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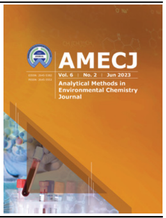

# A review: Analytical methods and health risk assessment for inorganic, organic, and total arsenic content in rice samples

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**ABSTRACT**

Determining the level of contaminants in rice is very important because it is one of the staple foods consumed by most people worldwide. Therefore, the quantity of arsenic in rice has become a health concern because rice cultivars have the property of accumulating arsenic in their grains. As a result, various societies have mandated the measurement of arsenic in rice by using different analytical chemistry methodologies, including atomic absorption spectrometry (AAS, ETAAS, HG-AAS) after sample preparation methods such as solid phase microextraction (SPME) and dispersive liquid-liquid extraction (DLLE). The content of arsenic in rice is an essential prerequisite data to incorporate in the health risk assessment. By having such information, it can be possible to determine the risk ratio calculations and identify which countries produce rice with less risk for human consumption. This review aimed to present the analytical methods used for the analysis of inorganic, organic, and total arsenic contents in rice and introduced the methodology for health risk assessment and its related calculations by using the data of inorganic and total arsenic quantifications in the rice along with the per capita of the consumption of rice.

## 1. Introduction

Heavy metals are among the potentially dangerous substances we encounter daily in various ways [1]. One of these heavy metals is arsenic (As), which is both toxic and carcinogenic. It is said that the word arsenic is derived from the Persian word *Zarnikh* which was converted into Greek as *arsenikon*, which means yellow orpiment in English. Arsenic has been renowned since ancient times as the king of poisons and the poison of kings [2]. Indeed, arsenic exists in different compounds and forms [3]. It has been a well-known toxicant since the ancient times of the Greece and Rome empires when its compounds, such as arsenic sulphide or orpiment ($As_2S_3$), were prescribed by those times of physicians and hakims in very tiny amounts to treat some kinds of diseases such as syphilis or abused by some evil poisoners to commit murders. Even it is an argument that Imam Hassan was poisoned by arsenic [4]. Arsenic compounds were harvested by ancient Chinese, Greek, and Egyptian miners from ore mines. Arsenic is among the first elements prepared and recognized by a kind of old chemistry known as alchemy. To some extent, the alchemists contributed to the sense of chemistry and toxicology by introducing methods for the identification and the techniques

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for the purification and analysis of some elements and compounds, such as arsenic [5]. The discovery of arsenic is attributed to the alchemist *Albertus Magnus* (1193–1280 AD). This German Dominican monk was famous for his advocacy for the peaceful coexistence of science and religion. He reportedly heated $As_2S_3$ with soap to produce elemental arsenic [6]. However, the first guidelines to produce arsenic can be obtained in the manuscripts of the father of modern toxicology, Paracelsus (1493–1541 AD) [7]. Arsenic has various applications, such as pesticides, sheep dips, wood preservatives, rat poisons, weed killers, electronic devices, glass making, bronzing process, pyrotechnics, and laser materials converting electricity directly into coherent light [8-10]. Among various usages of arsenic in industry, the hugest application of arsenic in the United states is reported for wood preservatives, especially as a form of chrome copper arsenate [3]. It can be argued that using novel forms of arsenic, such as arsenite and other 2D arsenic material in nanotechnology-based products and other high-tech industries, can enhance the possibility of the release of arsenic in the environment [11]. Nonetheless, the largest portion of arsenic exposure in the general population is via consuming foods. Arsenic causes different human toxicities, including neurotoxicity, mental impairment, hypertension, peripheral vascular disease, respiratory toxicity, diabetes, liver and pancreatic lesion, and skin problems such as hyperpigmentation and keratosis [12-14]. Moreover, epidemiological studies revealed that exposing to arsenic compounds are accompanying with the risk of cancers in different human organs including the skin, lung, digestive tract, liver, bladder, kidney, as well as lymphatic and hematopoietic systems. Also, arsenic is considered as a risk factor for cardiovascular diseases including atherosclerosis that are among the major causes of morbidities sand mortalities in the general public, both in developing and developed countries leading to a global burden of diseases [15-17]. In an interesting very recent study, the epigenetic mechanism of arsenic bearing cardiovascular diseases through DNA methylation was deciphered that once again is emphasizing the importance of considering arsenic as a seminal determinant of health and disease in the general population globally [18]. Arsenic has different forms, which we will explain in the next section of our manuscript. Interestingly, different species of arsenic can be seen in environmental air through various seasons [19,20] (Fig.1). Rice (*Oryza sativa* L.) is one of the most frequently served foods in many societies in the world [21]. Also, one of the most important agricultural products in the world is rice [22]. The three kinds of cereals with the highest global production rates are corn, rice, and wheat, with rice coming in second. In contrast to other cereal plants, rice is particularly unusual because it naturally accumulates arsenic due to various factors. It's interesting to note that different kinds of rice from around the world grown in the same soil accumulated different levels and types of arsenic [21]. Many communities have necessitated the measurement of arsenic in rice. Arsenic contamination of rice has several causes, including extraction of different metals during mining, irrigation of rice paddy fields with contaminated water with arsenic or the field application of arsenic pesticides for rice pest management. It is noteworthy to mention that even slight contamination of soil and water with arsenic need to be considered as an issue because arsenic can be concentrated in the contaminated water and soil and thus it can be accumulated ultimately in the rice grain. Since rice cultivated in soaked paddy lands, the transfer of arsenic in the soil and water can be much higher than other cereals that raised in the common soils with intermittent irrigation [23,24]. Due to this fact the possibility of the accumulation of arsenic in rice can be much augmented in comparison with other cereals. Therefore, consuming arsenic accumulated foods especially rice grains that constituted as a main dish in many countries can contribute to the high intake of arsenic in the human populations with deleterious chronic sequels such as various cancer [25,26]. Arsenite is the most detrimental and toxic form of arsenic, and because it has remarkable water solubility and soil mobility, it can be efficiently accumulated in seed rice. On the one hand, rice is the dominant and widely consumed food in many countries worldwide. On the other hand, arsenic is one of the most dangerous and well-known poisons [27,28]. Therefore, the consumption of food, especially rice contaminated with arsenic, can affect large populations of countries to be exposed to this dangerous poison and scrimmage with its consequences, especially the occurrence of various cancers and other known and even unknown morbidities and disease in lifelong. The authorities such as FAO's recommended maximum daily intake of inorganic arsenic need to be equal or below the level of 15 µg kg$^{-1}$ (ppb) in foods such as rice [27,29]. Consequently. It is possible for the human population to be exposed to this cumulative toxic metalloid. Nevertheless, the lack of data on the analytical methods to evaluate the level of arsenic in foods such as rice needs to be elucidated and also the approach of risk assessment required to be introduced. These are our concerns and thus we addressed these issues in this paper.

