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Diet's role in the toxicity of inorganic arsenic (iAs): A journey from soil to children's mouth

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ABSTRACT

Arsenic is widely distributed in the environment, particularly in soil. Absorption of arsenic and other metalloids from soil can alter the nutritional composition of some foods such as rice and vegetables. Rice has been found to contain a high amount of inorganic arsenic (iAs) that the plant accumulates from soil. A diet enriched of rice and rice based foods, such as in the case of children affected by celiac disease, can be therefore a toxicological issue. Vegetables are rich in antioxidants and folic acid that contribute to minimize some arsenic-induced toxic effects. Therefore, diet appears as a crucial determinant in the axis soil–food–human health. We preliminarily investigated the As exposure effects in *in vitro* models and we identified the principal interactors (mainly genes) involved in As-induced toxicity linked to specific metabolic pathways. We suggested that As-exposure and toxicity are more generally linked to diet and that diet can have a role in modulating and mitigating these toxic effects. In conclusion, we suggested that a more integrated view of 'exposure' to toxic elements should also include other factors, such as the diet contribution, other than environmental and toxicological data.

1. Introduction

1.1. Arsenic in the soil

Arsenic (As) is widely distributed in the environment, occurring as the 20th most abundant element in the earth's crust (Cullen and Reimer, 1989) with an overall amount estimated to be $4.01 \cdot 10^{16}$ kg (based on the concentrations in rock material) (Matschullat, 2000). Moreover, $1.715 \cdot 10^7$ kg/year are liberated from the lithosphere into the exogenic cycle by terrestrial volcanic exhalations and eruptions, while other $4.87 \cdot 10^6$ kg/year from submarine volcanism. Soil should not be considered as a homogenous medium as it may contain highly variable As concentrations. The humus layer has a crucial role: it acts as a natural biogeochemical barrier suppressing the percolation of As with the seepage water, and thus, facilitates its accumulation (Goldschmidt, 1937).

Of the almost 300 known As minerals, 60% are arsenates, 20% are sulphides and sulphosalts, 10% are oxides and the remaining fraction is represented by arsenites, arsenides, native elements and metal alloys (Bowell and Parshley, 2001). The most important primary As-bearing minerals are those where the As occurs as the anion (arsenide) or dianion (diarsenide), or as the sulfarsenide anion(s); these anions are bonded to metals such as Fe (löllingite, arsenopyrite), Co (cobaltite) and Ni (gersdorffite). The simple As sulphide minerals realgar and orpiment are also found. While As does not readily substitute into the structures of the major rock-forming minerals, it can easily occur as a minor component in the abundant Fe sulphide mineral pyrite (Blanchard et al., 2007; Savage, 2000). The association of As with these sulphide minerals (chalcophilic), has largely contributed to its release into the environment (Mudroch and Clair, 1986). In fact, when these primary minerals are exposed to the atmosphere and surface or groundwaters, secondary As minerals such as As oxides or more complex phases with As, oxygen and various metals are formed. The latter group of minerals comprises arsenite and arsenate minerals that are formed by linking As(III)- or As(V)-oxo-anion groups, respectively, to a variety of mono-, di- and trivalent metal cations. Arsenic exists mainly in three oxidation states (−3, +3, +5). The trivalent arsenic As(III) and the pentavalent arsenic As(V) are widely present in natural waters and their salts are soluble over a wide range of pH and Eh conditions (Bell, 1998). In oxidizing environmental conditions, the most stable species is As(V), whereas As(III) is the most predominant in reducing environmental conditions. Under aerobic conditions, As occurs in soils mainly in the form of arsenate (AsO_4^{3-}), bound to clays (Fe and Mn-oxi/hydroxides), and to organic substance. In acidic soils, Al and Fe-arsenates occur as $AlAsO_4$ and $FeAsO_4$, while Ca-arsenate, $Ca_3(AsO_4)_2$ is the dominant species in basic and limy soils (Fergusson, 1990). Under anaerobic conditions, arsenite can be reduced to arsine by microorganisms in soil (Gao and Burau, 1997; Hinchee et al., 1995). Some microorganisms, but also humans and animals, can transform As species into methylated as monomethylarsonic acid (MMAA),

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dimethylarsinic acid (DMAA) and trimethylarsine oxide (TMAO) species (Gadd, 1993). The trivalent compounds are generally more toxic than the pentavalent compounds (Cervantes et al., 1994; Smedley et al., 1996) with arsine gas (AsH_3) as the most toxic species. Moreover, it is generally recognized that organic arsenical compounds are generally less or not toxic with respect to inorganic species. However, arsenic is employed in several applications: hardening of alloys, semiconductor production, pigments and glass manufacturing, preparation of pesticides, fungicides and as component of drugs (i.e., Trisenox®) for the treatment of acute promyelocytic leukemia (APL) (Powell, 2011). Because of its exploitation, arsenic contamination is therefore widespread in the environment. As a direct consequence, As enrichment in soils may lead to root depression and growth defects in plants and to death of earthworms.

