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LAND POLLUTION (G HETTIARACHCHI, SECTION EDITOR)

How Does Contamination of Rice Soils with Cd and Zn Cause High Incidence of Human Cd Disease in Subsistence Rice Farmers

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Abstract Rice (*Oryza sativa* L.) grown on Zn mine waste contaminated soils has caused unequivocal Cd effects on kidney and occasional bone disease (*itai-itai*) in subsistence rice farmers, but high intake of Cd from other foods has not caused similar effects. Research has clarified two important topics about how Cd from mine waste contaminated rice soils has caused Cd disease: (1) bioaccumulation of soil Cd into rice grain without corresponding increase in Zn, and (2) subsistence rice diets potentiate Cd absorption/bioavailability and risk to farm families. Absorption of Cd by rice roots occurs on the NRAMP5 Mn^{2+} transporter. Although other transporters can influence Cd uptake-transport to shoots and grain, making NRAMP5 null greatly reduces grain Cd. Zn^{2+} has little ability to inhibit Cd^{2+} transfer in rice but clearly inhibits Cd uptake in other plant species. The bioavailability of dietary Cd is increased for subsistence rice diets. Research has identified that low levels and bioavailability of Zn and Fe in polished rice grain cause upregulation of Cd absorption on the Fe^{2+} transporter of duodenum cells (DMT1). Added dietary Zn can also inhibit intestinal Cd absorption somewhat. Nutritional stress (Fe, Zn deficiency) in humans consuming subsistence rice diets thus promotes Cd accumulation and adverse effects. No other dietary (crop) Cd exposure has caused unequivocal Cd-induced renal proximal tubular dysfunction (the first adverse Cd effect) in humans. Recognition of the very unusual nature of Cd risk from rice compared to other crops should be taken into account in setting international limits of Cd in rice and other foods.

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Introduction

Cadmium naturally occurs in Zn, Pb, and Cu ores with between 50 and 200 times more Zn than Cd on weight basis (Cd:Zn=0.005–0.02 g Cd(g Zn)$^{-1}$). One of the consequences of mining and smelting these ores has been the Cd contamination of surrounding soils which commonly occurred until recent times after environmental contamination was better understood. Cadmium contamination of soils has been a concern since it was determined that Zn mine wastes, containing high levels of Zn and Cd, had contaminated rice paddies and caused kidney and bone (*itai-itai*) diseases for subsistence rice farmers in the Jinzu Valley of Japan (see comprehensive review by Kobayashi [1]). The story of the discovery that Cd was the causal agent in *itai-itai* disease illustrates the unusual enrichment of Cd in diets of the subsistence rice farm families. The availability of a spectrograph which allowed measurement of Cd at low concentrations allowed analysis of soils, foods, and human tissues when few had previously studied Cd in biology. Subsequently, populations in many locations in Japan [2–5] and China [6, 7] and one location in Thailand [8] were similarly found to exhibit human Cd disease linked to subsistence rice farming although growing and smoking tobacco may have contributed to body Cd in some locations.

Cadmium in Zn mine waste contaminated soils is readily taken up by plants, is transported to different edible plant tissues, and thereby enters the food chain as a food contaminant [9, 10]. Food and smoking are the main pathways for human exposure to soil Cd. However, whether soil Cd reaches

edible parts of plants is complex, varying in plant species and cultivars [11], and with soil properties especially soil pH, soil E_h, soil Zn, and chloride levels and Cd sorbent levels (Fe and Mn oxyhydoxides and organic matter) [12].

Cadmium in Soils and Plants

With a normal geochemical Cd/Zn ratio of 1:100 or greater, crops other than rice grown in contaminated soil have a natural limit to Cd uptake due to Zn phytotoxicity [13]; as the crop Cd level increases, the crop Zn level also increases. Most crops such as leafy vegetables, legumes, storage roots/tubers, fruits, and grains maintain low levels of Cd in edible tissues when Cd and Zn soil levels are at 1:100 Cd/Zn (0.01) ratio. When foliar Zn exceeds about 400–500 mg kg^{-1} dry weight (DW), Zn causes phytotoxicity reducing crop yields and causing growers to identify the cause of the visual symptoms (yellowing, or chlorosis due to Zn-induced Fe deficiency) [13], limiting the transfer of soil Cd to humans or animals [10]. Further, for crops other than rice, when foliar Zn is greatly increased to the point of Zn phytotoxicity, grain Zn is substantially increased [9]. Most Zn phytotoxicity occurs in strongly acidic soils which promote uptake of Cd and Zn by plants, and normal limestone addition to increase pH and improve crop yields reduces crop Cd and Zn levels.