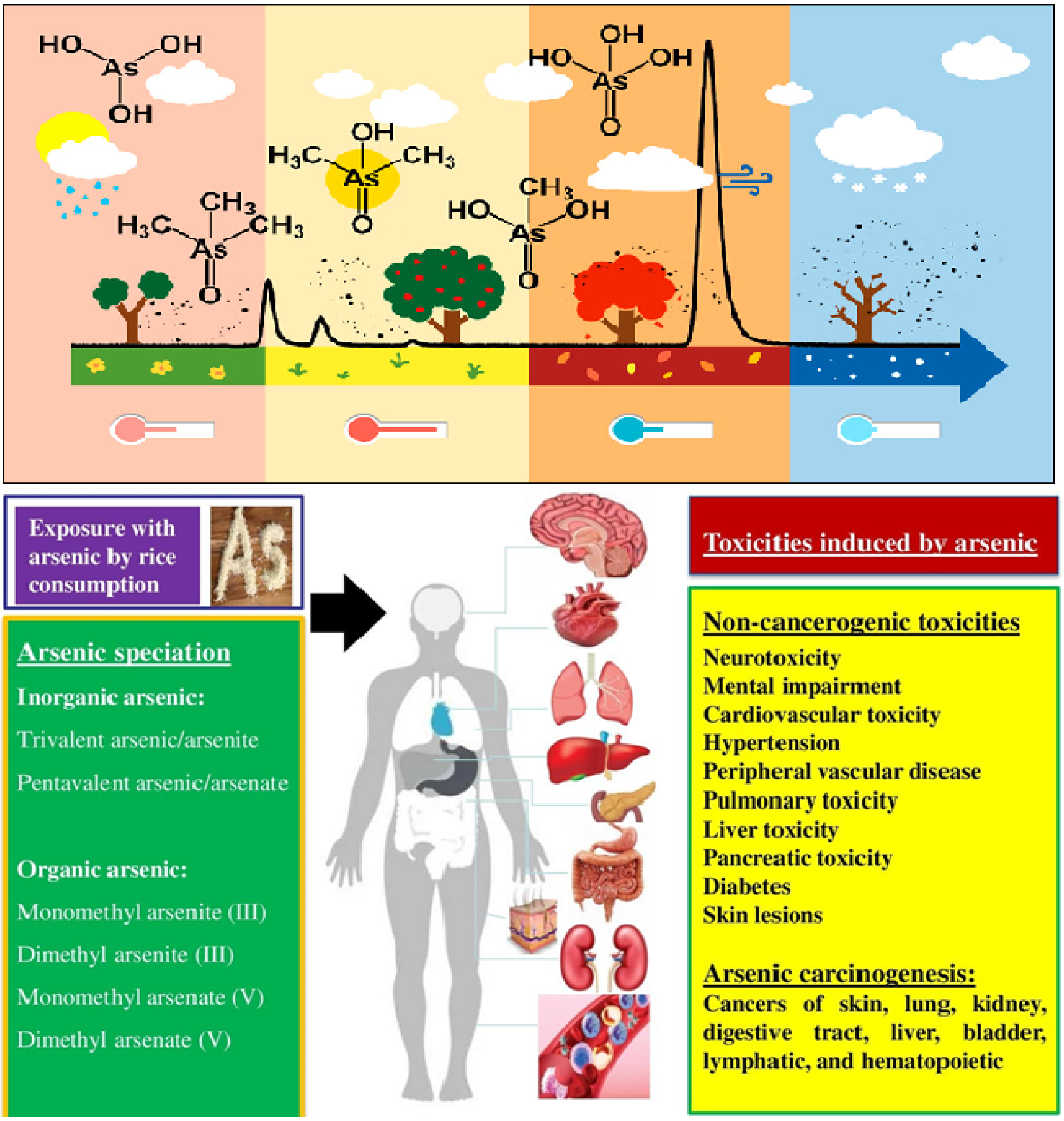
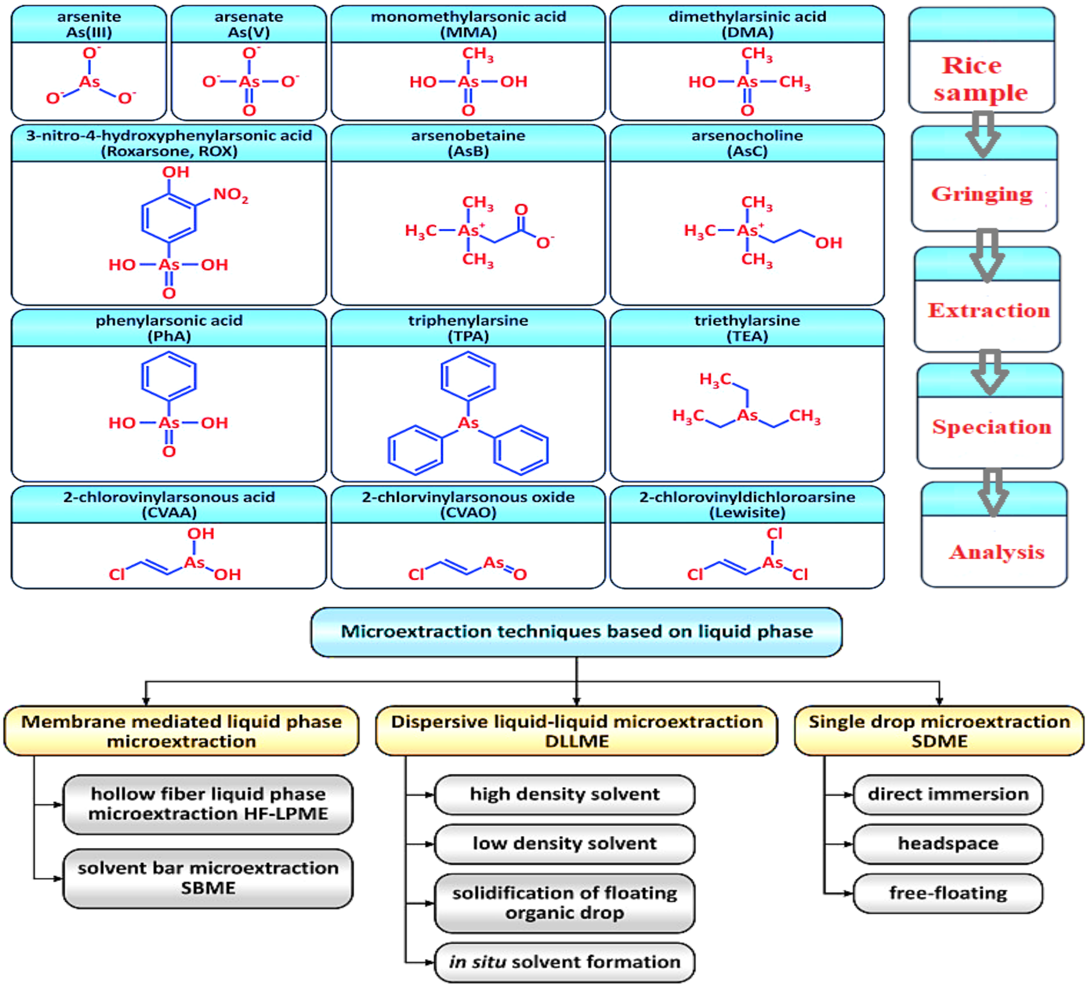


**Fig.1.** The upper part of this figure illustrates the occurrence of different arsenic species across seasonal changes. The lower part presents the toxicological profile of arsenic in the environment and the human body following consuming foods such as rice [12-14,19,20]

## 2. Experimental

### *2.1. Arsenic Speciation*

Arsenic has a variety of the speciation [30]. The following list summarizes the toxicities of various arsenic species: Monomethyl arsenite (III)> Dimethyl arsenite (III)> Arsenic (III)> Arsenic (V)> Monomethyl arsenate (V)> Dimethyl arsenate (V) [31]. Different spices of arsenic were shown in Schema 1, which were separated and extracted by other sample preparation methods, such as the microextraction procedure (DLLME and SDME), before being determined by the analyzer in the liquid phase. The type of arsenic species and their oxidation states directly impact the mutagenic, teratogenic, genotoxic, and neurotoxic effects of arsenic [32]. Trivalent arsenic (arsenite), which is more toxic and mobile than pentavalent arsenic (arsenate), is classified as a carcinogen in group I of the International Agency for Research on Cancer [33,34]. Also, arsenic is associated with maternal toxicity and low birth weight [35]. Since mineral arsenic (III and V), monomethyl arsenate (V), and dimethyl arsenate (V) make up the majority of the arsenic in rice, the risk assessment calculations used to determine the permissible limit of this element use 0.0003 mg $kg^{-1}$ body weight per day as the reference dose for mineral arsenic [36]. When compared to inorganic arsenic (III), monomethyl arsenate (V) and dimethyl arsenate (V) are at least a hundred times less toxic [36]. Therefore, the measurement of mineral arsenic is advised in place of total arsenic. It should be noted that regulatory institutions worldwide decide how much arsenic is present in rice [36]. Also, many nanotechnology methods are used for the extraction of metals/ heavy metals in various matrixes [37-39].



