

Cadmium and Contaminated Foods - A Risk Assessment

Quang Q. Bui, Ph.D., DABT

ABSTRACT

Cadmium is a naturally occurring metallic element that has no known beneficial functions in the human body. Interest on cadmium toxicity has recently been triggered due to its alleged presence in Jasmine-flavored rice grown in Thailand. Chronic exposure to cadmium is known to result in renal dysfunction, bone defects and cardiovascular complications. Pulmonary edema, emphysema and possibly lung and prostate cancer might develop from occupational exposure (inhalation) or cadmium fume (cigarette smoke). In light of its irreversible renal effects, regulatory agencies worldwide have established acceptable intake levels for cadmium in foods and drinking water. Exposure to foods contaminated with cadmium might become a health risk if the level of cadmium exceeds the safe level. In this risk assessment, the potential toxic effects of cadmium are discussed along with exposure assessment and risk characterization.

INTRODUCTION

Cadmium (Cd) is a naturally occurring metallic element that is used for galvanization processes, in the production of pigments, in batteries (Ni-Cd batteries), in fertilizers, in fungicides, and has other industrial applications. It is interesting to note that, although Cd occurs naturally in the earth's crust, it has no constructive purpose in the human body. This emphasizes the fact that it is not sensible to assume that natural chemicals are safe, just as it is not sensible to assume that synthetic chemicals are inevitably toxic.

Recently, cadmium was found in agricultural soils and crops in Thailand (Zarcinas et al., 2004) and numerous articles published in local newspapers warned that rice farmers have been sickened by cadmium passed from municipal sewage sludge through the rice crop. Contamination of rice from cadmium found in industrial sludge is anticipated since this is a common practice in many developing countries to use sewage sludge as fertilizer. Questions have been raised on the safety of Thailand jasmine-flavored rice, a favorite of the Vietnamese people.

There is risk associated with any chemical or drug and risk assessment is the process of characterizing the potential adverse effects of human exposure to a chemical or drug. In this article, a risk assessment for Cd and contaminated foods is presented. There are four steps in risk assessment - hazard identification, dose response assessment, exposure assessment and risk characterization - and each step is discussed below.

HAZARD IDENTIFICATION

Cadmium and Cd compounds (e.g., Cd oxide, Cd chloride, Cd sulfide, etc.) have a solubility ranging from very soluble to nearly insoluble and it's the solubility that determines the toxicity of Cd. Cd is more efficiently absorbed from the lungs (30 to

60%) than from the gastrointestinal tract (5 to 8%) (ATSDR, 1989). Gastrointestinal absorption is enhanced by deficiency of calcium, iron and diets low in protein. As much as 50% of Cd fumes (as in cigarette smoke) may be absorbed. Once absorbed, Cd is transported in the blood by binding to red blood cells and plasma proteins and is distributed primarily in the liver and kidneys.

Depending on the severity of oral exposure, clinical signs of Cd toxicity include nausea, vomiting, abdominal cramps, headache, shock and death (USAF, 1990). Dietary intake has also been implicated in hypertensive disorders. Exposure to high concentrations of Cd by inhalation might result in pulmonary edema, chronic bronchitis and emphysema.

The most serious chronic effect of Cd exposure is renal toxicity. Many studies have demonstrated an association between morphological and/or functional changes in the kidney and the renal concentration of Cd. The morphological changes are non-specific and are initially limited to proximal tubular degeneration followed by cellular atrophy, interstitial fibrosis and glomerular sclerosis. Renal tubular dysfunctions are characterized by proteinuria, glucosuria, hypercalciuria and aminoaciduria with β_2 -microglobulin as the predominant protein (WHO, 1992). Follow-up studies of persons with renal tubular dysfunction from occupational exposure to Cd have shown that the proteinuria is irreversible.

The role of the metal-binding protein metallothionein has been proposed to explain the nephrotoxicity of Cd. The accumulation of Cd in the kidneys to some extent without apparent toxic effects is due to the formation of Cd-thionein or metallothionein (Goyer and Clarkson, 2001). Metallothionein is a tissue protein and is ubiquitous in most organs, but it exists in the highest concentration in the liver. Metallothionein has low molecular weight and is rich in thiol ligands. These ligands provide the basis for high-affinity binding of metals such as Cd, Cu, Hg, Ag and Zn. Metallothionein protects against the toxicity of Cd by binding to it to form a complex that is non-toxic when stored within the cells. The metallothioneins are inducible by a number of metals, including Cd. Renal injury occurs when the concentrations of Cd exceed the critical concentration of methallothionein.

Cadmium also affects calcium metabolism and skeletal changes resulting from calcium loss are associated with chronic Cd exposure. Bone changes are part of *Itai-Itai* disease, a syndrome recognized in the Fuchu area of Japan during World War II. *Itai-Itai* translates to “ouch-ouch” reflecting the accompanying bone pain. The syndrome consists of bone deformities and chronic renal disease.

