# Arsenic and cadmium accumulation in rice and mitigation strategies

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# Arsenic and cadmium accumulation in rice and mitigation strategies

Fang-Jie Zhao · Peng Wang

**Abstract**

*Background* Arsenic (As) and cadmium (Cd) are two toxic elements that have a relatively high risk of transfer from paddy soil to rice grain. Rice is a major dietary source of these two elements for populations consuming rice as a staple food. Reducing their accumulation in rice grain is important for food safety and human health.

*Scope* We review recent progress in understanding the biogeochemical processes controlling As and Cd bioavailability in paddy soil, the mechanisms of their uptake, translocation and detoxification in rice plants, and strategies to reduce their accumulation in rice grain. Similarities and differences between the two elements are emphasized. Some knowledge gaps are also identified.

*Conclusions* The concentrations of As and Cd in rice grain vary by three orders of magnitude, depending on the bioavailability of the two elements in soil, rice genotype and growing conditions. The redox potential in paddy soil has a profound but opposite effect on As and Cd bioavailability, whereas soil pH affects Cd bioavailability more than As bioavailability. A number of key genes involved in As and Cd uptake, translocation, sequestration, and detoxification in rice have been characterized. Allelic variations of several genes underlying the variations in Cd accumulation have been identified, but more remains to be elucidated, especially for As. Two types of strategies can be used to reduce As and Cd accumulation, reducing their bioavailability in soil or their uptake and translocation in rice. Reducing the accumulation of both As and Cd in rice simultaneously remains a great challenge.

**Keywords** Arsenic · Cadmium · Food safety · Rice · Translocation · Uptake

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## Introduction

Soils contain a wide range of mineral elements, some of which are essential for living organisms while others are non-essential or even toxic. To grow, plants must acquire sufficient amounts of essential mineral elements. Uptake of these elements into the cell is carried out primarily via membrane transporters. However, some toxic elements can hitchhike onto these transporters and enter the cell, because of the similarities in their physiochemical properties with essential elements and the fact that membrane transporters are often imperfect in substrate selectivity. Toxic elements taken up by roots present a risk not only to plants but also to the consumers at the higher trophic levels. Plant-based foods are important, even dominant, source of some toxic elements for humans. Understanding how toxic elements are transferred from the soil to the food chain is an important field of research as it relates to food safety with potential impacts on human health.

In this review, we will focus on arsenic (As) and cadmium (Cd), two highly toxic elements that are particularly problematic due to a high risk in their transfer from soil to the food chain, especially with regard to paddy rice. Compared with other cereal crops, rice appears to have a higher ability to accumulate As and Cd (Su et al. 2010; Sui et al. 2018; Williams et al. 2007). Rice is a staple food for about half of the world's populations, and is also a major dietary source of both As and Cd for these populations (Li et al. 2011; Meharg et al. 2013; Song et al. 2017; Wang et al. 2019b). Chronic exposure to the two toxic elements can cause a number of diseases (Åkesson et al. 2014; Banerjee et al. 2013; Chen et al. 2009; Nordberg 2009). Arsenic and Cd behave very differently in their biogeochemical processes in paddy systems, making it difficult to develop common strategies to reduce their accumulation in rice grain simultaneously. Yet, As and Cd also share some common features. The similarities and contrasting behaviours of the two elements will be reviewed here, with the aim to identify strategies for controlling their accumulation in rice.

## Arsenic and cadmium have a high risk of transfer from paddy soil to rice grain

The transferability of toxic trace elements to the food chain depends on the element properties, as well as soil and plant factors. Chaney (1980) proposed the concept of "soil-plant barrier" to toxic element entry to the food chain. There are three barriers limiting the entry of toxic elements to the food chain: (1) Solubility. Some elements (e.g. Pb, Hg, $Cr^{3+}$, F, Ag, Au, Ti, Sn, Zr) have very low solubility in soil so that plants absorb only very small amounts of them; (2) Translocation. After absorption by the roots, some elements (e.g. Fe, Pb, Hg, Al) can be strongly sorbed on the root surfaces or strongly chelated in the root cells, limiting their translocation to plant shoots; (3) Phytotoxicity. Some elements (e.g. Cu, Zn, Ni, Co, Mn, B, As, Cd) can cause toxicity to plants and reduce yields, and the injured crops are less likely to be consumed by humans or domestic animals (Chaney 1980). The soil-plant barrier does not protect humans and animals from toxicities of all elements, especially Cd, Se and Mo, because they have relatively high solubility in soil and high translocation in plants, and are toxic to animals at levels that do not cause phytotoxicity (Chaney 1980). Although toxicities caused by excessive

levels of Se and Mo do exist, deficiencies of these elements in animals and humans, especially Se, are a much more widespread problem (Combs 2001). Cadmium is therefore the most prominent toxic metal threatening food safety through the soil to food chain transfer (Chaney 1980; Clemens et al. 2013). In the case of rice, we would add As to the list of elements with a high risk of soil to food chain transfer, as discussed below. Figure 1 depicts the concept of "soil-plant barrier" applied to paddy rice system.

Although both Cd and As have a high risk of soil-food chain transfer in paddy rice systems, the ratio of grain to soil total elemental concentration for Cd is one to two orders of magnitude higher than that for As. For example, Chen et al. (2018b) reported a range of 0.058–5.96 (mean = 1.38, median = 1.10, $n = 200$) for the ratio of grain to soil total Cd concentrations, compared with a range of 0.01–0.038 (mean = 0.011, median 0.009) for the ratio of grain to soil total As concentrations, in 200 paired soil-rice grain samples collected from southern China. Moreover, there is a significant, although not very strong, correlation between grain Cd concentration and soil total Cd concentration, but not between grain As concentration and soil total As concentration (Fig. 2). Figure 2 also shows that grain Cd concentration is more variable than grain As concentration. Similarly, Zhu et al. (2016) reported mean and median values of 1.05 and 0.84 ($n = 39,642$), respectively, of rice grain to soil Cd concentration ratio, whilst Williams et al. (2007) reported 0.04 for both mean and median values ($n = 72$) of rice grain to soil As concentration ratio. It is therefore clear that As has a much lower transferability from soil to rice grain than Cd. Nevertheless, because soils generally contain much higher levels of As than Cd, rice grains can still accumulate considerable amounts of As to pose a potential risk for human health.

## Intakes of Cd and As from consumption of rice

Rice is a dominant source of dietary intakes of both inorganic As (iAs) and Cd for populations consuming rice as the staple food (Li et al. 2011; Meharg et al. 2013; Meharg et al. 2009). Intakes of As and Cd from rice depends on the amount of rice consumed and the concentrations of these elements in rice grains. Average consumption rate of rice varies greatly among different countries, from 0.9 to 650 g/person/day (estimated by dividing national total rice consumption by population)

**Fig. 1** Soil-plant barrier and the risk of toxic element transfer to the food chain in paddy rice system. Based on the concept proposed by Chaney (1980) with modifications
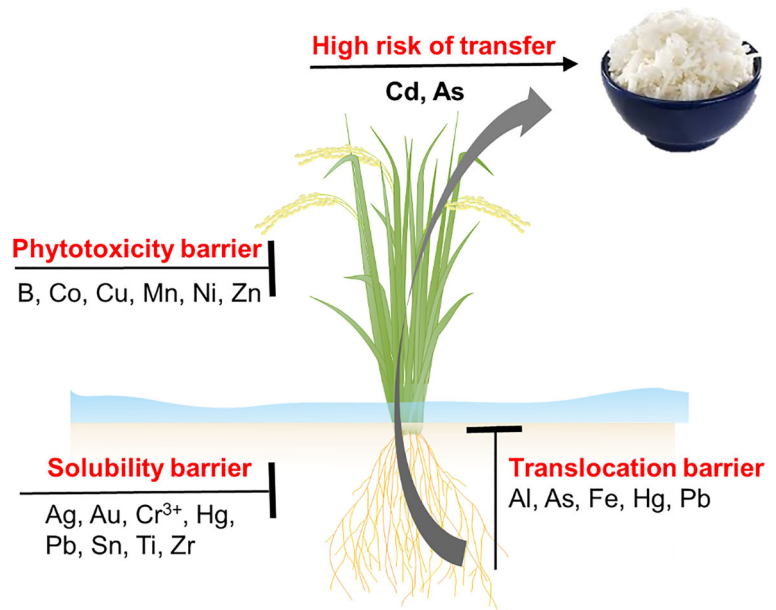
(Meharg and Zhao 2012). Forty six countries consume more than 100 g/person/day, with Myanmar, Laos, Viet Nam, Cambodia and Bangladesh consuming the largest amounts (>450 g/person/day). Rice consumption rate also varies within each country due to regional and/or ethnical variations in the diet. For example, northern and southern populations in China consume on average 124 and 327 g/person/day, with a national average of 238 g/person/day (Jin 2008). The concentrations of As and Cd in rice grain also vary markedly. Meharg et al. (2009, 2013) conducted global surveys of As and Cd