**Schema 1**. Different spices of arsenic for speciation by various microextraction procedures such as DLLME and SDME methods [30-36]

### *2.2. Analytical chemistry methods for the determination of arsenic*

Recently published literature on the measurement techniques for various species of arsenic has expanded significantly as chemical forms of arsenic are essential for health risk assessment [40].

One of the best strategies for measuring elemental species of arsenic is to use techniques to measure arsenic in rice, ensuring no change in species [41]. However, the selectivity and sensitivity of available methods hinder the feasibility of quantifying elements in small quantities. There are two mainstay steps in measuring an element's various species: extraction and measurement. It is essential to remember that for chemical analysis such as arsenic species in complex matrices such as rice, these steps must be optimized appropriately to ensure that there are as few changes in the measured element species [42]. Figure 2 depicts different extraction techniques that can be employed before the chemical analysis of arsenic in matrices, including rice.

There are several methodologies to measure various types of arsenic in rice (Fig. 3.).

These methods include I. Methods of measurement

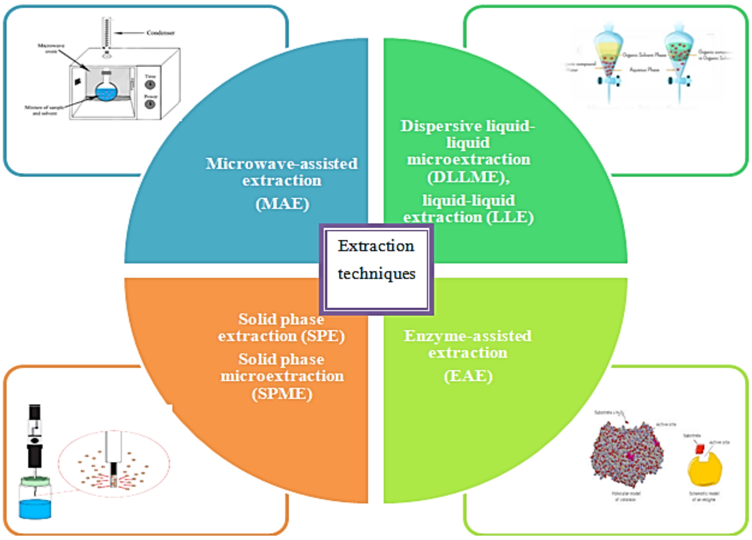


**Fig.2.** Different extraction techniques that can be employed for arsenic extraction before the instrumental analysis [43-50]

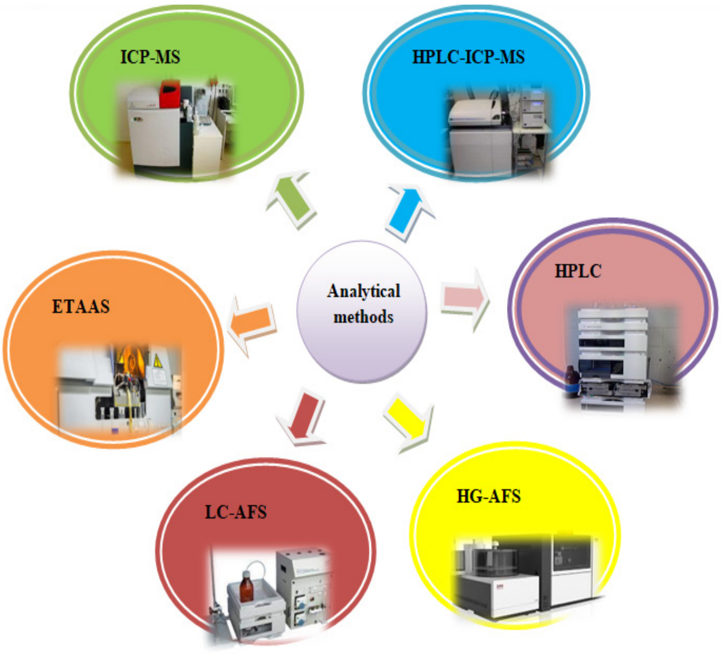


**Fig. 3**. Various methodologies for analyzing arsenic in rice [30-36]

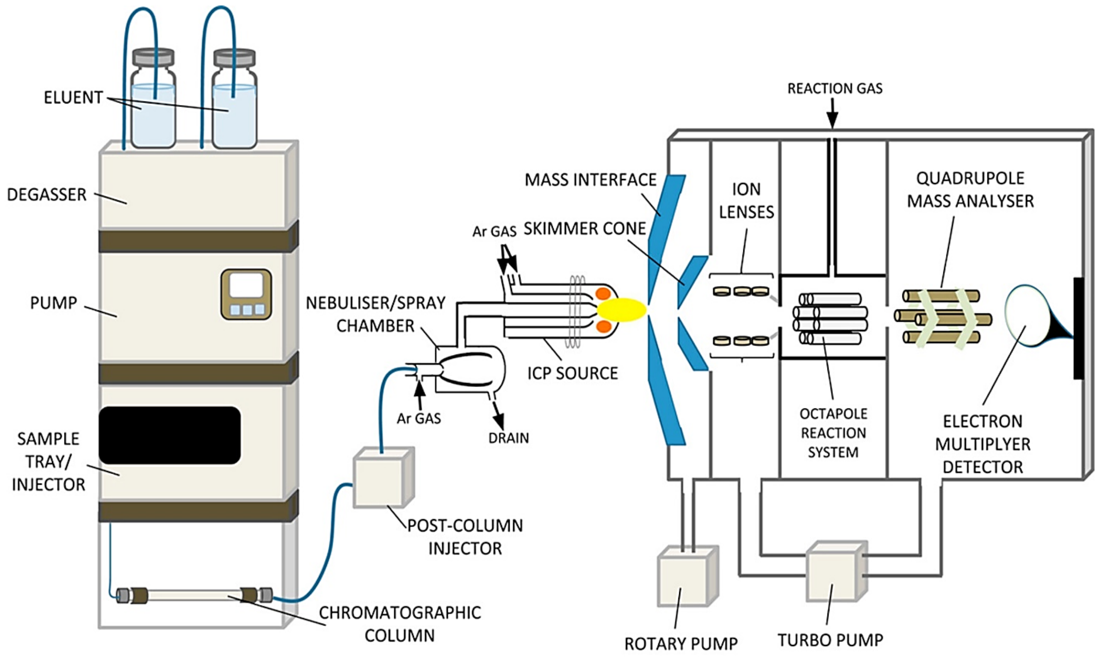
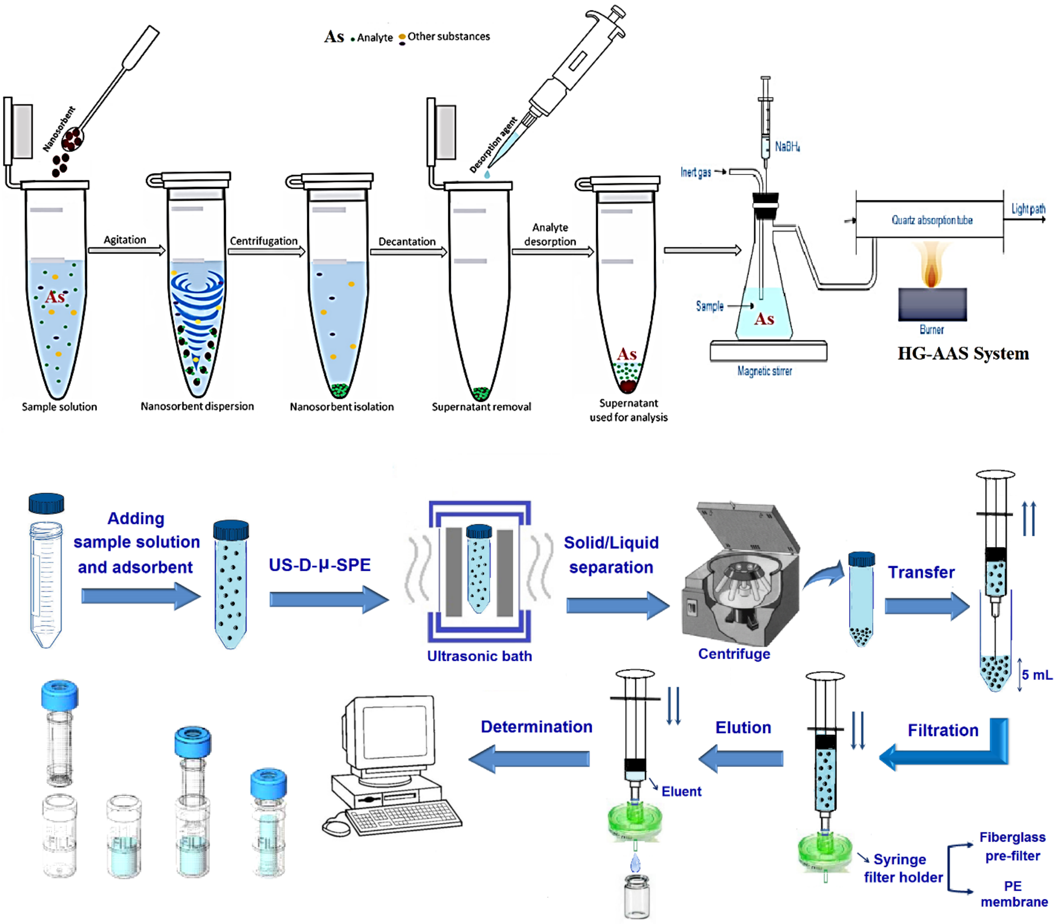