Although human Cd disease has occurred with as little as 5 mg Cd kg^{-1} soil in rice soils, there have been cases where, as a result of vegetable garden soil Cd+Zn contamination, soil Cd levels were as high as 50–150 mg Cd kg^{-1}, yet no kidney or bone diseases occurred in those consuming the produce, apparently because concurrent Zn levels were 5000–15,000 mg Zn kg^{-1} [10, 14–17]. However, while most rice paddies that are contaminated with Cd also have 100-fold higher Zn than Cd, this ratio did not provide the usual protection from Cd seen with other crops. Consumption of large amounts of seafood with Cd enrichment similarly had no effect on human Cd risk [18–20]. The interaction between Zn and Cd in rice is clearly an anomaly compared to other foods. In addition, Zn in test diets with food levels of Cd (not the high levels used by most toxicological researchers) limited increase of Cd in kidney and liver even when Cd was significantly increased compared to basal diets [21–25]. At food Cd levels, the co-contamination with Zn significantly reduces crop Cd bioavailability and risk except for rice consumption.

Cadmium accumulation by rice is anomalous compared to other staple crops. Takijima et al. [26, 27] found a wide range of Cd concentrations in rice paddy soils, yet found that total soil Cd was not correlated with Cd extractability nor with the Cd level in rice grain. Instead, flooding period and soil pH strongly affected rice grain Cd levels. In addition, the co-contamination with Zn had little influence on grain levels of Zn [28–30]. The paper by Fukushima et al. [31] on Cd and Zn in the rice consumed by the farm families at Jinzu Valley also reported that rice grain Cd could be sharply increased when soils were contaminated by Zn mine wastes, but grain Zn was not increased. In Thailand with extreme Cd+Zn contamination, grain Zn was not increased even when soils contained 7000 mg Zn kg^{-1} (Fig. 1) [32].

For rice culture, soil redox potential and pH control the amount of Cd in soil solution and Cd uptake by roots [26, 28, 30, 33]. Rice has traditionally been grown in flooded (anaerobic) soils. Under such anaerobic conditions, soil Mn and Fe oxyhydroxides are reduced to Mn^{2+} and Fe^{2+}, and pH rises toward 7. Zn is either strongly adsorbed to soil sorbents or transformed to insoluble ZnS and Cd can precipitate as CdS [28, 34], although it has been difficult to document the extent of CdS formation in flooded rice soils even using Extended X-Ray Absorption Fine Structure (EXAFS) [35–37]. Although early researchers who reported the very strong effect of soil reduction on Cd uptake suggested that this could be explained by sulfide formation in flooded soils and formation of CdS [28], EXAFS evidence of CdS was first reported by Khaokew et al. [35] with highly contaminated Thai rice soils. De Livera et al. [36, 38] argue that these results did not explain the reduced Cd uptake adequately and suggested that mixed solid Cd-ZnS nanoparticles of sulfides undergoing redox might play a role. Subsequently, Fulda et al. [37] clearly showed that CdS was unequivocally formed in flooded Cd-spiked soils and that if sulfate was low compared to sulfide forming metals, or if Cu was high, CdS formation was appreciably inhibited and Cd uptake increased. Perhaps this finding explains the unusually high transfer of Cd to rice grain grown in soils contaminated by Cu mine wastes which caused human Cd disease at lower soil Cd than other locations [5, 39].

Now it is clear that the main reason that rice accumulates Cd during grain filling is the role of NRAMP5 at the same time that soil oxidation with great lowering of soil solution Mn, and soil acidification increases Cd solubility in the rhizosphere. Fulda et al. [37] reported that soluble Mn dropped remarkably within 2 days after their flooded soils with CdS were made aerobic, which would strongly reduce competition for Cd uptake on NRAMP5.

