Cadmium and Lead Exposure

Subjects: Physiology

Contributor: Soisungwan Satarug

This entry provides information relevant to public health policy regarding advisable exposure limits for cadmium (Cd) and lead (Pb) that have no biologic role in humans. All of their perceptible effects are toxic. These metals exist in virtually all foodstuffs. Foods which are frequently consumed in large quantities such as cereals, rice, potatoes and vegetables contribute the most to total intake of these metals. Because Cd and Pb exposure are highly prevalent, even a small increase in disease risk can result in a large number of people affected by a disease that is preventable. Public measures to minimize environmental pollution and the food-chain transfer of Cd and Pb are required to prevent Cd- and Pb- related ailments and mortality as are risk reduction measures that set a maximally permissible concentration of Cd and Pb in staple food to the lowest achievable levels.

Keywords: cadmium ; lead ; dietary sources ; toxic mechanism ; chronic kidney disease ; safe intake levels

1. Introduction

Cadmium (Cd) and lead (Pb) are metals that have no biologic role in humans[1][2][3][4]. All of their perceptible effects are toxic[1][2][3][4]. Indeed, Cd and Pb are two of ten chemicals listed by the World Health Organization (WHO) as environmental pollutants of major public health concern[5]. Tissues and organs accumulate Cd and Pb because no excretory mechanism has evolved to eliminate these metals[6][7][8]. Consequently, tissue levels of Cd and Pb increase with age, as do risks of common ailments that are often viewed as outcomes of aging. Although the highest concentrations of Cd and Pb are found, respectively, in kidneys and bone, toxic effects of these metals are not confined to diseases of the kidney and skeleton[1][2][3][4][9][10]. It has been estimated that dietary intake of Cd, Pb, inorganic arsenic, and methylmercury have resulted in 56,000 deaths and more than 9 million disability-adjusted life-years worldwide[11]. For the nonsmoking population of adults, diet is the main exposure source of Cd and Pb[2][12][13][14][15][16].

Oxidative stress and inflammation have been identified as common toxic mechanisms of Cd and Pb even though neither metal undergoes a change in valence (redox inert)[17][18][19][20][21][22]. Both are primarily divalent[22][23][24]. In addition, Cd has a similar ionic radius to that of calcium (Ca) and electronegativity similar to that of zinc (Zn), and both Cd and Pb exhibit higher affinity than Zn for sulphur-containing ligands (Cd > Pb > Zn)[23][24][25][26]. Consequently, displacement of Zn and Ca and disruption of Zn and Cu homeostasis are other plausible toxic mechanisms[27][28][29][30][31][32][33][34][35]. All sulphur-containing amino acids, peptides and proteins with functional thiol (-SH) groups are potential ligands (molecular targets) for Cd and Pb. Examples include glutathione (GSH), numerous enzymes, zinc-finger transcription factors, and the metal-binding protein metallothionein (MT) [23][24][36]. Through Zn displacement, Pb impairs the activity of delta-aminolevulinic acid dehydratase (δ-ALAD), an enzyme required for the biosynthesis of heme, which is the functional group of hemoglobin, nitric oxide synthase, and cytochromes of the mitochondrial respiratory chain and xenobiotic metabolism[37]. Inhibition of the calcium-permeable acid-sensing ion channel may be the mechanism that accounts for the neurotoxicity of Pb[38][39].

2. Health Risk Assessment of Chronic Exposure to Cadmium and Lead

2.1. The Critical Target of Toxicity

Long-term chronic exposure to Cd and Pb has been associated with distinct pathologies in nearly every tissue and organ throughout the body[1][2][3][4][14][25]. However, in health risk assessment, the kidney was considered to be the critical target of Cd toxicity[1][8], while the brain was the critical target of Pb toxicity[3][4][25]. Accordingly, dietary intake estimates associated with a significant increase in the risk of nephrotoxicity of Cd or neurotoxicity of Pb were used to derive a tolerable intake level. One method to evaluate whether a given food contaminant poses a health risk is to compare dietary intake estimated by total diet studies with the provisional tolerable weekly intake (PTWI), as established by the Joint Expert Committee on Food Additives and Contaminants (JECFA) of the Food and Agriculture Organization (FAO) and the WHO of the United Nations (FAO/WHO).