**Fig. 2** Relationship between rice grain As or Cd concentration and soil As or Cd concentration ($n = 200$). Data are from a paired soil-rice grain survey conducted in Hunan Province, China (Chen et al. 2018b)

concentrations in polished rice grains produced in different countries. They reported a range of 0.01–0.82 mg kg$^{-1}$ for grain total As (mean = 0.15 mg kg$^{-1}$, median = 0.13 mg kg$^{-1}$, $n = 901$) and a range of <0.005–1.31 mg kg$^{-1}$ grain total Cd (mean = 0.047 mg kg$^{-1}$, median not reported, $n = 1147$). The Cd dataset in the study of Meharg et al. (2013) did not include any samples from China, a major rice producing country. National surveys in China reported a range of Cd concentration in polished rice grain of <0.001–0.74 mg kg$^{-1}$ (mean = 0.050 mg kg$^{-1}$, geometric mean = 0.026 mg kg$^{-1}$, $n = 712$) during the monitoring period between 2005 and 2008 (Qian et al. 2010) and a similar range but larger mean value (<0.004–0.77 mg kg$^{-1}$, mean = 0.093 mg kg$^{-1}$, median = 0.045 mg kg$^{-1}$, $n = 160$) in recent years (Chen et al. 2018a). A total diet study in China reported a mean Cd concentration of 0.062 mg kg$^{-1}$ in polished rice ($n = 19,782$, median not reported) (Song et al. 2017). In some regions of southern China, where Cd contamination in soil is serious, grain Cd concentrations are much higher (0.005–4.80 mg kg$^{-1}$, mean = 0.43 mg kg$^{-1}$, median = 0.38 mg kg$^{-1}$, $n = 39,642$) (Zhu et al. 2016). The concentrations of As and Cd reported above are based on either dry weight (e.g. Chen et al. 2018a; Zhu et al. 2016) or fresh weight (e.g. Song et al. 2017; Qian et al. 2010). Because fresh rice grains (i.e. air-dried) typically contain only 10–15% moisture, the difference between the concentrations based on fresh weight or dry
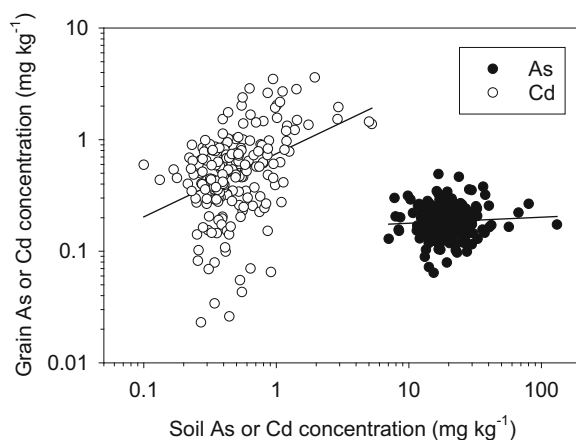
weight is small. There are also differences between polished and unpolished (brown) rice. Polishing reduces grain As concentration to a larger extent (by 30–70%) than grain Cd concentration (by 10–40%) (Meharg et al. 2013; Naito et al. 2015; Williams et al. 2009). This is because As is preferentially distributed in the outer layer of rice grain, whereas such preferential distribution is less apparent for Cd (Meharg et al. 2008, 2013; Moore et al. 2010; Sun et al. 2008).

Figure 3 shows the daily Cd intake for adults from rice as a function of rice consumption rate and the concentration of Cd in rice grain, assuming a body weight of 60 kg per person. The calculated intakes are compared with the tolerable intake level recommended by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) or the European Food Safety Authority (European Food Safety Authority 2012; Joint FAO/WHO Expert Committee on Food Additives 2010a). At a grain Cd concentration of 0.05 mg kg$^{-1}$, which is approximately the global mean value, consumption of 500 g of rice per adult per day would exceed the EFSA's Cd intake limit by 20% and reach half of the JECFA's limit. At a grain Cd concentration of 0.2 mg kg$^{-1}$ (fresh weight), which is the Chinese limit for concentration in rice (Ministry of Health of the People's Republic of China 2012), consumption of 105 and 250 g of rice per day would reach EFSA's and JECFA's Cd intake limit, respectively. At a grain Cd concentration of 0.4 mg kg$^{-1}$ (fresh weight), which is the current FAO/WHO limit for Cd concentration in rice (Codex Alimentarius Commission 2006), consumption of 300 and 500 g of rice per day would exceed EFSA's and JECFA's Cd intake limit by 2.4 and

4 times, respectively. These calculations serve to indicate that the current FAO/WHO limit for Cd concentration in rice is set at a far too high level, and is not protective for the populations consuming rice as a major staple food. Moreover, we would argue that it is an anomaly to set the maximum levels of Cd for wheat and polished rice at 0.2 and 0.4 mg kg$^{-1}$, respectively (Codex Alimentarius Commission 2006), because there is no evidence that Cd in rice is less bioavailable to humans than Cd in wheat. In fact, Cd in rice grain may even have a higher bioavailability because it is relatively poor in the essential micronutrients Zn and Fe (Chaney 2015). Rice is of course not the only dietary source of Cd; other food sources also add to the total dietary Cd exposure. For example, the contribution of rice to the total dietary Cd intake is 56% for the general population in China, rising from 38% for the northern population to 65% for the southern population (Song et al. 2017). In Japan, rice contributes about 40% of the total dietary Cd intake (Watanabe et al. 2000).

The intake of As from rice can also be calculated in the same way as for Cd, except for two important differences. Firstly, As speciation in rice grain has to be considered. Rice contains both inorganic As (iAs) and methylated As species, with iAs accounting for 20–90% of the total As in rice grains (Meharg et al. 2009; Zhao et al. 2013b). There are some interesting geographical differences in rice As speciation among different regions, with Asian rice generally containing a larger proportion of iAs than American rice (Meharg et al. 2009; Zhao et al. 2013b; Zhu et al. 2008). On average, iAs% is between 70 and 80% for rice produced in Bangladesh, India and China, approximately 60% for
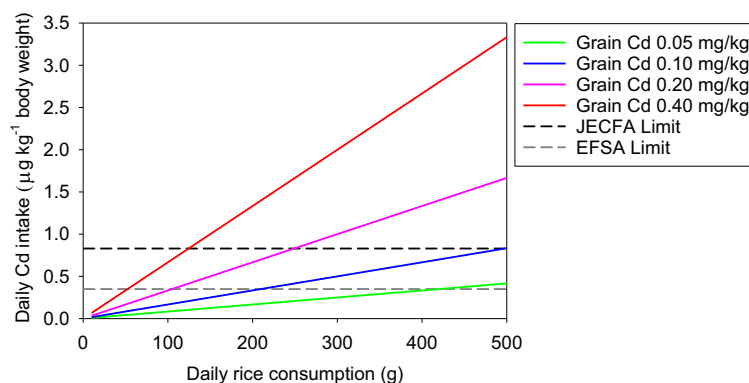


Fig. 3 Daily intake of Cd as a function of the amount of rice consumption and the concentration of Cd in rice grain. A body weight of 60 kg for adults is used in the calculation. JEFCA and ESFA limits refer to the tolerable Cd intake limits recommended by the Joint FAO/WHO Expert Committee on Food Additives (2010a) and the European Food Safety Authority (2012), respectively

European rice, and between 40 and 50% for US rice (Chen et al. 2018a; Torres-Escribano et al. 2008; Williams et al. 2005; Zavala et al. 2008; Zhu et al. 2008). The reasons for the geographical variation in rice As speciation are unknown, but could be due to differences in soil properties and microbial community (Zhao et al. 2013b). Inorganic As is considered to be more toxic to humans than pentavalent methylated As species (Zhao et al. 2013b). The United Nations food standards body Codex Alimentarius Commission has set a maximum level of iAs for polished rice of 0.2 mg kg$^{-1}$ (fresh weight), whilst EU proposed maximum levels of iAs in rice of 0.1 and 0.2 mg kg$^{-1}$ (fresh weight) for baby food and adult consumption, respectively (The European Commission 2015). Global mean for rice iAs is about 0.1 mg kg$^{-1}$, compared with the mean total As concentration of 0.15 mg kg$^{-1}$ (Meharg et al. 2009; Meharg and Zhao 2012). Secondly, iAs is considered to be a non-threshold Class I carcinogen (International Agency for Research on Cancer 2004; Smith et al. 2002) and JECFA has withdrawn a previous provisional dietary intake limit for iAs (Joint FAO/WHO Expert Committee on Food Additives 2010b). Intake of iAs from rice can be compared with that from drinking water, for which WHO has set an iAs limit of 10 μg L$^{-1}$ (World Health Organization 2011). Intake of iAs from 300 g rice at a global mean iAs concentration would amount to 30 μg per person per day, double the intake of iAs from drinking 1.5 L water at the WHO limit. Another way to assess the potential risk of As in rice is to use the slope of internal lifetime excess cancer risk of iAs. Meharg et al. (2009) estimated that the median excess cancer risk from rice iAs is 22, 15 and 7 per 10,000 people for Bangladesh, China and India, respectively, which are much higher than the WHO cancer risk standard of 1 per 100,000 with respect to As (World Health Organization 2011).