**Fig.4**. Schematic illustration of HPLC coupling with ICP-MS to set up HPLC-ICP-MS for arsenic analysis in rice [41,45].

based on unpaired techniques. Many of these techniques rely on spectroscopic devices to measure the selective separation of different arsenic species. II. Methods of direct measurement. III. Methods of measurement based on paired techniques. Other techniques using separation techniques and low concentrations have been proposed to measure various species of arsenic. HPLC-ICP-MS is among the best techniques for analyzing different forms of arsenic (Fig.4) [41,51].

The speciation method based on dispersive liquid-liquid microextraction (DLLME) was obtained for As (III and V) in urine/water samples at pH four by Zavvar Mousavi et al. Due to the procedure, As(III) was extracted based on ammonium pyrrolidine dithiocarbamate (APDC) and ionic liquid (IL) before being determined by ETAAS. Arsenic(V) was reduced (KI and ascorbic acid), and total arsenic (TAs) was determined. Finally, As(V) was measured by differentiating total AS and As(III) content. Various parameters' effect on arsenic ions' recovery has been studied [46]. Also, the speciation of arsenic (V, III) ions in water and human samples was achieved based on the functionalized graphene with carboxylate group (G–COOH) by ultrasound assisted-dispersive micro-solid phase extraction (US-D-μ-SPE). As(V) ions were only extracted on G–COOH at pH 3.5. Then, As(III) oxidized to As(V) using KMnO4 and TAs was determined by flow injection-hydride generation atomic absorption spectrometry (FI-HG-AAS). Finally, As(III) concentration was obtained by subtracting the As(V) from T-AS, as shown in Scheme 2. The G–COOH adsorbent characterization was analyzed by SEM, TEM, XRD, FT-IR, and BET equations [45].

Different researchers around the world have reported different methodologies. For instance, Nawrocka et al. (2022) introduced a rapid, sensitive, and qualitative method for determining total arsenic and other distinct arsenic species in food matrices, particularly seafood specimens. At first, they used a microwave-assisted extraction technique to isolate arsenic species after acid digestion. The conditions of this extraction technique were optimized by relying on the UAE 6 extraction module. They used a mixture of methanol and water to release the arsenic species in the analyzed samples. The sample with 0.1 g was lodged into a 14 mL conical polypropylene tube. Then, the volume reached 5