2.2. Tolerable Intake Levels

The PTWI for a chemical was defined as an estimate of the amount of a given chemical that can be ingested weekly over a lifetime without an appreciable health risk. The PTWI figures were first provided for Cd and Pb in 1989 and then amended in 1993 and 2010[40][41]. The 1993 PTWI figures for Cd and Pb were 7 and 25 µg per kg body weight per week, respectively. In 2010, the PTWI for Cd was amended to a tolerable monthly intake (TMI) level of 25 µg per kg body weight per month. This intake level is equivalent to 0.83 µg per kg body weight per day or 58 µg per day for a 70-kg person[41]. The model for deriving PTWI and TMI of Cd was based on elevated β_2-microglobulin (β_2MG) excretion as the sole evidence of nephrotoxicity[41].

For Pb, the previously established PTWI of 25 µg per kg body weight per week was withdrawn because it did not afford health protection[41]. A new tolerable Pb intake level could not be established as dose–response analyses indicated that no threshold levels exist for neurotoxicity of Pb. Thus, no amount of Pb intake is safe, and no tolerable Pb intake level has been officially identified. However, the U.S. Food and Drug Administration (FDA) has proposed a dietary Pb intake level of 12.5 µg/day as an interim safe intake level for the general population of adults[42][43]. This intake level corresponds to a blood concentration of Pb ($[Pb]_b$) of 0.5 µg/dL, which has not been found to be associated with an adverse effect in adults in any epidemiologic studies.

2.3. Urinary Cd Threshold Level

A urinary Cd excretion rate (E_{Cd}) of 5.24 µg/g creatinine was adopted as a threshold limit[41]. However, the established threshold level is questionable. Chronic environmental exposure to low-level Cd, producing urinary Cd one-tenth of the conventional threshold, has been associated with deterioration of kidney function, as assessed with estimated GFR (eGFR)[44][45][46]. A urinary Cd concentration ($[Cd]_u$) as low as 1 µg/L, corresponding to blood Cd concentration ($[Cd]_b$) of 0.5 µg/L, was associated with an increased risk of eGFR less than 60 mL/min/1.73 m^2 [44][47]. It can be argued that risk of nephrotoxicity of any toxicants, Cd and Pb included, should be based on eGFR, which is a reliable measure of kidney function and diagnosis and staging of CKD[48][49][50]. A dose–response analysis of urinary Cd and eGFR, rather than of urinary Cd and β_2MG, indicates that Cd-induced nephrotoxicity occurs at a much lower E_{Cd} than previously thought[12][51][52][53][54]. We believe that the established TMI for Cd is not protective of kidneys, just as the 1993 PTWI for Pb does not prevent neurotoxicity. The 1993 PTWI for Pb has now been withdrawn[41].

3. Exposure Sources and Dietary Intake Estimates

For the general nonsmoking population of adults, the diet is the major exposure source of both Cd and Pb. In this section, both natural and anthropogenic sources of Cd and Pb in the human diet are highlighted. In addition, a reliable dietary assessment and food safety monitoring method, such as a total diet study, is discussed, and estimated intake levels of Cd and Pb derived from recent total diet studies in various countries are provided.

3.1. Environmental Sources of Cadmium and Lead

Volcanic emissions, fossil fuel and biomass combustion, and cigarette smoke are sources of Cd and Pb released as CdO and PbO[69][70][71][72][73]. Experimental studies have shown that inhaled CdO and PbO are more bioavailable than oral Cd and Pb[74][75]. Typically, potable water is not a source of Cd or Pb, except in cases where significant amounts of Pb plumbing have been used, as occurred in the recent Flint, Michigan, water crisis[57][58].