The above calculations are based on average scenario. Dietary intakes of As and Cd from rice can be much higher due to soil contamination. Long-term irrigation of As-laden groundwater in south Asia has led to accumulation of As in paddy soils and elevated levels of As in rice grain (Dittmar et al. 2010; Meharg and Rahman 2003). Contamination of paddy soils with Cd from irrigation of mining-impacted Jinzu river in Toyama prefecture, Japan, has resulted in high Cd concentrations in rice grain, leading to the outbreak of Itai-Itai disease caused by weakening of bones and renal tubular dysfunction (Kobayashi et al. 2009). In some areas of southern China, large percentages of rice grain exceed the maximum permissible Cd limit (0.2 mg kg$^{-1}$) and the estimated Cd intakes in the local populations are well over the JECFA's tolerable intake level (Chen et al. 2018b; Wang et al. 2019b; Zhu et al. 2016).

The large variations in rice grain As and Cd concentrations, described above, are attributed to both genotypic and environmental factors. Genotypic variations are discussed in the latter sections. The environmental factors that affect As and Cd uptake by rice include the concentrations and speciation of the two contaminants in the soil, soil properties, paddy water management and climatic conditions. In particular, paddy water management has a strong impact on the biogeochemical cycling of As and Cd, thus affecting their bioavailability to rice plants (see below). With regard to climatic conditions, recent studies have shown that grain As concentration correlated positively with average air temperature during the middle period of grain filling (Arao et al. 2018) and elevated temperature and $CO_2$ concentration in a future climate scenario could increase As concentration in rice grain (Muehe et al. 2019).

## Contrasting biogeochemical behaviours of As and Cd in paddy soil

The availabilities of electrons and protons, measured as the redox potential (Eh) and pH, respectively, are two key drivers for the biogeochemical cycling of elements including As and Cd. Flooding of paddy fields causes dramatic changes in the redox potential and pH, thus impacting the biogeochemical processes of many elements in soil, including As and Cd. Paddy fields undergo episodic flooding and draining during the rice growing season, leading to large fluctuations in Eh, pH and the solubility of As and Cd. Typically, paddy water is drained during the late tillering stage to control excessive tillering, and during the mid-late grain filling stage for harvest. Upon flooding, Eh in paddy soil decreases rapidly as a result of the depletion of $O_2$ consumed by microbial activities, promoting a cascade of redox reactions, including the reduction of nitrate, manganese oxides, iron (oxy)hydroxides, arsenate, sulphate and finally the production of methane (Borch et al. 2010; Kirk 2004). These reduction reactions are coupled with the microbe-driven oxidation of organic substances in soil. Reduction of iron (oxy)hydroxides and manganese oxides may release As and Cd sorbed on these mineral

phases into the solution phase, whilst microbial reduction of As(V) to As(III) also renders As more soluble because the latter is less strongly adsorbed than the former (Rinklebe et al. 2016; Takahashi et al. 2004; Weber et al. 2010; Xu et al. 2017b; Yamaguchi et al. 2011). Reduction of sulphate to sulphide mediated by sulphate reducing bacteria can lead to precipitation of cadmium sulphide (de Livera et al. 2011; Fulda et al. 2013; Khaokaew et al. 2011; Wang et al. 2019a), which has a very low solubility ($\log K_{sp} = -14.36$) (Daskalakis and Heiz 1992). Formation of CdS depends on the availability of sulphate for microbial reduction and the competing ions such as Cu, which can form even more insoluble CuS (Fulda et al. 2013). Sulphate reduction may also decrease the solubility of As; this effect was evident only in paddy soils that produced large amounts of $Fe^{2+}$ under reducing conditions, probably due to co-precipitation or sorption As(III) by newly-formed FeS (Xu et al. 2019). Because many reduction reactions in soil also consume protons, soil pH generally increases to the neutral range if the initial pH is in the acidic range (Kirk 2004). In alkaline soils, soil pH tends to decrease to the neutral range after flooding due to the accumulation of $CO_2$ (Kirk 2004). Solubility of Cd in paddy soils decreases markedly as redox potential decreases upon flooding, largely as a result of CdS formation and increased pH in the acidic soils that promotes sorption of $Cd^{2+}$ (Fig. 4a). In contrast, solubility of As increases dramatically as redox potential decreases, primarily due to reductive dissolution of iron (oxy)hydroxides and reduction of As(V) to As(III) (Fig. 4b). When paddy water is drained, reverse processes occur rapidly, resulting in increased Cd solubility but decreased As solubility (de Livera et al. 2011; Fulda et al. 2013; Wang et al. 2019a). The contrasting behaviours of As and Cd in response to flooding and drainage in paddy soil represent a great obstacle for controlling the accumulation of the two toxic elements in rice grain simultaneously.

The redox status in paddy soil has a large impact on As and Cd accumulation in rice grain. In greenhouse experiments, growing rice in aerobic soil greatly decreased As accumulation in the grain, but increased Cd accumulation (Li et al. 2009b; Meharg and Zhao 2012; Xu et al. 2008). In contrast, growing rice under anaerobic soil conditions produced low Cd concentrations, but high As concentrations, in the grain. Intermittent flooding and draining during rice growth resulted in intermediate levels of As and Cd in the grain (Li et al. 2009b; Meharg and Zhao 2012). Similar results have
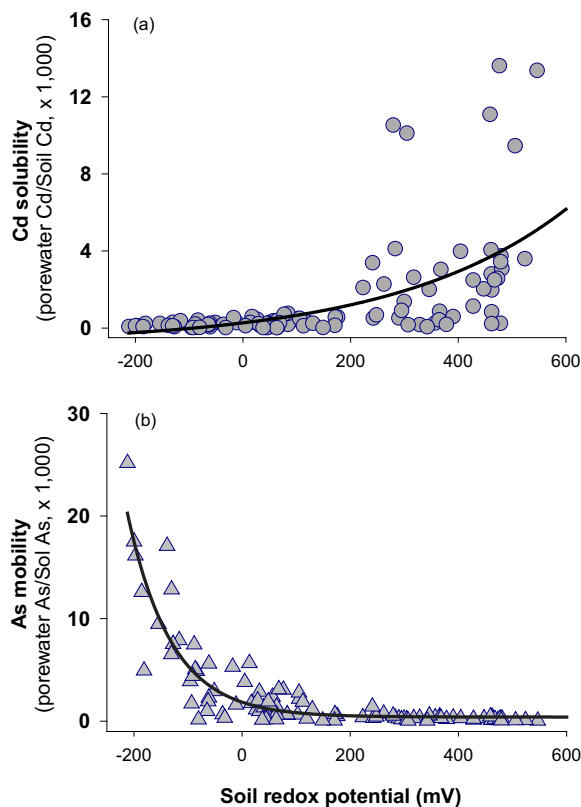


**Fig. 4** Relationships between Cd and As solubility and soil redox potential in paddy soils. Data are compiled from Wang et al. (2019a)

been found in field experiments, with continuous flooding leading to low grain Cd but high grain As concentrations, while draining during periods of rice growth decreased As but increased Cd accumulation in the grain (Arao et al. 2009; Honma et al. 2016; Hu et al. 2013; Ma et al. 2014). Paddy water management during the grain filling period had a greater impact on the Cd concentration than on the As concentration in rice grain (Arao et al. 2009). Similarly, As accumulated during the vegetative growth phase appears to be more important to grain As accumulation than that during the grain filling stage (Li et al. 2009b).