In common rice production, the paddies are drained at the beginning of flowering to promote higher yields, disease resistance, and convenience of harvest. As the drained paddy soils become aerobic and more acidic, CdS oxidizes, quickly becoming phytoavailable and causing rapid Cd uptake by rice (see [33, 40, 41]). A paper by Murakami et al. [42] testing phytoextraction of soil Cd using a Cd-accumulating cultivar of rice showed that while the soil remained flooded, rice shoot Cd did not exceed 0.5 mg kg^{-1} dry weight (DW), but after aerobic soil growth, shoots reached over 30–70 mg kg^{-1}. Part of the increased phytoavailability of soil Cd is due to a strong reduction in soil pH in soils which occurs in non-calcareous rice soils as conditions become aerobic (e.g., [43]). The

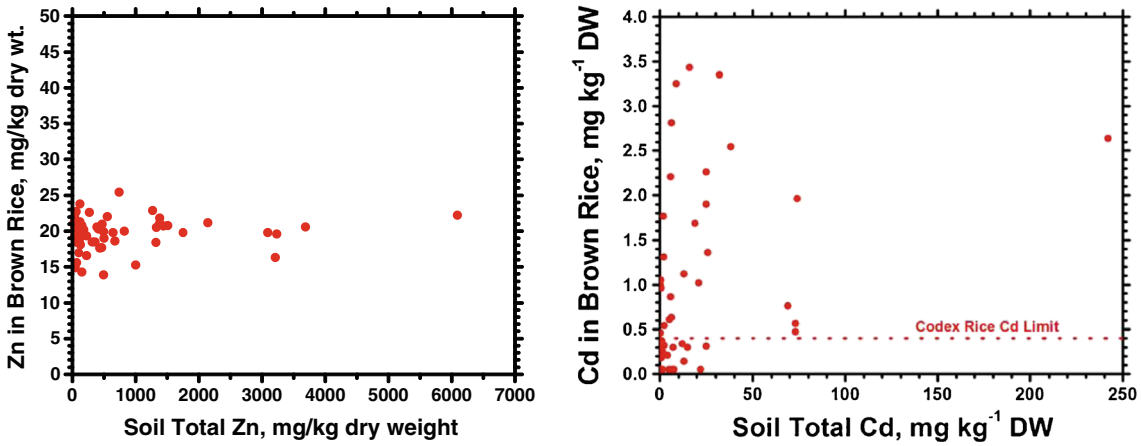

Fig. 1 Zn in rice grain is not increased despite massive Zn mine waste contamination of rice soils with Cd and Zn, while grain Cd is strongly increased with any contamination (based on data in [32])

combination of these factors makes Cd more available for plant uptake without the inhibition by the higher levels of Zn, leading to a high uptake of Cd into the grain.

Because of the change in redox and soil pH during grain filling, soil extractions have been poor predictors of Cd accumulation in rice when either flooded or air-dried soils were tested. But, testing of field moist soils collected during grain filling for 0.1 M $CaCl_2$-extractable Cd (1 g soil 5 mL^{-1}) showed a strong correlation of extractable Cd with grain Cd [44] (Fig. 2). The equation for predicting Cd in brown rice based on 0.10 M $CaCl_2$-extractable Cd of field-moist soil during the grain filling period was highly significant (Cd in brown rice=−0.007+3.32•Extr-Cd; R^2=0.95). Consuming such high Cd, low Zn and Fe rice grain caused human disease in many locations.

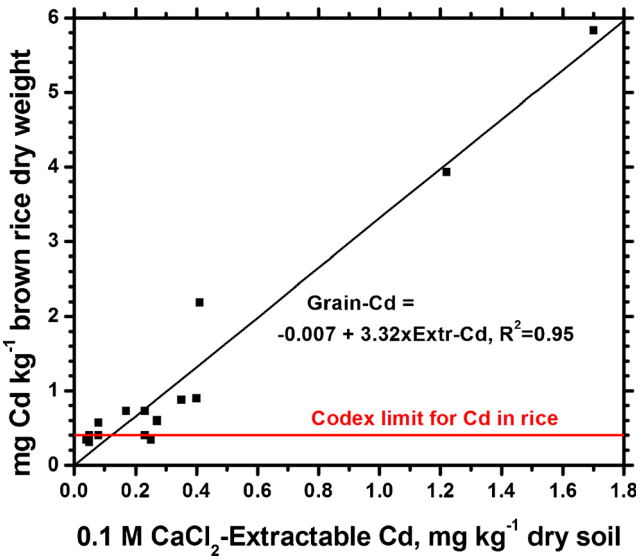

Fig. 2 Correlation of Cd concentration in brown rice grain with Cd extractable from field-moist soils collected during grain filling using 0.1 M $CaCl_2$ at 1 g soil $(5\ mL)^{-1}$ (based on data in [44])

Many studies of genetic variation in rice grain Cd have been reported. Some describe "pollution safe cultivars" [45], while others have identified the HMA3 genetic variation which when null so strongly increases Cd translocation to shoots and grain [46]. In most papers about "countermeasures" for contaminated rice fields, genetic improvement to lower Cd is included (e.g., [47]).

