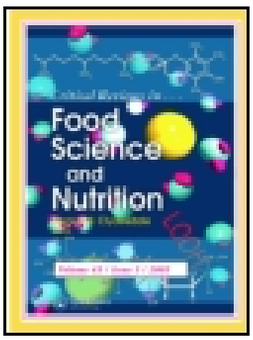

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Dietary compounds as modulators of metals and metalloids toxicity

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ABSTRACT

A large part of the population is exposed to metals and metalloids through the diet. Most of the in vivo studies on its toxicokinetics and toxicity are conducted by means of exposure through drinking water or by intragastric or intraperitoneal administration of aqueous standards, and therefore they do not consider the effect of the food matrix on the exposure. Numerous studies show that some components of the diet can modulate the toxicity of these food contaminants, reducing their effect on a systemic level. Part of this protective role may be due to a reduction of intestinal absorption and subsequent tissue accumulation of the toxic element, although it may also be a consequence of their ability to counteract the toxicity directly by their antioxidant and/or anti-inflammatory activity, among other factors. The present review provides a compilation of existing information about the effect that certain components of the diet have on the toxicokinetics and toxicity of the metals and metalloids of greatest toxicological importance that are present in food (arsenic, cadmium, lead, and mercury), and of their most toxic chemical species.

KEYWORDS

Arsenic; mercury; cadmium; lead; diet; toxicokinetics; toxicity

Introduction

Toxic metals and metalloids from the environment enter the food chain by various pathways. Some food products tend to accumulate these toxic elements, presenting concentrations that can exceed the legal limits or the values considered safe for consumers. For example, concentrations of mercury (Hg) (up to 3.3 mg/kg) higher than the legal limits have been found in seafood products, especially fish that are considered large predators (swordfish, tuna, bonito, some kinds of shark; EFSA, 2012a). The concentrations of arsenic (As) in inorganic form, the most toxic form found in foods so far, are notable in the brown seaweed *Hizikia fusiforme* (up to 100 mg/kg; Almela et al., 2002), in bivalves (up to 5.8 mg/kg; Sloth and Julshamn, 2008), and in rice (up to 0.3 mg/kg; Lamont, 2003; Torres-Escribano et al., 2008). Cadmium (Cd) can be present at high concentrations in seaweed (up to 1.9 mg/kg; Almela et al., 2002), mushrooms (up to 12 mg/kg; Kalač and Svoboda, 2000), seafood (up to 4.5 mg/kg; EFSA, 2009), and cocoa-based products (up to 1.8 mg/kg; Mounicou et al., 2003). Elevated amounts of lead (Pb) are found in game meat (up to 110 mg/kg; Lindboe et al., 2012), alga-based supplements (up to 0.9 mg/kg; EFSA, 2012b), and seafood products, especially crustaceans and mollusks (up to 6 mg/kg; Abi-Ghanem et al., 2014). The magnitude of the absorption and subsequent distribution and excretion are the parameters that, to a large extent, govern the toxic effects of the orally ingested elements.

These metals and metalloids are ingested as part of the diet. Currently, numerous studies show that some components of the diet could modulate the toxicity of these food contaminants. This modulation can take place on various levels, and in some cases it can be beneficial by bringing about a reduction in the toxicity of the metal/metalloid. The present review provides a compilation of existing information about the effect that certain components of the diet have on the toxicokinetics and toxicity of the metals and metalloids of greatest toxicological importance that are present in food (Cd, As, Hg, and Pb). For As and Hg, the review concentrates on the most toxic forms that exist in water and food: inorganic As [arsenite As(III) and arsenate As(V)], methylmercury (CH_3Hg), and inorganic divalent mercury [Hg(II)].

Diet modifies the toxicokinetics of metals and metalloids

Studies on toxicokinetics in metals and metalloids have mainly been conducted by dosing laboratory animals through drinking water or by gavage, using saline solutions of standards. However, in many cases these toxic elements that are present in the food matrix are bound to proteins or molecules of some other kind, and during digestion they are not always released in a chemical form similar to that of the standards that are commercially available. The form of these contaminants that is available for absorption may be different, depending on the food, and therefore also the mechanisms involved in their absorption. Moreover, once the toxic elements have been released from the matrix in the lumen, they may interact with other compounds derived from the digestion. These interactions may modify transport across the intestinal epithelium, or may even cause formation of complexes that are insoluble and, therefore, not

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absorbable. Furthermore, components of the diet may affect intestinal transport by competing with metals and metalloids for the same transport mechanisms. Therefore, it is necessary to consider the diet when evaluating intestinal absorption of these contaminants ingested orally, as it may modulate this process.

Cadmium toxicokinetics

Intestinal absorption of Cd is characterized by high accumulation in the intestinal mucosa and a low rate of transfer into the organism (Elsenhans et al., 1997). Indeed, it has been reported that after inorganic Cd ingestion, only 0.5–8% is absorbed in rodents. In humans, the average amount absorbed varies between 2.9% (males) and 7.5% (females) (Flanagan et al., 1978). The bioavailability of Cd from food is also low. In fact, in rats the bioavailability of Cd in drinking water is not significantly different from the bioavailability of Cd in food when dosages are less than 4 mg/kg body weight (bw)/day (Ruoff et al., 1994). Vahter et al. (1996) evaluated absorption of Cd in women fed a diet containing shellfish once a week or more (median intake 22.3 μg Cd/day) and demonstrated almost complete elimination by feces, indicating a low average absorption of dietary Cd.

The role of intracellular metallothioneins (MT) in Cd absorption is controversial. According to Ohta and Cherian (1991), although the intracellular presence of MT in the gastrointestinal epithelium does not affect uptake of Cd from the lumen, it may reduce both the release of Cd from the intestine and its eventual deposition in the liver. However, other studies show that the absorption and initial distribution of orally administered Cd is dose dependent but not influenced by MT (Liu et al., 2001).

After absorption, the main storage sites for Cd in the body are the liver and the kidneys, especially the renal cortex (Piotrowski et al., 1996; Hiratsuka et al., 1999). The retention of Cd in various tissues is MT-dependent (Klaassen et al., 2009). The rate of urinary excretion in humans of Cd accumulated in the kidneys is estimated at 0.000042/day, corresponding to a half-life of 45 years (Fransson et al., 2014).

The low intestinal absorption and accumulation in organs increases when there are certain mineral deficiencies in the diet. Intestinal absorption of Cd is influenced by body iron (Fe) status. In human subjects, the average absorption of 25 μg of Cd from a test meal was 8.9 $\pm$ 2.0% in 10 people with low body Fe stores (serum ferritin $\sim$ 20 ng/mL), and 2.3 $\pm$ 0.3% in 12 subjects with normal Fe stores (serum ferritin $>$ 23 ng/mL) (Flanagan et al., 1978). It is believed that this is a result of the participation in the transport of Cd of the main intestinal transporters of Fe [divalent metal transporter 1 (DMT1, SLC11A2) at apical level and ferroportin 1 (FPN1, MTP1, SLC40A1) in the basolateral domain of the mucosa]. Park et al. (2002) indicate that functional DMT1 protein is upregulated in the small intestine by body Fe depletion, and that upregulation probably increases Cd uptake from the gastrointestinal tract. Ryu et al. (2004) found a correlation between expression of duodenal DMT1 and FPN1 and Cd body burden, which suggests an important role of Fe transporters in Cd absorption. Elevated Cd absorption in animals with a dietary deficiency of Fe results in a greater accumulation of this metal in the small intestine, liver, and kidneys (Flanagan et al., 1978).

Deficiency in zinc (Zn) also leads to an increase in Cd absorption. Vance and Chun (2015) found a relationship between Zn status and Cd blood levels in US adults. In adjusted regression models, a 10% increase in serum Zn was associated with a 2% decrease in blood Cd and a 4% increase in urinary Cd. Waalkes (1986) also found that Zn-deficient diets in rats markedly enhanced accumulation of Cd in the liver, kidney, and testes. Ohta and Cherian (1991) explained this effect in terms of induction of synthesis of intestinal MT after oral feeding with Zn salts. They suggested that a high intestinal MT contents reduce transfer of Cd from the intestine to the liver owing to greater accumulation in the intestinal mucosa. However, Reeves et al. (2005) later demonstrated that MT induction is not involved in duodenal Cd accumulation in animals with marginal Zn dietary status. Sarić et al. (2002) also reported a reduction in the quantity of Cd in organs and carcasses of suckling rats exposed orally to Cd (0.5 mg/kg bw/day) co-administered with calcium (Ca, 1–6%). This reduction produced by Ca was not found after parenteral Cd exposure, indicating that the interaction took place at a gastrointestinal level.

Dietary fiber also has an effect on intestinal absorption and tissue accumulation of Cd. Berglund et al. (1994) showed that fecal Cd corresponded to 93% in a mixed-diet group and 100% in a high-fiber diet group, indicating an inhibitory effect of fiber on gastrointestinal absorption of Cd. House et al. (2003) demonstrated that the bioavailability of Cd in rats was depressed when wholegrain wheat, rich in fiber, was part of the regular diet. Turecki et al. (1994), using everted rat intestinal sacs, showed that, in the presence of Ca, phytic acid reduced transport of Cd across the intestinal wall and the percentage of Cd retained by intestinal tissue. The formation of insoluble phytate–Ca–Cd complexes appears to be the mechanism responsible for this protective effect. The greatest decrease was observed at a Ca:phytic acid molar ratio of 5:1, the ratio of maximum precipitation of phytic acid by Ca. Wing (1993) also found that accumulation of Cd in liver and kidneys was 34–48% lower in rats fed on whole-wheat or wheat-bran diets compared with rats fed on a low-fiber diet.

The effect of proteins on gastrointestinal absorption of Cd has also been demonstrated, and it seems to depend on the length of the treatment. Lower levels of Cd in the liver, kidney, and whole body were observed in mice fed high-protein diets for 24 hours before and after an oral dose of ^{115}Cd (Revis and Osborne, 1984). However, in long-term exposures the high-protein diet was associated with high tissue levels of Cd (Revis and Osborne, 1984). Kojima et al. (1985) showed that the type of protein is also a factor to be taken into account. They demonstrated that glycinin and ovalbumin significantly depressed gastrointestinal absorption of Cd, decreasing the contents of Cd in liver, kidneys, spleen, and testes; however, gelatin did not have this effect. They determined the Cd-binding capacity of gastrointestinal digests of glycinin and gelatin and showed that gelatin has a low ability to chelate this metal.

There have also been reports on intestinal Cd-sequestering properties of probiotics. Zhai et al. (2013) showed that *Lactobacillus plantarum* CCFM8610 produced an increase in fecal excretion, and therefore, a reduction in intestinal

absorption and in accumulation of Cd in the liver and kidneys after acute exposures. They demonstrated that the reduction was more notable when the probiotic treatment occurred after intake of the metal. The protective effect observed in acute exposures was also observed in prolonged treatments (8-week treatment period; Zhai et al., 2014). The authors showed that not all bacterial strains have this capability, as the commercial yogurt starter culture *Lactobacillus bulgaricus* CCFM8004 failed to reduce organ accumulation (Zhai et al., 2013).

Arsenic toxicokinetics

Absorption of the inorganic forms of As has been shown to be high in laboratory animals. A study conducted by Juhasz et al. (2006) demonstrated very high absolute bioavailability in swine for As(III) (103.9 ± 25.8%) and for As(V) (92.5 ± 22.3%). In monkeys, the estimated absolute As(V) bioavailability was slightly lower, 74.4 ± 4.7% (Roberts et al., 2002). After absorption, inorganic As is mainly transformed in the liver by the action of arsenic (+3 oxidation state) methyltransferase (AS3MT) into a series of mono- and dimethylated metabolites with oxidation states +3 and +5, which may be bound to thiol groups (Thomas et al., 2007; Figure 1). Dimethylated forms (DMA) are the final products of the process, so a greater presence of these forms indicates an adequate progress of the metabolic process. Contrarily, accumulation of monomethylated species (MMA), intermediate metabolites, or of inorganic As indicates a lower rate of metabolism. This metabolic process affects As tissue distribution and excretion. Indeed, *As3mt* knockout mice retain significantly higher percentages of inorganic As and present slower whole body clearance than do wild-type mice (Drobna et al., 2009).

