PUBLIC HEALTH GOALS FOR CHEMICALS IN DRINKING WATER

Cadmium

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Governor of the State of California
Arnold Schwarzenegger

Secretary for Environmental Protection
California Environmental Protection Agency
Linda S. Adams

Director
Office of Environmental Health Hazard Assessment
Joan E. Denton, Ph.D.

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CADMIUM
in Drinking Water

Prepared by

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
Pesticide and Environmental Toxicology Branch

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PREFACE

Drinking Water Public Health Goal
Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances that may cause chronic disease shall be based solely on health effects and shall be set at levels that OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider potential adverse effects on members of subgroups that comprise a meaningful proportion of the population, including but not limited to infants, children, pregnant women, the elderly, and individuals with a history of serious illness.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. OEHHA shall consider additive effects of exposure to contaminants in media other than drinking water, including food and air, and the resulting body burden.
7. In risk assessments that involve infants and children, OEHHA shall specifically assess exposure patterns, special susceptibility, multiple contaminants with toxic mechanisms in common, and the interactions of such contaminants.

8. In cases of insufficient data for OEHHA to determine a level that creates no significant risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
9. In cases where scientific evidence demonstrates that a safe dose response threshold for a contaminant exists, then the PHG should be set at that threshold.
10. The PHG may be set at zero if necessary to satisfy the requirements listed above in items seven and eight.
11. PHGs adopted by OEHHA shall be reviewed at least once every five years and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations or technical feasibility, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each primary drinking water standard adopted by DHS shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By state and federal law, MCLs established by DHS must be at least as stringent as the federal MCL, if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not intended to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA Web site at www.oehha.ca.gov.

LIST OF CONTRIBUTORS

PHG PROJECT MANAGEMENT	REPORT PREPARATION	SUPPORT
Project Director	***Authors***	***Administrative Support***
Anna Fan, Ph.D.	Richard Sedman, Ph.D.	Hermelinda Jimenez
		Sharon Davis
PHG Program Leader	***Primary Reviewers***	***Library Support***
Robert A. Howd, Ph.D.	David Morry, Ph.D.	Charleen Kubota, M.L.S.
	David Chan, D. Env.	
Comment Coordinator	***Final Reviewers***	***Web site Posting***
Thomas Parker, M.S.	Anna Fan, Ph.D.	Laurie Monserrat
	George Alexeeff, Ph.D.	
	Robert Howd, Ph.D.	

TABLE OF CONTENTS

PUBLIC HEALTH GOAL FOR CADMIUM IN DRINKING WATER

SUMMARY

The Office of Environmental Health Hazard Assessment (OEHHA) has reviewed available data on the toxicity of cadmium in order to update the previous Public Health Goal (PHG) document, published in 1999. Many studies on the carcinogenic and non-carcinogenic activity of this chemical were identified and evaluated. Other studies that characterized the toxicokinetics of cadmium were also reviewed.

Renal toxicity in humans after long-term exposure to cadmium is the basis of the revised PHG, as it was for the earlier risk assessment. Kidney is a sensitive organ because of the gradual accumulation of cadmium in this tissue over the first several decades of life. Changes in the level of certain urinary proteins, urinary biomarker that are very sensitive indicators of the onset of renal toxicity, were used to identify an exposure level that would not result in renal toxicity. A number of studies in humans showed that when urinary cadmium levels exceed 2 to 5 μg/g creatinine, proteinuria indicative of renal damage begins to occur. When urinary cadmium levels remain at or below 1 μg/g creatinine, proteinuria and other more severe signs renal toxicity are not detected.

Toxicokinetic studies in humans were employed to estimate the long-term daily oral cadmium intake associated with urinary cadmium levels of 1 μg/g creatinine after 50 years of exposure. Studies in humans indicated first order elimination of cadmium, that is, the rate of urinary excretion is a function of body burden. A terminal half-life of 14 years was estimated based on first order kinetics and the findings of Ellis and coworkers (Ellis *et al.*, 1979). Given a terminal half-life of 14 years, a daily oral intake of cadmium of 19 μg/day would yield a urinary cadmium level of 1 μg/g creatinine after 50 years of exposure, which is considered by OEHHA to be equivalent to a no observed adverse effect level (NOAEL) for cadmium in humans.