Whilst Eh affects the solubility of both As and Cd greatly, pH has a much larger effect on Cd solubility within the normal range of soil pH. Cadmium sorption on the soil solid phases is strongly dependent on pH (Bolan et al. 2013; Naidu et al. 1994; Smolders and Mertens 2013), whereas sorption of As(III), the predominant As species in flooded paddy soils, is only weakly dependent on pH (Dixit and Hering 2003). On average, Cd solubility in soil increased by approximately 4 fold

with one unit decrease in pH (Smolders and Mertens 2013; Wang et al. 2019a). The inverse relationship between soil pH and Cd availability is demonstrated clearly in a large scale paired soil-rice grain survey ($n = 39,642$) (Zhu et al. 2016). The study showed that the median Cd transfer ratio (i.e. rice grain to soil Cd concentration ratio) increases by 10 fold (from 0.08 to 0.85) when soil pH decreases from 7.0 to 5.0 (Zhu et al. 2016) (Fig. 5). It should be pointed out that there is a large variation in the Cd transfer ratio at each soil pH, which is caused by other factors that influence Cd availability. It may appear rather paradoxical that soil pH should have such a large effect on Cd accumulation in rice grain, considering that pH in paddy soils converges to the neutral range upon flooding. The main reasons are that paddy fields are usually drained during the mid to late phase of grain filling, when soil pH reverts to their initial values, and it is suggested that about 80% of Cd accumulation in rice grain occurs during the grain filling stage (Arao et al. 2009; Inahara et al. 2007). One of the key reasons for high Cd concentrations in rice grain produced in some areas of southern China is soil acidification, which occurs during the last three decades due to the cumulative effect of nitrogen fertilizer applications (Zhao et al. 2015; Zhu et al. 2016).

Arsenic differs from Cd not only in the redox cycle, but also in its propensity of being methylated. Many organisms, including some archaea, bacteria, fungi, algae and animals (e.g. humans), are able to methylate iAs to different methylated As species, the most common species being monomethylarsonic acid (MMA), dimethylarsinic acid (DMA), and trimethylarsine (TMA) (Cullen and Reimer 1989; Qin et al. 2006, 2009; Tseng 2009; Zhu et al. 2014). Paradoxically,
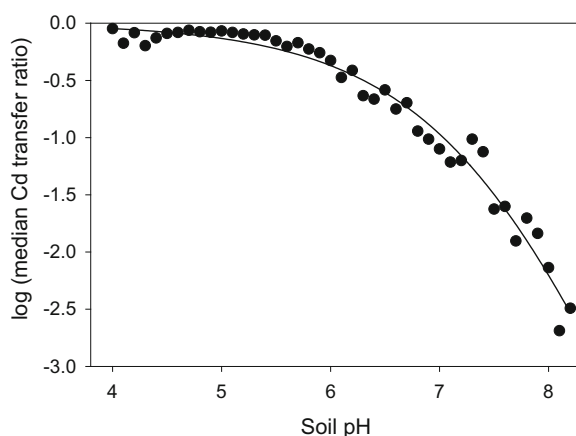


**Fig. 5** Median Cd transfer ratio (rice grain Cd / soil Cd concentration) as a function of soil pH. Redrawn from Zhu et al. (2016)

higher plants, such as rice, do not appear to possess the ability to methylate iAs (Lomax et al. 2012). Flooding of soil and additions of organic matter enhance As methylation (Mestrot et al. 2009, 2011), suggesting that anoxic conditions may favour As methylation. DMA is the predominant methylated As species in paddy soil solutions and in rice gains (Chen et al. 2018a; Williams et al. 2005; Zavala et al. 2008; Zhao et al. 2013a). In incubation experiments with paddy soils under flooded conditions, DMA initially accumulated in the soil solution and then disappeared (Chen et al. 2019a). Further investigations using metabolic inhibitors, microbial enrichment cultures and $^{13}C$ labelled DMA showed that As methylation in flooded paddy soils was driven primarily by the sulphate-reducing bacteria, whereas DMA was demethylated by some methanogenic archaea (Chen et al. 2019a). Under oxic or sub-oxic conditions, e.g. when paddy water is drained or in the rice rhizosphere, some aerobic microorganisms may also contribute to As methylation (Huang et al. 2016; Kuramata et al. 2015). Paddy water management has a large effect on As speciation in rice grain. Continuous flooding and additions of organic matter increase DMA concentration and its proportion in the total As in rice grain (Arao et al. 2009; Li et al. 2009b; Ma et al. 2014; Xu et al. 2008; Yang et al. 2018b). Flooding of paddy soil also promotes volatilization of As, primarily as pentavalent and O-free methylated species of TMA, DMA and MMA (Chen et al. 2017a; Mestrot et al. 2009, 2011). In general, the amounts of As volatilization are negligible compared with the total As in paddy soils (Mestrot et al. 2009, 2011).

In flooded paddy soils, some methylated thioarsenical species, such as dimethylmonothioarsinic acid (DMMTA), dimethyldithioarsinic acid (DMDTA), and monomethylmonothioarsonic acid (MMMTA), may also exist (Planer-Friedrich et al. 2017). These As species are likely formed from the thiolation of DMA and MMA in the presence of $H_2S$ (Kim et al. 2016), which is produced by sulphate-reducing bacteria under anoxic conditions. Methylated thioarsenical species can be taken up by rice roots and partially de-thiolated (Kerl et al. 2019), although the mechanisms remain unclear.

## Uptake of As and Cd in rice

Understanding the molecular mechanisms of As and Cd uptake and translocation (see next section) provides

potential targets for marker-assisted breeding or genetic engineering of rice varieties with low accumulation. In both physiological and molecular biology studies, it is important to consider chemical speciation of As and Cd in soil and the rhizosphere, as different chemical species are likely taken up by roots via different mechanisms. Cadmium is a cationic element and is present as free ions and soluble complexes in soil solution. Cadmium may form soluble complexes with both organic ligands (e.g. dissolved organic matter, particularly low molecular weight organic acids secreted from the roots) and inorganic ligands (e.g. $Cl^-$, $SO_4^{2-}$). Formation of soluble Cd complexes increases its mobility towards the root surfaces, but it is generally assumed that free $Cd^{2+}$ ions are the main Cd species transported across the plasma membranes into the root cells. Arsenic speciation in soil solution is strongly influenced by both Eh and pH. Under anoxic conditions in flooded paddy soil, arsenite [As(III)] is the predominant As species, which is present mainly as undissociated neutral molecules due to its high $pK_a$ (9.2). Small amounts of arsenate [As(V)] may also be detected in the solution of flooded paddy soil, typically accounting for 10–30% of the total soluble As (Khan et al. 2010; Stroud et al. 2011a). The presence of As(V) could be due to anaerobic microbial oxidation of As(III) coupled to denitrification (Zhang et al. 2017). Release of oxygen by rice roots could also promote As(III) oxidation to As(V) in the rhizosphere. As(V) is present as anions due to its low $pK_a$ (2.2). DMA and to a less extent, MMA, may also be present in the soil solution (Zhao et al. 2013a). The intermediate $pK_a$ of DMA (6.1) means that it is present both as anions and undissociated neutral molecules within the normal pH range in soil. Another point to consider is the typical concentrations of As and Cd in soil solutions. Soluble Cd concentrations are typically in the nM range, rarely exceeding 1 μM range (Smolders and Mertens 2013), whereas soluble As(III) concentrations in flooded paddy soils are in the range from sub μM to tens μM (Khan et al. 2010; Panaullah et al. 2009; Stroud et al. 2011b). These concentration ranges should be borne in mind when designing hydroponic experiments to investigate As and Cd uptake by rice plants.

As(III) is taken up by rice roots mainly through the silicon uptake pathway (Ma et al. 2008) (Fig. 6). Loss-of-function mutations of the Si influx transporter Lsi1 (OsNIP2;1) or the efflux transporter Lsi2 resulted in large decreases in As(III) uptake and accumulation in the shoots (Ma et al. 2008). Silicon inhibited As(III) uptake in wild-type rice plants, but not in the mutants of *lsi1* or *lsi2*, either through a direct competition for the transporters or through a down-regulation of the expression of the two genes (Ma et al. 2008; Mitani-Ueno et al. 2016). Rice is more efficient than wheat or barley in As(III) uptake and translocation, because of the highly efficient pathway for silicon/As(III) uptake in rice (Su et al. 2010). A highly expressed and efficient transport pathway for Si in rice inadvertently allows As(III), which is mobilized markedly under flooded paddy soil conditions, to be taken up and accumulated in rice (Zhao et al. 2010b). Several other rice NIP channel proteins are also permeable to As(III) (Chen et al. 2017b; Ma et al. 2008; Mitani-Ueno et al. 2011; Sun et al. 2018). OsNIP3;2 contributes to As(III) uptake in lateral roots, although its overall contribution to As(III) accumulation in rice is small (Chen et al. 2017b). OsNIP1;1 and OsNIP3;3 do not contribute to As(III) uptake due to their low levels of expression in rice roots (Sun et al. 2018). Surprisingly, overexpression of *OsNIP1;1* or *OsNIP3;3* decreased As(III) translocation to and accumulation in rice shoots and grain, which is interpreted as providing a leakage route for As(III) out of the stele (Sun et al. 2018). Lsi1 (OsNIP2;1) is also permeable to undissociated molecules of MMA and DMA, and contributes substantially to their uptake by rice roots (Li et al. 2009a). In contrast, Lsi2 plays no role in the uptake and accumulation of MMA and DMA (Li et al. 2009a).