1.2. Arsenic accumulation in rice and vegetables

The European Food Safety Authority (EFSA) Panel on Contaminants in the Food Chain (CONTAM Panel) has summarized the results of several risk assessment studies related to the presence of As in food in a Scientific Opinion (European Food Safety Authority (EFSA), 2009). EFSA has also determined that diet is the main source of As: fish and fish products, cereal grains and derived products, fruit and vegetables juices, baby rice, drinking water, milk and infant formula and cocoa powder contain the highest amount of total As. In fact, As contamination in soils affects the physiology of vegetal species such as rice, the staple food for half of humanity. Paddy rice has enhanced As accumulation with respect to other cereal crops (Xu et al., 2008). Flooding of soil leads to a rapid mobilization of As in the form of arsenite. Arsenic accumulation in rice shoots and grain is markedly increased (10–15 fold) under flooded conditions with respect to aerobically grown rice. Arsenate has been recognized as the main As species in the aerobic soil. Therefore, it has been demonstrated that a greatly increased bioavailability of As under the flooded conditions is the main reason for an enhanced As accumulation by flooded rice. A recent study reported that two different types of transporters mediate the transfer of arsenite from the external medium to the xylem (Ma et al., 2008). In rice, transporters belonging to the NIP subfamily of aquaporins are permeable to arsenite but not to arsenate. This could explain why As accumulation in rice is higher in the flooded conditions (where arsenite is the main species) with respect to aerobic conditions (where arsenate is the prevalent species). The mechanisms of As accumulation within grain has been recently studied by Carey et al. who showed that As species are delivered through cut flag leaves during grain fill (Carey et al., 2011). This kind of food contamination has been also reported when As-contaminated groundwater has been used for crop irrigation in affected countries such as Asian countries (del Ninno and Dorosh, 2001; Meharg and Rahman, 2003; Rahman and Hasegawa, 2011). The problem of arsenic contamination in groundwater affecting Bangladesh, West Bengal (India), Vietnam, Thailand, Nepal and Taiwan with high levels of As in groundwater and the generally low concentration of micronutrients in rice have become a real major concern for human health (Dahal et al., 2008; Nordstrom, 2002). A recent study analyzed the arsenic accumulation in 32 types of vegetables and 7 types of pulses produced in the Nadia district, one of the most severely polluted areas in West Bengal (India) (Biswas et al., 2012). A higher arsenic content with respect to unpolluted sites has been found in vegetables cultivated in this area and irrigated with contaminated water. Similar results have been found in another study where a high accumulation of As was found in grain crops obtained from the agricultural soil irrigated with tub well as compared to soil irrigated with surface water (Baig and Kazi, 2012). On the contrary, the accumulation of other metalloids such as selenium (Se) can have opposite effects and display beneficial effects on human health. In fact, Se is essential for humans and has a beneficial role in cardiovascular disease (Lymbury et al., 2008) and cancer prevention (Abdulah et al., 2005; Clark et al., 1996). The main Se source for humans is dietary although Se concentration in foods correlates with the metalloid concentration in the soil where the food was grown. Moreover, Se supplementation has been employed to treat Se-deficiency (Alfthan et al., 2000) and Kashin-Beck osteoarthropathy in children (Zou et al., 2009). Interestingly, selenium enrichment of broccoli vegetables has been reported to increase chemosensitivity and apoptosis of prostate cancer cells (Abdulah et al., 2009) and to decrease intestinal tumorigenesis in mice intestinal neoplasia (Davis et al., 2002). Therefore, these data emphasize once more that the soil composition is a crucial issue to take into account when dealing with metal and metalloids accumulation in vegetable species and other foods. Therefore, this is even more important when dealing with infants' and children's health. Infants and children, with an exposure from 2 to 3-fold that of adults, appear to be the most vulnerable category that needs a specific protection because other foods consumed during childhood such as crackers, biscuits, crisped and puffed rice cereals, pasta, noodles, puddings, plain polished and whole grain rice might contribute to increase their As intake (Da Sacco and Masotti, 2012). A special attention should be deserved to those children affected by celiac disease, a particular health condition that obligate them to eat gluten-free foods, such as rice based foods or other kind of cereals. This appears to be a high-risk category of people considered that rice and rice based foods contain high levels of inorganic As.

1.3. Arsenic, rice and celiac disease

Celiac disease is an immune-mediated enteropathy associated with malabsorption of most nutrients and vitamins, characterized by an abnormal response to gluten that ultimately damages the lining of the small intestines (Rodrigo, 2006). Celiac disease may occur during childhood or adolescence but also during infancy. The only viable treatment for infants and children affected by celiac disease is a gluten-free diet, with rice and rice based foods as the main edible substitutes of wheat based products. For infants under 1 year of age, pre-cooked, milled rice is currently employed for weaning owing to its properties: it has a low allergenic potential and nutritional value, a poor taste and scarce nutritional value (Meharg et al., 2008; Mennella et al., 2006). For infants and children, rice may be of concern for the high content of inorganic arsenic in its grains as reported above. Moreover, it has been evaluated that the arsenic bioavailability from rice is quite high (~90%) (Ackerman et al., 2005). Two recent studies emphasized the presence of a positive correlation between rice content and As level in foods (Burlo et al., 2012; Carbonell-Barrachina et al., 2012). In the first study, the authors found that arsenic concentration in gluten-free infant rice (0.057 mg/kg) doubles that of gluten based products, such as cereal mixtures (0.024 mg/kg) (Burlo et al., 2012). This data reflects the different composition of these foods: gluten-free products have a mean rice content of 80.6% with respect to 10–15% of gluten based products. In the second study, Carbonell-Barrachina et al. assessed the arsenic concentration of a wide range of infant foods (infant rice, infant cereals, pureed meat and fish foods and special foods) from different countries (China, USA, UK, and Spain) (Carbonell-Barrachina et al., 2012). They found that gluten-free rice samples had the second highest total As content (126 ± 26 μg/kg), after the food that included fish, but the highest content of inorganic As (69 ± 8 μg/kg). Therefore, all together these data suggest that infants and children with celiac disease, who are recommended to have a gluten-free diet most often with high percentages of rice products, are at serious risk due to their high intake of inorganic arsenic. Some potential options to limit this problem are currently investigated: to identify rice varieties that have low inorganic As contents or rice cultivars with restricted As uptake (i.e. aerobic growing practices) and upward transport to the edible grain, sourcing rice from low arsenic regions, a different cooking procedure or simply reduce the rice content of baby foods.