Epidemiologic studies suggest that cadmium is an etiologic agent for essential hypertension and cardiovascular effects. Clinical investigations have also substantiated a relationship between occupational (respiratory) exposure to Cd and lung cancer and possibly prostate cancer. The International Agency for Research on Cancer classifies cadmium as a Category B1, i.e. probable human carcinogen (IARC, 1994).

There is no evidence to suggest that Cd is toxic to the reproductive system or the developing fetus.

DOSE RESPONSE ASSESSMENT

In humans, cadmium is virtually absent at birth but accumulates with time. Blood cadmium levels in adults without excessive exposure is usually less than 1 $\mu\text{g}/\text{dL}$ (for nonsmokers). However, it should be noted that blood Cd generally reflects recent exposure rather than accumulated body burden since up to 75% of the total body burden is found in the liver and renal cortex. Cadmium half life may be as long as 30 years. With continued retention, there is progressive accumulation in the kidneys with age and the critical concentration of Cd in the renal cortex that produces tubular dysfunction is about 200 $\mu\text{g}/\text{gm}$ wet human renal cortex. This 200 $\mu\text{g}/\text{gm}$ level is the highest renal level not associated with significant proteinuria (US.EPA, 1985).

Fatality has been reported after acute oral ingestion of 20 – 30 g Cd or by inhalation exposure to a level of 5000 $\mu\text{g}/\text{m}^3$. Exposure to 1 mg/m^3 is considered to be immediately dangerous. OSHA limits workplace air to 100 $\mu\text{g}/\text{m}^3$ as cadmium fumes and 200 $\mu\text{g}/\text{m}^3$ as cadmium dust (1989).

WHO (1992) indicated that daily intake of food of 140 to 260 μg Cd/day or exposure to Cd in air at 50 $\mu\text{g}/\text{m}^3$ for more than 10 years has produced renal dysfunction. In the US, the average person consumes about 30 μg cadmium in food daily. In Japan, the mean dietary intake of Cd by nonsmokers women is 26 $\mu\text{g}/\text{day}$.

The US.EPA allows a maximum of 5 ppb (parts per billion) of Cd in drinking water and the level of Cd in most drinking water in the US is less than 1 ppb. The US.FDA limits the amount of cadmium in food colors to 15 ppm (parts per million).

An epidemiologic study of the dose-response relationship of Cd intake from rice consumption and β_2 -microglobulin as an index of renal dysfunction, found that the total Cd intake over a lifetime that produced an adverse health effect was 2000 mg (Nogawa et al., 1989).

EXPOSURE ASSESSMENT

For the general population, the major source of cadmium is food. Plants readily take up Cd from the soil contaminated with Cd. This results from the use of Cd-containing fertilizers and the use of commercial sludge to fertilize agricultural fields, a practice quite common in Southeast Asia. Shellfish such as mussels, scallops and oysters may contain up to 1000 μg Cd/kg. In mammals, the highest concentrations of Cd are found in animal liver and kidneys.

The joint FAO/WHO Expert Committee on Food Additives (JECFA, 2003) has set the Provisional Tolerable Weekly Intake (PTWI) for Cd at 7 $\mu\text{g}/\text{kg}$ body weight equivalent to 1 $\mu\text{g}/\text{kg}$ body weight/day (0.001 mg/kg bw/day).

The US.EPA has established the oral reference dose (RfD) for cadmium in drinking water at 0.0005 mg/kg/day and in food at 0.001 mg/kg/day (US.EPA, 1994). The US.EPA oral reference dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg/day. In general, the RfD is an estimate of a daily exposure to the human population that is likely to be without an appreciate risk of deleterious effects during a lifetime. The US.EPA RfD for Cd in food is thus similar to that of the FAO/WHO recommended maximum intake of 1 µg/kg body weight/day.

Exposure to Cd can occur from food, water, smoking or occupational. However, due to the objective of this article, the risk assessment discussed here is limited to food. The estimated average intake (µg/kg bw/day) varies from 0.5 (China) to 0.75 (Greece), 0.22 (France), 0.36 (Japan), to 0.15 (USA). So, for an average person of 60 kg, the total daily intake of Cd from food, water and air in North America and Europe is estimated to be about 10 to 40 µg/day equivalent to 0.16 to 0.65 µg/kg body weight/day using an average human body weight of 60 kg.

Rice alone contributes from 0.002 to 0.224 µg/kg body weight or 0.12 to 13.5 µg/day. The European Community currently sets a Maximum Permissible Level of Cd in rice at 0.2 mg/kg of rice.

RISK CHARACTERIZATION

There are several studies providing evidence of an association between Cd exposure (inhalation, cigarette smoke) and lung and prostate cancer in cadmium smelter workers (Sorahan and Waterhouse, 1983). However, there are no positive studies correlating orally ingested Cd and cancer. Therefore, a risk characterization on cancer after ingestion of Cd-contaminated food is not necessary.

Risk characterization would thus focus on the primary endpoint of systemic toxicity, i.e., nephrotoxicity and dietary intake.