Experiments tested the ability of rice to accumulate solution Cd at different growth stages and to transport the Cd absorbed at several growth stages to the grain during filling. These studies showed that rice grown in aerobic nutrient solutions could absorb ^{109}Cd and translocate it to leaves, and subsequently to grain at any time during growth [5, 29, 48]. Recently, Rodda et al. [49] studied Cd uptake and redistribution during grain filling and confirmed that part of the Cd absorbed into leaves during vegetative growth could move into grain but that most grain Cd was absorbed during the grain filling period and translocated directly to grain. As noted elsewhere, Cd is translocated from roots in xylem and transferred to phloem at shoot nodes and can be efficiently translocated to grain [50, 51]. Thus, it was not the ability of rice plants to only transport Cd to grain only during grain filling but that the uptake of Cd was greatly increased at the time of grain filling (due to aerobic soil conditions with lower pH, higher Cd^{2+}, and lower Mn^{2+} in soil solution) that is the important factor in why rice accumulates Cd in grain so much more effectively than other cereal grains.

Recently, it was learned that Cd uptake by rice occurs largely on the NRAMP5 transporter, a Mn^{2+} transporter in rice roots [52–54]. Ishikawa et al. [52] generated heavy ion mutants of rice and tested Cd accumulation by 2592 M2 plants grown in Cd+Zn contaminated rice soils. They subsequently tested these lines in three contaminated fields in Japan, finding that the three lines had almost no Cd (undetected to 0.03 mg kg^{-1}) accumulation in grain when the parent wild-type rice accumulated 0.55 to 1.8 mg Cd kg^{-1}. Shoot Cd was similarly greatly reduced by the mutation.

During flooded culture, Mn^{2+} concentration in soil solution is greatly increased due to microbial reduction of soil MnO_2, which inhibits Cd uptake on NRAMP5. Whether high soil solution Mn represses expression of NRAMP5 has not been clarified to date although the gene was reported to be constitutively expressed [54]. Levels of Mn^{2+} used in testing repression may not have been representative of reduced paddy soils. Further study of the interaction of Mn^{2+} with Cd^{2+} uptake by rice showed that soil solution levels of Mn^{2+} in flooded soils strongly inhibited Cd uptake [55] extending the findings of Fulda et al. [37] and Sasaki et al. [54]. Further, in contrast with Cd absorption by other plant species, increased Zn^{2+} had little effect on Cd absorption by NRAMP5. In previous studies of Cd uptake by wheat [56, 57], lettuce and spinach [58], and sunflower [59], increased activities of Zn^{2+} significantly reduced Cd accumulation to shoots when environmentally relevant Cd and Zn levels were used.

Environmentally relevant activities of microelement cations are stressed because in early study of microelement divalent cation uptake by pea, it was suggested that Cd uptake could occur on the IRT1 Fe^{2+} transporter of roots [60]. However, subsequent testing at other metal ion activities more similar to soil solution showed that IRT1 was only a Fe^{2+} transporter that likely played no role in accumulation of ions such as Zn^{2+}, Cd^{2+}, Ni^{2+}, and Cu^{2+} [61]. Study of Zn uptake by rice has shown that there are at least two levels of uptake affinity, a high affinity transporter with a K_m (concentration which gives half maximal uptake rate) of 0.010 to 0.020 μM and a low affinity transporter with K_m of 6–20 μM [62]. Study at Cd levels >0.1 μM are irrelevant in understanding practical Zn accumulation from soils. Similar high affinity Zn transport activity was reported by Hacisalihoglu et al. [63] for bread wheat. Study at lower Cd^{2+} activity levels is difficult unless chelator buffering is used to control Cd and Zn activities at levels similar to soil solution. Green and Chaney (unpublished) showed that with Cd activity which gives rice Cd levels found in the field, increased Zn activity had little effect on Cd uptake, confirming the field observations that Zn does not inhibit Cd accumulation by rice. On the other hand, the "Chino" solution supplied more Mn and gave significantly lower Cd accumulation in rice shoots and grain than the "Grusak" solution both with the same buffered Cd^{2+} and Zn^2 activity [64] (Table 1).

