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Arsenic in baby foods: health effects and dietary exposure

M. Medina-Pizzali*, N. Damián-Bastidas and M. Vargas-Reyes

Facultad de Ciencias de la Salud, Universidad Peruana de Ciencias Aplicadas, Av. Alameda San Marcos, Cuadra 2, Chorrillos, Lima, Perú; pcnummed@upc.edu.pe

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REVIEW ARTICLE

Abstract

Health effects of arsenic in adults have been studied and documented more extensively than in infants and children, despite the fact that the younger population is more sensitive and is more exposed. Although rice has the highest concentrations of inorganic arsenic among foods, it is widely consumed by infants and children. The present article discusses the latest global literature on the presence of inorganic arsenic and total arsenic in foods consumed by infants, focusing on the adverse chronic health effects as well as dietary exposure and risk assessment in this population. It also discusses international regulations related to arsenic in rice and other products consumed by infants. Finally, it reviews mitigation strategies to reduce arsenic intake or its effects. It was concluded that the limits regarding $_{i}$As in rice-based products need to be included in the Codex Alimentarius standards since these standards are currently used by countries that have not developed their own regional or national regulations. Early-life chronic exposure to arsenic has the potential to affect several systems of the human body, and while some of these effects are likely to remain latent, others become evident in the short term. Worldwide, numerous foods intended for infants and children, including infant formula, contain high levels of $_{i}$As, particularly rice and rice-based products.

Keywords: rice, infant, intake, risk

1. Introduction

Arsenic is found in both its inorganic and organic forms in the environment from natural occurrence and from anthropogenic activity (JECFA, 2011). Inorganic arsenic ($_{i}$As) is generally more toxic than organic arsenic (EFSA, 2010; WHO, 2010) and is considered responsible for most of the effects of arsenic in humans (EFSA, 2010; FDA, 2016).

In the European Union (EU), the following foods were identified as largely contributing to $_{i}$As daily exposure: cereal grains and cereal-based products, food for particular dietary uses, beer and coffee, bottled water, fish and vegetables, rice grains and rice-based products, (EFSA, 2010; Huang *et al.*, 2012) but food supplements might also be a matter of concern (Martena *et al.*, 2010). The Joint FAO/WHO Expert Committee on Food Additives (JECFA) concluded that the highest total arsenic ($_{T}$As) concentrations have been found in seaweed, fish and shellfish, mushrooms and fungi, rice and rice products and some meat products. However, seaweed, rice, and some fish and seafood have higher $_{i}$As levels, as do food crops grown in arsenic-contaminated soils (JECFA, 2011). According to the Food and Drug Administration, rice and rice-based food products have the highest concentrations of $_{i}$As among foods and are a major source of exposure due to their widespread consumption, especially by infants (FDA, 2016; Rasheed *et al.*, 2016).

Particular subpopulations could be at a higher risk for adverse health effects as a consequence of exposure to arsenic. This may result from altered metabolism or underlying genetic risk factors, life stages that represent developmental windows of unique sensitivity to $_{i}$As toxicity, and factors that may increase dietary exposure such as individual preferences, age group, cultural factors, and dietary restrictions (Nachman *et al.*, 2017). Among these subpopulations, we find coeliac disease patients (Da Sacco *et al.*, 2013; Munera-Picazo *et al.*, 2014), keen rice consumers (Rintala *et al.*, 2014) and children (Jackson *et al.,* 2012; Rasheed *et al.*, 2016).

In this review, we will discuss current standards and legislation with regards to arsenic in rice, rice-based products, and foods intended for infants and children; recent findings on chronic health effects of early-life arsenic exposure in humans, and estimations of this exposure and risk assessment in different countries around the world.

Throughout the month of November 2017, we indexed publications from 2010 to 2017 in the Web of Science and Scopus. The keywords used for Web of Science were: arsenic, infant, and food, resulting in 59 records, and the keywords used for Scopus were: arsenic, baby, and food, for a total of 886 records. For both Web of Science and Scopus, we applied the following exclusion criteria: original research and articles written in English and Spanish, which gave us 49 and 480 records, respectively, totalling 529 records from both databases. In Scopus, we further excluded research related to other elements rather than arsenic and research related to results other than adverse health effects of arsenic in babies. Finally, we excluded 28 records that we considered not relevant or were duplicate but included 39 records found in the grey literature and/or identified through additional search, totalling 84 records. The whole process is schematised in Figure 1.

2. Standards and legislation on arsenic in rice and other products consumed by infants

Relevant international and nation-specific safety limits are shown in Table 1. The rice related terminology is based on the European Classification of Goods for rice and related products (EC, 2019).

Maximum limits were set by the Codex Alimentarius (Codex Alimentarius Commission, 2014), the European Commission (EC, 2015) and the Food and Drug Administration, USA (FDA, 2016). The limits set by the Codex Alimentarius and the Food and Drug Administration are non-mandatory guidelines, while those established by the European Commission are mandatory in member states. National mandatory maximum limits were implemented by China (USDA Foreign Agricultural Service, 2013), India (FSSAI, 2017) and Australia (FSANZ, 2017). To date, international safety limits for $_{T}$As and $_{i}$As in infant formula have not been established.