Years of production and industrial use of Cd and Pb have mobilized these metals from nonbioavailable geologic matrices to biologically accessible sources from which they can enter food chains[69]. Like all other metals, Cd and Pb are not biodegradable and thus can persist indefinitely in the environment[69]. The use of contaminated phosphate fertilizers has also added these toxic metals to agricultural soils[6][7], causing a further increase in Cd and Pb in the food chain][59][60][61]. Livestock that graze on contaminated pastures can accumulate Cd in the kidney and liver at levels that make these organs unsafe for human consumption[62]. In Pb-exposed cattle, blood Pb levels correlated with levels of Pb in liver, bone and kidney, but not in brain or skeletal muscle (beef)[63]. Of note, a detectable amount of Pb was found in beef at a blood Pb concentration of 4.57 µg/dL. This blood Pb level was close to the exposure limit for neurotoxicity of Pb in children (5 µg/dL)[63]. Molluscs and crustaceans accumulate Cd and are also notorious hyperaccumulators of other metals[65][66][67][68]. For most species, fish muscle does not appear to be a significant source of Cd and Pb, but there are exceptions[76].

In a similar manner to molluscs and crustaceans, plants have the propensity to concentrate Cd and Pb from the soil. Plants have evolved multiple metal detoxification mechanisms, including an array of metal-binding ligands such as MT, phytochelatins (PCs), other low-molecular-weight thiols, GSH, cysteine, γ-glutamylcysteine, and cysteinylglycine[77][78][79].

As Cd exerts toxicity in the “free” ion or unbound state, complexes of Cd and metal-binding ligands, such as CdMT and CdPC, are viewed as detoxified forms[80]. Accordingly, the various types of metal-binding ligands render plants capable of tolerating levels of Cd and Pb that are toxic to animals and humans.

Owing to their phylogenic characteristics, tobacco, rice, other cereal grains, potatoes, salad vegetables, spinach, and Romaine lettuce accumulate Cd more efficiently than other plants[81]. An outbreak of “itai-itai” disease, a severe form of Cd poisoning from contaminated rice, serves as a reminder of the health threat from Cd contamination of a staple food crop[82].

3.2. Total Diet Studies and Dietary Intake Estimates

Reliable methodology is vital to assess the levels of contaminants in commonly eaten foods and to set food safety standards. The total diet study has been widely used by authorities to estimate intake levels and identify sources of Cd and Pb in the human diet[83][84][85][86][87]. It is also known as the “market basket survey” because samples of foodstuffs are collected from supermarkets and retail stores to determine levels of nutrients, food additives, pesticide residues and contaminants[2][83][84][85][86][87]. It serves as a food safety monitoring program that provides a basis to define a maximally permissible concentration of a given contaminant in a specific food group.

In a typical total diet study, an intake level of a given contaminant from a study food item (rice as an example) is computed based on an amount of the food item consumed per day and the concentration of a contaminant in the rice samples that are analyzed in a study. The median and 90th percentile concentration levels of a contaminant are used to represent the intake levels of a contaminant by average and high consumers, respectively[88].

Table 1 summarizes most recent total diet studies showing intake levels of Cd among adult consumers in China [88][89][90][91], Korea[92][93], Germany[94] Spain[95][96] and the U.S.[97][98][99] along with the list of foods that contributed significantly to total intake of the metal. Table 1 summarizes also food products that contributed significantly to total intake of Pb and the estimated intake levels of the metal among adult consumers in China [89–91], Korea [92], Germany[100], Spain[95] and the U.S.[84]. Furthermore, Cd intake levels estimated for consumers in Sweden [88] France[101], Belgium[102] and a region with Cd pollution of Japan[103] are provided.

Table 1. Estimated intake levels of cadmium and lead and their sources.