Various studies on the distribution of inorganic As in rodents show that it depends on the oxidation state, dose, and type of dosage. In general, tissue concentrations are substantially lower for the pentavalent form of inorganic As than for the trivalent form. It has also been shown that the profile of accumulated metabolites depends on the duration of the treatment. Two hours after a single oral exposure of As(V) (0.5 mg As/kg), DMA was the predominant form in the liver (Kenyon et al., 2005). After nine repeated exposures the proportion of DMA decreased, while the proportion of inorganic

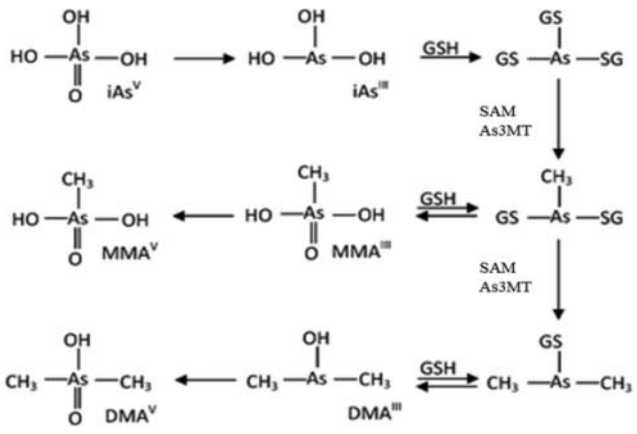

Figure 1. Inorganic arsenic metabolism.

As increased, probably owing to a saturation of the metabolic pathway (Hughes et al., 2003). In normal conditions, As is excreted primarily in the urine, with DMA(V) being the main product eliminated.

Kenyon et al. (1997) showed that dietary selenium (Se) status alters As metabolism and disposition. Arsenic methylation decreased in mice on a high-Se diet, probably owing to depletion of S-adenosylmethionine (SAM) pools, the methyl donor in the metabolism of inorganic As (Figure 1). According to those authors, this may lead to higher or longer As retention in tissues of animals on a Se-excessive diet. In contrast, when working in conditions of sufficient but not excessive Se, it can bring about a reduction in retention of As in tissues. Gregus et al. (1998) found that selenite [Se(IV)] increased biliary excretion of inorganic As in rats exposed intravenously, with the increase in As(V) excretion (7.8-fold) being larger than that of As(III) (2.4-fold). Structural studies of the bile of rabbits exposed to As(III) and Se(IV) by means of X-ray absorption spectroscopy revealed the presence of seleno-bis (S-glutathionyl) arsinium ion, $[(GS)_2AsSe]^-$, formed from As (III), Se(IV), and glutathione (GSH; Gailer et al., 2000).

Folic acid, a vitamin essential for biosynthesis of SAM, also affects the toxicokinetics of inorganic As. A double-blind placebo-controlled trial in a population in Bangladesh with low plasma folate showed that after 12 weeks of folic acid supplementation the proportion of total urinary As excreted as DMA increased, suggesting an improvement in As metabolism (Gamble et al., 2006). In another study conducted in Bangladesh, Heck et al. (2007) showed that other nutrients connected with methylation processes also affect metabolism and accumulation of inorganic As. Dietary intakes of cysteine, methionine, vitamin B-12, calcium, and protein were inversely associated with the percentage of inorganic As in urine, indicating an increase in metabolic rate and greater excretion.

In addition to an effect on metabolism, it has also been demonstrated that there is interaction of some components of the diet with the process of intestinal absorption of inorganic As. González et al. (1995) showed that phosphate produces a pronounced decrease in intestinal absorption of As(V). These authors suggested that the reduction is because the two oxyanions share the same transport mechanisms. Later studies showed that the sodium-dependent phosphate transporters that are present in the apical membrane of enterocytes may intervene in absorption of As(V) (Villa-Bellosta and Sorribas, 2010; Calatayud et al., 2012). Clemente et al. (2016) showed, in vitro, that iron salts reduce the quantity of soluble As after digestion (bioaccessibility) of rice and seaweed, with reductions exceeding 60%. This reduction in bioaccessibility means that the quantity of As available for intestinal absorption is smaller. The effectiveness of Fe(III) in reducing bioaccessibility of As (III) (15–37%) was also shown in a study conducted by Yu et al. (2016) using an in vitro dynamic gastrointestinal digestion model (SHIME).

Bisanz et al. (2014) carried out an intervention in an African population to study the effect of probiotics on plasma levels of As. In this study, during a period of 24 days they administered either a locally produced yogurt containing *Lactobacillus rhamnosus GR-1* (10^{10} CFU/250 g) or an equivalent portion of ultra-heat-treated milk as a control devoid of lactic acid

bacteria. The authors reported a significant reduction in As levels in the blood of the people treated with the probiotic, although it was not relevant from a toxicological point of view.

Mercury toxicokinetics

Assays on animals and humans indicate that absorption of Hg(II) is variable (1 and 38%) and depends on the degree of solubility in water of the mercury salt used (JECFA, 2011). The kidney, and specifically the pars recta of the proximal tubule, is the organ that presents the greatest accumulation of the inorganic form of Hg (Zalups, 2000). Owing to its low intestinal absorption, it is eliminated mainly through feces (JECFA, 2011). Unlike what has been observed for the inorganic forms, CH_3Hg presents absorption rates higher than 80% (EFSA, 2012a). After its absorption the highest concentrations are found in the kidneys and the liver (NRC, 2000). Approximately 80–90% of the dose absorbed is eliminated in the form of inorganic Hg through feces (US EPA, 1997; NRC, 2000). Biliary elimination plays an import role in the process of excretion of the CH_3Hg absorbed. In the liver it is conjugated with GSH, and in this form it is eliminated in the bile. At that point the intestinal microbiota comes into play, with their ability to demethylate CH_3Hg to Hg(II) (Rowland et al., 1980), which facilitates its fecal elimination.

Selenium is considered an antagonist of the toxic effect of Hg. Part of this protective effect may be due to the fact that Se affects the absorption, distribution, and elimination of the metal. In fact, in a study conducted with suckling rats exposed simultaneously to Se(IV) and Hg(II) for four days, Orct et al. (2009) showed that the Hg concentration in organs and plasma decreased with higher oral doses of Se. Magos and Webb (1977) observed the opposite effect in mice co-exposed to CH_3Hg and Se(IV) by gastric gavage. At 48 hours after administration, Se(IV)-treated animals had significantly more Hg in the brain and a decrease of Hg in blood in comparison with rats given only CH_3Hg.

Edible fats also affect the toxicokinetics of Hg(II) and CH_3Hg, although the data from studies are contradictory. Højbjerg et al. (1992), working with various kinds of fat (cod liver oil, coconut oil, and soy oil), demonstrated that the type and amount of fat in the diet affects the whole-body retention and relative organ distribution of CH_3Hg and Hg(II) administered orally to mice. However, in a study conducted with rats, Jin et al. (2007) showed that dietary fats (soy oil, seal oil, docosahexaenoic acid, fish oil, or lard) may not be a determining factor in brain/blood Hg distribution.

Fiber mainly affects the metabolism of CH_3Hg. Dietary bran increases the rate of elimination of Hg in mice dosed with CH_3Hg. The incorporation of 30% bran in the diet of mice decreased the total Hg concentration in the brain, blood, and small intestine (Rowland et al., 1986). These authors showed that there was a higher concentration of Hg(II) in the liver, kidneys, brain, and intestine of animals treated with bran. They concluded that bran exerts its effects on Hg retention by increasing the metabolic activity of the gut microflora. Milk has an effect opposite to that of bran. Landry et al. (1979) showed that a milk diet in mice enhanced reabsorption of CH_3Hg after enterohepatic circulation. They suggested that this was due to a decrease in CH_3Hg demethylation by the intestinal microflora.

Finally, mention must be made of the first intervention carried out to reduce absorption of Hg in populations by the use of probiotics (Bisanz et al., 2014). This study, cited earlier in relation to As (Arsenic toxicokinetics section), showed a significant reduction in levels of Hg in blood of pregnant women treated with *Lactobacillus rhamnosus GR-1*, although it was not effective in children.

Lead toxicokinetics

Rabinowitz et al. (1980) conducted a study with five volunteers whose controlled diet was supplemented from day 2 to day 124 with various Pb salts. Lead absorption was calculated from the difference between intake and fecal excretion. During fasting, the mean Pb absorption varied from 30 to 37%. This absorption decreased very significantly when Pb was ingested with food (7–10%). These data show that components of the diet can reduce the entry of Pb into the systemic circulation. After absorption, about 94% of the total amount of Pb in adults is accumulated in the bones versus about 73% in children; the rest is associated with soft tissues (liver, kidneys, brain). The half-life for Pb in blood and other soft tissues is about 28–36 days, but it is much longer in bones (WHO, 1995). The release of bone Pb into blood can maintain increased blood Pb concentrations for years after the end of exposure (Ambrose et al., 2000). Elimination may be accelerated in decalcification processes related to elderly people, pregnancy, acidosis, thyrotoxicosis, or active remodeling processes in the bones of children (WHO, 2001).

As with the other toxic elements evaluated in this review, the presence of some minerals affects intestinal absorption of Pb and its accumulation in tissues. Bradman et al. (2001) demonstrated a correlation between Fe-deficient diets and a higher concentration of Pb in blood in children living in highly contaminated environments. Flanagan et al. (1979) suggested that Pb absorption occurs by two simultaneous processes: the first is a diffusion-type mechanism, and the second is a carrier-mediated process, which is enhanced by feeding a low-Fe diet. Later studies demonstrated that, like Cd, Pb can be transported by DMT1, which transports Pb and Fe with similar affinity (Bannon et al., 2002). Thus, in situations of Fe deficiency, the expression of this transporter in the intestine increases, which indirectly leads to an increase in the transport of Pb. This would explain why supplementation with Fe only brings about a reduction in absorption of Pb in populations with anemia. Rosado et al. (2006) gave Fe supplementation to a population of children with normal Fe status who attended elementary schools located within a 3.5 km radius of a metal smelter ($n = 602$) and, they did not observe a reduction in blood Pb levels.

Mahaffey et al. (1986) showed that dietary Ca intake was inversely associated with blood Pb level, after the examination of 2926 children. In a randomized, double-blind, placebo-control trial, Hernández-Avila et al. (2003) showed that supplementation with Ca (1200 mg/day) among lactating women reduced maternal blood Pb levels (15–20%) over the course of lactation. Several studies also demonstrate that Ca supplementation

reduces Pb absorption and accumulation in osseous and non-osseous tissues in animals (Mahaffey, 1990). The mechanism by which systemic homeostasis of Ca affects the entry and accumulation of Pb has proved to be complex (Fullmer, 1990). Studies show that the major interactions between these two elements are mediated via changes in blood concentration of the metabolite of vitamin D, 1,25 dihydroxyvitamin D3 [1,25$(OH)_2$D3], rather than direct effects on the intestine (Fullmer, 1997). In diets deficient in Ca there is an increase in synthesis of 1,25$(OH)_2$D3, the major regulator of intestinal Ca absorption, which stimulates Ca^{2+} transporter proteins at the intestinal level (Christakos, 2012). It is believed that Pb can be transported by these proteins, especially during their translocation inside the epithelium and in their passage across the basolateral domain (Diamond, 2000). Therefore, a Ca deficiency would favor intestinal transport of Pb. Phosphate has an effect similar to that of Ca. The presence of high concentrations of phosphate results in lower absorption of Pb, which is connected with the formation of highly insoluble salts with Pb (Barton and Conrad, 1981). Mykkanen et al. (1984) also link the effect of phosphate to 1,25$(OH)_2$D3, as phosphate deficiency is known to enhance its production.