In 2010, JECFA withdrew the provisional tolerable weekly intake (PTWI) for $_{i}$As of 15 μg/kg body weight (equivalent to 2.1 μg/kg body weight per day) considering that it was too close to the benchmark dose for a 0.5% increased incidence ($BMDL_{0.5}$) of lung cancer, 3.0 μg/kg body weight per day (FAO/WHO, 2010). Additionally, the European Food Safety Authority (EFSA) stated that the PTWI of 15 μg/kg body weight was no longer adequate since a number of harmful health effects have been reported at $_{i}$As exposures below that level (EFSA, 2010).

3. Toxicity

Arsenic has a negative effect on multiple biological and biochemical processes which, in turn, would manifest themselves as toxicity. These processes are summarised in Table 2 (Medina-Pizzali *et al.*, 2018).

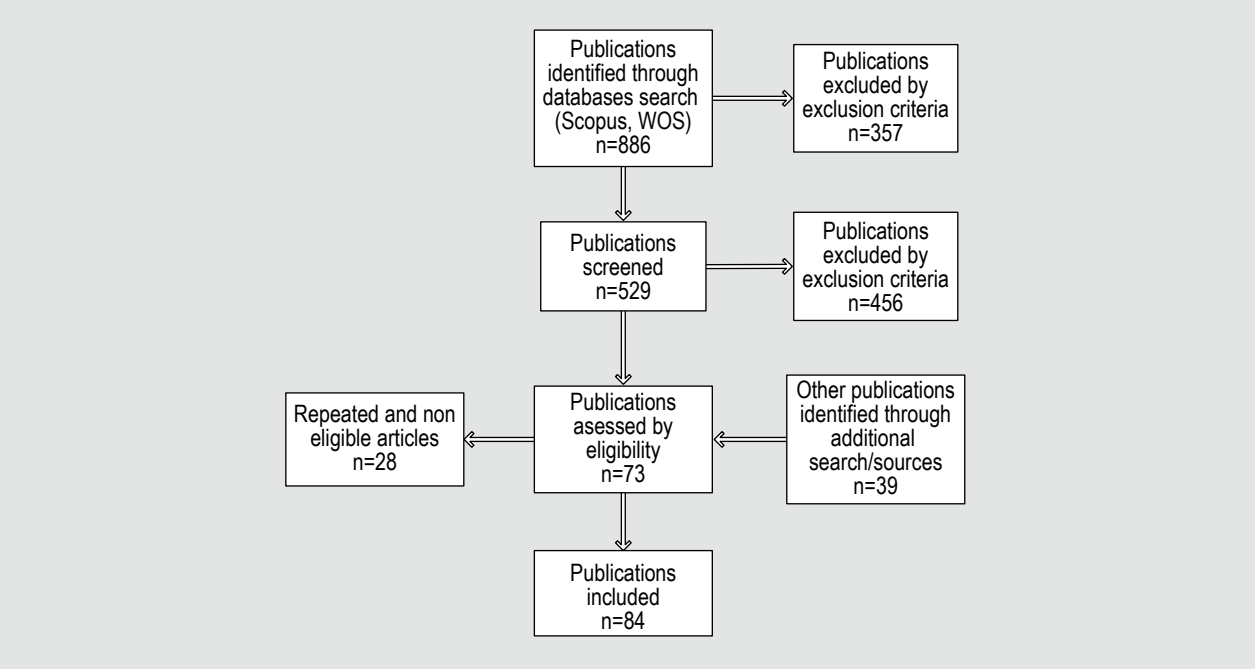

Figure 1. Indexing of publications to be included in this review.

Table 1. Standards and legislation on arsenic in foods around the world.

Country/organisation	Food item	Year	Maximum level (mg/kg)	Arsenical species[1]
China[2]	rice[3] (including brown rice)	2014	0.20	$_{i}$As
	cereal-based complementary foods for infants and young children	2014	0.20	$_{i}$As
	canned complementary foods for infants and young children	2014	0.10	$_{i}$As
Codex Alimentarius Commission	polished rice	2014	0.20	$_{i}$As
	husked rice	2014	0.35	$_{i}$As
European Union	non-parboiled milled rice	2015	0.20	$_{i}$As
	parboiled rice and husked rice	2015	0.25	$_{i}$As
	rice-based waffles, wafers, crackers, and cakes	2015	0.30	$_{i}$As
	rice used for production of food for infants and young children	2015	0.10	$_{i}$As
Food and Drug Administration[4]	infant rice cereals	2016	0.10	$_{i}$As
India	non-specified foods (including rice)	2017	1.1	$_{T}$As
	infant milk substitute and infant foods	2017	0.05	$_{T}$As
Australia	cereal grains and milled cereal products	2017	1	$_{T}$As

[1] $_{i}$As = inorganic arsenic; $_{T}$As = total arsenic.
[2] China is the world's major producer of rice.
[3] The rice terms used throughout this article have a connection with the degree of processing that the grains have undergone: paddy rice or whole grain rice refers to grains still enveloped by the husk. Husked or brown rice refers to rice grains without the husk. Milled rice refers to rice grains processed to remove the pericarp which is still present in brown rice. Polished rice refers to wholly milled rice grains which have been brushed to improve their appearance. Parboiled rice refers to paddy rice grains steamed or soaked in hot water and then dried before other processes are carried out.
[4] The FDA limit is not mandatory in the USA; it is a recommendation for producers.