The US.EPA has established an oral RfD for Cd in food at 1 µg/kg body weight per day. Non-contaminated rice contributes from 0.002 to 0.224 µg Cd/kg body weight per day. Drinking water contains 1 ppb or 1 µg Cd per liter. Assuming a person consumes 2 L of water (from all sources – drinking, cooking, brushing, etc.), then the daily exposure to Cd would be 2 µg per day or 0.03 µg/kg body weight. Exposure from all other sources (e.g., Cd in air, second-hand cigarette smoke, sea foods, organ meats, etc.) would push our average daily intake from 0.25 to 0.65 µg Cd/kg body weight. Our normal daily exposure to Cd already occupies 25 to 65% of the oral RfD, a level considered as without risk.

If rice contains Cd at 0.4 mg/kg rice, an average daily consumption of 100 g of rice would contribute 40 µg Cd per day or 0.65 µg Cd/kg body weight/day. This additional exposure from contaminated rice alone already occupies 65% of the oral RfD and would make our total daily exposure to Cd to exceed the oral RfD - an unacceptable risk.

The Cd-contaminated rice is a significant threat to children' health since rice and rice-based products are frequently eaten by young children. A daily consumption of 50 g of rice contaminated with Cd at 0.4 mg/kg rice would result in an exposure of 20 µg per day or 1.33 µg/kg body weight/day, assuming a child weighs 15 kg. This exposure level from rice alone already exceeds the oral RfD of 1.0 µg Cd/kg body weight/day. The following table summarizes the exposures and margins of safety.

Source	Daily Exposure µg Cd/kg bw	Cumulative Exposure µg Cd/kg bw ^(a)	Margins of Safety ^(b)
Expected exposure (from all sources (foods, rice, water, 2 nd hand smoke, environment)	0.25 – 0.65	0.25 – 0.65	4.0 to 1.50
Rice contaminated at 0.4 mg Cd/kg rice	0.65	0.90 – 1.30	1.1 to 0.76 Unacceptable

(a) Cumulative Exposure = Expected Exposure + Additional Exposure from rice

(b) Margins of safety = $\frac{\text{Oral Reference Dose}}{\text{Cumulative Exposure}}$

CONCLUSION

In summary, exposure to cadmium poses a health risk to both adults and children since Cd has an extremely long biological half life in humans and accumulates in the liver and kidney. The toxic manifestations of Cd are on the kidneys and information from the published literature indicates that a proportion of the general population may be at increased risk for tubular dysfunction when exposed at the current oral RfD of 1 µg/kg body weight/day or the cumulative WHO/FAO PTWI of 7 µg/kg body weight.

Additional exposure to Cd-contaminated rice would make the cumulative daily exposure to exceed the oral RfD, an unacceptable risk for the general population. However, it is not possible to predict whether renal dysfunction would occur with the additional exposure from contaminated rice since Cd toxicity is influenced by many factors including (a) alcohol consumption, (b) smoking, (c) occupation, (d) age due to increased body burden and (e) levels of methallothionein.

However, it is recognized that children are more susceptible to Cd toxicity due to lower body weight and their susceptibility for skeletal deformities.

REFERENCES

ATSDR (Agency for Toxic Substances and Disease Registry). Toxicological properties of Cadmium. ATSDR/US Public Health Service, ATSDR/TP-88/08, 1989.

IARC. *Monograph on the Evaluation of Risks to Humans*. Vol 58: *Cadmium, Mercury, Borellium and the Glass Industry*. Lyon, France, 1994.

Goyer RA and Clarkson TW: Toxic effects of metals. In Casarett & Doull's Toxicology, The Basic Science of Poisons, ed. Curtis Klaassen, 6th edition, McGraw Hill, 2001.

Nogawa K, Tsuritami I, Kido T et al.: Mechanisms for bone disease found in inhabitants environmentally exposed to cadmium. *Int Arch Occup Environ Health*, Vol 59, pp. 21-30, 1987.

OSHA (Occupational Safety and Health Administration). Air contaminants. 29CFR1910, Federal Registers, 1989.

Sorahan T and Waterhouse JAH. Mortality study of nickel-cadmium battery workers by the method of regression models in life tables. *Br. J Ind Med*. Vol 40, pp 293-300, 1983.

USAF. Cadmium. In: Installation restoration program toxicology guide, Armstrong Aerospace Medical Research Laboratory, Wright Patterson AFB, OH, 1990.

US.EPA, IRIS, Cadmium (CASRN 7440-43-9), Integrated Risk Information System, 1994.

US.EPA. Drinking Water Criteria Document on Cadmium. Office of Drinking Water, Washington DC, 1985.

WHO (World Health Organization) *Cadmium*, Environmental Health Criteria No. 134, Geneva, 1992.

Zarcinas BA, Pongsakul P, McLaughlin MJ and Cozens G. Heavy metals in soils and crops in Southeast Asia 2. Thailand. *Environ Geochem Health*, Vol 26 (4), pp. 359-371, 2004.