Countries	**Estimated Intake Levels as µg Per Day and Dietary Sources**	
	Cadmium (Atomic Weight 112.4)	**Lead (Atomic Weight 207.2)**
China [89,90] 67% of population	Average consumers: 32.7 µg/day. Rice and vegetables as the main sources for most Chinese. Potato was the main source in Mongolia. High Cd foods: Nori, peanuts, squid, cuttlefish, and mushrooms.	Average consumers: 35.1 µg/day. Cereals, meats, vegetables, and beverages and water together contributed to 73.26% of total intake. High Pb foods: Kelp, nori, processed and preserved soybean, meat, and fungus. products.
Korea [92] *n* = 4867	Average consumers: 12.6 µg/day. Sources: Grain and grain-based products (40.4%), vegetables and vegetable products (16.5%), and fish and shellfish (17.9%). High Cd foods: Seaweed, shellfish and crustaceans, molluscs, nuts and seeds, and flavourings, with median values of 594, 186, 155, 15.7, and 6.23 µg/kg, respectively.	Average consumers: 9.8 µg/day. High Pb foods: Seaweed, shellfish and crustaceans, molluscs, fish, and sugar and sugar products, with respective median values of 94.2, 91.4, 62.4, 8.13, and 4.61 µg/kg, while the median value for beverages (fruit juice, carbonated fruit juice, carbonated drinks, sports drinks, and coffee) was 11.0 µg/kg.

Germany [94,100] *n* = 15,371	Average consumers: 14.6 µg/day. High consumers: 23.5 µg/day. Sources: Cereals and vegetables, beverages, fruits and nuts, and dairy products (milk included). High Cd foods: Cereals, oily seeds and fruits, and vegetables.	Average consumers: 37.1 µg/day. High consumers: 50.4 µg/day. Sources: Beverages, vegetables, fruits and nuts and cereals. High Pb foods: Meat (offal included), fish (seafood), vegetables and cereals.
Spain [95] *n* = 1281	Average consumers: 7.7 µg/day. Sources: Cereals and fish contributed to 38% and 29% of total intake. High Cd foods: Cereals (16.25 µg/kg), fish group (11.40 µg/kg).	Average consumers: 14.7 µg/day. Cereals contributed to 49% of total intake. High Pb foods: Sweeteners and condiments, vegetable oils, meat, and fish, with respective median levels of 32.5, 15.25, 14.90 and 13.21 µg/kg.
U.S. [84,97] *n* = 14,614 FDA 2014–2016 total diet study	Average consumers: 4.63 µg/day. Sources: Cereals and bread, leafy vegetables, potatoes, legumes and nuts, stem/root vegetables, and fruits contributed to 34%, 20%, 11%, 7% and 6% of total intake, respectively. High Cd foods: Spaghetti, bread, potatoes and potato chips contributed the most to total Cd intake, followed by lettuce, spinach, tomatoes, and beer. Lettuce was a main Cd source for whites and blacks. Tortillas and rice were main Cd sources for Hispanic Americans, and Asians plus other ethnicities. Cd concentration of raw leaf lettuce and iceberg lettuce were 0.066 and 0.051 mg/kg, respectively.	Average consumers: 1.7−5.3 µg/day. High consumers: 3.2−7.8 µg/day. Sources: Grains, beverages, vegetables, dairy, fruits, meat, and poultry plus fish contributed to 24.1%, 14.3%, 10.7%, 9.7%, 9.3% and 3.4% to total intake, respectively. High Pb foods: Chocolate syrup, liver, canned sweet potatoes, brownies, low-calorie buttermilk, salad dressing, raisins, English muffins, canned apricots, milk chocolate, candy bars, chocolate cake, chocolate chip cookies, wine and oat ring cereal with respective median levels of 14, 14, 14, 13, 13, 12, 10, 10, 9, 8, 8, 7 and 7 µg/kg.

A current tolerable Cd intake level established by FAO/WHO for the population of adults is 25 µg per kg body weight per month (58 µg per day for a 70-kg person)[41]. No tolerable Pb intake level has been identified after a previously established guideline was withdrawn in 2010[41]. U.S. FDA interim safe intake level of Pb for the population of adults is 12.5 µg per day[42].

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