It is well known that As(V) is taken up via phosphate transporters. In the case of rice, it has been shown that OsPT1, OsPT4 and OsPT8 are involved in the uptake of As(V) by roots (Cao et al. 2017; Kamiya et al. 2013; Wang et al. 2016; Ye et al. 2017) (Fig. 6). Whilst organisms cannot avoid taking up As(V) because of their need for phosphate, they have evolved a common mechanism to get rid of cellular As via As(V) reduction and As(III) efflux. This mechanism has also been shown to be important in plants (Xu et al. 2007). Typically, 60–80% of As(V) taken up by roots is extruded as As(III). A key component of this mechanism is As(V) reductases, which have recently been identified in *Arabidopsis* (Chao et al. 2014; Sanchez-Bermejo et al. 2014) and rice (Shi et al. 2016; Xu et al. 2017a). OsHAC1;1, OsHAC1;2 and OsHAC4 are involved in reducing As(V) to As(III) in rice roots (Fig. 6). Knockout of these genes resulted in decreased As(V) reduction in the roots and decreased As(III) efflux to the external medium, and increased As accumulation in the shoots, whereas overexpression of these genes decreased As accumulation in
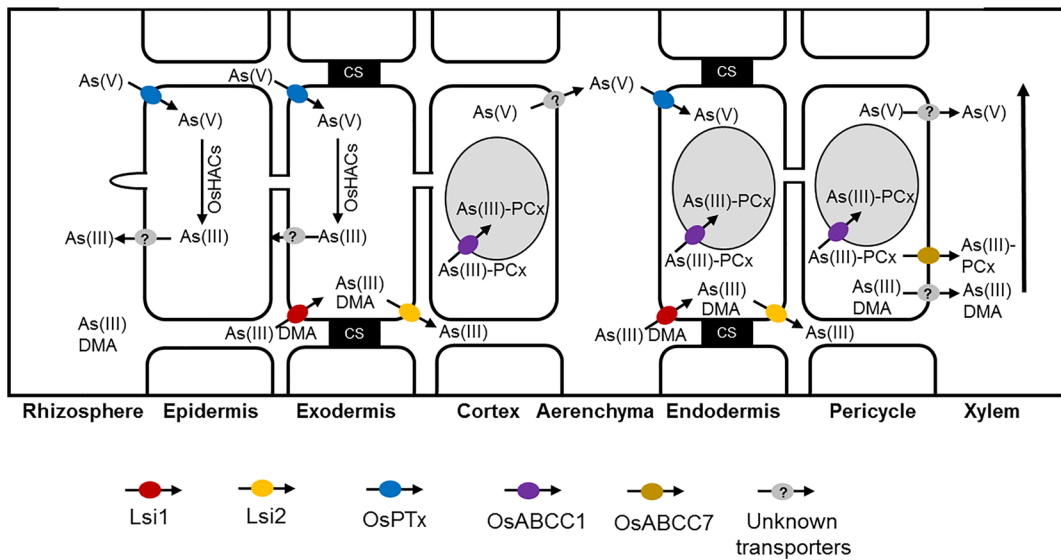
**Fig. 6** Transporters and arsenate reductases involved in arsenic uptake, transformation and translocation in rice roots. CS, Casparian strip; OsHACs, rice As(V) reductases; PCx, phytochelatins. Based on Salt (2017) with modifications

the shoots (Shi et al. 2016; Xu et al. 2017a). The HAC As(V) reductases play a critical role in limiting As accumulation in plant shoots when plants are exposed to As(V). Efflux of As(III) following As(V) reduction may be through bi-directional As(III) permeable channels, such as Lsi1 (Zhao et al. 2010a), and other unidentified transporters.

Cadmium is taken up by rice roots primarily via the manganese (Mn) transporter OsNRAMP5 (Natural Resistance Associated Macrophage Protein 5) (Sasaki et al. 2012) (Fig. 7). *OsNRAMP5* is expressed

predominantly in rice roots and the protein is polarly localized at the plasma membranes of the distal side of both exodermis and endodermis cells, a localization pattern consistent with its role in the influx of Mn and Cd into the cells (Sasaki et al. 2012). Knockout of *OsNRAMP5* gene resulted in greatly decreased Cd uptake by roots and Cd accumulation in the shoots and grains (Ishikawa et al. 2012; Sasaki et al. 2012; Yang et al. 2014). In a short-term influx experiment, active influx of Cd into rice roots was almost completely abolished in a *OsNRAMP5* knockout mutant (Sasaki
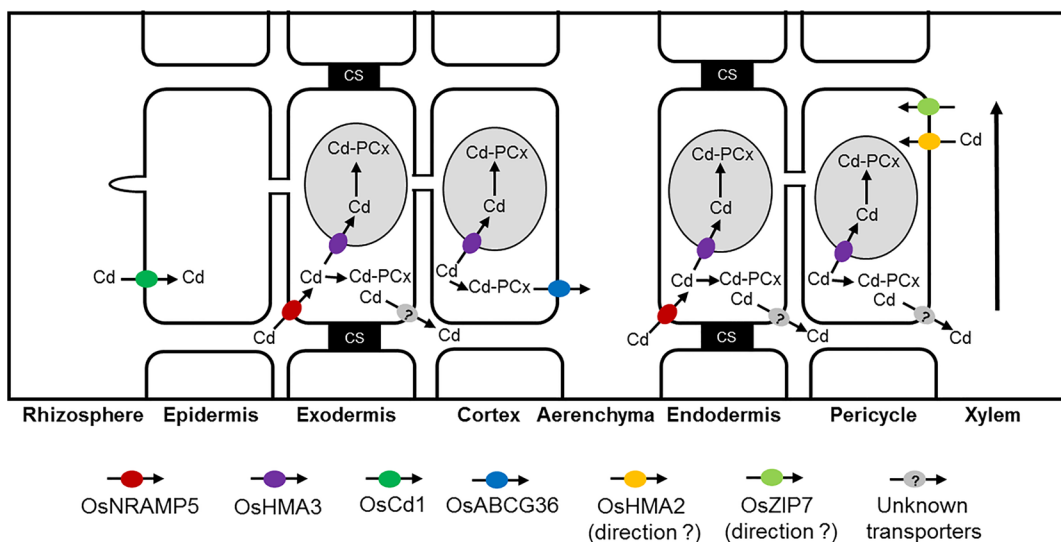


**Fig. 7** Transporters involved in cadmium uptake and translocation in rice roots. CS, Casparian strip; PCx, phytochelatins

et al. 2012). In hydroponic experiments, Mn inhibited Cd uptake in wild-type rice plants, but not in *osnramp5* mutant, suggesting a competition between Mn and Cd for uptake (Yang et al. 2014). The maximum Cd influx velocity of rice was found to be 6.5 and 2.2 times that in wheat and maize, respectively, indicating that rice has a higher capacity for Cd uptake than the other two cereal species (Sui et al. 2018). This difference may be attributed to different expression levels of the orthologous *NRAMP5* genes, with rice roots having a 4–5 times higher expression than wheat and maize roots (Sui et al. 2018). Similarly, rice roots also express a higher level of *NRAMP5* than barley roots (Wu et al. 2016).

Other transporters may also contribute to Cd uptake by rice, although the contributions are likely to be relatively small compared with that from OsNRAMP5. Within the NRAMP family, OsNRAMP1 shows a Cd transport activity in yeast heterologous expression assays (Takahashi et al. 2011). Overexpression of *OsNRAMP1* in rice increased Cd accumulation in the leaves (Takahashi et al. 2011), but the contribution of OsNRAMP1 to Cd uptake in rice remains unclear, which should be addressed by a gene knockout approach. Recently, Yan et al. (2019) identified a new Cd transporter in rice, named OsCd1, which belongs to the major facilitator family (MSF) (Fig. 7). Knockout of *OsCd1* gene decreased Cd concentrations in the roots and shoots by approximately 20–50%, and decreased grain Cd concentration by 15–30%. The knockout mutants also accumulated less Mn and showed reduced growth and fertility.