The high affinity Zn transporter in rice is believed to be ZIP1 which is expressed in the epidermal membrane of root cells [53, 65–68]. There have been many studies of Zn accumulation in rice in recent years because of the clear evidence that subsistence rice consumers may suffer Zn and Fe malnutrition (see [69]). Both agronomic and genetic methods to biofortify rice grain with Zn have been studied [70]. Improved bioavailable Zn in rice grain is also being evaluated for more water saving production methods (alternate wetting and drying). Even with aerobic soils, adding significant soluble Zn fertilizers has little effect on grain Zn concentration (e.g., [71]), while spray application of soluble Zn to leaves post-flowering (during grain filling) has significantly increased rice

Table 1 Effect of solution Zn activity on rice accumulation of Cd and Zn in chelator-buffered nutrient solutions based on nutrient solutions used by M. Grusak and M. Chino in rice metals research (from [64])

Constituent			Grusak Solution		Chino Solution	
			μM		μM	
FeHEDTA			10.		20.	
$MnCl_2$			1.0		4.61	
$ZnSO_4$			2.0		1.53	
$CuSO_4$			2.0		2.0	
$NiSO_4$			0.1		.	
EGTA in excess of CdEGTA			50.		50.	
Tissue composition:						
Solution Cd	Leaf Cd, mg kg^{-1} DW		Leaf Mn, mg kg^{-1} DW		Leaf Zn, mg kg^{-1} DW	
	Grusak	Chino	Grusak	Chino	Grusak	Chino
0.0 Cd	<0.1	<0.10	41.1	410.	23.8	23.0
0.5 Cd	0.37	0.18				
2.0 Cd	0.79	0.75				
Solution Cd	Grain Cd, mg kg^{-1} DW		Grain Mn, mg kg^{-1} DW		Grain Zn, mg kg^{-1} DW	
	Grusak	Chino	Grusak	Chino	Grusak	Chino
0.0 Cd	<0.01	<0.01	5.45	10.9	42.0	38.6
0.5 Cd	0.2202	0.02				
2.0 Cd	0.90	0.22				

grain Zn levels [72, 73]. Stomph et al. [74] note the remarkable difference between rice and other studied grains in Zn uptake and transfer to grain in relation to soil applications. Further, although brown rice is increased appreciably in Zn by foliar Zn sprays during grain filling, endosperm is only slightly increased in Zn [75, 76].

The transition to more aerobic rice production (AWD) effect on rice grain Zn concentration and bioavailability are also complex [77, 78], while more aerobic soils invariably increase grain Cd (Fig. 3).

The interaction between metals in the uptake process can either be antagonistic (the addition of one decreasing the uptake of the other one) or synergistic (the addition of one increasing the uptake of the other). Antagonism between Cd and Zn has been reported by Honma and Hirata (see [29]) with rice, and Chaney et al. [59] with sunflower). Still other studies have reported synergism between Zn and Cd in rice, with an increase in Zn increasing the translocation of Cd from the roots to the shoots (see [29]). Yet when Cd and Zn were added in a ratio of 1:50 Cd:Zn, Cd concentration in the shoots decreased [29].

The demonstration of a key role of NRAMP5 in Cd accumulation in rice came from several research programs. In one, the researchers made mutants and grew out thousands of seeds to find any with lower accumulation of Cd in grain [52–54]. They characterized localization of the protein and expression, concluding that NRAMP5 was a significant transporter of Cd^{2+}, Mn^{2+} and possibly Fe^{2+}, but not Zn^{2+} into epidermal cells. Although in testing to date the NRAMP5 null rice genotypes maintain yields and grain quality, uptake of Mn is strongly reduced. If soils had not been flooded during the growth cycle in the research with the NRAMP5 null genotypes, it is possible that Mn would have become deficient for rice. Over a period of years of aerobic culture of low Mn soils such as long term rice soils which have undergone repeated reduction and oxidation over centuries, Mn phytoavailability can decline even to deficient levels (e.g., [80]). In that study, application of high rates of a high Fe biosolids to a low Mn Maryland soil caused Mn deficiency of wheat and soybean after about 15 years post biosolids application. It took that long for the soil redox and Mn chemistry to reach low phytoavailable Mn and cause Mn deficiency in wheat and even in maize. So it is not clear if the NRAMP5 null rice cultivar will maintain agronomic performance in the long term with aerobic production.