Hart and Smith (1981) showed that cholecalciferol (vitamin D3) supplementation resulted in increased net intestinal absorption of Pb and uptake into femurs and kidneys. They demonstrated that the increased Pb tissue uptake was not a consequence of a direct effect of cholecalciferol on gastrointestinal Pb absorption. The effect of vitamin D3 on absorption and retention of Pb may be due to an action similar to that reported for Ca and P, an increase in the blood level of its renal metabolite 1,25$(OH)_2$D3.

Vitamin C (ascorbic acid) is another nutritional factor associated with Pb levels in blood and tissues. A cross-sectional analysis of 19,578 participants suggests that high serum levels of ascorbic acid are associated with decreased blood Pb levels (Simon and Hudes 1999). Dalley et al. (1989) demonstrated that in the presence of vitamin C (intraperitoneal dose), Pb concentrations in femur, kidneys, and liver of rats were reduced by 56, 22, and 41%, and the half-life of Pb in femur and plasma decreased by 27 and 51%, respectively. The effect of ascorbic acid on Pb is related to its chelating ability (Simon and Hudes, 1999). However, this effect does not always appear, for example, in a study conducted with suckling rats treated with a daily oral dose of vitamin C (650 mg/kg bw) and Pb (2 mg/kg bw) during eight days, Varnai et al. (2003) showed that ascorbic acid supplementation did not reduce Pb retention; in fact, they even detected an increase in Pb concentration in the carcass. These contradictory data among studies may be due to differences in the type of dosage of vitamin C (intraperitoneal versus oral) and the age of the animals (adults versus suckling rats).

Dietary fiber is another food component that affects metabolism of Pb. A study conducted with rats fed on diets with different fiber sources (cellulose, pectin, guar gum, or carboxymethylcellulose) and 0.1% of Pb for four weeks showed that guar gum is the most effective fiber for reducing absorption of Pb and accumulation of it in femurs, kidneys, and liver (Kim and Lee, 1990).

Macronutrients have also been linked to the toxicokinetics of Pb. High fat diets increased blood and liver Pb concentration in rats fed with diets containing 0.075% $PbCl_2$ (Barltrop and Khoo, 1975, 1976). The authors suggested the possibility that Pb, fatty acids, and perhaps bile salts could form a soluble diffusible complex in the intestine, which might be more readily absorbed. The effect of protein is concentration-dependent. Diets with 10–15% protein have no effect on Pb absorption; diets with low protein (<5%) increase Pb concentrations in blood, kidney, liver, femur, and spleen, and diets with high protein (40–80%) result in greater Pb concentrations in kidneys and femurs (Barltrop and Khoo, 1975).

Finally, it has also been shown that probiotics can have an effect on the toxicokinetics of Pb. Tian et al. (2012) demonstrated that living and dead cells of *Lactobacillus plantarum* CCFM8661 decreased Pb levels in mice blood and tissues in an oral co-administration assay, suggesting that this metal forms complexes with lactic bacteria in the intestinal lumen.

Diet modifies the toxic effect of metals and metalloids

It has been shown that some components of foods can counteract the toxic effect of metals and metalloids. Part of this protective effect may be due to a decrease in intestinal absorption and in tissue accumulation of the toxic element. It may also be a consequence of an ability to counteract the toxicity directly by their antioxidant and/or anti-inflammatory activity, among other things. Micronutrients such as vitamin E, vitamin C, polyphenols, carotenoids, Se, and minerals mitigate oxidative stress through their radical-scavenging capacity (Fang et al., 2002; Brewer, 2011). It has also been reported that some nutrients such as n-3 polyunsaturated fatty acids or polyphenols have anti-inflammatory properties (Calder, 1998; González et al., 2011). The extent to which these compounds can moderate the effects of toxicant exposure is still poorly explained (Colacino et al., 2014).

Modulation of cadmium toxicity

The International Agency for Research on Cancer (IARC) has classified Cd and Cd compounds as group 1 human carcinogens by inhalation (IARC, 1993); however, oral exposure is not associated with greater prevalence of cancer. The most serious chronic effect of oral exposure to Cd is renal toxicity. The first sign of Cd-induced renal lesions is tubular proteinuria, which results from damage to proximal tubular cells (UNEP, 2010). There have also been reports about effects on the skeletal (Berglund et al., 2000) and the reproductive systems (Thompson and Bannigan, 2008). The toxicity mechanisms of this metal are very diverse (Waisberg et al., 2003; Matović et al., 2011; Bernhoft, 2013): induction of oxidative stress, inflammation, interactions with essential elements such as Zn and magnesium (Mg), alteration in gene expression, inhibition of DNA repair, and alteration of cellular signaling pathways.

The fact that some components of the diet reduce absorption and tissue accumulation of Cd (Cadmium toxicokinetics section) is a first indication that the diet can reduce the toxicity of Cd ingested orally. Colacino et al. (2014) examined associations between the antioxidant and anti-inflammatory dietary potential and markers of oxidative stress and inflammation associated with Cd exposure. They concluded that dietary interventions may provide a route to reduce the impact of Cd toxicity on the population level. So far, however, there have not

been interventions aimed at palliating the effects existing in populations exposed to Cd.

In laboratory animals, it has been shown that the administration of minerals reduces the toxicity of Cd. Amara et al. (2008) demonstrated that Zn administration (40 mg/L) minimized oxidative damage and reversed the impairment of spermatogenesis and testosterone production induced by subchronic oral exposure to $CdCl_2$ (40 mg/L, 30 days). This may be attributable to a smaller absorption of Cd and/or induction of MT owing to the administration of Zn. It is thought that the increased MT binds Cd in the cytosol, thus reducing Cd content in critical organelles (Goering and Klaassen, 1983). Several studies show high susceptibility to Cd toxicity in MT I/II/III-null mice (Habeebu et al., 2000; Honda et al., 2010). Zinc protection against Cd-induced oxidative stress may also be due to its role in the antioxidant machinery of the cell, acting as a cofactor of the enzyme copper-zinc superoxide dismutase.

The protective effect of administration of Fe on the oxidative stress generated by Cd has also been shown in rats (Jamakala and Rani, 2014). These authors showed that combining Fe and Zn is more effective than individual treatments with these elements. Groten et al. (1991) also showed that a combination of minerals, specifically Ca, P, Zn, and Fe, reduces anemia, plasma transaminase activities, and alterations of Fe metabolism caused by Cd.

Protection against hepatic, renal, skeletal, and reproductive disorders caused by exposure to Cd has also been shown after administration of polyphenols with substantial antioxidant activity, such as naringenin (Renugadevi and Prabu, 2009), quercetin (Renugadevi and Prabu, 2010), curcumin (Oguzturk et al., 2012), or polyphenolic extracts of plants such as green tea (Muhammed, 2014), *Aronia melanocarpa* berries (Brzóska et al., 2015), or garlic (Ayakeme et al., 2012). Argüelles et al. (2012) found that oral administration of grapefruit juice to pregnant rats during days 0 to 17 of gestation provides teratogenic and genotoxic protection against Cd exposure, which they assumed to be related to its antioxidant potential.

The use of lactic acid bacteria has also proved to be effective in reducing the toxic effect of Cd. After treatment of male Wistar rats for five weeks with $CdCl_2$ (70 mg/L in drinking water) and a mixture of lyophilized bacteria [*Lactobacillus rhamnosus, L. acidophilus*, and *Bifidobacterium longum* (5×10^8 CFU/g of food)], probiotics significantly reduced Cd-induced genotoxicity (around 20%) (Jama et al., 2012). The authors suggested binding of Cd to probiotic bacteria as the most probable protection mechanism. Zhai et al. (2014) also showed that *L. plantarum* CCFM8610 (10^9 CFU once daily by gavage) reduced oxidative stress caused by exposure to Cd (10 mg/mL in drinking water during eight weeks). They showed that this protection was not just a consequence of the ability of bacteria to bind Cd in the intestinal lumen. *Lactobacillus plantarum* also reduced oxidative stress when the exposure was intraperitoneal, and in this case the probiotic was unable to significantly sequester Cd in the intestine. The authors suggested that this reduction was due to induction of MT and gene expression changes in several Cd-toxicity-related pathways.

Modulation of arsenic toxicity

IARC has classified inorganic As in drinking water as carcinogenic to humans (Group 1; IARC, 2004). Most epidemiological studies show greater prevalence of cancers of skin, bladder, kidneys, and lungs in chronic exposure (Smith et al., 1999). In addition to cancerous processes, epidemiological studies have shown that chronic exposure to inorganic As also increases the prevalence of type 2 diabetes (Wang et al., 2014), vascular diseases (Tseng et al., 2005), and alterations in childhood development and cognitive ability (Tyler and Allan, 2014). The mechanisms of action of inorganic As are multiple and depend on its oxidation state (Hughes, 2002). Arsenate [As(V)] can replace phosphate in many biochemical reactions owing to the physicochemical similarity of these two oxyanions (Tawfik and Viola, 2011). On the other hand, arsenite [As(III)] acts mainly by binding to thiol groups of molecules (Shen et al., 2013). Some proposed mechanisms of action for inorganic As carcinogenesis include genotoxicity, cell proliferation, altered DNA repair and DNA methylated oxidative stress, co-carcinogenesis, and tumor promotion (Hughes, 2002).

Numerous studies have shown that the toxicity of inorganic As depends partly on its metabolism. It has been reported that an enhancement of the metabolic process is linked to a reduction of the risk of As-related health outcomes. In fact, persons whose urine contains low proportions of dimethylated forms (DMA) and high proportions of monomethylated species (MMA) or inorganic As are at greater risk of skin and bladder cancers and peripheral vascular diseases (Kile et al., 2011). Furthermore, it is also believed that nutrition is an important susceptibility factor in As toxicity (Vahter, 2007).

Selenium is one of the components of the diet whose antagonist role has been most analyzed. Some population studies support the protective effect of this element, for example, in a case-cohort study, Chen et al. (2007) concluded that dietary Se intake may reduce the incidence of premalignant skin lesions among populations exposed to As from drinking water. Studies in animals showed that diets based on high-Se lentils counteract As toxicity and reduce As-related atherosclerosis (Sah et al., 2013; Krohn et al., 2016a). Based on these studies, Krohn et al. (2016b) are currently conducting an intervention using high-Se lentils in communities of Bangladesh, where As levels in tube well water frequently exceed 50 ng/L. Sun et al. (2014) hypothesize that there are two types of interactions between As and Se; at low concentration Se can decrease As toxicity, but at high concentration excessive Se can enhance As toxicity. The reduction in toxicity brought about by Se may be connected with increased biliary excretion of As (see the arsenic toxicokinetics section). With regard to the enhancement of the toxicity of As, Styblo and Thomas (2001) showed that micromolar Se(IV) concentrations inhibited methylation of As in rat hepatocytes. Song et al. (2010) suggested that this inhibitory effect of Se(IV) on AS3MT activity may be via interactions with free cysteine residues of the enzyme to form inactive protein adducts. In addition to inorganic Se, the effect of organic forms of Se has also been evaluated. Rodríguez-Sosa et al. (2013) showed that supplementation with selenomethionine (0.2 and 2 mg/L) improved basal immunological parameters (maintenance of CD4/CD8 ratio of lymphocytes in the spleen) but did not reduce damage caused by oxidative stress after exposure of mice to As(III) (3–10 mg/kg, nine days).