Table 2. Main molecular and cellular processes involved in arsenic toxicity.

Interference with a number of enzymatic systems	• Binding to sulfhydryl groups (in proteins, glutathione, cysteine) affecting enzymes for cellular respiration, gluconeogenesis, glucose uptake and glutathione metabolism (As^{+3}) • As^{+5} changes to As^{+3} *in vivo*, and has a direct effect on the decoupling of oxidative phosphorylation
Altered expression of various growth factors	
Suppression of cell cycle checkpoint proteins	
Promotion of and resistance to apoptosis	
Aberrations and chromosomal anomalies	
Genotoxicity	• DNA damage • Inhibition of DNA repair causing mutations • Activation of oncogenic pathways
Alterations of the epigenetic regulation of DNA	• Perturbation of DNA methylation • Expression of microRNA • Histone modifications
Immune suppression	
Oxidative stress	
Alteration and dysfunction of mitochondria	

Arsenic's toxicity to the human body depends on its chemical form. $_{i}$As is more toxic than the organic forms (EFSA, 2010; WHO, 2010), and trivalent arsenite (As^{+3}) is more toxic than pentavalent arsenate (As^{+5}) (as cited in Hong *et al.*, 2014). Its toxicity depends on the oxidation state and solubility of the arsenical species; the exposure amount, length, and frequency; the biological species; age; sex; individual sensitivity; genetics; and nutritional factors (as cited in Hong *et al.*, 2014).

Another factor that influences arsenic's toxicity is its metabolism in the human body. $_{i}$As goes through

a series of oxidation and methylation steps to yield monomethylarsonic acid (MMA) and then dimethylarsinic acid (DMA), which aids arsenic elimination, given that DMA has a shorter circulating half-life than $_{i}$As and is rapidly excreted in urine (Howe *et al.*, 2014; Pierce *et al.*, 2013). These reactions require S-adenosyl methionine (SAM) as the methyl donor via one-carbon metabolism and are catalysed by methyltransferase enzymes, mainly, arsenite methyltransferase (AS3MT) (Kaur *et al.*, 2011; Pierce *et al.*, 2013). The main metabolites eliminated in urine are MMA and DMA, together with a certain amount of unmethylated $_{i}$As (Löveborn *et al.*, 2016). All of them are considered biomarkers of recent exposure as their half-life is 3 to 4 days (Saoudi *et al.*, 2012). Higher levels of $_{i}$As and MMA in urine correlate with higher retention in the body and a higher risk of adverse health effects. Among the factors that influence the efficiency of the arsenic metabolism we find polymorphisms in the AS3MT gene, gender, nutrition, smoking, and pregnancy (Löveborn *et al.*, 2016), but folate and cobalamin levels of adult individuals is important since they affect the production of SAM via one-carbon metabolism (Howe *et al.*, 2014). Arsenic bioaccumulates when it binds to proteins containing sulfhydryl groups such as keratin, so bioaccumulation is confirmed by determination of biomarkers such as hair and nails (Rasheed *et al.*, 2016), (Hanh *et al.*, 2011; Shen *et al.*, 2013).

According to the International Agency for Research on Cancer (IARC), arsenic and $_{i}$As species belong to Group I (carcinogenic to humans), DMA and MMA are included in Group IIB (possibly carcinogenic to humans), while arsenobetaine and other organic species are part of Group III (not classifiable as to their carcinogenicity to humans) (IARC, 2012). In addition to being able to induce various types of cancer, arsenic has harmful chronic effects in humans such as skin lesions, central and peripheral neurotoxicity, cardiovascular diseases, abnormal glucose metabolism and diabetes (EFSA, 2010; Hong *et al.*, 2014). Furthermore, this contaminant negatively affects almost all organs and systems, and causes a diversity of chronic effects including haemolytic anaemia, renal dysfunction, infertility, reduced immunity and cirrhosis (Medina-Pizzali *et al.*, 2018).

4. Health effects of early exposure to arsenic in children

Figure 2 shows a summary of the health effects of early-life exposure to arsenic.

Although children may be exposed to arsenic through food, they may also be exposed *in utero*. In pregnant women, $_{i}$As and its methylated metabolites easily pass the placenta (Vahter, 2009) and can be found in the meconium and cord blood (Jiang *et al.*, 2014). Arsenic inhibits thioredoxin reductase which is the main protection system against placental stress, causing placental pathology and preeclampsia (Vahter, 2009). Other effects are foetal growth impairment and low weight at birth, stillbirths and