Long-term performance under aerobic conditions is an important question because of the newly understood need to produce rice aerobically to minimize accumulation of inorganic As (*i*As) in rice grain. Because arsenate is reduced to the much more soluble (less strongly adsorbed) arsenite in flooded soils, and because arsenite is accumulated into rice on the silicate transporter [81], rice grown with traditional flood culture is higher in *i*As than other food crops and may exceed the newly established CODEX limit of 0.20 mg *i*As kg^{-1}. Unfortunately, aerobic production to reduce grain *i*As simultaneously causes grain Cd to increase as discussed above (see [40, 82] [Fig. 3]).

Other transporters are important in Cd accumulation in rice and other plant species. In particular, the HMA3 protein pumps Cd^{2+} into root vacuoles of rice [46, 83, 84] and soybean [85]. Over-expression of the HMA3 protein greatly reduced Cd transport to shoots and grain without changing uptake or transport of Zn or other nutrients [84]. However, adoption of transgenic improved cultivars over-expressing HMA3 is not accepted in many nations, and simple breeding using normal genotypes offers little hope of lowering crop Cd through change in HMA3 expression. HMA3-null rice has been identified as a potentially valuable phytoextraction crop because growing these genotypes under aerobic soil conditions, especially with acidic soils, allows high Cd accumulation in rice shoots, and the high shoot yields allow

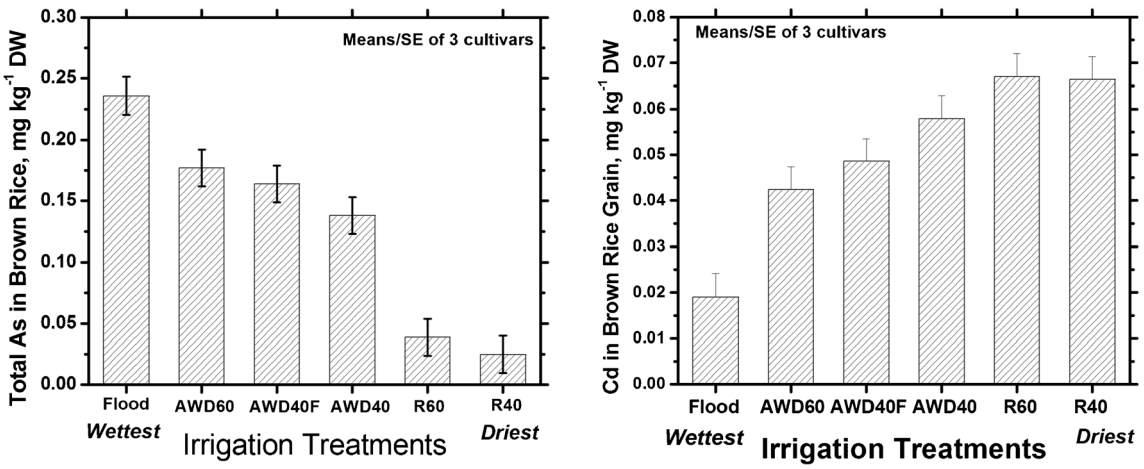

Fig. 3 Effect of alternate wetting and drying flood management on accumulation of As and Cd in rice grain [79]. The water management varied from traditional full season flood, through alternative wetting and drying, to furrow irrigation only when the soil reached 40 or 60 % of water holding capacity

significant removal of Cd from the field [42, 86]. Another gene, HMA2, is involved in translocation of Cd and Zn from roots to shoots [87, 88], and yet another (LCT1) may affect low affinity Cd transport from leaves into grains [89].

An important advance in understanding of Cd uptake and translocation in rice was achieved by Fujimaki et al. [51] who used a positron-emitting tracer imaging system (PETIS) to follow Cd uptake and translocation in real time. This work illustrated the rapid transfer of Cd from xylem to phloem in basal nodes of the rice plant, helping to explain the highly efficient transfer of absorbed Cd into the grain after field drainage (see also [50]).