**Schema 2.** The speciation of arsenic (V, III) ions in water and human samples by nanotechnology [37-39]

mL by adding the $CH_3OH$ extractant solution (3:1, v/v) and shaking mechanically through a bench mixer for 15 min at 800 rpm. After that, the tubes were placed into TFM™-PTFE vessels filled with water to half the height of the tube and microwave heated programming to a two-step temperature setting as follows: at the first step, the temperature was 70$^{O}$C,, ramp 10 min, hold 10 min, power 80%, and in the second step the temperature reached to 70$^{O}$C, ramp 5 min, hold 15 min., power 80%, and finally in the cooling step the temperature was 50$^{O}$C; ramp 1 min, hold 10 min, power 0%). The extracts must be centrifuged after cooling for 10 min, 3500 rpm, and at 21$^{O}$C. The gained supernatants were carefully decanted into new conical tubes and evaporated to approximately 0.5 mL at 70$^{O}$C under a continuous nitrogen flow. The evaporated extracts were dissolved to obtain a 10 mL solution with MQ water and filtered using PVDF syringe filters (Nylon 25 mm, 0.45 µm, Kinesis Inc., USA) directly into polypropylene LC vials before the analysis without additional dilution. They determined the extracted extracts' total arsenic content via ICP-MS to confirm the extraction efficiency. Six arsenic forms were identified and quantified using high-performance liquid chromatography combined with inductively coupled plasma mass spectrometry (HPLC-ICP-MS) with an anion exchange column. They used ion-exchange chromatography coupled with a quadrupole inductively coupled plasma mass spectrometry (ICP-MS) to separate and quantify arsenic species. They used this method since the ICP-MS in one chromatographic run used ammonium carbonate-based buffers, which has little effect on ICP-MS sensitivity compared to commonly used phosphate buffers. To separate the arsenic species, an anion exchange column (4.6 × 250 mm, 10 µm, PEEK, Hamilton, Bonaduz, Switzerland) with a PRP X-100 anion exchange guard column (3 × 8 mm, 10 µm, PEEK, Hamilton Bonaduz, Switzerland) was applied. The column was maintained at an ambient temperature. Ultimately, a mobile phase of 50 mM $NH_4(CO_3)_2$ at pH 8.5 adjusted by $NH_4OH$, 1% MetOH (v/v) and 0.2 mM EDTA was utilized. The mobile phase was degassed using an ultrasonic bath before the analysis. The separation was performed under an isocratic condition at a 0.8 mL min-1 flow rate. An interesting part of the study is that they worked on real samples of the most common bivalve molluscs and fish available on the Polish Market, including Atlantic jackknife clam (*Ensis directus*), blue mussel (*Mytilus edulis*), Pacific oyster (*Crassostrea gigas*), common cockle (*Cardium edule*), tuna (*Thunnu*s sp.) and Atlantic salmon (*Salmo salar*) for arsenic speciation analysis. Their results revealed that the inorganic arsenic was within the range of 33.70–436.56 µg $kg^{-1}$ dry mass in 61% of seafood samples. Ultimately, they suggested that further analysis and characterization of arsenic species in a larger sample must be able to use that data for human exposure assessment, a part of risk assessment [52]. Llorente-Mirandes et al. (2012) reported an analytical method for determining total, organic, and inorganic arsenic species in rice and infant cereals from Spain. Initially, they provided 29 rice products, representing all types of rice and rice-based baby cereals consumed in Spain. Using a commercial coffee mill, they ground rice samples to prepare a fine powder (Moulinex, Vidrafoc). Then they stored powdered samples in the refrigerator at -4$^{O}$C until analysis after placing them in the plastic containers. Their used rice-certified reference materials (CRMs) included SRM 1568a Rice Flour that catered from NIst (Gaithersburg, MD, USA), NMIJ CRM 7503a White Rice Flour purchased from NMIJ (Japan), and NCS ZC73008 Rice that acquired from NCS (Beijing, China). To determine the samples' total arsenic content and the CRMs, the ICP-MS was used following microwave digestion. The analysis was performed in triplicate. In short, the procedure was as follows: the 0.5 g aliquots of the samples or the CRMs were weighed in the digestion vessels, and 8 mL of nitric acid solution (diluted 1:1 with doubly deionized water) and 2 mL of hydrogen peroxide was added. The mixtures were digested at room temperature and ramped to 190°C in 45 minutes. After cooling to room temperature, the digested samples were diluted with water to reach 20 mL. For the final measurements, further dilution was performed when necessary. The Helium gas was used in the collision cell to remove interferences in the ICP-MS analysis. $^{103}Rh$ was applied as an internal standard, and the samples' analytes were quantified using an external calibration curve prepared from the arsenate standards. The calibration curve standards were run before and after each sample, run to do quality control. The corresponding digestion blanks (one for each sample digestion series) were also measured. The quality control standard solutions at two concentration levels were measured after every 10 samples. Then, arsenic speciation was determined on the extracted samples using LC-ICP-MS. To this end, 0.25 g aliquots of the powdered rice samples were weighed in the digestion vessels. After that, the extraction was done by adding 10 mL of 0.2 % (w/v) nitric acid and 1 % (w/v) hydrogen peroxide solution in a microwave digestion system. The temperature was raised to 95 °C in 45 min. Samples were cooled to room temperature and centrifuged at 3000 rpm for 12 min. The supernatant was filtered through PET filters (pore size 0.45 µm). The extracts were kept at 4 °C until analysis (up to 24 h). The arsenic species determination was carried out by comparing the retention times of chromatograms with those of the standards. Meanwhile, the external calibration curves were employed to quantify organic and inorganic arsenic species against the relevant standards. LC-ICP-MS also analyzed extraction blanks in each run. Two concentration levels of quality control standard solutions were measured in each speciation run. Their results show that the total arsenic levels in all analyzed samples ranged from 40.1 to 323.7 micrograms of arsenic per kg. In comparison, the mean concentration of arsenic in all forms of rice and rice product samples was 169.5 micrograms of arsenic per kg [53]. In another report, Urango-Cárdenas et al. (2021) endeavoured to set up and validate an analytical method for determining arsenic species in rice grains. The research team purchased rice grain samples from the local Market in the northwest of Colombia. They macerated the samples by using a mortar to make them homogenous. Then, they separated the fractions passed through a 50 mesh (0.297 mm) for analysis. To perform the extraction, approximately 1.0 g of sample was weighed, 15 mL of extraction solution (HNO3 0.28 M) was added to a 50 mL digestion tube. Then samples digested under controlled conditions at 90 °C for 2 h in a microwave digester (Milestone Ethos One). After cooling, the extracted samples were diluted to 25 mL with deionized water. After that the extracted samples were filtered through a 0.45 µm nylon syringe filter before the analysis with the high-performance liquid chromatography coupled to hydride generator with atomic fluorescence detector (HPLC-HG-AFS). Meanwhile, their instrumental conditions were as follow: 250 µL of sample solution were injected into a Hamilton PRP-X100 anion exchange column with 250 mm long and 4.1 mm internal diameter (contain 10 µm particle size) and an isocratic program was employed to separate the arsenic species. As each of the species eluted from the column, they mixed with a stream of hydrochloric acid and $NaBH_4$ /NaOH to produce volatile hydrides that were removed from the liquid gas separator (LGS) in a stream of argon gas. This stream flows through a hygroscopic membrane to remove moisture and then to the detector. The separation and detection of the arsenic species took 8 minutes. The identification of the arsenic species was certified by comparing the retention times of a standard mixture of arsenic species with the extracts of real rice grains samples. It is needless to mention that in order to ensure the quality of the analytical method, an appropriate certified rice reference material, namely the rice flour NIst-SRM-1568b, was employed that is a certified reference material that is generally accepted to be used for quality control the analytical methods for arsenic in rice. The final results of this study show that the total arsenic concentration in rice grain samples was 38 to 272 µg kg $^{-1}$ with an average of 165 µg kg $^{-1}$. Also, it is noteworthy to say that they found that Arsenic (III) or arsenite was the main arsenic species in the analyzed rice grain samples [54]. Other researchers tried to introduce arsenic determination and quantification methodologies in other matrices, such as drinking water [55] and biological samples, including human urine and whole blood [56]. Moreover, research teams are interested in developing portable, fast, cheap, easy-to-use field tests and sensors using novel technologies [57-60]. Nonetheless, regarding regulatory toxicology, only a few methods have been validated and approved practically, even though numerous methodologies have been reported in the abovementioned scientific papers and other scholarly literature for measuring various arsenic species. To determine the amount of mineral arsenic in food, the European Committee for standardization (CEN TC 327/WG 4) developed two methods (EN 16278 and PD CEN/TS 16731) that use a flame atomic absorption system (HG-AAS) after microwave extraction and solid phase extraction [61]. The CEN TC 275/WG 10 method for measuring inorganic arsenic based on high-performance liquid chromatography-inductivity coupled plasma mass spectroscopy (HPLC-ICP-MS) is certified and approved. still, the detection limit of this method is not appropriate due to the maximum allowable concentration of arsenic in food [52,61]. 200 micrograms per kilogram and 150 micrograms per kilogram of mineral arsenic are the upper limits for rice set by the World Health Organization (WHO) and China, respectively, in recently enacted acts. Although the United states Food and Drug Administration (FDA) has initiated projects to establish standardized methods for determining the mineral arsenic in food, since rice is an important component of many different materials, the country has not placed a limit on the amount of arsenic in rice. When used as infant and child food, the rice should have a maximum arsenic content declared [62,63]. According to the European Union's Regulation (EC) No. 1881/2006's Annex, the permissible limit for mineral arsenic is as follows: I. White rice (not parboiled) contains 200 micrograms per kilogram. II. 250 micrograms of husked and parboiled rice per kilogram. III. 300 micrograms of brass per kilogram are present in brass wafers, crackers, and cakes. IV. 100 micrograms per kilogram of rice are required to produce food for infants and young children [64,65]. Table 1 showed the various analytical chemistry methods for the analysis of the contents of arsenic in rice in different countries and Table 2 lists the maximum levels of total arsenic in various nations. According to studies, the toxicity of the mineral arsenic is significant [66-85]. The risk of arsenic in white rice is higher because white rice is consumed, even though brown rice has an average concentration of arsenic higher than white rice.