Evaluations of the potential protective role of Zn in mitigating adverse effects of inorganic As exposure have also been

conducted. Ahmad et al. (2013) demonstrated a perinatal protective effect of Zn on mice offspring exposed to inorganic As. Prenatal exposure to As(V) (40 mg/kg bw/day) caused delay in morphological development and retardation in the development of all sensory motor reflexes of pups and a decrease in motor behavior in young mice. However, animals exposed to As(V) in the presence of Zn (40 mg/kg bw/day) showed a remarkable reduction in all observed teratological effects, which is attributable to the antioxidative role of Zn. Other dietary antioxidants have also proved to be effective in reducing the toxicity of inorganic As in laboratory animals. Kadirvel et al. (2007) demonstrated that co-administration of ascorbic acid (200 mg/kg bw/day) or α-tocopherol (400 mg/kg bw/day) to As(III)-exposed rats (100 mg/L in drinking water for 30 days) produced a substantial reduction in As-induced oxidative stress, with reductions in the levels of protein oxidation, DNA strand breaks, and DNA–protein cross-links. Curcumin has proved to be effective in ameliorating As(III)-induced hepatotoxicity, by decreasing hepatic lipoperoxidation and serum alanine and aspartate aminotransferases activity, as well as increasing blood and hepatic GSH levels (Gao et al., 2013). These authors demonstrated that part of this protection is through activation of the Nrf2 pathway and promotion of arsenic methylation and urinary excretion. The effects of curcumin against As genotoxicity were also proven in field trials conducted in West Bengal (Biswas et al., 2010; Roy et al., 2011). The main problem with this antioxidant is its low bioavailability, which makes it necessary to administer large concentrations to achieve therapeutic doses. To overcome this handicap, curcumin nano-encapsulated in chitosan has been employed, achieving reductions in As(III) toxicity at a much lower dose than with free curcumin (Yadav et al., 2012). Other plant antioxidants that have demonstrated their usefulness in the reduction of As(III)-induced oxidative stress are β-carotene (Das et al., 2015), naringenin (Roy et al., 2014), and tea polyphenols (Raihan et al., 2009).

The study of effectiveness in reducing the toxicity of compounds that modulate the metabolism of inorganic As has concentrated on folate. Persons possessing polymorphisms in certain genes involved in folate metabolism excrete a lower proportion of urinary As as DMA, which may influence susceptibility to As toxicity (Kile and Ronnenberg, 2008). In a case–control study of 177 urothelial carcinoma cases and 488 controls in a population exposed to low concentrations of As in drinking water, the authors found that higher plasma folate concentrations were associated with a decreased risk of carcinoma (Huang et al., 2008). Similarly, nutrients involved in the generation of SAM, such as methionine, homocysteine, choline, betaine, and vitamin B12, may influence the toxicity of this metalloid (Gamble et al., 2005).

Modulation of mercury toxicity

As happens with arsenic, the toxicity of Hg largely depends on the chemical form in which it is present. CH_3Hg is classified by IARC (1993) as possibly carcinogenic to humans. Renal tumors have been observed in mice chronically exposed to CH_3HgCl (Mitsumori et al., 1990). Inorganic Hg is included in group 3, not classifiable as carcinogenic to humans (IARC, 1993). CH_3Hg is a neurotoxic compound and also affects fetal development. Prenatal exposure has been associated with neurodevelopmental delays and cognitive deficits (Grandjean et al., 1997). The main target organ of Hg(II) is the kidney. Long-term studies (two years, dosing five days/week, concentrations of 0.3–5 mg/kg bw/day) in rats showed a high incidence of nephropathy, characterized by tubule regeneration, basement membrane thickening, and dilated tubules containing hyaline casts (NTP, 1993). The molecular mechanisms involved in the toxicity of Hg are related to its high affinity for molecules that present thiol groups (proteins or peptides), because this binding makes these molecules susceptible to structural and functional modifications. Furthermore, some studies indicate that Hg can affect the expression of numerous genes connected with control and regulation of the cell cycle, transcription factors, components of the DNA repair machinery, and some signaling pathways (Syversen and Kaur, 2012).

Various studies with animals have shown that the dietary Se/Hg ratio is an important variable in the risk associated with exposure to CH_3Hg (Fredriksson et al., 1993; Ralston et al., 2007). This mercury species is highly inhibitory of Se-dependent enzymes, which are required to prevent and reverse oxidative damage. Inhibition of selenoenzyme activities appears to be one of the causes of CH_3Hg toxicity, which takes place as a result of the ability of CH_3Hg to sequester Se (Ralston and Raymond, 2010). An excess of Se with respect to CH_3Hg in the diet reduces this enzymatic inhibition, because there is always Se available for synthesis of selenoenzymes. Although most of the studies refer to the protective effect of inorganic Se, this role has also been shown for organic Se, which is the major form in food. Sakamoto et al. (2013) demonstrated the protective effects of selenomethionine against CH_3Hg-induced neurotoxicity in the developing rat cerebrum. Another element that has been studied as a possible protector, in this case only for Hg(II), is Zn (Fukino et al., 1984; Peixoto et al., 2003; Franciscato et al., 2011). This antagonism is related to synthesis of metallothioneins and to participation of Zn in the cell antioxidant system (Fukino et al., 1984; Peixoto et al., 2003).

The action of polyunsaturated acids (PUFA) is also due to their antioxidant capacity. The association of PUFA with Hg toxicity is complex. The findings of the Seychelles Child Development Nutrition Study showed, after adjusting for model covariates, that larger maternal n-3 PUFA levels were associated with improved psychomotor developmental index scores in children (Stokes-Riner et al., 2011). In a study conducted by Jin et al. (2007), in which they evaluated the effect of various kinds of fat (soy oil, seal oil, docosahexaenoic acid, fish oil, and lard) on the toxicity of CH_3Hg in rats, the authors showed that dietary fats modulate CH_3Hg toxicity, which may translate into more severe or protective clinical outcomes. For example, the seal oil diet provided more resistance, while the fish oil diet rendered greater sensitivity to the effects of CH_3Hg on the immune system.

Some vitamins have also been noted as antagonists of the toxic effect of Hg. In a study conducted in rats treated with CH_3Hg (2.0 mg/kg bw/day), the animals presented morphological changes in neuronal cell bodies and in dorsal root fibers. In the animals co-administrated with vitamin E (50 mg/kg bw/day), these negative effects were not observable (Yip and

Chang, 1982). Vitamin C has also proved to be effective. In mice treated with $HgCl_2$ (65 mg/L) for 28 days through drinking water, reductions were observed in hematological parameters, together with an increase in hepatic enzymes and liver and kidney lesions. All these toxic effects decreased in the presence of vitamin C (250 mg/L) or vitamin E (100 mg/L), although a combination of both vitamins was the most effective treatment (Huq et al., 2008). A combination of vitamin C and folic acid also showed an antagonistic effect in chick embryos treated with CH_3Hg (2.5 mg), reducing the teratogenic effects observed when CH_3Hg was injected into fertilized eggs (Bekhet et al., 2013).

There are also studies concerning natural extracts or supplements that reduce the effect of Hg. The cyanobacterium *Spirulina platensis* has been shown to have a protective effect on Hg(II)-induced oxidative damage and histopathological alterations in the testis of rats (El-Desoky et al., 2013). Aqueous extract of *Ocimum sanctum* (Sharma et al., 2002), extract of leaves of *Ginkgo biloba L.* (Sener et al., 2007), and *Bacopa monniera* extract (Sumathi et al., 2012) are some of the plant extracts that have been used to reduce oxidative tissue damage produced by Hg(II) or CH_3Hg in rodents.

Modulation of lead toxicity

Inorganic Pb and Pb compounds are classified as probably carcinogenic to humans (group 2A; IARC, 2006). Lead acetate administered orally or intraperitoneally causes kidney, brain (gliomas), and lung cancers in rodents, and acts synergistically with other carcinogens (Steenland and Boffetta, 2000). Several studies have focused on cancer risks among workers exposed to Pb, in which stomach cancer was consistently elevated, and which also showed a greater risk of lung cancer and gliomas (Steenland and Boffetta, 2000). However, in most of these studies there are various uncertainties that cast doubt on the results (no direct exposure data, no inclusion of important confounders, low sample size, co-exposure with other possible carcinogens). The most sensitive end-points for Pb toxicity are those related to neurodevelopmental, cardiovascular, renal, and hematological disorders (ATSDR, 2007). Many studies report negative associations between intellectual function and increased blood Pb in children (Téllez-Rojo et al., 2006; Roy et al., 2009). Lead has multiple mechanisms of action at many different levels that affect many enzyme systems and cellular processes (ATSDR, 2007). Oxidative stress plays an important role in pathogenesis of Pb-induced toxicity; heme synthesis enzymes, thiol-containing antioxidants, and enzymes (superoxide dismutase, catalase, GSH peroxidase, glucose 6-phosphate dehydrogenase) are prime targets of this metal (Nemsadze et al., 2009). Its ability to substitute other divalent cations such as Ca, Mg, and Fe, and monovalent cations such as sodium (Na) also affects various fundamental biological processes (Flora et al., 2012).

As occurs with Cd, the minerals that influence absorption of Pb also reduce its toxic effect. Prasanthi et al. (2006) demonstrated that Zn or Ca (0.02–0.1%) administered together with Pb (0.2–1%, postnatal day 1–21) reduces aberrations produced in cognitive and non-cognitive behavior in rats. It has been shown that Ca and Zn supplementation reverses Pb-induced alterations in the aminergic system of the developing mouse brain by recovery in monoamine levels and monoamine oxidase activity (Jaya Prasanthi et al., 2005). This supplementation also reduces effects on antioxidant enzymes, lipid peroxidation, and free radical formation (Prasanthi et al., 2010). Another mineral that has been reported as a protector against the toxicity of Pb is Se, in this case because of its antioxidant capacity. A study conducted in *Caenorhabditis elegans*, established as a model for studying neurotoxicity, showed that Se(IV) (0.01 μM) pretreatment ameliorated the decline of locomotion of *C. elegans* produced by Pb (100 μM), mainly by reducing accumulation of intracellular reactive oxygen species (ROS; Li et al., 2013).

Dietary antioxidants are the compounds that have been most investigated as reducers of the toxic effects of Pb (Hsu and Guo, 2002). Patra et al. (2001) showed that treatment with ascorbic acid, α-tocopherol, and L-methionine (daily dose of 100 mg/kg bw) results in reversal of oxidative stress in kidney, liver, and brain of rats exposed to Pb (1 mg/kg bw, four weeks) without a significant decline in tissue burden. Vitamin E reduces the impact of Pb toxicity in the male genital organs (degenerative changes in the seminiferous tubules and cellular abnormalities in testosterone-producing cells; El-Tohami and Ali, 2014). Liu et al. (2012) showed inhibition of Pb-induced kidney inflammation by quercetin. They suggested that this was due to its antioxidant activity and its ability to modulate the MAPK and NF-κB signaling pathway. Rats exposed to Pb acetate (500 mg/L) for 75 days with quercetin co-administration (25 and 50 mg/kg) presented kidney antioxidant capacity and plasma levels of proinflammatory cytokines IL-1β, IL-6, and TNF-α similar to those observed for control groups. The reduced and oxidized form of lipoic acid, another powerful antioxidant, can chelate Pb, although it has been shown that its protection against the toxicity of Pb may be due to its potential for bolstering thiol antioxidant capacity (Gurer et al., 1999).

Extracts of plant origin with known antioxidant capacity, such as garlic extract, olive leaf extract, and green tea extract, have demonstrated their effectiveness in reducing the toxicity of Pb at different levels in experimental animals (Mehana et al., 2012; Asadpour et al., 2013; Wang et al., 2013). A combination of antioxidants may have a greater protective effect against Pb than individual supplementation, as shown by Wang et al. (2007), who combined ascorbic acid and thiamine (vitamin B1). Their study also shows that at high doses the effect of antioxidants may be inverted or reduced. Wang et al. (2008) also reported that lipoic acid (25 mg/kg) rebalances the increased prooxidant/antioxidant ratio induced by Pb and repairs synaptic plasticity in rats; however, at higher concentrations (50 or 100 mg/kg) the protective effect is lower.