## Translocation of As and Cd in rice

Root-to-shoot translocation is a critical step controlling the accumulation of As and Cd in the shoots and grain. Variation in grain Cd concentration among 69 accessions of rice was found to correlate closely with the concentration of Cd in the xylem sap, indicating the importance of root-to-shoot translocation (Uraguchi et al. 2009). The efficiency of root-to-shoot translocation depends on both vacuolar sequestration in the roots and the efficiency of xylem loading. These two processes often show an inverse relationship; more vacuolar sequestration in the roots means less translocation to the shoots and vice versa. Translocation of As and Cd to rice grain also involves intervascular and xylem-to-phloem transfer.

### Vacuolar and apoplastic sequestration

Arsenic is sequestered by both the iron plaques on the root surfaces and inside the vacuoles. Iron plaques, consisting primarily of ferrihydrite (Liu et al. 2006), are formed on the surfaces of rice roots as a result of the oxidation of Fe(II) by oxygen released from the root aerenchyma. Iron plaques are strong adsorbent for As, particularly As(V), and there is a strong co-localization of Fe and As in the plaque (Moore et al. 2011; Seyfferth et al. 2010). Although iron plaques act as a barrier for the entry of As into the root cells, they may also serve as a sink to attract soluble As from the bulk soil to the root surfaces. In situ measurements using diffusive gradients in thin films (DGT) showed maximal fluxes of both soluble As and Fe(II) in the root surfaces near the root tips, suggesting mobilization of both elements (Williams et al. 2014). Inside the cells, As is sequestered in the vacuoles as As(III)-thiol complexes, particularly in the pericycle and endodermal cells in rice roots (Moore et al. 2011). The ATP-binding cassette transporter OsABCC1 has been identified as a tonoplast transporter for phytochelatins (PCs) or As(III)-PC complexes (Song et al. 2014) (Fig. 6). *OsABCC1* is expressed in the roots, leaves, nodes, peduncle, and rachis, and knockout of this gene resulted in higher As accumulation in the grain (Hayashi et al. 2017; Song et al. 2014). Vacuolar sequestration of As(III) also depends on the synthesis of PCs; a rice mutant of phytochelatin synthase gene *OsPCS1* showed increased As accumulation in the grain, similar to *osabcc1* mutant (Hayashi et al. 2017). Although DMA is taken up by rice roots more slowly than iAs, it is much more easily translocated to the shoots (Li et al. 2009a; Lomax et al. 2012; Raab et al. 2007). The reason for the high mobility of DMA is probably that it is not complexed with thiol compounds and not sequestered in the vacuoles (Raab et al. 2005; Zhao et al. 2013b).

Recent studies have shown that OsHMA3, a member of the $P_{1B}$ subgroup of the P-type ATPase family, is a key tonoplast transporter for Cd sequestration into the root vacuoles (Miyadate et al. 2011; Ueno et al. 2010) (Fig. 7). Importantly, coding sequence variation in *OsHMA3* can affect the Cd transport activity of the protein, giving rise to large variation in Cd translocation among rice cultivars (Miyadate et al. 2011; Sui et al. 2019; Ueno et al. 2010; Yan et al. 2016). Cultivars possessing weak or loss-of-function alleles of *OsHMA3* are less able to sequester Cd in the vacuoles

and, consequently, accumulate more Cd in the shoots and grain. In contrast, cultivars with strong alleles of *OsHMA3* accumulate lower levels of Cd in the shoots and grain. Using positron-emitting [107]Cd tracer to monitor the real-time distribution of Cd, Ishikawa et al. (2011) showed that rice cultivars possessing weak or null alleles of *OsHMA3* transported Cd from the roots to the shoots much more rapidly than cultivars with functional *OsHMA3*.

Xylem loading

The traditional paradigm is that the radial transport of nutrients and contaminants into the stele takes place via the apoplastic or symplastic pathways. This paradigm needs to be modified to account for the distinct anatomic structure of rice roots, which have two Casparian bands and the formation of aerenchyma for oxygen release into the rhizosphere (Sasaki et al. 2016). The apoplastic pathway occurs in the young root zone where the Casparian band has not fully formed or near the region where lateral roots break through the Casparian band. The formation of the Casparian band in both the exodermis and endodermis in rice roots stops the apoplastic pathway, forcing nutrients and contaminants to move through the symplastic pathway, i.e. influx into the cells and movement between cells through the plasmodesmata connections (Figs. 5 and 6). In the mature zone of rice roots, most of the cortical cells between the exodermis and endodermis are broken as a result of the formation of the aerenchyma, which breaks the symplastic pathway. Therefore, radial transport of nutrients and contaminants in rice roots involve multiple steps of influx and efflux and is a mixture of both apoplastic and symplastic pathways (Sasaki et al. 2016). The Casparian band in the endodermis seals the stele from apoplastic entry and also prevents the leakage of the solutes in the stele. Cadmium and As reaching the endodermis, pericycle and parenchyma cells in the steles via the symplastic pathway have to exit these cells prior to loading into the xylem vessels for translocation to the shoots. Efflux is the critical step, as loading into the xylem vessels is a passive process driven by the transpiration stream.

Lsi2 is an efflux pump for Si and As(III) in rice (Ma et al. 2008). It is polarly localized to the plasma membranes in the proximal side (facing the direction of the stele) of the exodermal and endodermal cells (Ma et al. 2007). Because of this polar localization, As(III) effluxed from the endodermis cells via Lsi2 can move

in the apoplastic space to the xylem vessels (Fig. 6). Mutants of *Lsi2* showed greatly reduced concentrations of As(III) in the xylem sap (by 70–90%) compared with wild-type plants (Ma et al. 2008). The fact that rice is more efficient in As(III) translocation than wheat and barley could be explained by the strong expression of *Lsi2* and its polar localization in the endodermis in rice roots (Su et al. 2010). The rice C-type ABC transporter OsABCC7 showed efflux transport activities for As(III)-glutathione and As(III)-PC complexes when the gene was expressed in *Xenopus laevis* oocytes (Tang et al. 2019). The transporter is localized to the plasma membranes of the parenchyma cells in the stele region. Knockout of *OsABCC7* decreased As concentration in the xylem sap by about 25% (Tang et al. 2019). It appears that OsABCC7 makes only moderate contribution to root-to-shoot translocation in rice. Although As(III) is the predominant As species in the xylem sap of rice, As(V) is also detected as a minor species (Su et al. 2010). Presumably, As(V) is loaded into the xylem vessels via the phosphate transport pathway. Very little is known about how methylated As species are loaded into the xylem for translocation.

Several transporters are involved in the root-to-shoot translocation of Cd in rice. OsHMA2 (Satoh-Nagasawa et al. 2012; Takahashi et al. 2012; Yamaji et al. 2013) and OsZIP7 (Tan et al. 2019) are plasma membrane transporters for Zn and Cd localized to the pericycle in the roots (Fig. 7) and the parenchyma cells in the vascular bundles in the nodes of rice. Knockout of either genes decreased root-to-shoot translocation of Zn and Cd. There is disagreement as to whether OsHMA2 is an efflux transporter allowing Zn and Cd to be loaded into the xylem (Satoh-Nagasawa et al. 2012; Takahashi et al. 2012), or an influx transporter for the uptake of Zn and Cd into the pericycle cells in the roots and the phloem cells in the node for redistribution to the root tips and the reproductive organs (Yamaji et al. 2013). OsZIP7 is suggested as an influx transporter (Tan et al. 2019). It is not clear how influx transporter located at the pericycle cells facilitate xylem loading of Cd and Zn. A defensin-like protein in rice, named OsCAL1, is expressed mainly in the root exodermis and the xylem parenchyma cells. (Luo et al. 2018). This protein can bind Cd and facilitate its efflux to the apoplastic spaces. Knockout of *OsCAL1* decreased Cd translocation to the shoots, but did not affect Cd accumulation in the grain.

Intervascular and xylem-to-phloem transfer

The majority (>90%) of As and Cd delivered to rice grain is via the phloem, with the exception of DMA which is transported to the grain via both xylem and phloem at approximately equal portions (Carey et al. 2010; Tanaka et al. 2007). This means that Cd and As have to be transferred from the xylem to the phloem at some point during their long-distance translocation from the roots to the grain. The transfer likely takes place in the nodes, which house different types of vascular bundles to regulate the distribution of minerals to leaves and panicles (Yamaji and Ma 2017). In the nodes, certain portions of minerals transported from the roots or lower nodes via xylems of the enlarged vascular bundles are transferred across to the diffuse vascular bundles, which are connected to the upper nodes or panicles, a process called intervascular transfer (Yamaji & Ma, 2017). During this process, xylem-to-phloem transfer may also occur. Compared with other organs in the shoots, nodes accumulate much higher levels of As and Cd (Fujimaki et al. 2010; Moore et al. 2014).