In other plant species, Zn strongly inhibits Cd uptake and translocation. The interaction can occur due to correction of Zn deficiency reducing upregulation of the Zn^{2+} transporter thereby reducing Cd uptake [90, 91], or the simple competition of Zn with Cd uptake by the ZIP1 discussed above.

Another important aspect of subsistence rice farming is that locally (home) grown crops are consumed by the farm family. For most other staple foods, crops are processed off-farm so that individuals do not consume only crops grown on contaminated soils for long periods. For urban populations, crops from many farms are commingled preventing consumption of only highly contaminated crop for long periods. Some other subsistence crops are consumed locally but are not known to accumulate bioavailable Cd as effectively as rice (maize, sorghum, bean, potato, casava) from common Cd+Zn mine or smelter contamination. It should be recognized that some Cd sources for soils lack the Zn of mine wastes, which allows high Cd phytoavailability and bioavailability thru all crops (e.g., [92]).

Absorption of Cd in Animal Intestine

Research using food levels of Cd has clearly shown that absorption of Cd is inhibited by Zn in the test meal [23–25, 93] and strongly increased by Fe deficiency status of the individual [94–96]. Research by Reeves and collaborators attempted to clarify the role of the nutrient deficiencies of rice subsistence diets in increased Cd absorption [97]. These studies showed that under marginal Fe-Zn-Ca malnutrition which did not reduce growth rates of rats, Cd absorption was increased as much as 10-fold compared to adequately nourished rats (not high levels) and that Cd in sunflower kernels had lower bioavailability than Cd in polished rice [98, 99]. They then did a pulse-chase kinetic study of ^{109}Cd absorption and retention in tissues from Zn-Fe-Ca marginal diets versus adequate Zn-Fe-Ca diets which showed about 10-fold higher Cd absorption into enterocytes on the marginal diets, and long turnover in the intestine which caused much higher net Cd absorption (Fig. 4). After the dose, ^{109}Cd continued to accumulate in the kidney until after the intestine had released all ^{109}Cd. Further, a test with metallothionein-null mutant versus wild-type mice showed that metallothionein (a protein previously believed to play a significant role in Cd and Zn absorption into enterocytes) played no role in Cd absorption at dietary levels of Cd exposure in contrast with toxicological studies at high doses commonly reported [100]. This work illustrates the error in understanding animal Cd physiology which resulted from toxicological type testing with rats and other animals. In those studies, diet Cd is often higher than diet Zn or Fe, changing absorption patterns and competitions, and causing induction of metallothionein biosynthesis which traps Cd in the intestine cells. Huge numbers of papers on Cd absorption are irrelevant due to the use of toxicological doses rather than food Cd levels [10, 93, 97].

Limits to Protect Humans from Cd in Contaminated Soils

Misunderstanding of food Cd risks has led to difficulty in setting limits for allowable Cd in foods. After years of review, the Joint Expert Committee on Contaminants and Food Additives (JECFA) [101] established 7 μg Cd(kg body weight)$^{-1}$ week^{-1} as a limit for chronic ingestion of dietary Cd. A later

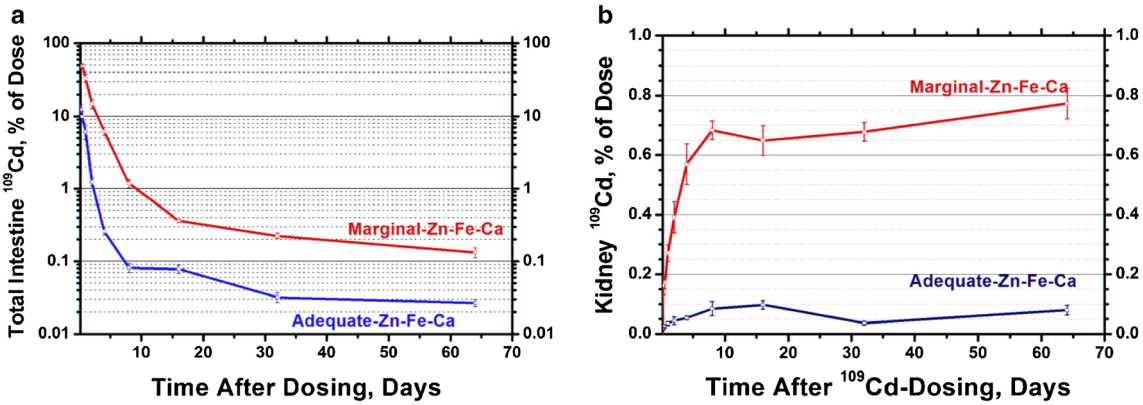

Fig. 4 **a** Concentration of ^{109}Cd in whole intestine of rats fed with Fe-Zn-Ca marginal or adequate diets during 64 days post-feeding; **b** concentration of ^{109}Cd in kidney of rats fed with Fe-Zn-Ca marginal or adequate diets during 64 days post-feeding (based on [99])