Studies with lactic bacteria show the effectiveness of some strains in reducing the toxicity of Pb. Living and dead cells of *L. plantarum* CCFM8661 offered a significant protective effect against Pb toxicity in rats. Probiotic treatment recovered blood δ-aminolevulinic acid dehydratase activity, and prevented alterations in the levels of GSH, GSH peroxidase, malondialdehyde, superoxide dismutase, and ROS in blood and kidneys. The treatment was more effective when administered consistently during the entire Pb exposure than after the exposure (Tian et al., 2012). The protective effect of *L. plantarum* CCFM8661

against oxidative stress is greater than that of meso-2,3-dimercaptosuccinic acid, a chelator widely used in cases of Pb poisoning.

Conclusions

This review shows that the harmful effect on human health of exposure through food and drinking water to toxic trace elements such as Cd, As, Hg, and Pb may be modulated by several dietary components. This modulation may take place during the transit of the metal(loid) along the gastrointestinal tract, due to the interactions of the toxic compound with the components of the diet, or to a direct competition for the transport mechanisms that favor their intestinal absorption. This type of interaction results in an increased fecal excretion of the metaloids. Likewise, there are dietary components that do not affect metal(loid)s toxicokinetics but exert a positive effect by counteracting the systemic toxicity generated by the metal (loid)s. This protective effect may be due to properties of the dietary component such as its anti-oxidant or anti-inflammatory capacity. Therefore, foods considered as presenting a risk because of their high concentrations of toxic metaloids may, as a result of the effect of the nutrients that they contain or of those that are provided by other foods included in the daily diet, have a lower negative effect on consumer health than might be expected. This circumstance, which has already been verified in vitro and in laboratory animals for some toxic trace element/nutrient combinations, opens up the possibility of adopting dietary strategies based on the use of food components or dietary supplements to reduce the bioavailability and/or toxicity of these food contaminants in human populations. Studies aimed at establishing the effectiveness of these strategies are proposed as a line of future research in food safety and toxicology, successful results of which could be beneficial for the food industry, vulnerable population groups, and populations chronically exposed to these contaminants.

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References

Abi-Ghanem, C., Khalaf, G. and Najjar, E. (2014). Distribution of lead, cadmium, and vanadium in Lebanese coastal sediments and mussels. *J. Coast. Res.* **30**:1074–1080.

Ahmad, M., Wadaan, M. A., Farooq, M., Daghestani, M. H. and Sami, A. S. (2013). Effectiveness of zinc in modulating perinatal effects of arsenic on the teratological effects in mice offspring. *Biol. Res.* **46**:131–138.

Almela, C., Algora, S., Benito, V., Clemente, M. J., Devesa, V., Suñer, M. A., Velez, D. and Montoro, R. (2002). Heavy metal, total arsenic, and inorganic arsenic contents of algae food products. *J. Agric. Food Chem.* **50**:918–923.

Amara, S., Abdelmelek, H., Garrel, C., Guiraud, P., Douki, T., Ravanat, J. L., Favier, A., Sakly, M. and Ben Rhouma, K. (2008). Preventive effect of zinc against cadmium-induced oxidative stress in the rat testis. *Reprod. Dev.* **54**:129–134.

Ambrose, T. M., Al-Lozi, M. and Scott, M. G. (2000). Bone lead concentrations assessed by in vivo X-ray fluorescence. *Clin. Chem.* **46**:1171–1178.

Argüelles, N., Alvarez-González, I., Chamorro, G. and Madrigal-Bujaidar, E. (2012). Protective effect of grapefruit juice on the teratogenic and genotoxic damage induced by cadmium in mice. *J. Med. Food* **15**:887–893.

Asadpour, R., Azari, M., Hejazi, M., Tayefi, H. and Zaboli, N. (2013). Protective effects of garlic aqueous extract (*Allium sativum*), vitamin E, and N-acetylcysteine on reproductive quality of male rats exposed to lead. *Vet. Res. Forum* **4**:251–257.

ATSDR (Agency for Toxic Substances and Disease Registry). (2007). *Toxicological Profile for Lead.* U.S. Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA. Available from http://www.atsdr.cdc.gov/toxprofiles/tp13.pdf. Accessed July 2, 2016.

Ayakeme, T., Ibeh, G. O., Nwinuka, M. N. and Nwachoko, N. C. (2012). Effects of garlic extract on cadmium-induced toxicity in Wistar Albino rat. *Indian J. Drugs Dis.* **1**:68–73.

Bannon, D., Portnoy, M. E., Olivi, L., Lees, P. S., Culotta, V. C. and Bressler, J. P. (2002). Uptake of lead and iron by divalent metal transporter 1 in yeast and mammalian cells. *Biochem. Biophys. Res. Commun.* **295**:978–984.

Barltrop, D. and Khoo, H. E. (1975). The influence of nutritional factors on lead absorption. *Postgrad. Med. J.* **51**:795–800.

Barltrop, D. and Khoo, H. E. (1976). The influence of dietary minerals and fat on the absorption of lead. *Sci. Total Environ.* **6**:265–273.

Barton, J. C. and Conrad, M. E. (1981). Effect of phosphate on the absorption and retention of lead in the rat. *Am. J. Clin. Nutr.* **34**:2192–2198.

Bekhet, G. M., Al-Kahtani, M. A. and Abdel-Moneim, A. M. (2013). The protective effects of vitamin C and folic acid against methylmercury teratogenicity in chick embryo. *J. Cell Anim. Biol.* **7**:77–84.

Berglund, M., Akesson, A., Bjellerup, P. and Vahter, M. (2000). Metal-bone interactions. *Toxicol. Lett.* **112–113**:219–225.

Berglund, M., Akesson, A., Nermell, B. and Vahter, M. (1994). Intestinal absorption of dietary cadmium in women depends on body iron stores and fiber intake. *Environ. Health Perspect.* **102**:1058–1066.

Bernhoft, R. A. (2013). Cadmium toxicity and treatment. *Sci. World J.* **2013**:394652.

Bisanz, J., Enos, M., Mwanga, J., Changalucha, J., Jeremy, P., Burton, J. P., Gloor, G. B. and Reid, G. (2014). Randomized open-label pilot study of the influence of probiotics and the gut microbiome on toxic metal levels in Tanzanian pregnant women and school children. *mBio* **5**:e01580–14.

Biswas, J., Sinha, D., Mukherjee, S., Roy, S., Siddiqi, M. and Roy, M. (2010). Curcumin protects DNA damage in a chronically arsenic exposed population of West Bengal. *Hum. Exp. Toxicol.* **29**:513–524.

Bradman, A., Eskenazi, B., Sutton, P., Athanasoulis, M. and Goldman, L. R. (2001). Iron deficiency associated with higher blood lead in children living in contaminated environments. *Environ. Health Perspect.* **109**:1079–1084.

Brewer, M. S. (2011). Natural antioxidants: Sources, compounds, mechanisms of action, and potential applications. *Compr. Rev. Food Sci. Food Saf.* **10**:221–247.

Brzóska, M. M., Rogalska, J., Galazyn-Sidorczuk, M., Jurczuk, M., Roszczenko, A. and Tomczyk, M. (2015). Protective effect of *Aronia melanocarpa* polyphenols against cadmium-induced disorders in bone metabolism: A study in a rat model of lifetime human exposure to this heavy metal. *Chem. Biol. Interact.* **229**:132–146.

Calatayud, M., Barrios, J. A., Vélez, D. and Devesa, V. (2012). In vitro study of transporters involved in intestinal absorption of inorganic arsenic. *Chem. Res. Toxicol.* **25**:446–453.

Calder, P. C. (1998). Immunoregulatory and anti-inflammatory effects of n-3 polyunsaturated fatty acids. *Braz. J. Med. Biol. Res.* **31**:467–490.

Chen, Y., Hall, M., Graziano, J. H., Slavkovich, V., van Geen, A., Parvez, F. and Ahsan, H. (2007). A prospective study of blood selenium levels

and the risk of arsenic-related premalignant skin lesions. *Cancer Epidemiol. Biomarkers Prev.* **16**:207–213.

Christakos, S. (2012). Mechanism of action of 1,25-dihydroxyvitamin D3 on intestinal calcium absorption. *Rev. Endocr. Metab. Disord.* **13**:39–44.

Clemente, M. J., Devesa, V. and Vélez, D. (2016). Dietary strategies to reduce the bioaccessibility of arsenic from food matrices. *J. Agric. Food Chem.* **64**:923–931.

Colacino, J. A., Arthur, A. E., Ferguson, K. K. and Rozek, L. S. (2014). Dietary antioxidant and anti-inflammatory intake modifies the effect of cadmium exposure on markers of systemic inflammation and oxidative stress. *Environ. Res.* **131**:6–12.

Dalley, J. W., Gupta, P. K., Lam, F. C. and Hung, C. T. (1989). Interaction of L-ascorbic acid on the disposition of lead in rats. *Pharmacol. Toxicol.* **64**:360–364.

Das, R., Das, A., Roy, A., Kumari, U., Bhattacharya, S. and Haldar, P. K. (2015). β-Carotene ameliorates arsenic-induced toxicity in albino mice. *Biol. Trace Elem. Res.* **164**:226–233.

Diamond, G. L. (2000). Transport of metals in the gastrointestinal system and kidneys. **In**: *Molecular Biology and Toxicology of Metals*, pp. 300–345. Zalups, R. K. and Koropatnick, D. J., Eds., New York: Taylor and Francis Ltd..

Drobna, Z., Narenmandura, H., Kubachka, K. M., Edwards, B. C., Herbin-Davis, K., Styblo, M., Le, X. C., Creed, J. T., Maeda, N., Hughes, M. F. and Thomas, D. J. (2009). Disruption of the arsenic (+3 oxidation state) methyltransferase gene in the mouse alters the phenotype for methylation of arsenic and affects distribution and retention of orally administered arsenate. *Chem. Res. Toxicol.* **22**:1713–1720.

EFSA (European Food Safety Authority). (2009). Cadmium in food. Scientific opinion of the panel on contaminants in the food chain (Question No EFSA-Q-2007-138). *EFSA J.* **80**:1–139.

EFSA (European Food Safety Authority). (2012a). Scientific opinion on the risk for public health related to the presence of mercury and methylmercury in food. *EFSA J.* **10**:1–2985.

EFSA (European Food Safety Authority). (2012b). Lead dietary exposure in the European population. *EFSA J.* **10**:1–2831.

El-Desoky, G. E., Bashandy, S. A., Alhazza, I. M., Al-Othman, Z. A., Aboul-Soud, M. A. and Yusuf, K. (2013). Improvement of mercuric chloride-induced testis injuries and sperm quality deteriorations by Spirulina platensis in rats. *PLoS One* **8**:e59177.

Elsenhans, B., Strugala, G. J. and Schäfer, S. G. (1997). Small-intestinal absorption of cadmium and the significance of mucosal metallothionein. *Hum. Exp. Toxicol.* **16**:429–434.

El-Tohami, A. A. and Ali, E. K. (2014). Effect of vitamin E supplementation on testicular tissues of mice exposed to sub-chronic lead intoxication. *Trends Med. Res.* **9**:33–43.

Fang, Y. Z., Yang, S. and Wu, G. (2002). Free radicals, antioxidants, and nutrition. *Nutrition* **18**:872–879.

Flanagan, P. R., Hamilton, D. L., Haist, J. and Valberg, L. S. (1979). Interrelationships between iron and lead absorption in iron-deficient mice. *Gastroenterology* **77**:1074–1081.

Flanagan, P. R., McLellan, J. S., Haist, J., Cherian, G., Chamberlain, M. J. and Valberg, L. S. (1978). Increased dietary cadmium absorption in mice and human subjects with iron deficiency. *Gastroenterology* **74**:841–846.

Flora, G., Gupta, D. and Tiwari, A. (2012). Toxicity of lead: A review with recent updates. *Interdiscip. Toxicol.* **5**:47–58.

Franciscato, C., Moraes-Silva, L., Duarte, F. A., Oliveira, C. S., Ineu, R. P., Flores, E. M., Dressler, V. L., Peixoto, N. C. and Pereira, M. E. (2011). Delayed biochemical changes induced by mercury intoxication are prevented by zinc pre-exposure. *Ecotoxicol. Environ. Saf.* **74**:480–486.