The efflux transporter Lsi2 is also involved in the intervascular transfer of As(III) (Chen et al. 2015). Lsi2 is highly expressed not only in the roots, but also in the nodes. The protein is polarly localized at the distal side of bundle sheath cells of the enlarged vascular bundles, which also have an apoplastic barrier (Yamaji et al. 2015). Compared with wide type, lsi2 mutant distributed more As(III) to the node and flag leaf but less As(III) to the grain (Chen et al. 2015). In addition to Lsi2, two other Si transporters, Lsi6 and Lsi3, are involved in the intervascular transfer of Si (Yamaji et al. 2015). Whether they play a role in As(III) transfer has not been reported. Strong As accumulation in the vacuoles of the companion cells in the phloem of both enlarged and diffuse vascular bundles in rice nodes was visualized using synchrotron X-ray fluorescence and high-resolution secondary ion mass spectrometry (Moore et al. 2014). Moreover, there was a strong co-localization of As and S, suggesting that As is complexed with thiol compounds. In addition to the role in the roots, OsABCC1 also plays an important role in transporting PCs or As(III)-PC complexes into the vacuoles in the phloem companion cells in the nodes (Song et al. 2014). Both OsABCC1 mutation and inhibition of PC synthesis by an inhibitor of GSH decreased the sequestration of As(III) in the nodes and increased its distribution to the grain (Chen et al. 2015; Hayashi et al. 2017; Song et al. 2014).

Mutation in OsPCS1 also increased As accumulation in rice grain (Hayashi et al. 2017). Therefore, in addition to vacuolar sequestration of the root cells, sequestration of As(III)-PC complexes in the vacuoles of the phloem companion cells in the nodes is important for restricting As(III) transfer to the grain. These mechanisms do not apply to DMA, as it is not permeable through Lsi2 and is also not complexed by PCs (Chen et al. 2015). DMA fed through cut stems or cut leaves is transferred to the grain highly efficiently (Carey et al. 2011; Chen et al. 2015). OsPTR7 (also named as OsNPF8.1), a putative peptide transporter, showed an influx transport activity for DMA in assays using Xenopus laevis oocytes (Tang et al. 2017b). Knockout of OsPTR7 decreased the translocation of DMA from the roots to the shoots and grain, suggesting that the transporter is involved in the translocation of DMA (Tang et al. 2017b).

Several transporters play important roles in the intervascular and xylem-to-phloem transfer of Cd. The low-affinity cation transporter OsLCT1 is a plasma membrane efflux transporter for Cd (Uraguchi et al. 2011). The gene is expressed in both the enlarged and diffuse vascular bundles in rice nodes. Knock down of OsLCT1 by RNAi did not affect the Cd concentration in the xylem sap, but decreased the Cd concentration in the phloem sap, suggesting that the transporter is involved in the xylem-to-phloem transfer of Cd (Uraguchi et al. 2011). OsHMA2 not only is involved in the root-to-shoot translocation of Cd and Zn, but also takes part in the distribution of Cd and Zn in the nodes (Yamaji et al. 2013). The transporter is localized to the phloem parenchyma cells and companion cells in the diffuse and enlarged vascular bundles, functioning as an influx transporter to absorb Zn and Cd arriving from the xylem. Mutation of OsHMA2 reduced Zn and Cd distribution to both the panicle and the flag leaf (Yamaji et al. 2013). Note the disagreement on the transport direction of OsHMA2 with regard to Zn and Cd loading into the xylem in the roots (see the section on xylem loading), which would also affect the transport direction in the node. OsZIP7 appears to play a similar role in the intervascular transfer of Zn and Cd in the nodes (Tan et al. 2019). Another transporter involved in the transfer of Cd is the putative cation/Ca exchanger OsCCX2. OsCCX2 is highly expressed in the xylem region of the enlarged vascular bundles in the nodes, possibly functioning as an efflux transporter for Cd and Ca (Hao et al. 2018). Knockout of this gene decreased Cd concentration in rice grain by about half.

## Detoxification of As and Cd in rice

Paddy soils in some areas may be contaminated with As and Cd due to mining, smelting, industrial activities, applications of agrochemicals, or irrigation of contaminated water. In general, Cd levels in paddy soils are not high enough to cause phytotoxicity to rice plants, although Cd can accumulate in rice grain to levels that are unsafe for human consumption. In contrast, As contamination in paddy soil can cause phytotoxicity to rice plants, owing to the fact that As in paddy soil becomes much more bioavailable under flooded conditions. For example, long-term irrigation of As-laden groundwater in Bangladesh has led to build up of As in paddy soils and substantial reductions in grain yield (Huhmann et al. 2017; Panaullah et al. 2009). Accumulation of DMA can cause straight-head disease, a physiological disorder in rice with infertile spikelets and deformed husk, leading to large yield losses (Limmer et al. 2018; Meharg and Zhao 2012; Zheng et al. 2013). Therefore, Cd in rice is primarily a food safety issue, whereas As can cause both food safety and phytotoxicity problems.

Detoxification of As and Cd in plants shares some common features, including efflux, complexation with thiol-rich compounds and vacuolar sequestration. OsHAC4 plays an important role in As(V) tolerance by reducing As(V) to As(III), which allows As(III) to be extruded out of the root cells (Xu et al. 2017a). Mutants of *oshac4* are more sensitive to As(V), but not As(III) (Xu et al. 2017a). Efflux of Cd or Cd conjugates mediated by plasma membrane transporter OsABCG36 contributes to Cd tolerance in rice (Fu et al. 2019).

Both As and Cd are detoxified by complexation with phytochelatins (Cobbett and Goldsbrough 2002). Rice mutants lacking the PC synthase OsPCS1 are more sensitive to both Cd and As (Uraguchi et al. 2017), although not as sensitive as the Arabidopsis *AtPCS1* mutant (*cad1;3*) (Ha et al. 1999; Howden et al. 1995). There is possibly a degree of functional redundancy between OsPCS1 and OsPCS2, which should be investigated further by knocking out both genes. There is some confusion in the naming of OsPCS1 and OsPCS2; OsPCS1 named by Hayashi et al. (2017) is called OsPCS2 by Uraguchi et al. (2017) and vice versa.

Sequestration of As and Cd in the vacuoles is also important for tolerance. Knockout of *OsABCC1* in rice renders the mutants much more sensitive to As than wild-type plants, because vacuolar sequestration of As is weakened in the mutants (Song et al. 2014). Although *Arabidopsis* AtABCC1 and AtABCC2 can also transport Cd-PC complexes into the vacuoles and contribute to Cd tolerance (Park et al. 2012), OsABCC1 appears to have no such function and its knockout mutants are no more sensitive to Cd than wild type (Song et al. 2014). Transport of $Cd^{2+}$ ions into the vacuoles is carried out by OsHMA3, as discussed above. Overexpression of *OsHMA3* in rice increased Cd tolerance markedly (Lu et al. 2019; Sasaki et al. 2014). Inside the vacuoles, Cd may form complexes with PCs and high molecular weight complexes with additions of sulphide (Cobbett and Goldsbrough 2002). It is not known if intact Cd-PC complexes are transported into the vacuoles in rice.

## Strategies to reduce As and Cd accumulation in rice grain

Two types of approaches can be used to reduce As and Cd accumulation in rice grain: reducing their bioavailability in soil or their uptake/translocation to the grain. Key considerations include the feasibility, durability, cost and public acceptance.