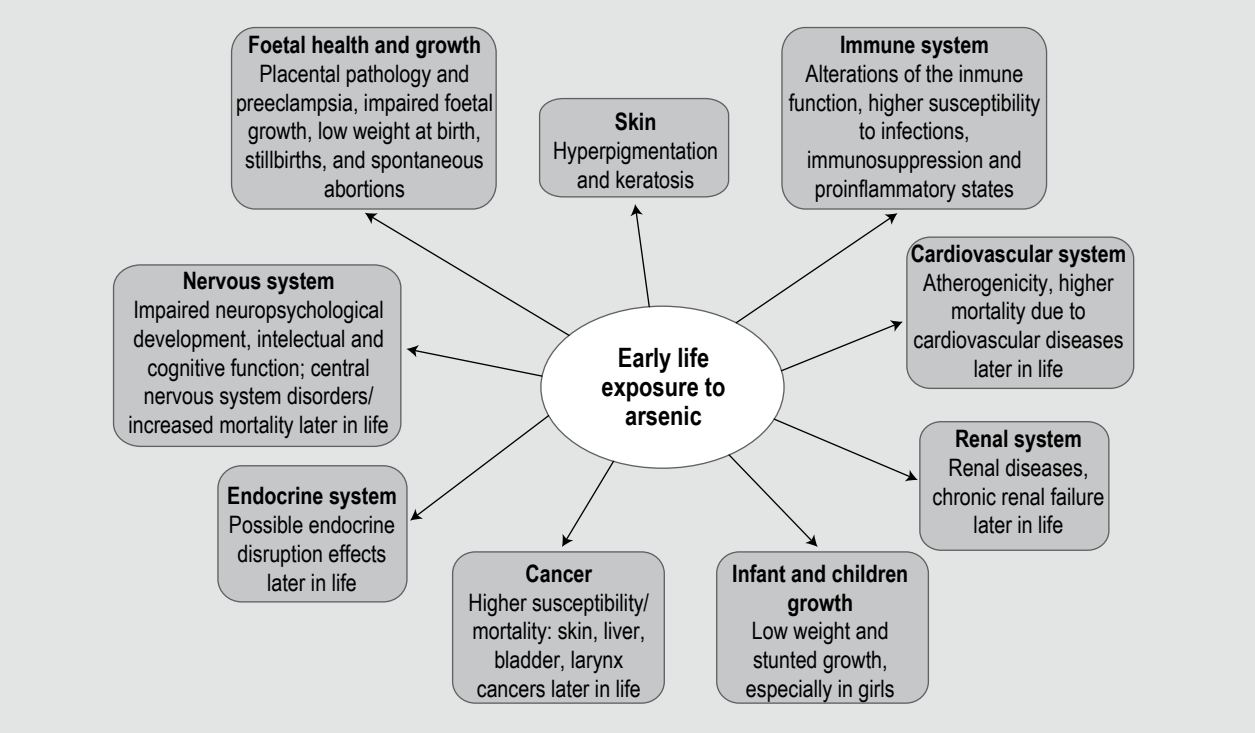

Figure 2. Diagram showing the effects of early-life exposure to arsenic.

spontaneous abortions (Chakraborti *et al.*, 2016; Luo *et al.*, 2017; Shih *et al.*, 2017; Vahter, 2009). Lower birth weight may lead to rapid adiposity increase in young children and a higher risk for cardiometabolic disorders in adulthood (Luo *et al.*, 2017).

In a cohort follow-up study on children in Taiwan, results indicated that the atherogenic capacity of $_{i}$As may initiate early in life, due to dyslipidaemias (Kuo *et al.,* 2018). The identified postnatal exposure window for arsenic-derived atherogenicity is consistent with animal studies, and the association between cardiovascular abnormalities and diseases and arsenic exposure has been studied and documented in adults (as cited in Kuo *et al.*, 2018) and well as in children (as cited in Farzan *et al.*, 2013). There is strong evidence of an association between early life arsenic exposure and mortality due to cardiovascular diseases in adults, based on a study in Chile (Yuan *et al.*, 2007) and a recent study demonstrated that *in utero* arsenic exposure in humans alters DNA methylation at sites involved in the expression of low-density-lipoproteins (Kaushal *et al.*, 2017).

The effects that arsenic exposure has, both *in utero* and in children, on the mortality rate decades later, were studied in a large population in Chile. In young adults exposed to water $_{T}$As levels of 870 µg/l, the study found marked increased rates of mortality from bladder, larynx, and liver cancers, as well as from renal diseases linked to chronic renal failure (Smith *et al.*, 2012).

A similar approach was applied in a study in Japan where excess mortality was assessed among a population who had survived a poisoning event with arsenious acid (As^{+3}) as children. The survivors showed a much higher mortality from nervous-system related conditions than the overall population (Tanaka *et al.,* 2010).

Exposure to arsenic in children (younger than 3 years old) is estimated to be two or three times higher than in adults. This can be explained by the higher metabolic rate children have, drinking and eating more water and food per kilogram of body weight than adults do. This higher metabolic rate is at its peak in the first 6 months of life. Increased exposure in children has been associated with impaired intellectual function and neuropsychological development in children and adolescents (Bae *et al.*, 2017).

A study carried out on a population of children in Mexico, showed that $_{i}$As contamination affected children's cognitive function in terms of memory, attention, problem-solving, and vocabulary processes (Rosado *et al.*, 2007) and other studies have reported various long term mental and neuropsychological effects of its exposure in children affecting their intellectual and cognitive functions (Arroyo and Fernández, 2013; Yorifuji *et al.*, 2016). Similar results were obtained in a longitudinal study on children in Bangladesh, showing that early-life arsenic exposure negatively affected IQ measures in girls (Hamadani *et al.*, 2011; Saha *et al.*, 2012).