Fransson, M. N., Barregard, L., Sallsten, G., Akerstrom, M. and Johanson, G. (2014). Physiologically-based toxicokinetic model for cadmium using Markov-chain Monte Carlo analysis of concentrations in blood, urine, and kidney cortex from living kidney donors. *Toxicol. Sci.* **141**:365–376.

Fredriksson, A., Gårdlund, A. T., Bergman, K., Oskarsson, A., Ohlin, B., Danielsson, B. and Archer, T. (1993). Effects of maternal dietary supplementation with selenite on the postnatal development of rat offspring exposed to methyl mercury in utero. *Pharmacol. Toxicol.* **72**:377–382.

Fukino, H., Hirai, M., Hsueh, Y. M. and Yamane, Y. (1984). Effect of zinc pretreatment on mercuric chloride-induced lipid peroxidation in the rat kidney. *Toxicol. Appl. Pharmacol.* **73**:395–401.

Fullmer, C. S. (1990). Intestinal lead and calcium absorption: Effect of 1,25-dihydroxycholecalciferol and lead status. *Proc. Soc. Exp. Biol. Med.* **194**:258–264.

Fullmer, C. S. (1997). Lead-calcium interactions: Involvement of 1,25-dihydroxyvitamin D. *Environ. Res.* **72**:45–55.

Gailer, J., George, G. N., Pickering, I. J., Prince, R. C., Ringwald, S. C., Pemberton, J. E., Glass, R. S., Younis, H. S., DeYoung, J. D. W. and Aposhian, H. V. (2000). A metabolic link between arsenite and selenite: The seleno-bis(S-glutathionyl) arsinium ion. *J. Am. Chem. Soc.* **122**:4637–4639.

Gamble, M. V., Liu, X., Ahsan, H., Pilsner, J. R., Ilievski, V., Slavkovich, V., Parvez, F., Chen, Y., Levy, D., Factor-Litvak, P. and Graziano, J. H. (2006). Folate and arsenic metabolism: A double-blind, placebo-controlled folic acid-supplementation trial in Bangladesh. *Am. J. Clin. Nutr.* **84**:1093–1101.

Gamble, M. V., Liu, X., Ahsan, H., Pilsner, R., Ilievski, V., Slavkovich, V., Parvez, F., Levy, D., Litvak, P. and Graziano, J. H. (2005). Folate, homocysteine, and arsenic metabolism in arsenic-exposed individuals in Bangladesh. *Environ. Health Perspect.* **113**:1683–1688.

Gao, S., Duan, X., Wang, X., Dong, D., Liu, D., Li, X., Sun, G. and Li, B. (2013). Curcumin attenuates arsenic-induced hepatic injuries and oxidative stress in experimental mice through activation of Nrf2 pathway, promotion of arsenic methylation and urinary excretion. *Food Chem. Toxicol.* **59**:739–747.

Goering, P. L. and Klaassen, C. D. (1983). Altered subcellular distribution of cadmium following cadmium pretreatment: Possible mechanism of tolerance to cadmium-induced lethality. *Toxicol. Appl. Pharmacol.* **70**:195–203.

González, M. J., Aguilar, M. V. and Martinez Para, M. C. (1995). Gastrointestinal absorption of inorganic arsenic (V): The effect of concentration and interactions with phosphate and dichromate. *Vet. Hum. Toxicol.* **37**:131–136.

González, R., Ballester, I., López-Posadas, R., Suárez, M. D., Zarzuelo, A., Martínez-Augustin, O. and Sánchez de Medina, F. (2011). Effects of flavonoids and other polyphenols on inflammation. *Crit. Rev. Food Sci. Nutr.* **51**:331–362.

Grandjean, P., Weihe, P., White, R. F., Debes, F., Araki, S., Yokoyama, K., Murata, K., Sørensen, N., Dahl, R. and Jørgensen, P. J. (1997). Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. *Neurotoxicol. Teratol.* **19**:417–428.

Gregus, Z., Gyurasics, A. and Koszorú, S. L. (1998). Interactions between selenium and group Va-metalloids (arsenic, antimony and bismuth) in the biliary excretion. *Environ. Toxicol. Pharmacol.* **5**:89–99.

Groten, J. P., Sinkeldam, E. J., Muys, T., Luten, J. B. and van Bladeren, P. J. (1991). Interaction of dietary Ca, P, Mg, Mn, Cu, Fe, Zn and Se with the accumulation and oral toxicity of cadmium in rats. *Food Chem. Toxicol.* **29**:249–258.

Gurer, H., Ozgunes, H., Oztezcan, S. and Ercal, N. (1999). Antioxidant role of alpha-lipoic acid in lead toxicity. *Free Radic. Biol. Med.* **27**:75–81.

Habeebu, S. S., Liu, J., Liu, Y. and Klaassen, C. D. (2000). Metallothionein-null mice are more sensitive than wild-type mice to liver injury induced by repeated exposure to cadmium. *Toxicol. Sci.* **55**:223–232.

Hart, M. H. and Smith, J. L. (1981). Effect of vitamin D and low dietary calcium on lead uptake and retention in rats. *J. Nutr.* **111**:694–698.

Heck, J. E., Gamble, M. V., Chen, Y., Graziano, J. H., Slavkovich, V., Parvez, F., Baron, J. A., Howe, G. R. and Ahsan, H. (2007). Consumption of folate-related nutrients and metabolism of arsenic in Bangladesh. *Am. J. Clin. Nutr.* **85**:1367–1374.

Hernández-Avila, M., Gonzalez-Cossio, T., Hernandez-Avila, J. E., Romieu, I., Peterson, K. E., Aro, A., Palazuelos, E. and Hu, H. (2003). Dietary calcium supplements to lower blood lead levels in lactating women: A randomized placebo-controlled trial. *Epidemiology* **14**:206–212.

Hiratsuka, H., Satoh, S. I., Satoh, M., Nishijima, M., Katsuki, Y., Suzuki, J., Nakagawa, J. I., Sumiyoshi, M., Shibutani, M., Mitsumori, K., Tanaka-Kagawa, T. and Ando, M. (1999). Tissue distribution of cadmium in

rats given minimum amounts of cadmium-polluted rice or cadmium chloride for 8 months. *Toxicol. Appl. Pharmacol.* **160**:183–191.

Højbjerg, S., Nielsen, J. B. and Andersen, O. (1992). Effects of dietary lipids on whole-body retention and organ distribution of organic and inorganic mercury in mice. *Food Chem. Toxicol.* **30**:703–708.

Honda, A., Komuro, H., Shimada, A., Hasegawa, T., Seko, Y., Nagase, H., Hozumi, I., Inuzuka, T., Hara, H., Fujiwara, Y. and Satoh, M. (2010). Attenuation of cadmium-induced testicular injury in metallothionein-III null mice. *Life Sci.* **87**:545–550.

House, W. A., Hart, J. J., Norvell, W. A. and Welch, R. M. (2003). Cadmium absorption and retention by rats fed durum wheat (*Triticum turgidum L.* var. durum) grain. *Br. J. Nutr.* **89**:499–508.

Hsu, P. C. and Guo, Y. L. (2002). Antioxidant nutrients and lead toxicity. *Toxicology* **180**:33–44. DOI: 10.1016/S0300-483X(02)00380-3.

Huang, Y. K., Pu, Y. S., Chung, C. J., Shiue, H. S., Yang, M. H., Chen, C. J. and Hsueh, Y. M. (2008). Plasma folate level, urinary arsenic methylation profiles, and urothelial carcinoma susceptibility. *Food Chem. Toxicol.* **46**:929–938.

Hughes, M. F. (2002). Arsenic toxicity and potential mechanisms of action. *Toxicol. Lett.* **133**:1–16.

Hughes, M. F., Kenyon, E. M., Edwards, B. C., Mitchell, C. T., Razo, L. M. and Thomas, D. J. (2003). Accumulation and metabolism of arsenic in mice after repeated oral administration of arsenate. *Toxicol. Appl. Pharmacol.* **191**:202–210.

Huq, M. A., Awal, M. A., Mostofa, M., Ghosh, A. and Das, A. R. (2008). Effects of vitamin E and vitamin C on mercury induced toxicity in mice. *Progress Agric.* **19**:93–100.

IARC (International Agency for Research on Cancer). (1993). Beryllium, cadmium, mercury, and exposures in the glass manufacturing industry. **In**: *IARC Monographs on the Evaluation of Carcinogenic Risk to Humans*, Vol. 58, IARC, Lyon. WHO Press, 1–444.

IARC (International Agency for Research on Cancer). (2004). Summaries and evaluations: Arsenic in drinking-water (Group 1). **In**: *IARC Monographs on the Evaluation of Carcinogenic Risk to Humans*, Vol. 84, IARC, Lyon. WHO Press, 1–9.

IARC (International Agency for the Research on Cancer). (2006). Inorganic and organic lead compounds. **In**: *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Vol. 87, IARC, Lyon. WHO Press, 1–529.

Jama, A. M., Mitić-Ćulafić, D., Kolarević, S., Đurašević, S. F. and Knežević-Vukčević, J. (2012). Protective effect of probiotic bacteria against cadmium-induced genotoxicity in rat hepatocytes *in vivo* and in vitro. *Arch. Biol. Sci.* **64**:1197–1206.

Jamakala, O. and Rani, A. U. (2014). Mitigating role of zinc and iron against cadmium induced toxicity in liver and kidney of male albino rat: A study with reference to metallothionein quantification. *Int. J. Pharm. Sci.* **6**:411–417.

Jaya Prasanthi, R. P., Hariprasad Reddy, G., Bhuvaneswari Devi, C. and Rajarami Reddy, G. (2005). Zinc and calcium reduce lead induced perturbations in the aminergic system of developing brain. *Biometals* **18**:615–626.

JECFA (Joint FAO/WHO Expert Committee on Food Additives). (2011). Safety evaluation of certain contaminants in food. Seventy-second meeting of JECFA. **In**: *FAO JECFA Monographs, Vol. 8*, JECFA, Rome.

Jin, X., Lok, E., Bondy, G., Caldwell, D., Mueller, R., Kapal, K., Armstrong, C., Taylor, M., Kubow, S., Mehta, R. and Chan, H. M. (2007). Modulating effects of dietary fats on methylmercury toxicity and distribution in rats. *Toxicology* **230**:22–44.

Juhasz, A. L., Smith, E., Weber, J., Rees, M., Rofe, A., Kuchel, T., Sansom, L. and Naidu, R. (2006). *In vivo* assessment of arsenic bioavailability in rice and its significance for human health risk assessment. *Environ. Health Perspect.* **114**:1826–1831.

Kadirvel, R., Sundaram, K., Mani, S., Samuel, S., Elango, N. and Panneerselvam, C. (2007). Supplementation of ascorbic acid and alpha-tocopherol prevents arsenic-induced protein oxidation and DNA damage induced by arsenic in rats. *Hum. Exp. Toxicol.* **26**:939–946.

Kalač, P. and Svoboda, L. (2000). A review of trace element concentrations in edible mushrooms. *Food Chem.* **69**:273–281.

Kenyon, E. M., Del Razo, L. M. and Hughes, M. F. (2005). Tissue distribution and urinary excretion of inorganic arsenic and its methylated metabolites in mice following acute oral administration of arsenate. *Toxicol. Sci.* **85**:468–475.

Kenyon, E. M., Hughes, M. F. and Levander, O. A. (1997). Influence of dietary selenium on the disposition of arsenate in the female B6C3F1 mouse. *J. Toxicol. Environ. Health* **51**:279–299.

Kile, M. L., Hoffman, E., Rodrigues, E. G., Breton, C. V., Quamruzzaman, Q., Rahman, M., Mahiuddin, G., Hsueh, Y. M. and Christiani, D. C. (2011). A pathway-based analysis of urinary arsenic metabolites and skin lesions. *Am. J. Epidemiol.* **173**:778–786.

