice-based products**

**Rice**

First, Sun et al44 proved that the pattern of tAs concentration in rice grain fractions was endosperm < whole grain < bran, with mean values being 560 μg kg⁻¹, 760 μg kg⁻¹, and 3,300 μg kg⁻¹, respectively, in rice samples from People’s Republic of China and Bangladesh. This pattern of concentration in the different grain parts leads to the fact that brown rice has higher contents of tAs and iAs than polished/white rice. Commercial bran can reach values as high as 1,000 μg kg⁻¹.44

Lombi et al45 reported large differences in the distribution and speciation between the husk, bran, and endosperm of rice (Figure 2). The high content of As in the bran is probably the most important result because nowadays rice bran is widely used as a food additive and as a major health food product.44 It should be noted that while pure rice bran is used as a health food supplement, perhaps of greater concern is soluble rice bran, which is marketed as a “superfood” and as a supplement to malnourished children in international aid programs, without adequate toxicological research. Concentrations of As increased significantly from endosperm (540 μg kg⁻¹), to bran (6,240 μg kg⁻¹), and to husk (12,420 μg kg⁻¹).

Among many other authors (Figure 3),44,46-62 Meharg et al52 studied the geographical variation in tAs and iAs contents of polished rice. An extensive data set of tAs analysis for 901 polished grain samples, originating from ten countries in four continents, was compiled. Egypt (40 μg kg⁻¹) and India (70 μg kg⁻¹) had the lowest tAs content, while the US (250 μg kg⁻¹) and France (280 μg kg⁻¹) had the highest content. A subset of 63 samples from Bangladesh, People’s Republic of China, India, Italy, and the US was analyzed for As species. The relationship between iAs content versus tAs content significantly differed among countries, with Bangladesh and India having the steepest slope in linear regression, and the US having the shallowest slope.42

**Infant feed**

Milled rice is a dominant carbohydrate source for weaning babies up to 1 year of age due to its blandness, material properties, low allergenicity, and high nutritional value. As the child develops, the rice porridge is used as the basis of more complex meals, by mixing it initially (from 6 months of age onward) with puréed fruits or vegetables and later (from 8 months onward) with meat (mainly chicken) and fish (mainly hake), either home-made mixtures with baby rice or pre-prepared commercial products. This dependence on rice is exacerbated in infants with food intolerances.

Several studies have proved that high iAs levels are also present in rice products intended for babies and infants. First, Meharg et al63 and, later, Carbonell-Barrachina et al64 studied the contents of iAs in baby foods based on rice and cereals from Spain, the UK, People’s Republic of China, and the US. The iAs contents were significantly higher in gluten-free rice than in cereal mixtures with gluten, placing infants with celiac disease at high risk. All rice-based products displayed a high iAs content, with values being >60% of the tAs content and the remainder being basically DMA. Pure rice samples for infants from Spain showed lower iAs content (85 μg kg⁻¹) compared to samples from other countries such as People’s Republic of China (148 μg kg⁻¹), the USA (125 μg kg⁻¹), and the UK (162 μg kg⁻¹). The products with the highest contents of both tAs and iAs were those manufactured using organic brown rice, which nowadays has a huge demand among consumers wanting natural and/or ecological products. Hernández-Martínez and Navarro-Blasco65 obtained similar results in Spain, where organic samples of infant foods had higher levels of As than conventional food samples. Juskelis et al66 determined the contents of the main As species in 30 American infant cereals that were considered to be a potential health risk to the infant population. The results indicated...
high levels of iAs contamination, with values ranging from 55 µg kg⁻¹ to 158 µg kg⁻¹.

Celiac disease and lactose intolerance

Celiac disease is a digestive illness that damages the mucous membrane of the small intestine and interferes with absorption of nutrients from food. This illness is caused by intolerance to gluten proteins. The diet for people suffering from this disease basically consists of eliminating all foods having wheat, rye, and barley. Rice is therefore essential for the manufacture of supplies for celiac disease-affected people and reaches high percentages in their formulations.67,68

Munera-Picazo et al69,70 conducted two studies evaluating the occurrence of As in foods intended for children and adults who suffer from celiac disease. A positive relationship between rice percentage and As content was clearly observed (Figure 4). Moreover, gluten-free products that do not contain rice in their formulations do not contain As above the detection limit. The highest values of tAs and iAs found were 256 µg kg⁻¹ and 128 µg kg⁻¹, respectively, and corresponded to samples of pasta for children. In adults, tAs and iAs reached contents as high as 120 µg kg⁻¹ (pasta) and 85.8 µg kg⁻¹ (baking flour). The daily estimated intake of iAs from the studied rice-based products ranged from 0.61 µg kg⁻¹ bw to 0.78 µg kg⁻¹ bw for children and 0.47 µg kg⁻¹ bw to 0.46 µg kg⁻¹ bw for adults. These levels are within the BMDL₀₁ values identified by the EFSA, and, consequently, a risk to this segment of consumers cannot be excluded.