Exposure to arsenic in childhood is believed to cause damage mainly at the level of the central nervous system, compared to the peripheral nerves, and could affect different domains of the brain or cause diffuse alterations (Yorifuji *et al.*, 2016).

Regarding the mechanism of action of arsenic in the effects on neurodevelopment, it was proposed that it would cross the blood-brain barrier and alter the white matter of the brain, as well as interfere with neurotransmitters and reduce neuronal growth. Since arsenic is a pro-oxidant, it may also generate oxidative stress in the developing brain. It may also have interactions with oestrogen and thyroid hormones which are crucial for brain development (Jiang *et al.*, 2014). Epigenetic alterations caused by arsenic *in utero* might also explain the negative effects in the foetal brain but more research has yet to be done (Lo and Zhou, 2009).

Studies in Bangladesh and Korea show that exposure to $_{T}$As influences the weight and length of infants, even at low concentrations (Choi *et al.*, 2017), and also show that the effects are more significant than during prenatal exposure, with a higher incidence in the female population (Saha *et al.*, 2012), which correlates with the results of other studies (Gardner *et al.*, 2013). The main effect of exposure to arsenic is a restriction in growth and although the mechanism is not entirely clear, it is thought that it generates endocrine alterations that cause the suppression of the insulin-like growth factor 1 (Choi *et al.*, 2017).

Arsenic interactions with DNA methylation and steroid hormones in early life may lead to adverse health effects many years later. High exposure to arsenic in early life is associated with increased cancer mortality, while animal-based and human-based genetic studies indicate that at low levels of exposure, arsenic may interfere with the long term programming of the individual, leading to problems such as predisposition to increased risk of cancer, endocrine disruption and depressive behaviour (Kaushal *et al.*, 2017; Vahter, 2009). Epigenetic reprogramming and alterations in gene expression caused by $_{i}$As may affect a diversity of genes such as those implicated in cancer, atherosclerosis, and diabetes, and may have a negative effect on the immune system, leading to immunosuppression and proinflammatory states which could not only explain long term effects but short term effects as well (Bailey *et al.*, 2016).

In a cohort study conducted in the USA, $_{T}$As exposure and its impact on the risk of respiratory infections during the first year of life were evaluated (arsenobetaine was

excluded). A strong association was found between prenatal exposure to $_{T}$As and an increased risk of respiratory infections, especially in the first four months of life, suggesting that the first months of life are a critical period for the effects of arsenic. This might be explained by modifications in the immune system (Farzan *et al.*, 2016), mainly innate immunity, as well as inflammatory response and integrity of the cellular matrix (Farzan *et al.*, 2013).

Studies carried out in India, showed that skin lesions such as hyperpigmentation and keratosis which lead to skin cancer in children are linked to chronic $_{T}$As exposure by water and consumption of rice (Chakraborti *et al.*, 2016; Liao *et al.*, 2010). The prevalence ratios of skin lesions were notably higher with increasing arsenic levels of exposure and with the children's age, but they were also influenced by gender, with male children showing higher ratios which could be explained by differences in methylation capacity (Liao *et al.*, 2010).

5. Mitigating arsenic intake or its effects

Breastfeeding might protect infants against the negative effects of arsenic. Its protective properties derive from the high levels of antioxidant substances such as taurine and thioredoxin, and the high concentrations of choline, which promotes efficient methylation (Fängström *et al.*, 2008; Todoroki *et al.*, 2005; Vahter, 2009). Arsenic exposure through breast milk has been reported, but studies indicate that the contaminant's concentration is low in breast milk (Carignan *et al.*, 2015; Salmani *et al.*, 2018) even at high levels of exposure in the mother (Fängström *et al.*, 2008).

Appropriate cooking methods could be applied to reduce arsenic intake in populations. Besides its levels in cooking water, the kind of processing that food undergoes, cooking medium, time and temperature, and the amount of water used, can all have an impact on arsenic concentrations in the prepared foods (Cottingham *et al.*, 2013; Hanh *et al.*, 2011; JECFA, 2011).

Research shows that selenium, an essential nutrient, could be used to reduce the cytotoxic and teratogenic effects of arsenic (Abass *et al.*, 2017). However, there is evidence of a synergistic effect as well, causing selenium to enhance arsenic's toxicity, depending on their intracellular concentrations (Sun *et al.*, 2014).

Folate has a critical role in all methylation reactions. Methylated arsenic species are more easily excreted; therefore, increasing folate intake may be a way of facilitating arsenic excretion. Methylation and excretion of arsenic may be hindered by low folate status and its toxicity could be enhanced (Bae *et al.*, 2017). Folic acid supplementation is a low-cost strategy to treat populations at risk for arsenic-induced diseases (Peters *et al.*, 2015).

On the other hand, it is considered that a good intervention strategy for arsenic in any population should focus on ways to reduce the population's exposure from common dietary sources, as it is done for the case of methyl mercury in fish (Nachman *et al.*, 2017). Updated food science and nutritional education and dissemination of research in the community are essential to promote a change in dietary patterns.