## *2.3. Health risk assessment analysis in terms of inorganic and total arsenic content in rice in different countries*

### *2.3.1.Health risk assessment methodology*

Health policy and planning related to toxic chemicals are based on risk management and risk assessment [86]. While risk assessment offers scientific guidelines for legislation on public health, the environment, and other settings [87], risk management is a process where risk assessment outcomes are considered from various economic, political, legal, and ethical perspectives [88]. The process of estimating the likelihood and magnitude of the loss, harm, or damage caused by a potential threat to one's health is known as risk assessment

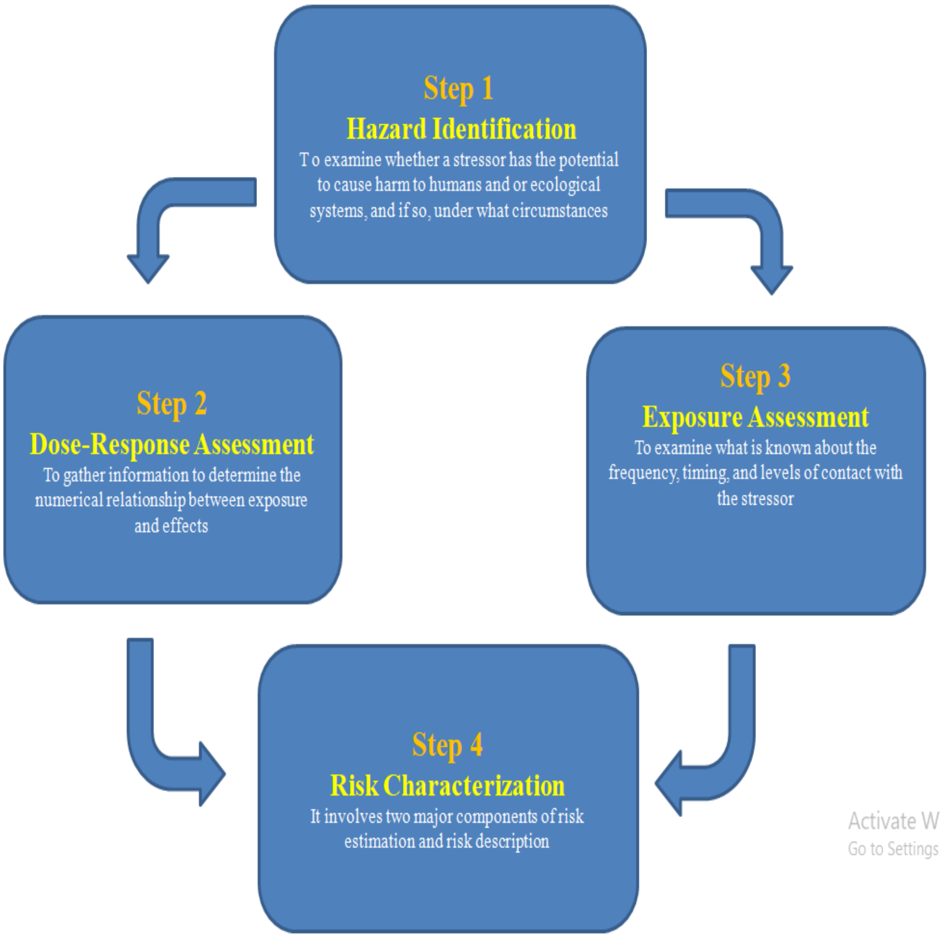


**Fig.5.** The diagram represents the four main steps of risk assessment

**Table 1.** Review of the various analytical chemistry methods for the analysis of the contents of arsenic in rice in different countries

| **Arsenic speciation** | **Detection methods** | **Countries** | **Ref.** |
|---|---|---|---|
| T-As, I-As | ICP-MS, HPLC-ICP-MS | USA, Spain, China, UK | [66] |
| T-As, I-As | HPLC-ICP-MS | Czech Republic | [67] |
| T-As, I-As | ICP-MS | Italy | [68] |
| T-As, I-As, As(III), As(V) | ETAAS | Greece | [69] |
| T-As | ICP-MS | Cambodia | [70] |
| T-As | ICP-MS | Australia, Egypt | [71] |
| T-As, I-As | HPLC-ICP-MS | Turkey | [72] |
| I-As | LC-AFS | China | [73] |
| I-As | HG-AFS | China | [74] |
| As(III), As(V), MMA, DMA | HPLC-ICP-MS | Japan | [75] |
| As(III), As(V), DMA, MMA | HPLC-ICP-MS | Australia | [76] |
| T-As, As(III), As(V), DMA, MMA | HPLC-ICP-MS | India, Bangladesh | [77] |
| As(III) and As(V) | HG-AAS | Brazil | [78] |
| As(V), As(III), DMA, MMA | HPLC-ICP-MS/MS | Vietnam | [79] |
| T-As, As(III), As(V), DMA, MMA | ICP-MS | Taiwan | [80] |
| T-As, As(III), As(V), DMA, MMA | HG-AAS, HPLC | Iran | [81] |
| T-As, I-As | HPLC–ICP-MS | Uruguay | [82] |
| T-As | ICP-MS | Canada | [83] |
| T-As, I-As | HG-AFS | Thailand | [84] |
| T-As, I-As, As(III), As(V), DMA, MMA | HPLC–HG–AFS | Argentina | [85] |

T-As: total arsenic
I-As: inorganic arsenic
MMA: monomethyl arsenate
DMA dimethyl arsenate
ETAAS: electrothermal atomic absorption spectrometry
HPLC: High-performance liquid chromatography
ICP-MS: Inductively coupled plasma-mass spectrometer
LC-AFS: liquid chromatography-atomic fluorescence spectrometry
HG-AFS: hydride-generation atomic fluorescence spectrometry
HPLC–ICP-MS: high-performance liquid chromatography coupled to inductively coupled plasma-mass spectrometry.
HPLC–HG–AFS: high-performance liquid chromatography–hydride generation–atomic fluorescence spectrometry

**Table 2.** Percapita consumption of rice, total arsenic (T-AS), inorganic arsenic (I-AS) concentration (μg kg $^{-1}$), and its allowable limit in different countries

| Country | Capita annual consumption (kg) | Classification of consumption | (T-AS) | (I-As) | Maximum residue level (I-AS) | Maximum residue level (T-AS) |
|---|---|---|---|---|---|---|
| Vietnam | 191 | High | * | 200 | 85 | 126 |
| Indonesia | 163 | High | * | 200 | 30 | 33 |
| Thailand | 143 | High | * | 200 | 85 | 126 |
| China | 76 | High | * | 150 | 108 | 143 |
| India | 73 | High | * | 200 | 100 | 180 |
| Japan | 58 | Medium | * | 200 | 110 | 190 |
| Egypt | 42 | Medium | * | 200 | 38 | 40 |
| Brazil | 40 | Medium | * | 200 | 77 | 212 |
| Iran | 39 | Medium | 120 | * | 99 | 110 |
| Australia | 15.9 | Low | 1000 | 200 | 92 | 220 |
| Uruguay | 12 | Low | 300 | 200 | 80 | 269 |
| Argentina | 11 | Low | 300 | 200 | 64 | 370 |
| U.S.A | 11 | Low | * | 200 | 92 | 214 |
| Canada | 4.5 | Low | * | 200 | 57 | 60 |
| Europe | 5 | Low | * | 200 | 80 | 230 |

*No data was reported.