Kile, M. L. and Ronnenberg, A. G. (2008). Can folate intake reduce arsenic toxicity? *Nutr. Rev.* **66**:349–353.

Kim, M. K. and Lee, H. Y. (1990). Effect of high dietary fiber diet on lead absorption and metabolic changes in growing rats. *Korean J. Nutr.* **23**:492–503.

Klaassen, C. D., Liu, J. and Diwan, B. A. (2009). Metallothionein protection of cadmium toxicity. *Toxicol. Appl. Pharmacol.* **238**:215–220.

Kojima, S., Kiyozumi, M., Mishima, M., Honda, T. and Nakagawa, M. (1985). Effects of three proteins on absorption of cadmium in rats. *Toxicology* **34**:161–171.

Krohn, R. M., Lemaire, M., Negro Silva, L. F., Lemarie, C., Bolt, A., Mann, K. K. and Smits, J. E. (2016a). High-selenium lentil diet protects against arsenic-induced atherosclerosis in a mouse model. *J. Nutr. Biochem.* **27**:9–15.

Krohn, R. M., Raqib, R., Akhtar, E., Vandenberg, A. and Smits, J. E. (2016b). A high-selenium lentil dietary intervention in Bangladesh to counteract arsenic toxicity: study protocol for a randomized controlled trial. *Trials* **17**:218–225.

Lamont, W. H. (2003). Concentration of inorganic arsenic in samples of white rice from the United States. *J. Food Compost. Anal.* **16**:689–695.

Landry, T. D., Doherty, R. A. and Gates, A. H. (1979). Effects of three diets on mercury excretion after methylmercury administration. *Bull. Environ. Contam. Toxicol.* **22**:151–158.

Li, W. H., Shi, Y. C., Tseng, I. L. and Liao, V. H. C. (2013). Protective efficacy of selenite against lead-induced neurotoxicity in *Caenorhabditis elegans*. *PLoS ONE* **8**:e62387.

Lindboe, M., Henrichsen, E. N., Høgåsen, H. R. and Bernhoft, A. (2012). Lead concentration in meat from lead-killed moose and predicted human exposure using Monte Carlo simulation. *Food Addit. Contamin. Part A* **29**:1052–1057.

Liu, C. M., Sun, Y. Z., Sun, J. M., Ma, J. Q. and Cheng, C. (2012). Protective role of quercetin against lead-induced inflammatory response in rat kidney through the ROS-mediated MAPKs and NF-κB pathway. *Biochim. Biophys. Acta* **1820**:1693–1703.

Liu, Y., Liu, J. and Klaassen, C. D. (2001). Metallothionein-null and wild-type mice show similar cadmium absorption and tissue distribution following oral cadmium administration. *Toxicol. Appl. Pharmacol.* **175**:253–259.

Magos, L. and Webb, M. (1977). The effect of selenium on the brain uptake of methylmercury. *Arch. Toxicol.* **38**:201–207.

Mahaffey, K. R. (1990). Environmental lead toxicity: Nutrition as a component of intervention. *Environ. Health Perspect.* **89**:75–78.

Mahaffey, K. R., Gartside, P. S. and Glueck, C. J. (1986). Blood lead levels and dietary calcium intake in 1- to 11-year-old children: The Second National Health and Nutrition Examination Survey, 1976 to 1980. *Pediatrics* **78**:257–262.

Matović, V., Buha, A., Bulat, Z. and Đurić-Ćosić, D. (2011). Cadmium toxicity revisited: Focus on oxidative stress induction and interactions with zinc and magnesium. *Arh. Hig. Rada. Toksikol.* **62**:65–76.

Mehana, E. E., Meki, A. R. and Fazili, K. (2012). Ameliorated effects of green tea extract on lead induced liver toxicity in rats. *Exp. Toxicol. Pathol.* **64**:291–295.

Mitsumori, K., Hirano, M., Ueda, H., Maita, K. and Shirasu, Y. (1990). Chronic toxicity and carcinogenicity of methylmercury chloride in B6C3F1 mice. *Fund. Appl. Toxicol.* **14**:179–190.

Mounicou, S., Szpunar, J., Andrey, D., Blake, C. and Lobinski, R. (2003). Concentrations and bioavailability of cadmium and lead in cocoa powder and related products. *Food Addit. Contam.* **20**:343–352.

Muhammed, Z. I. (2014). Effect of phenolic compound extract of green tea to ameliorate the cadmium sulphate toxicity on the female rat kidneys. *IOSR J. Pharm. Biol. Sci.* **9**:44–50.

Mykkanen, H. M. and Fullmer, C. S. and Wasserman, R. H. (1984). Effect of phosphate on the intestinal absorption of lead (^{203}Pb) in chicks. *J. Nutr.* **114**:68–74.

Nemsadze, K., Sanikidze, T., Ratiani, L., Gabunia, L. and Sharashenidze, T. (2009). Mechanisms of lead-induced poisoning. *Georgian Med. News* **172–173**:92–96.

NRC (United States National Research Council). (2000). *Commission on Life Sciences, Board on Environmental Studies and Toxicology. Toxicological Effects of Methylmercury*, Vol. 22, pp. 568–577, Washington, DC: National Academy Press.

NTP (National Toxicology Program). (1993). Toxicology and carcinogenesis studies of mercuric chloride (CAS No. 7487-94-7) in F344 rats and B6C3F1 mice (gavage studies). *Natl. Toxicol. Program Tech. Rep. Ser.* **408**:1–260.

Oguzturk, H., Ciftci, O., Aydin, M., Timurkaan, N., Beytur, A. and Yilmaz, F. (2012). Ameliorative effects of curcumin against acute cadmium toxicity on male reproductive system in rats. *Andrologia* **44**:243-–249.

Ohta, H. and Cherian, M. G. (1991). Gastrointestinal absorption of cadmium and metallothionein. *Toxicol. Appl. Pharmacol.* **107**:63–72.

Orct, T., Lazarus, M., Jurasović, J., Blanusa, M., Piasek, M. and Kostial, K. (2009). Influence of selenium dose on mercury distribution and retention in suckling rats. *J. Appl. Toxicol.* **29**:585–589.

Park, J. D., Cherrington, N. J. and Klaassen, C. D. (2002). Intestinal absorption of cadmium is associated with divalent metal transporter 1 in rats. *Toxicol. Sci.* **68**:288–294.

Patra, R. C., Swarup, D. and Dwivedi, S. K. (2001). Antioxidant effects of alpha tocopherol, ascorbic acid and L-methionine on lead induced oxidative stress to the liver, kidney and brain in rats. *Toxicology* **162**:81–88.

Peixoto, N. C., Roza, T., Flores, E. M. and Pereira, M. E. (2003). Effects of zinc and cadmium on $HgCl_2$-delta-ALA-D inhibition and Hg levels in tissues of suckling rats. *Toxicol. Lett.* **146**:17–25.

Piotrowski, J. K., Orlowski, C., Bem, E. M., Brys, M. and Baran, E. (1996). The monitoring of cadmium, zinc and copper in the kidneys and liver of humans deceased in the region of Cracow (Poland). *Environ. Monit. Assess.* **43**:227–236.

Prasanthi, R. P., Devi, C. B., Basha, D. C., Reddy, N. S. and Reddy, G. R. (2010). Calcium and zinc supplementation protects lead (Pb)-induced perturbations in antioxidant enzymes and lipid peroxidation in developing mouse brain. *Int. J. Dev. Neurosci.* **28**:161–167.

Prasanthi, R. P. J., Reddy, G. H. and Reddy, G. R. (2006). Calcium or zinc supplementation reduces lead toxicity: Assessment of behavioral dysfunction in young and adult mice. *Nutr. Res.* **26**:537–545.

Rabinowitz, M. B., Kopple, J. D. and Wetherill, G. W. (1980). Effect of food intake and fasting on gastrointestinal lead absorption in humans. *Am. J. Clin. Nutr.* **33**:1784–1788.

Raihan, S. Z., Chowdhury, A. K., Rabbani, G. H., Marni, F., Ali, M. S., Nahar, L. and Sarker, S. D. (2009). Effect of aqueous extracts of black and green teas in arsenic-induced toxicity in rabbits. *Phytother. Res.* **23**:1603–1608. DOI: 10.1002/ptr.2827.

Ralston, N. V., Blackwell, J. L. and Raymond, L. J. (2007). Importance of molar ratios in selenium-dependent protection against methylmercury toxicity. *Biol. Trace Elem. Res.* **119**:255–268.

Ralston, N. V. and Raymond, L. J. (2010). Dietary selenium's protective effects against methylmercury toxicity. *Toxicology* **278**:112–123.

Reeves, P. G., Chaney, R. L., Simmons, R. W. and Cherian, M. G. (2005). Metallothionein induction is not involved in cadmium accumulation in the duodenum of mice and rats fed diets containing high-cadmium rice or sunflower kernels and a marginal supply of zinc, iron, and calcium. *J. Nutr.* **135**:99–108.

Renugadevi, J. and Prabu, S. M. (2009). Naringenin protects against cadmium-induced oxidative renal dysfunction in rats. *Toxicology* **256**:128–134.

Renugadevi, J. and Prabu, S. M. (2010). Quercetin protects against oxidative stress-related renal dysfunction by cadmium in rats. *Exp. Toxicol. Pathol.* **62**:471–481.

Revis, N. W. and Osborne, T. R. (1984). Dietary protein effects on cadmium and metallothionein accumulation in the liver and kidney of rats. *Environ. Health Perspect.* **54**:83–91.

Roberts, S. M., Weimar, W. R., Vinson, J. R., Munson, J. W. and Bergeron, R. J. (2002). Measurement of arsenic bioavailability in soil using a primate model. *Toxicol. Sci.* **67**:303–310.

Rodríguez-Sosa, M., García-Montalvo, E. A., Del Razo, L. M. and Vega, L. (2013). Effect of selenomethionine supplementation in food on the excretion and toxicity of arsenic exposure in female mice. *Biol. Trace Elem. Res.* **156**:279–287.

Rosado, J. L., López, P., Kordas, K., García-Vargas, G., Ronquillo, D., Alatorre, J. and Stoltzfus, R. J. (2006). Iron and/or zinc supplementation did not reduce blood lead concentrations in children in a randomized, placebo-controlled trial. *J. Nutr.* **136**:2378–2383.

Rowland, I. R., Davies, M. J. and Evans, J. G. (1980). Tissue content of mercury in rats given methylmercuric chloride orally: influence of intestinal flora. *Arch. Environ. Health* **35**:155–160.

Rowland, I. R., Mallett, A. K., Flynn, J. and Hargreaves, R. J. (1986). The effect of various dietary fibres on tissue concentration and chemical form of mercury after methylmercury exposure in mice. *Arch. Toxicol.* **59**:94–98.

Roy, A., Bellinger, D., Hu, H., Schwartz, J., Ettinger, A. S., Wright, R. O., Bouchard, M., Palaniappan, K. and Balakrishnan, K. (2009). Lead exposure and behavior among young children in Chennai, India. *Environ. Health Perspect.* **117**:1607–1611.

Roy, A., Das, A., Das, R., Haldar, S., Bhattacharya, S. and Haldar, P. K. (2014). Naringenin, a citrus flavonoid, ameliorates arsenic-induced toxicity in Swiss albino mice. *J. Environ. Pathol. Toxicol. Oncol.* **33**:195–204.

Roy, M., Sinha, D., Mukherjee, S. and Biswas, J. (2011). Curcumin prevents DNA damage and enhances the repair potential in a chronically arsenic-exposed human population in West Bengal, India. *Eur. J. Cancer Prev.* **20**:123–131.

Ruoff, W. L., Diamond, G. L., Velazquez, S. F., Stiteler, W. M. and Gefell, D. J. (1994). Bioavailability of cadmium in food and water: A case study on the derivation of relative bioavailability factors for inorganics and their relevance to the reference dose. *Regul. Toxicol. Pharmacol.* **20**:139–160.