In the USA, a coordinated approach for reducing $_{i}$As exposure through diet was proposed and it included a combination of three elements: prioritisation of foods for additional evaluation and intervention; development of a recommended limit in the food based on a relative source contribution approach which guarantees that no specific food contributes a steep amount to the aggregate dose; and finally intervention strategies, that reduce the $_{i}$As concentration in the food, or provide dietary advice that limits intake of that food to meet exposure goals (Nachman *et al.*, 2017). The relative source contribution approach was developed originally by the U.S. EPA and takes into account multiple or cumulative sources of exposure to a chemical, by using a factor to indicate what percentage of a population's exposure might derive from a particular source of exposure (Gadagbui *et al.*, 2012).

In order to protect infants and children, rice and rice products should be regulated and products containing rice should declare their content of $_{i}$As. Interventions should be made to favour the use of other cereals, so as to lower the intake of arsenic from rice (Hojsak *et al.*, 2015). Unfortunately, regulation on rice and rice products cannot be achieved if scientific research is lacking and monitoring programmes are not correctly implemented nationwide.

6. Infant foods and arsenic exposure

In a study done in New Hampshire, USA, researchers compared urinary arsenic (not including arsenobetaine) in breastfed infants and bottle-fed infants; and concluded that breastfed infants had much lower exposure. The population, a subset sample of a larger cohort study, had low urinary arsenic but infants fed only with formula showed levels 7.5 times greater than those exclusively breastfed. For formula-fed infants, the estimated daily $_{T}$As intake was 0.22 µg/kg/day, while for breastfed infants in the larger cohort study it was 0.04 µg/kg/day. The difference might be explained by the contribution of the formula powder and the water used to reconstitute the formula (Carignan *et al.*, 2015).

In an exploratory study done on baby foods in the Serbian and Spanish markets, $_{T}$As was detected in samples of porridge (average arsenic daily intake 1.44 µg/kg body weight per day), whose main ingredients were vegetables and fish, but the arsenical species were not identified (Škrbić *et al.*, 2017). Speciation would have been necessary,

considering that arsenic in fish is mainly organic and less toxic.

After analysing a number of fish and chicken-based infant foods, a study carried out in the UK showed that, in terms of $_{T}$As levels, these foods were not of concern since their concentrations were below the detection limit (Zand *et al.*, 2012). The formulations contained also vegetables which might explain why the concentrations were so low, despite the presence of fish.

A study done in Poland showed that among infant foods, mean middle bound levels for $_{T}$As were significant for rice gruel and fish-based food but did not exceed 0.14 mg/kg and 0.18 mg/kg, respectively. The study was based on a national monitoring programme, but again arsenical species were not identified. They concluded that arsenic concentrations in infant foods were comparable to those in other European countries (Mania *et al.*, 2015).

7. Arsenic in rice-based baby foods

Since rice grows in flooded fields it takes up higher amounts of arsenic, and this fact is supported by rice having the highest levels among foods (Rasheed *et al.*, 2016). Rice and its sub-products are ingredients in many processed baby foods, such as formula, jarred purees and strained foods, and also snacks (Jackson *et al.*, 2012). Rice is also used in homemade preparations for infants (Burló *et al.*, 2012). All the studies found in this review analysed processed baby foods or rice, but not homemade infant foods.

In a study in Spain, samples of rice marketed in Spain were analysed for $_{T}$As content, and the mean concentration in all rice samples was 0.186±0.015 mg/kg, with values ranging from 0.102 to 0.351 mg/kg, exceeding the EU limits for infant foods (0.10 mg/kg) and polished rice (0.20 mg/kg) (Burló *et al.*, 2012). A more recent study showed that 26% of all Spanish rice samples taken would exceed $_{i}$As limits under the latest EU regulations for the production of infant and children food (Signes-Pastor *et al.*, 2016a). Coeliac infants would be under serious risk since they have to consume gluten-free products and therefore have a higher percentage of rice in their diet (Carbonell-Barrachina *et al.*, 2012; Signes-Pastor *et al.*, 2016b). Another study in Spain analysed samples of cereals intended for infants, assessing them in terms of the different cereal types, the predominating cereal in the formulation, the added ingredients used, and whether the cereal was organically or conventionally grown. Rice-based cereals showed the highest levels of $_{T}$As, but organic cereals had much higher concentrations. This would be explained by the use of brown rice in these products (Hernández-Martínez and Navarro-Blasco, 2013).

In Sweden, a study conducted on infant formulas and infant foods was carried out to assess the concentrations for various essential and toxic elements. Alarming results were obtained: three out of five rice-based foods showed $_{T}$As concentrations close to 30 µg/kg, while two foods with added fruit had slightly lower concentrations (Ljung *et al.*, 2011).

In a study carried out in Ireland, UK, it was found that formula-fed infants had higher concentrations of urinary DMA and MMA than exclusively or partially breastfed infants; DMA and MMA being metabolites found in urine as a consequence of exposure to $_{i}$As through diet. The comparison between levels of DMA and MMA in infants before and after weaning, lead to the conclusion that the weaning process increased their exposure to $_{i}$As. Rice-based infant and children foods were also analysed for comparison, exceeding in most cases the EU limit of 0.1 mg/kg (Signes-Pastor *et al.*, 2017).

A study carried out in the USA analysed samples of various brands of rice snacks for $_{T}$As, and it subsequently analysed the samples with the highest concentrations to determine the arsenical species present. One-third of all the samples were marketed for infants and toddlers, and the study found that 22% of them exceeded the EU standard for $_{i}$As for this category of products (0.10 mg/kg) (Karagas *et al.*, 2016).