[89]. The four steps of a health risk assessment are typically: 1) hazard identification, 2) dose-response evaluation, 3) exposure evaluation, and 4) risk characterization (Fig.5) [90]. The main objectives of risk assessment are to evaluate the contamination of food, soil, air, water, or sediment, to look at all potential exposure routes, to determine the amount of contaminant that enters each living thing's body, and to evaluate the effects on the organisms [91,92]. The two primary categories into which the risk of heavy metals is spat are carcinogenic and non-carcinogenic effects [93]. The non-carcinogenic effects of heavy metals are determined using a function called hazard quotient (HQ), which is the comparison of the given pollutant concentration to a reference value (RfD)[94]. RfD is the daily introduction of a contaminant into a person's body throughout their lifetime with little to no risk. It is usually expressed as milligrams per kilogram of body weight per day [95]. RfD can be calculated using the division of the NOAEL (No Observable Adverse Effect Level) on the safety factor between 10 and 100, as well as for comparisons between species and studies involving chronic, sub-chronic, sub-acute, and acute exposure to a single variable. This aspect is connected to extrapolating data from

animal experiments to people [96]. The codex has set a limit of 200 micrograms per kilogram (ppb) for mineral arsenic in rice [97]. China is the only nation to have established an acceptable amount of arsenic in rice at 150 micrograms per kilogram (ppb). Total arsenic levels in Iran range from 120 to 150 micrograms per kilogram (ppb) [62]. Because paddy rice contains 10–20 times more arsenic than rice grains, brown rice has more arsenic than white rice [98]. Various arsenic levels in rice produced in different nations have been assessed so far, and it has been discovered that rice consumption has not been regulated by international standards [99]. On the other hand, rice husk and rice germ contain the most arsenic, according to research that involved imaging a component of the rice grain [100]. One notable point is that cooking rice and washing the rice before cooking can significantly reduce the amount of total and inorganic arsenic in the finished food [40,101]. Accordingly, gathering data on various topics, such as the type and amount of arsenic in rice and its per capita consumption, comparing them across nations, and so forth, will directly affect public health.

#### *2.3.1.1. Rice consumption per capita*

China, the world's largest rice producer, is also the largest rice consumer [102]. Annual rice consumption in this nation is about 160 million tons [102,103]. Regarding per capita consumption, South Americans and Africans became prominent after Asians [103]. Iranians consume 7 times as much rice as Europeans, according to statistics on rice consumption worldwide [104]. The average person in Iran consumes 39 kg of rice annually, compared to just 5 kg for those living in the EU. Iran consumes less rice per capita than the global average of 57.2 kg [105,106]. This number is 68 kg per year in developing nations, while in developed countries, it is 12 kg. China, India, Japan, Egypt, the United states, Russia, and China each consume 76 kilograms of rice per person each year. Thailand, India, China, and Bangladesh are among the top-ranked nations, with a per capita consumption of more than 70 kg of rice. With less than 10 kg consumed per person, Australia and Europe consume rice at the lowest rates worldwide [24,107-112].

#### *2.3.1.2. Health risks of consuming rice with arsenic content*

The following equation is used to calculate the hazard quotient or health risk index:

$$HQ = \frac{CDI}{R_f DO}$$

$$CDI\,(mgkg^{-1}day^{-1}) = \frac{CF \times IR \times EF \times ED}{BW \times AT}$$

The rate of chronic arsenic consumption (CDI) is affected by the average arsenic concentration in rice, the daily amount of rice consumption, the frequency of exposure, the duration of exposure, and the body weight. The higher the CDI, the higher the HQ, and the higher the HQ, the more concerning it will be. To put it another way, if the value of HQ to each of the chosen toxic elements is less than one, that element does not present a significant risk of being toxic, and ratios greater than one for HQ pose a potential hazard. International organizations set the value of oral reference dose (RfDO), and its numerical amount represents the concentration of analyte that has no harmful effects on humans during their lifespan. The Cancer Slope Factor (CSF) method is employed in the risk assessment of carcinogenic effects of metals. The formula for calculating the CSF with a 95% confidence interval is as follows.

CR = Cancer Risk; CDI = Lifetime Average Daily Dose; CSF = Cancer Slope Factor;

$CR = CDI \times CFS$

The risk of cancer is shallow if the outcome (CR) is less than and equal to 6-10 (less than one million people), and the risk of the element's carcinogenicity can be disregarded if it is greater than 4-10. It has a tolerable carcinogenic risk for humans, ranging from 6–10 to 4–10 for human cancer. The risk ratio (HQ) for total arsenic was calculated by information on rice consumption and the concentration of total arsenic in rice produced in that nation. Table 3 showed the risk ratios for

**Table 3.** Chronic intake, risk ratio, and cancer risk index for total arsenic in rice in different countries [110-112]

| Country | mg kg$^{-1}$ day$^{-1}$<br>CDI | mg kg$^{-1}$<br>C (T-As) | kg<br>IR | HQ | Carcinogenic risk (CR) |
|---|---|---|---|---|---|
| Vietnam | 0.0011 | 0.126 | 0.523 | 3.66 | 2.E-03 |
| Indonesia | 0.0002 | 0.033 | 0.447 | 0.82 | 4.E-04 |
| Thailand | 0.0008 | 0.126 | 0.392 | 2.74 | 1.E-03 |
| China | 0.0017 | 0.500 | 0.208 | 5.78 | 3.E-03 |
| India | 0.0006 | 0.18 | 0.200 | 2.00 | 9.E-04 |
| Japan | 0.0005 | 0.19 | 0.159 | 1.68 | 8.E-04 |
| Egypt | 0.0001 | 0.04 | 0.115 | 0.26 | 1.E-04 |
| Brazil | 0.0004 | 0.212 | 0.110 | 1.29 | 6.E-04 |
| Iran | 0.0002 | 0.11 | 0.107 | 0.65 | 3.E-04 |
| Australia | 0.0002 | 0.22 | 0.044 | 0.53 | 2.E-04 |
| Uruguay | 0.0001 | 0.37 | 0.033 | 0.49 | 2.E-04 |
| Argentina | 0.0002 | 0.37 | 0.030 | 0.62 | 3.E-04 |
| U.S.A | 0.0001 | 0.214 | 0.030 | 0.36 | 2.E-04 |
| Canada | 0.0000 | 0.06 | 0.012 | 0.04 | 2.E-05 |
| Europe | 0.0001 | 0.23 | 0.014 | 0.18 | 8.E-05 |

**Table 4.** Chronic intake, risk ratio, and cancer risk index for inorganic arsenic in rice in different countries [110-112]

| Country | mg kg$^{-1}$ day$^{-1}$<br>CDI | kg$^{-1}$ mg<br>C (i-As) | kg<br>IR | HQ | Carcinogenic risk (CR) |
|---|---|---|---|---|---|
| Vietnam | 0.000741 | 0.085 | 0.523 | 2.47 | 1.E-03 |
| Indonesia | 0.000223 | 0.03 | 0.447 | 0.74 | 3.E-04 |
| Thailand | 0.000555 | 0.085 | 0.392 | 1.85 | 8.E-04 |
| China | 0.001215 | 0.35 | 0.208 | 4.05 | 2.E-03 |
| India | 0.000333 | 0.1 | 0.200 | 1.11 | 5.E-04 |
| Japan | 0.000291 | 0.11 | 0.159 | 0.97 | 4.E-04 |
| Egypt | 0.000073 | 0.038 | 0.115 | 0.24 | 1.E-04 |
| Brazil | 0.000141 | 0.077 | 0.110 | 0.47 | 2.E-04 |
| Iran | 0.000176 | 0.099 | 0.107 | 0.59 | 3.E-04 |
| Australia | 0.000067 | 0.092 | 0.044 | 0.22 | 1.E-04 |
| Uruguay | 0.000044 | 0.08 | 0.033 | 0.15 | 7.E-05 |
| Argentina | 0.000032 | 0.064 | 0.030 | 0.11 | 5.E-05 |
| U.S.A | 0.000046 | 0.092 | 0.030 | 0.15 | 7.E-05 |
| Canada | 0.000012 | 0.057 | 0.012 | 0.04 | 2.E-05 |
| Europe | 0.000018 | 0.08 | 0.014 | 0.06 | 3.E-05 |

Vietnam, Thailand, China, India, Japan, and Brazil are all greater than one, indicating the possibility of risk. According to carcinogenic risk values, total arsenic has a high risk of causing cancer in humans, greater than 4-10 worldwide [113-115].