Reducing As and Cd bioavailability in paddy soil

The first action to take is to stop the source of contamination, e.g. irrigation with contaminated waters. If soil acidity is the main reason for high Cd uptake in rice, liming can be used to increase soil pH. Field experiments showed that liming is highly effective at decreasing Cd concentrations in rice grain in an acidic paddy soil (Chen et al. 2018c). One-off application of 7.5 t ha$^{-1}$ of $CaCO_3$ before rice planting raised soil pH from the initial value of 5.5 to 6.5 and decreased grain Cd concentrations by 70–80% in three successive seasons, and there were no negative effects on grain yield or the concentrations of essential micronutrients in the grain (Chen et al. 2018c; Wang et al. 2019b). Liming did not affect As concentration in the grain. Other liming materials can also be used, if the cost and effect analysis is favourable. Field experiments have shown that applications of biochar can decrease Cd accumulation in rice grain, and the effect can be attributed mainly to increased soil pH (Bian et al. 2014; Bian et al. 2013). Because large amounts of biochar (>20 t ha$^{-1}$) are needed, the cost would be much higher than liming with $CaCO_3$. Ideal materials would be to immobilize (or fix) Cd in the soil strongly and specifically. However, such

materials may be difficult to come by, because Cd is a trace level contaminant in soil that is swamped by massively larger amounts of other divalent and trivalent cations that may compete with the sorption or fixation processes. Materials to facilitate immobilization of As include iron oxides/hydroxides and manganese oxides. Pot and field experiments have shown that As availability in paddy soils and As accumulation in rice grain can be decreased by amendments with Fe-rich materials or manganese oxides (Honma et al. 2016; Xu et al. 2017b; Yu et al. 2017). Manganese oxides promote oxidation of As(III) to As(V) under flooded conditions, thus increasing As sorption on the solid phase (Xu et al. 2017b). The effectiveness and durability of these materials need to be tested under field conditions.

Management of paddy water is effective for controlling As and Cd availability in paddy soil, but, as described above, the effects are opposite. The options for paddy water management depend on the relative risks of As and Cd accumulation. Where the risk of high As accumulation is low, delaying paddy water drainage during grain filling can be an effective method to decrease Cd accumulation in rice grain. In contrast, where the risk of excessive Cd accumulation is low (e.g. in neutral and alkaline paddy soils), intermittent irrigation can reduce grain As accumulation. Growing rice plants on raised beds above the water level in the surrounding furrows was also effective at decreasing As accumulation in the grain (Duxbury and Panaullah 2007). Whether this cultivation method would increase grain Cd concentration was not reported.

Reducing uptake or translocation of As and Cd to the grain

Large variations in grain As and Cd concentrations have been reported among rice germplasm (Duan et al. 2017; Norton et al. 2012; Pinson et al. 2015). It is possible to screen low accumulating rice cultivars for As and Cd based on multiple environment trials (Duan et al. 2017). Multiple field trials across sites and seasons should be conducted to assess the effect of genotype x environment interactions. However, it appears to be difficult to select cultivars low in the accumulation of both As and Cd. It was found that grain Cd concentration correlated positively with heading date among a large panel of rice cultivars, whereas grain As concentration correlated negatively with heading date (Duan et al. 2017). The reasons for these opposite correlations are not clear.

In the medium to long term, it is possible to breed rice cultivars with low As or Cd accumulation in the grain. A number of quantitative trait loci (QTLs) controlling grain As and Cd concentrations have been identified (e.g. Yang et al. 2018a; Zhang et al. 2014). Multiple QTLs with low accumulating traits can be combined using molecular marker-assisted breeding programme. Causal genes for several Cd accumulation QTLs have been identified (Luo et al. 2018; Ueno et al. 2010; Yan et al. 2019). In particular, strong functional alleles of OsHMA3 are very useful for limiting Cd translocation to the shoots and accumulation in the grain (Yan et al. 2016). By introgressing qCd7 from the Japonica cultivar Nipponbare, containing a strong OsHMA3, to Indica rice hybrids, grain Cd concentration was reduced by about 50% (Zhou et al. 2019). It has been shown that allelic variation in the promoter of OsNRAMP5 can cause variation in Mn accumulation by affecting the expression level of OsNRAMP5 (Liu et al. 2017). The effect of this allelic variation on Cd accumulation is unknown, because OsNRAMP5 and OsHMA3 genes are very close in the genome and difficult to segregate in the mapping population. It would not be a surprise if the weak OsNRAMP5 allele is associated with a low Cd uptake, and if so, combining a weak allele of OsNRAMP5 with a strong allele of OsHMA3 should lead to further reduction in Cd accumulation in the grain. Low-Cd OsNRAMP5 mutants of rice generated by ion beam irradiation can also be used as a parental line in the breeding of low-Cd rice cultivars (Ishikawa et al. 2012), although the potential effect of Mn deficiency on grain yield should be evaluated. Compared with Cd, little is known about the causal genes underlying grain As QTLs, making molecular breeding of low As rice more difficult.

Genetic engineering can be used to either knock out or overexpress specific genes to reduce uptake or translocation of As and Cd in rice. Tang et al. (2017a) used CRISPR/Cas9 gene editing technology to knock out OsNRAMP5 gene in both parental lines of a rice hybrid, producing hybrid rice with >90% reduction in grain Cd concentration when grown on a contaminated paddy soil. Although Mn uptake in the gene-edited hybrid rice was also reduced substantially, plant growth and grain yield were normal, possibly due to the high availability of Mn in the flooded paddy soil. In Mn limiting soils, there may be a risk of Mn deficiency when OsNRAMP5 is inactivated (Ueno et al. 2010; Yang et al. 2014). Another highly effective approach is to overexpress a

functional allele of *OsHMA3* to enhance Cd sequestration in the vacuoles of roots and other vegetative tissues. Overexpression of *OsHMA3* in both Japonica and Indica cultivars of rice produced dramatic decreases (>90% reduction) in grain Cd concentration with little effects on grain yield or the concentrations of essential trace elements (Lu et al. 2019; Sasaki et al. 2014; Ueno et al. 2010). *OsLCT1* is another target gene for editing, which may decrease Cd translocation to rice grain (Uraguchi et al. 2011). In the case of As, overexpression of *OsNIP1;1* or *OsNIP3;3* reduced grain As concentration by about half (Sun et al. 2018). Deng et al. (2018) developed transgenic rice with a targeted overexpression of *OsABCC1* in the root cortical and internode phloem cells and also overexpression of a bacterial γ-glutamylcysteine synthetase. Enhanced synthesis of thiol compounds coupled with increased expression of *OsABCC1* helped trap more As in the vacuoles and reduced grain As concentration by two thirds. Another way to increase As(III) sequestration in the vacuoles is to express *PvACR3.1*, which encodes a tonoplast As(III) transporter in the As-hyperaccumulator *Pteris vittata* (Chen et al. 2019b). Transgenic rice expressing *PvACR3.1* contained 26–46% lower levels of iAs in rice grain than wild type when grown in an As-contaminated soil.

Some fertilizers and amendments can be used to reduce As and Cd uptake. It has been shown that Si suppresses the expression of *Lsi1* and *Lsi2* (Mitani-Ueno et al. 2016; Sun et al. 2018), which in turn can result in a significant reduction of As(III) uptake (Ma et al. 2008; Sun et al. 2018). Silicon may also compete with As(III) for the transporters directly. Additions of Si fertilizers or Si-rich materials to soil significantly decreased As accumulation in rice grain (Li et al. 2009b; Seyfferth and Fendorf 2012). Interestingly, Si also suppresses the expression of *OsNRAMP5* and *OsHMA2*, resulting in decreased Cd uptake and translocation (Shao et al. 2017). This effect may explain why foliar application of Si decreased Cd accumulation in rice in a pot experiment (Liu et al. 2009). Foliar sprays of $ZnSO_4$ solution at the grain filling stage were found to decrease grain Cd concentration to certain extents (Lv et al. 2019).

## Concluding remarks

Much progress has been made in understanding the biogeochemical processes of As and Cd in paddy soil and the molecular mechanisms of their uptake and translocation in rice plants. However, there are still significant knowledge gaps in a number of areas. Firstly, predictions of As or Cd uptake by rice from simple soil tests remain difficult, hampering the effort to adopt a risk-based management approach. This difficulty mainly arises from the large impact of the redox potential on the bioavailability of As and Cd in paddy soil, and the fact that the redox potential fluctuates widely in paddy soil depending on the paddy water status. Secondly, causal genes for many QTLs for grain Cd and, particularly, As concentrations remain unknown. Further efforts are needed to clone these QTLs and reveal the mechanisms underlying the natural variations in As and Cd accumulation among rice germplasm. This information is crucial for breeding low accumulating cultivars using molecular marker-assisted breeding method. Thirdly, the effects of genetic x environment interactions are large for both As and Cd accumulation in rice. Related to this question is how key genes involved in As or Cd uptake and translocation are regulated in response to environmental factors. A better understanding of these interactions could improve the mitigation efforts under different environmental conditions. Fourthly, reducing the bioavailability of both As and Cd in paddy soil simultaneously remains a great challenge. More research is needed to develop innovative methods to tackle the two contaminants together. Finally, there is a need for more epidemiological studies to assess the risk on human health associated with elevated levels of As and Cd in rice grain.

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