On the other hand, in a study carried out in the UK to compare different brands of processed rice-based baby foods, it was found that many factors affected the concentrations of $_{i}$As in the products: the amount of rice used, processing (milled rice vs brown rice), and geographical origin. The latter also affects $_{T}$As levels and speciation (Signes-Pastor *et al.*, 2016a,b). Products containing whole-grain rice had higher concentrations of $_{i}$As and were produced under organic standards, some of them exceeding the JECFA maximum limits. Organic products are usually associated with a healthier and safer product. (Signes-Pastor *et al.*, 2016b). In another study carried out in the USA, the difference in concentrations of $_{i}$As between organic and conventional infant rice cereals was not significant, probably due to the high levels of DMA (Juskelis *et al.*, 2013).

8. Estimations of arsenic dietary intake and risk assessment

Age, ethnicity, culture, and preferences may affect people's consumption patterns of a certain food. Consumption patterns for high-risk foods are used to assess the degree of exposure of consumers in terms of total dietary arsenic (Wilson, 2015). Studies have been done to estimate the daily consumption of rice and rice products by the younger population in many countries where previous data for levels of $_{T}$As or $_{i}$As is available.

In the EU, rice is one of the main contributors to $_{i}$As daily exposure. Children under 3 years of age are most exposed and their $_{i}$As dietary exposure is about 2 or 3-fold that of adults (EFSA, 2010). Infants are weaned when they reach 4-6 months of age, and they are introduced to pureed infant foods and infant cereals (Carbonell-Barrachina *et al.*, 2012). In infants up to one year of age, pre-cooked, milled rice is the preferred source of carbohydrates, so its contribution to the $_{i}$As daily exposure is very high and this could be higher in children suffering from milk intolerances, since rice drinks or rice-based infant formula is the substitute to milk (EFSA, 2010).

In the previously mentioned Swedish study, it was estimated that two portions of the rice-based infant foods analysed would contribute about 2 µg/kg body weight, which is close to the outdated PTWI (Ljung *et al.*, 2011).

In a study conducted in Spain, it was concluded that all infants above 4 months of age consuming gluten-free infant rice products were receiving more dietary $_{i}$As than the maximum limit for adults under to EU and U.S. regulations (0.17 µg/kg/day), while infants consuming cereals with gluten surpassed the same maximum limit for adults after 8 months of age. The study assumed that infants were fed only one portion of infant rice, meat-based infant food and fish-based infant food per day (Carbonell-Barrachina *et al.*, 2012).

A nation-wide study conducted in Italy showed that the mean chronic dietary exposures for infants and toddlers, and for children were in the range of 0.190-0.215 and 0.152-0.179 µg/kg body weight per day, respectively. Foods that contributed the most to the mean exposure of arsenic in infants and toddlers were water (bottled water, mainly) and non-alcoholic drinks, cereals and cereal products, especially rice and pasta. Fruit and dairy products contributed to a lesser extent. Rice and rice-based products represented more than 50% of the $_{i}$As exposure from cereals and cereal products, being the dominant dietary source of $_{i}$As for children in Italy. The exposure of infants and toddlers to dietary $_{i}$As was the highest. The study compared the estimated exposures to the benchmark dose lower confidence limit (BMDL) value by EFSA for 1% excess risk of lung cancer (lowest $BMDL_{01}$) equal to 0.3 µg/kg body weight per day (EFSA, 2010) and calculated the margin of exposure, which for infants and toddlers was 2.8 and for children was 2.4 times that of adults (Cubadda *et al.*, 2016).

A monitoring programme in Poland carried out between 2009 and 2013, showed concentrations of arsenic in baby (6-12 m.o.) foods and calculated their mean dietary exposure at between 0.11 and 0.99 µg/kg body weight per day (4-33% $BMDL_{0.5}$ value) (Mania *et al.*, 2015). Using the more stringent lower limit of the $BMDL_{0.1}$ would have been more adequate since it is the one recommended by the CONTAM Panel (EFSA, 2010).

In Finland, a study was carried out to determine $_{T}$As and $_{i}$As content in rice-based baby foods and to estimate its daily intake of children of different age groups. The $_{i}$As intake from rice-based baby food was near the lower $BMDL_{0.1}$ value, 0.3 µg/kg body weight per day (Rintala *et al.*, 2014).

In the USA, infant formulas, purees and Stage 2 and 3 foods were analysed to determine $_{T}$As concentration and its species. Results showed low concentrations of $_{T}$As (mainly $_{i}$As), but when expressed on a µg/kg/day basis, those concentrations resulted in exposures that exceeded the WHO/EPA safe drinking water exposure for adults (0.17 µg $_{T}$As /kg/day), without taking into account other dietary sources (Jackson *et al.*, 2012). Likewise, a modelling approach to estimate the daily intake of arsenic was applied to a large cohort of infants in the USA, based on their consumption of breast milk and formula. The estimated median exposure to arsenic was 5.5 times higher in solely formula-fed infants (0.22 µg/kg/day) compared with exclusively breastfed infants (0.04 µg/kg/day). Formula powder may have contributed with 71% of the median estimated exposure, so it may be the main source of exposure for many of the formula-fed infants in this population (Carignan *et al.*, 2015).