Lactose intolerance is the inability to digest and metabolize lactose due to the lack of lactase, the enzyme required to break down lactose in the digestive system.71 An alternative to breast milk and animal milk is soybean milk or rice milk. An increase in the intake of rice products can imply an increase in the intake of As. Results of two studies on rice milk proved that all samples of the EU and the US fail the maximum residue limit established for water (10 µg L⁻¹).70,72

Ways to reduce arsenic in rice and rice-based products

The feasible options to reduce the intake of iAs through rice range from using rice varieties with restricted As uptake and upward transport of As and cultivating rice in geographical areas with low contents of soil As (this would be easily achievable through knowledge of historical contamination of rice-growing areas) to the most drastic and dramatic option of not using rice as a source of carbohydrates and proteins but using other grains, such as oat, corn, or wheat. But this last option would create a huge crisis and it is not feasible at all.
While an appropriate selection of cultivars is routinely conducted and rice plants with reduced uptake are fully available to farmers, intermediate options have to be used. These include changing farming practices, pretreating rice before entering it into the normal processing chain of the food industry, and optimizing the working conditions of key unit operations to reduce the content of As in rice, if possible.

**Agronomic practices**

It has been shown that different growing regions of a country can produce rice with different As contents. For example, in Spain, the As contents in rice for Andalusia (Cadiz and Seville) are generally much lower than those of other areas (Valencia, Tarragona, and Calasparra). Therefore, the first step in reducing the content of As in rice is to determine the levels of contamination and identify areas that have low levels of As. These comparisons will allow the identification of cultivars that have been used in these geographical areas with reduced As content and also highlight farming practices that could be specific for these areas.

Studies by Norton et al have clearly demonstrated that As uptake, transport, and accumulation in edible rice grain are affected by cultivar. Therefore, an appropriate selection of cultivars is the first issue to be studied.

In general, French rice has very high As content. This may be due to the specific cultivars used in the Camargue or may be due to the availability of land and/or management practices. One option to reduce this problem through farming practices could be the addition of organic matter or usage of organic matter–rich soils, leading to intensified As methylation, which may be a desirable process because, as previously mentioned, oAs forms are less toxic than iAs forms.

Finally, we should mention that the aerobic culturing of rice is starting to be considered around the world in order to increase efficiency in the management of nitrogen fertilizers and mainly because water is becoming less and less available worldwide. Compared to continuous flooding of rice fields, aerobic management significantly reduces As availability for plant uptake by conserving As-adsorbent materials such as iron hydro(oxides), and thereby reducing the final As content in edible grain. However, aerobic conditions may affect the availability of other toxic elements, such as cadmium (Cd). Moreno-Jiménez et al conducted an experiment over 7 consecutive years, evaluating the impact of water management on accumulation of As and Cd in rice. Sprinkler irrigation was compared to traditional flooding irrigation. Successive sprinkler irrigation over 7 years decreased tAs to one-sixth of its initial concentration in the flooded system, while one cycle of sprinkler irrigation also reduced tAs by one-third. iAs concentration increased up to two-folds under flooded conditions compared to sprinkler-irrigated fields, while oAs was also lower in sprinkler system treatments, but to a

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**Figure 4** Relationship between iAs and rice percentage in samples of rice-based foods for children and adults with the celiac disease. **Abbreviation:** iAs, inorganic arsenic.
lesser extent. This suggests that methylation is favored under water logging. However, sprinkler irrigation increased Cd transfer to the grain by a factor of 10. Sprinkler systems in paddy fields are able to mitigate excessive As accumulation, but this experiment showed that an increased Cd load in rice grain may result. In summary, it is desirable to reduce iAs content of rice, by altering agronomic practices, but it is essential that these changes do not detrimentally impact the nutritional value of rice, including essential minerals (Fe and Zn) and vitamins, or increase the content of other toxic elements, such as Cd.76

Rice processing

Rice processing is a combination of several operations to convert paddy into well-milled, silky white rice, which has superior cooking quality attributes.77,78

Rice can be classified, according to its different processing steps, into paddy, wholegrain brown rice, and milled white rice. During rice processing, different by-products or coproducts are produced, including hull and bran. Moreover, white rice (the final product) can also reach its final commercial stage in different forms: large broken rice, small broken rice, and rice flour.79

Signes et al78 compared the two rice dehusking processes (removal of the external hull or husk of the rice grain) currently in use in India, wet (soaking and boiling of rice and mechanical hulling, leading to parboiled rice) and dry (mechanical hulling, leading to atab rice). The dry method was recommended if As-free water was not available; however, soaking and light boiling resulted in lower As concentrations if nonpolluted water was used. Therefore, the use of high volumes of water for washing and boiling the rice could be good ways of easily and significantly reducing the As content of rice, before starting the production of rice flour for rice-based infant foods. Later, brown or white rice can be cooked before entering the final manufacture of rice-based products.78

Recommendations for limiting the final intake of As and for improving consumer confidence on rice and rice-based products

When consumers have already made the purchase of rice or rice-based products, there are still other options available to reduce the possible presence of As in this food at home. Mainly, these options are based on the safety of the water used for cooking, and the cooking process (temperature and time).