European Food Safety Agency (EFSA) [102] examined the same data and suggested that maximum daily intakes of Cd should be no higher than 2.5 μg Cd(kg body weight)$^{-1}$week^{-1}. The JECFA [103] panel re-evaluated the Cd limit and lowered it slightly and made the recommendation to use a monthly intake limit (25 rather than 30 μg Cd(kg body weight)$^{-1}$month^{-1}) to stress the long-term nature of food Cd risks. Even with this international opinion, the EFSA panel continued with their lower Cd intake recommendation [104].

Based on the summary of dietary Cd exposure to Cd+Zn contaminated soils above, and the improved understanding of animal absorption of Cd at dietary levels, it seems clear that several important over-estimations of dietary Cd risk are being made by many scientists. If humans exposed to a number of food Cd contamination sources have been shown to consume the Cd but not have increased Cd in blood, kidney, or urine [19, 105], important differences in food Cd bioavailability are not being taken into account in derivation of food Cd limits. In addition, some foods have significantly lower Cd bioavailability due to the presence of oxalate, phytate, and fiber in the food. Spinach is a known Cd accumulator crop, but the presence of oxalate in this food substantially reduces net Cd absorption compared to other foods [23, 106] apparently due to formation of a Ca-Cd-oxalate co-precipitate in the digestive system. Numerous papers have illustrated that added Zn reduces absorption of Cd from test diets [24], even from intrinsic labelled diets [23, 97]. When crops are grown with geogenic ratios of Cd to Zn, Zn inhibits Cd uptake by the crop, limits yield of the crop with smaller increases in crop Cd, and also reduces Cd bioavailability in the edible crop to the consumer [107]. Because most Cd absorption research does not include the "natural" 100-fold increased crop Zn that accompanies Cd in mine waste contaminated soils and crops, predictions of risk from that source are greatly over-estimated for crops other than rice.

In addition, adverse effects of Cd in humans are often overstated. Examination of the extensive human Cd exposure and disease in Japan suggests that no one would experience initial proximal renal tubular dysfunction until urinary Cd exceeded 10–12 μg(g creatinine)$^{-1}$ in urine [108]. Examination of over 10,000 middle-aged non-smoking Japanese urban women consuming considerably higher daily Cd in their diet than Europeans (because of the background higher Cd in rice in Japan) showed that even when urine contained 3 μg Cd(g creatinine)$^{-1}$, there was no evidence of renal tubular disease [109, 110] in direct contradiction of the views of the EFSA panel [102, 104]. One needs to recognize potential bias from selection of a cutoff of urinary β_2-microglobulin or other proximal tubular dysfunction indicators in urine when the normal geometric mean is 100 and strong Cd disease causes β_2-microglobulin to rise above 100,000 μg(g creatinine)$^{-1}$ [111]. Further, when smoking is a more significant source of kidney Cd in smokers than food Cd for non-smokers, evaluating Cd effects in mixed populations of smokers and non-smokers may give artifacts. Many diseases are induced by chronic smoking, while chronic ingestion of Cd is only connected clearly with high consumption of rice homegrown on mine waste contaminated paddy soils which causes proximal tubular renal dysfunction and occasionally osteomalacia (*itai-itai*) after prolonged Cd kidney disease.

The new concerns about As in rice make Cd in rice a more important issue to be considered in management of rice production. As discussed above, growing rice with more aerobic soil management can significantly reduce ***i***As in rice grain, a desired outcome. However, any increase in aerobic condition during growth and especially during grain filling can significantly increase grain Cd (Fig. 3). Efforts to reduce rice ***i***As must balance this goal against the potential increase in rice Cd with more aerobic production practices.

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Conflict of Interest The author has no conflict of interest.

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