Furthermore, in a risk assessment study in the same country, it was estimated that rice cereals for infants would represent more than half of the $_{i}$As exposure in babies, assuming they consumed these products daily. In terms of acute effects, the rice cereal associated risk would be below minimal or acceptable while the risk for non-carcinogenic chronic effects would be more than minimal for some infants and toddlers in that country (Shibata *et al.*, 2016). Another study carried out in the USA applied the total dietary intake minimum risk level for chronic exposures set up by the Agency for Toxic Substances and Disease Registry (ATSDR) as a standard for comparison against former results in multiple foods and beverages. It was concluded that infant formula sweetened with organic brown rice syrup contributed with 221-520% of the ATSDR minimum risk level (0.3 mg $_{i}$As /kg body weight per day) in the mid-range level of consumption (Wilson, 2015).

In Brazil, the estimated daily intake of $_{i}$As in baby foods and rice-based products was calculated based on arsenic concentrations of Brazilian and imported samples. The estimated daily intake of $_{i}$As was 0.30 µg/kg body weight per day. The study did not focus on estimating what percentage from the total exposure this daily intake represented but concluded that the levels of $_{i}$As in rice-based baby products were lower compared to other rice-based foods (Pedron *et al.*, 2016).

In Peru, an official surveillance report showed results for contaminants in a variety of foods, including milled and whole grain rice, in 2016. However, rice was not analysed for arsenic (SENASA, 2016). In the national surveillance plan for 2018, rice was not even included in the list of foods to be analysed for contaminants (SENASA, 2018) even though Peru is a major producer and consumer of rice in the region (MINCETUR, 2018).

A study conducted in Qatar estimated the total dietary intake for $_{T}$As in infants based on the consumption of infant cereals. The total dietary intake ranged from 0.850 to 2.02 µg/kg body weight per day, and these values were compared to the former provisional tolerable daily intake set by JOINT FAO/WHO Expert Committee on Food Additives (JECFA, 2011) resulting in an average of 70% of the provisional tolerable daily intake (Rowell *et al.*, 2014).

In Thailand, a variety of foods generally consumed by Thai children were analysed and the daily intake of a number of elements was estimated (Nookabkaew *et al.*, 2013) and compared to the outdated PTWI (JECFA, 2011). Samples included not only rice and infant formula but other foods including soybean milk, drinking water, bottled water, vegetables, banana, meat and other foods of animal origin. For many samples such as poultry, pig liver, rice and wheat, $_{T}$As daily intakes greatly surpassed the PTWI, but it was concluded that $_{T}$As levels were not of concern in most foods since they were lower than international standards. (Nookabkaew *et al.*, 2013). However, this conclusion is misleading since the study used a PTWI which is no longer in use.

A study carried out in Australia estimated the daily intake of $_{T}$As from rice and rice products at 7.9 µg/day for young children. However the study was based on consumption data per day for 12 to 15-year-old children from a previous national survey (Tinggi *et al.*, 2015), so it probably may not be an accurate reflection of daily consumption of rice in infants and toddlers.

9. Conclusions

International recommended limits for $_{i}$As in rice and rice products have been established by the European Commission, yet the Codex Alimentarius Commission guidelines do not include rice-based products or rice for infant food. Some countries have mandatory national safety limits. For instance, China has established stringent $_{i}$As limits not only for rice but for infant cereals and foods. On the other hand, international safety limits for $_{T}$As and $_{i}$As in infant formula have not been established so far, despite the evidence found on arsenic exposure through ingestion of infant formula (Carignan *et al.*, 2015; Jackson *et al.*, 2012; Signes-Pastor *et al.*, 2017).

Most countries use international recommended limits since they have not established their own safety limits for $_{T}$As and $_{i}$As in rice and rice-based products. Worldwide, improved surveillance programmes of arsenic levels in foods are necessary in order to identify potentially harmful foods, assess daily intake in infants and children, and eventually establish preventative measures.

Early-life chronic exposure to arsenic has the potential to affect several systems of the human body, and while some of these effects are likely to remain latent, manifesting themselves long after the exposure has ceased, others become evident during or shortly after the duration of the exposure. There is a consistent association between arsenic exposure and negative short-term effects such as impaired foetal growth and spontaneous abortions, stunted growth, impaired nervous system development and cognitive function, and decreased immunity in infants and children. Long-term latent effects include cardiovascular and neurological disorders, cancer, and possibly endocrine disruptive effects, but more research is needed in relation to the latter.

A variety of foods contribute to the exposure to arsenic in infant and child populations. In many countries, foods intended for infants and children contain high levels of $_{T}$As and $_{i}$As, particularly rice and rice-based products, and the $_{i}$As dietary exposure of these populations is estimated to be about 2 or 3-fold that of adults (EFSA, 2010). Reduced exposure to arsenic is derived from breastfeeding, but once infants are weaned or introduced to formula (Carignan *et al.*, 2015) and other foods, they are most likely exposed to potentially harmful concentrations of arsenic (Cubadda *et al.,* 2016). This exposure implies a major public health problem which contributes to the disease burden in future adult populations. This can be addressed by means of different strategies, such as emphasising responsible surveillance, research, and dissemination of updated information and education in the community.

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