The three most common methods of cooking rice in Asia are known as 1) traditional, 2) intermediate, and 3) contemporary. In the traditional method, the rice is washed until the washings become clear, the washings are discarded, and the rice is boiled in excess of water until cooked; finally, the remaining water is discarded. The intermediate method of cooking is similar to the traditional one but rice is boiled using less water, and cooking is finished when no water is left. Finally, in the contemporary method, rice is not washed and it is boiled with a low water volume until there is no water left.77 Signes et al80 simulated three cooking methods in their facilities, and the use of the traditional method is recommended (using large volumes of water for the cooking and washing steps); this method significantly reduces the content of tAs to 387–258 μg kg⁻¹. Similar conclusions were previously reached by Sengupta et al,77 who cooked rice using water with low As content (<3 μg L⁻¹) using traditional and modern methods and found that the traditional method (wash until clear; cook with rice: water ratio of 1:6; and discard excess water) removed up to 57% As from the initial rice. Approximately half of the As was lost in the wash water and the other half in the discard water.77

Simultaneously, Signes et al.80 cooking simulated rice with different levels of As (>50 μg L⁻¹) species in the cooking water, concluded that As concentration in cooked rice was always higher than that of the raw rice and varied in the range of 227–1,642 μg kg⁻¹. Mondal and Polya61 reported values of As in cooked rice (170 μg kg⁻¹) from two surveys of households in West Bengal, Nadia district, India; Smith et al1 reported As values of 350 μg kg⁻¹ in a survey of households in Bangladesh; Bae et al81 reported values of 270 μg kg⁻¹ for a site survey in Bangladesh; Rahman et al82 reported As levels of 320 μg kg⁻¹ during a field study in Bangladesh; and Roychowdhury et al83 reported values of 370 μg kg⁻¹ from a household survey in West Bengal, India. Finally, Raab et al84 systematically investigated tAs and iAs in different types of basmati, long grain, polished, and whole rice samples that had been subjected to various types of cooking processes using uncontaminated water. The effects of washing–rinsing, low volume of water (rice-to-water ratio 1:2.5), and high volume of water (ratio of water to rice: 1:6) during cooking and steaming were investigated. Rinsing and washing were effective in eliminating about 10% of tAs and iAs in basmati rice, but these were less effective for other types of rice. While steaming reduced tAs and iAs contents in rice, it did not consistently affect all types of rice investigated. The use of a large water volume for cooking effectively reduced both
tAs and iAs, 35% and 45%, respectively, in the long-grain basmati rice as compared to the reduction in raw rice. This study indicated that washing and rinsing with high volumes of clean water are effective in reducing the As (especially iAs) content of cooked rice.

Furthermore, Signes et al. demonstrated that As speciation was not significantly affected by the cooking process, probably because the temperature reached during cooking of rice, 100°C, is lower than that required for promoting exchange of species. Van Elteren and Slejokovek studied the effect of high temperature on As speciation in aqueous As standard solutions and concluded that temperatures above 150°C are required to establish significant changes. A later study by Devesa et al agreed with this statement and concluded that these high temperatures can be achieved in some cooking treatments in which the food surface is in direct contact with the source of heat (grilling, frying, or baking); temperatures as high as 250°C can be reached. Similar results were found by Hanaoka et al. and Torres-Escribano et al.

As the final conclusion, proper labeling is essential for this type of product. It is required to express the percentage of rice used, in addition to the variety and its origin. This information will be useful and improve consumer confidence in these products.

In summary, the rice industry has to know the possible options to limit this problem. Here are some objectives to be reached:

- To identify rice varieties accumulating low levels of iAs.
- To use rice cultivars that show restricted As uptake, use aerobic cultivation practices, and avoid upward As transport to the edible grain.
- To facilitate increased production of rice in regions with low contents of As.
- To optimize rice cooking, by using more water to facilitate the migration of As to the rinsing/washing/cooking water.
- To limit the use of whole grain rice (containing bran) for the segment of population with high intake of rice, for instance, people with celiac disease.

Disclosures
The authors report no conflicts of interest in this work.

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