The risk ratio (HQ) on mineral arsenic for the consumer of that same country was calculated by the data on rice consumption and concentrations of mineral arsenic in that country's rice production. As shown in Table 4, the risk ratios are more significant than 1, indicating the possibility of risk only in Vietnam, Thailand, China, and India. Total arsenic has higher than 4-10 carcinogenicity values in China, Vietnam, Thailand, India, Japan, Iran, Indonesia, and Brazil, respectively. This indicates a high risk of cancer in humans.

The HQ to total arsenic was calculated by the Iranians' per-capita rice consumption data and the total arsenic amount in imported rice. The risk ratio index for rice imported from China, India, Japan, Brazil, Australia, Uruguay, Argentina, and Europe is greater than 1, as shown in Table 5, indicating the possibility of potential risk to the consumer. Except for Indonesia and Egypt, imported rice has carcinogenic risk values for total arsenic greater than 4-10, putting Iranian consumers at a high risk of developing cancer.

The HQ for mineral arsenic was calculated using the data on the amount of rice consumed per person in Iran and the amount of mineral arsenic in imported rice. Table 6 shows that the risk ratio for rice imported from various countries, except for China, is less than one and does not suggest that there may be a risk to consumers. In addition, the carcinogenic risk values for the mineral arsenic show that, except for Indonesia and Egypt, imported rice from other countries is slightly larger than 4-10, is close to each other and is less likely to indicate a cancer risk in Iranian consumers.

## 3. Conclusion

Inorganic arsenic (I-AS) has a much higher toxicity than organic arsenic in rice and other foods. The values of I-AS concentration in rice are considered

**Table 5.** Chronic intake, risk ratio and cancer risk index for imported rice consumption in Iran relative to total arsenic concentration according to per capita consumption in Iran [110-112]

| Country | mg kg$^{-1}$ day$^{-1}$ | mg kg$^{-1}$ | kg | HQ | Carcinogenic risk (CR) |
|---|---|---|---|---|---|
| | CDI | C (T-As) | IR | | |
| Vietnam | 0.0002 | 0.126 | 0.107 | 0.75 | 3.E-04 |
| Indonesia | 0.0001 | 0.033 | 0.107 | 0.20 | 9.E-05 |
| Thailand | 0.0002 | 0.126 | 0.107 | 0.75 | 3.E-04 |
| China | 0.0009 | 0.5 | 0.107 | 2.97 | 1.E-03 |
| India | 0.0003 | 0.18 | 0.107 | 1.07 | 5.E-04 |
| Japan | 0.0003 | 0.19 | 0.107 | 1.13 | 5.E-04 |
| Egypt | 0.0001 | 0.04 | 0.107 | 0.24 | 1.E-04 |
| Brazil | 0.0004 | 0.212 | 0.107 | 1.26 | 6.E-04 |
| Iran | 0.0002 | 0.11 | 0.107 | 0.65 | 3.E-04 |
| Australia | 0.0004 | 0.22 | 0.107 | 1.31 | 6.E-04 |
| Uruguay | 0.0005 | 0.269 | 0.107 | 1.60 | 7.E-04 |
| Argentina | 0.0007 | 0.37 | 0.107 | 2.20 | 1.E-03 |
| U.S.A | 0.0004 | 0.214 | 0.107 | 1.27 | 6.E-04 |
| Canada | 0.0001 | 0.06 | 0.107 | 0.36 | 2.E-04 |
| Europe | 0.0004 | 0.23 | 0.107 | 1.37 | 6.E-04 |

**Table 6.** Chronic intake, risk ratio, and cancer risk index for imported rice consumption in Iran relative to total arsenic concentration according to per capita consumption in Iran [110-112]

| **Country** | **mg kg$^{-1}$ day$^{-1}$** | **kg$^{-1}$ mg** | **kg** | **HQ** | **Carcinogenic risk (CR)** |
|---|---|---|---|---|---|
| | **CDI** | **C (i-As)** | **IR** | | |
| Vietnam | 0.000151 | 0.085 | 0.107 | 0.50 | 2.E-04 |
| Indonesia | 0.000053 | 0.03 | 0.107 | 0.18 | 8.E-05 |
| Thailand | 0.000151 | 0.085 | 0.107 | 0.50 | 2.E-04 |
| China | 0.000623 | 0.35 | 0.107 | 2.08 | 9.E-04 |
| India | 0.000178 | 0.1 | 0.107 | 0.59 | 3.E-04 |
| Japan | 0.000196 | 0.11 | 0.107 | 0.65 | 3.E-04 |
| Egypt | 0.000068 | 0.038 | 0.107 | 0.23 | 1.E-04 |
| Brazil | 0.000137 | 0.077 | 0.107 | 0.46 | 2.E-04 |
| Iran | 0.000176 | 0.099 | 0.107 | 0.59 | 3.E-04 |
| Australia | 0.000164 | 0.092 | 0.107 | 0.55 | 2.E-04 |
| Uruguay | 0.000142 | 0.08 | 0.107 | 0.47 | 2.E-04 |
| Argentina | 0.000114 | 0.064 | 0.107 | 0.38 | 2.E-04 |
| U.S.A | 0.000164 | 0.092 | 0.107 | 0.55 | 2.E-04 |
| Canada | 0.000102 | 0.057 | 0.107 | 0.34 | 2.E-04 |
| Europe | 0.000142 | 0.08 | 0.107 | 0.47 | 2.E-04 |

the permissible arsenic level. The amount of inorganic arsenic in rice is significant because it is more toxic than organic arsenic. So, arsenic has a toxic effect on water, soil, and foods and must be determined with high-resolution instruments and perfect technology. Arsenic speciation was obtained in water samples based on sample treatment methods such as DLLM, LLE, DLLME, USA-D-µ-SPE, SPME, and MSPME by the different analyzer (ET-AAs, HG-AAS, ICP-MS, HPLC, HPLC-ICP-MS). Total arsenic was determined in rice samples with a microwave digestion procedure before being determined by HG-AAS. PH has a critical role in the extraction of arsenic species in liquid solutions by different adsorbents such as carbon nanotubes (CNTs), graphene oxide (GO), activated carbon (AC), Metal-Organic Framework (MOF), and mesoporous silica nanoparticles (MSN) or functionalized nanoadsorbents with different groups such as COOH, OH, NH$_2$, SH, and CO. According to the data on rice consumption per person in Iran and the amount of total arsenic in imported rice, the risk ratio index for rice imported from countries including China, India, Japan, Brazil, Australia, Uruguay, Argentina, and Europe is higher than one. Only rice imported from Vietnam, Thailand, China, and India has a risk ratio index that is greater than one and indicates the possibility of potential risk, according to data on per capita rice consumption in Iran and the concentration of the mineral arsenic in imported rice. This index is less than one in other nations that were studied. The carcinogenic risk values for inorganic and organic arsenic also demonstrate that imported rice is larger than 4-10 except for Indonesia and Egypt and indicates a high risk of cancer in Iranian consumers.

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