Ryu, D. Y., Lee, S. J., Park, D. W., Choi, B. S., Klaassen, C. D. and Park, J. D. (2004). Dietary iron regulates intestinal cadmium absorption through iron transporters in rats. *Toxicol. Lett.* **152**:19–25.

Sah, S., Vandenberg, A. and Smits, J. (2013). Treating chronic arsenic toxicity with high selenium lentil diets. *Toxicol. Appl. Pharmacol.* **272**:256–262. DOI: 10.1016/j.taap.2013.06.008.

Sakamoto, M., Yasutake, A., Kakita, A., Ryufuku, M., Chan, H. M., Yamamoto, M., Oumi, S., Kobayashi, S. and Watanabe, C. (2013). Selenomethionine protects against neuronal degeneration by methylmercury in the developing rat cerebrum. *Environ. Sci. Technol.* **47**:2862–2868.

Sarić, M. M., Blanusa, M., Piasek, M., Varnai, V. M., Juresa, D. and Kostial, K. (2002). Effect of dietary calcium on cadmium absorption and retention in suckling rats. *Biometals* **15**:175–182.

Sener, G., Sehirli, O., Tozan, A., Velioğlu-Ovunç, A., Gedik, N. and Omurtag, G. Z. (2007). Ginkgo biloba extract protects against mercury (II)-induced oxidative tissue damage in rats. *Food Chem. Toxicol.* **45**:543–550.

Sharma, M. K., Kumar, M. and Kumar, A. (2002). Ocimum sanctum aqueous leaf extract provides protection against mercury induced toxicity in Swiss albino mice. *Indian J. Exp. Biol.* **40**:1079–1082.

Shen, S., Li, X.-F., Cullen, W. R., Weinfeld, M. and Le, X. C. (2013). Arsenic binding to proteins. *Chem. Rev.* **113**:7769–7792.

Simon, J. A. and Hudes, E. S. (1999). Relationship of ascorbic acid to blood lead levels. *JAMA* **281**:2289–2293.

Sloth, J. J. and Julshamn, K. (2008). Survey of total and inorganic arsenic content in blue mussels (*Mytilus edulis L.*) from Norwegian fiords: Revelation of unusual high levels of inorganic arsenic. *J. Agric. Food Chem.* **56**:1269–1273.

Smith, A. H., Biggs, M.L, Moore, L., Haque, R., Steinmaus, C., Chung, J., Hernandez, A. and Lopipero, P. (1999). Cancer risks from arsenic in drinking water: Implication for drinking water standards. **In**: *Arsenic Exposure and Health Effects*, pp. 191–199. Chappell, W. R., Abernathy, C. O., and Calderon, R. L., Eds., New York: Elsevier Science.

Song, X., Geng, Z., Li, C., Hu, X. and Wang, Z. (2010). Transition metal ions and selenite modulate the methylation of arsenite by the

recombinant human arsenic (+3 oxidation state) methyltransferase (hAS3MT). *J. Inorg. Biochem.* **104**:541–550.
Steenland, K. and Boffetta, P. (2000). Lead and cancer in humans: Where are we now? *Am. J. Ind. Med.* **38**:295–299.
Stokes-Riner, A., Thurston, S. W., Myers, G. J., Duffy, E. M., Wallace, J., Bonham, M., Robson, P., Shamlaye, C. F., Strain, J. J., Watson, G. and Davidson, P. W. (2011). A longitudinal analysis of prenatal exposure to methylmercury and fatty acids in the Seychelles. *Neurotoxicol. Teratol.* **33**:325–328.
Styblo, M. and Thomas, D. J. (2001). Selenium modifies the metabolism and toxicity of arsenic in primary rat hepatocytes. *Toxicol. Appl. Pharmacol.* **172**:52–61.
Sumathi, T., Shobana, C., Christinal, J. and Anusha, C. (2012). Protective effect of Bacopa monniera on methyl mercury-induced oxidative stress in cerebellum of rats. *Cell. Mol. Neurobiol.* **32**:979–987.
Sun, H.-J., Rathinasabapathi, B., Wu, B., Luo, J., Puc, L.-P. and Ma, L. Q. (2014). Arsenic and selenium toxicity and their interactive effects in humans. *Environ. Int.* **69**:148–158.
Syversen, T. and Kaur, P. (2012). The toxicology of mercury and its compounds. *J. Trace Elem. Med. Biol.* **26**:215–226.
Tawfik, D. S. and Viola, R. E. (2011). Arsenate replacing phosphate: Alternative life chemistries and ion promiscuity. *Biochemistry* **50**:1128–1134.
Téllez-Rojo, M. M., Bellinger, D. C., Arroyo-Quiroz, C., Lamadrid-Figueroa, H., Mercado-García, A., Schnaas-Arrieta, L., Wright, R. O., Hernández-Avila, M. and Hu, H. (2006). Longitudinal associations between blood lead concentrations lower than 10 microg/dL and neurobehavioral development in environmentally exposed children in Mexico City. *Pediatrics* **118**:e323–e330.
Thomas, D. J., Li, J., Waters, S. B., Xing, W., Adair, B. M., Drobna, Z., Devesa, V. and Styblo, M. (2007). Arsenic (+3 oxidation state) methyltransferase and the methylation of arsenicals. *Exp. Biol. Med.* **232**:3–13.
Thompson, J. and Bannigan, J. (2008). Cadmium: Toxic effects on the reproductive system and the embryo. *Reprod. Toxicol.* **25**:304–315.
Tian, F., Zhai, Q., Zhao, J., Liu, X., Wang, G., Zhang, H., Zhang, H. and Chen, W. (2012). *Lactobacillus plantarum* CCFM8661 alleviates lead toxicity in mice. *Biol. Trace Elem. Res.* **150**:264–271.
Torres-Escribano, S., Leal, M., Vélez, D. and Montoro, R. (2008). Total and inorganic arsenic concentrations in rice sold in Spain, effect of cooking, and risk assessments. *Environ. Sci. Technol.* **42**:3867–3872.
Tseng, C. H., Huang, Y. K., Huang, Y. L., Chung, C. J., Yang, M. H., Chen, C. J. and Hsueh, Y. M. (2005). Arsenic exposure, urinary arsenic speciation, and peripheral vascular disease in blackfoot disease-hyperendemic villages in Taiwan. *Toxicol. Appl. Pharmacol.* **206**:299–308.
Turecki, T. R. C., Ewan, R. C. and Stahr, H. M. (1994). Effect of phytic acid and calcium on the intestinal absorption of cadmium *in vitro*. *Bull. Environ. Contam. Toxicol.* **53**:464–470.
Tyler, C. R. and Allan, A. M. (2014). The effects of arsenic exposure on neurological and cognitive dysfunction in human and rodent studies: A review. *Curr. Environ. Health Rpt.* **1**:132–147.
UNEP (United Nations Environment Programme). (2010). Final review of scientific information on cadmium, Chemicals Branch, DTIE. Available from http://www.unep.org/hazardoussubstances/Portals/9/Lead_Cadmium/docs/Interim_reviews/UNEP_GC26_INF_11_Add_2_Final_UNEP_Cadmium_review_and_apppendix_Dec_2010.pdf. Accessed June 27, 2016.
US EPA (United States Environmental Protection Agency). (1997). Mercury study report to Congress. Vol. V. Health effects of mercury and mercury compounds (EPA-452/R-97-007), Available from https://www3.epa.gov/airtoxics/112nmerc/volume5.pdf. Accessed June 30, 2016.
Vahter, M., Berglund, M., Nermell, B. and Akesson, A. (1996). Bioavailability of cadmium from shellfish and mixed diet in women. *Toxicol. Appl. Pharmacol.* **136**:332–341.
Vahter, M. E. (2007). Interactions between arsenic-induced toxicity and nutrition in early life. *J. Nutr.* **137**:2798–2804.
Vance, T. M. and Chun, O. K. (2015). Zinc intake is associated with lower cadmium burden in U.S. adults. *J. Nutr.* **145**:2741–2748.
Varnai, V. M., Piasek, M., Blanusa, M., Juresa, D., Sarić, M. and Kostial, K. (2003). Ascorbic acid supplementation does not improve efficacy of meso-dimercaptosuccinic acid treatment in lead-exposed suckling rats. *Pharmacol. Toxicol.* **93**:180–185.
Villa-Bellosta, R. and Sorribas, V. (2010). Arsenate transport by sodium/phosphate cotransporter type IIb. *Toxicol. Appl. Pharmacol.* **247**:36–40.
Waalkes, M. P. (1986). Effect of dietary zinc deficiency on the accumulation of cadmium and metallothionein in selected tissues of the rat. *J. Toxicol. Environ. Health* **18**:301–313.
Waisberg, M., Joseph, P., Hale, B. and Beyersmann, D. (2003). Molecular and cellular mechanisms of cadmium carcinogenesis. *Toxicology* **192**:95–117.
Wang, C., Liang, J., Zhang, C., Bi, Y., Shi, X. and Shi, Q. (2007). Effect of ascorbic acid and thiamine supplementation at different concentrations on lead toxicity in liver. *Ann. Occup. Hyg.* **51**:563–569.
Wang, H. L., Chen, X. T., Yin, S. T, Liu, J., Tang, M. L., Wu, C. Y. and Ruan, D. Y. (2008). Opposite effects of alpha-lipoic acid on antioxidation and long-term potentiation in control and chronically lead-exposed rats. Naunyn Schmiedebergs. *Arch. Pharmacol.* **378**:303–310.
Wang, W., Xie, Z., Lin, Y. and Zhang, D. (2014). Association of inorganic arsenic exposure with type 2 diabetes mellitus: A meta-analysis. *J. Epidemiol. Community Health* **68**:176–184.
Wang, Y., Wang, S., Cui, W., He, J., Wang, Z. and Yang, X. (2013). Olive leaf extract inhibits lead poisoning-induced brain injury. *Neural Regen. Res.* **8**:2021–2029.
WHO (World Health Organization). (1995). *Environmental Health Criteria 165. Inorganic lead. International Programme on Chemical Safety*, Geneva, Switzerland: WHO.
WHO (World Health Organization). (2001). Lead. **In**: *Air Quality Guidelines-Second Edition, Chapter 6.7.* WHO Regional Office for Europe, Copenhagen, Denmark. WHO Regional Publications, European Series, No. 91.
Wing, A. M. (1993). The effects of whole wheat, wheat bran and zinc in the diet on the absorption and accumulation of cadmium in rats. *Br. J. Nutr.* **69**:199–209.
Yadav, A., Lomash, V., Samim, M. and Flora, S. J. (2012). Curcumin encapsulated in chitosan nanoparticles: A novel strategy for the treatment of arsenic toxicity. *Chem. Biol. Interact.* **199**:49–61.
Yip, R. K. and Chang, L. W. (1982). Protective effects of vitamin E on methylmercury toxicity in the dorsal root ganglia. *Environ. Res.* **28**:84–95.
Yu, H., Wu, B., Zhang, X. X., Liu, S., Yu, J., Cheng, S., Ren, H. Q. and Ye, L. (2016). Arsenic metabolism and toxicity influenced by ferric iron in simulated gastrointestinal tract and the roles of gut microbiota. *Environ. Sci. Technol.* **50**:7189–7197.
Zalups, R. K. (2000). Molecular interactions with mercury in the kidney. *Pharmacol. Rev.* **52**:113–143.
Zhai, Q., Wang, G., Zhao, J., Liu, X., Narbad, A., Chen, Y. Q., Zhang, H., Tian, F. and Chen, W. (2014). Protective effects of *Lactobacillus plantarum* CCFM8610 against chronic cadmium toxicity in mice indicate routes of protection besides intestinal sequestration. *Appl. Environ. Microbiol.* **80**:4063–4071.
Zhai, Q., Wang, G., Zhao, J., Liu, X., Tian, F., Zhang, H. and Chen, W. (2013). Protective effects of *Lactobacillus plantarum* CCFM8610 against acute cadmium toxicity in mice. *Appl. Environ. Microbiol.* **79**:1508–1515.