While a number of studies yielded key information regarding the toxicity and toxicokinetics of cadmium, only limited information was available regarding the cadmium toxicokinetics in women. Studies in humans indicate that women are likely to be a sensitive population because they have a higher body burden of cadmium. The elevated levels of cadmium in women appear to be due to a higher level of oral absorption but other factors may be involved. Sensitivity of women to cadmium is also indicated by the observation that Itai Itai disease, a disease caused by cadmium, occurs principally in women. Also a recent study revealed significant increases in mortality in women but not men exposed to cadmium in rice in Japan (Kobayashi *et al.*, 2002). Accordingly, a 5-fold uncertainty factor was included in the derivation of the PHG to insure protection of this sensitive population.

OEHHA (2005), IARC (1993), and U.S. EPA (2005) have determined that there is sufficient evidence that cadmium is carcinogenic to humans. No oral studies in humans or animals were identified that were judged suitable for developing an oral cancer potency for cadmium. Available information that would allow an extrapolation

of the inhalation potency to the oral route was determined by OEHHA to be inadequate and therefore extrapolation of the inhalation potency to the oral route was judged to be inappropriate. To address cancer risk due to oral exposure to cadmium, an additional 10-fold uncertainty factor was employed in the derivation of the PHG. A relative source contribution of 20 percent was selected for calculation of the PHG because most exposure is attributable to sources other than drinking water.

A NOAEL of 19 μg/day, an overall uncertainty factor of 50 and a relative source contribution of 20 percent, yield a PHG of 0.04 μg/L for cadmium. The previous PHG for cadmium was 0.07 μg/L, set in 1999. The California and U.S. EPA Maximum Contaminant Level (MCL) for cadmium is 5 μg/L.

INTRODUCTION

Exposure to cadmium in both occupational and non-occupational settings has resulted in notable human toxicity. Worker exposure to cadmium has occurred because it is used in a number of industrial processes. Worker exposure to cadmium is also a consequence of the mining and smelting of non-ferrous metals (in processes not intended to recover cadmium) because the ores of non-ferrous metals contain cadmium.

The mining and smelting of non-ferrous ores has also resulted in the release of substantial amounts of cadmium into the environment. High public exposure to cadmium occurred when mining operations contaminated sources of irrigation water used to grow rice in Japan. More typically, the release of cadmium into the environment from ore smelting or combustion of fossil fuels resulted in a steady increase in ambient levels of cadmium.

The increase in cadmium levels in the environment appears to be reflected in increases in public exposure to cadmium. Increased levels of cadmium have been detected in plants and animals. Human exposure to cadmium outside the workplace appears to be due to the consumption of food and tobacco. Drinking water does not appear to be an important source of cadmium exposure. No known nutritional role has been identified for cadmium.

CHEMICAL PROFILE

Chemical Identity

Cadmium (CAS Registry Number 7440-43-9) is a soft silver-white metal, atomic number 48, that occurs in nature as a mixture of eight isotopes: ^{106}Cd; ^{108}Cd; ^{110}Cd; ^{111}Cd; ^{112}Cd; ^{113}Cd; ^{114}Cd and ^{116}Cd (U.S. EPA. 1986). The most abundant isotopes in nature are ^{112}Cd (24 percent) and ^{114}Cd (29 percent). None of these natural isotopes is radioactive, but artificially-created radioactive forms are available (Weast, 1988).

Physical and Chemical Properties

With a valance state of +2, cadmium occurs in a number of different inorganic salts that govern its solubility and appearance (color). Carbonate, hydroxide, oxide and sulfide salts of cadmium are essentially insoluble in water while chloride, fluoride, iodide, nitrate and sulphate salts are relatively soluble in water (Agency for Toxic Substances and Disease Registry (ATSDR), 1999; U.S. EPA, 1986). Water insoluble forms of cadmium salts such as cadmium carbonate and cadmium oxide are much more soluble in dilute acids. The vapor pressure of cadmium (Table 1) is 1.4 mm at 400 ^{o}C and 16 mm at 500 ^{o}C. Smelting of ores and scrap metal, and welding metals containing cadmium, result in release of the metal into the air.

Table 1. Physical Properties of Cadmium

Molecular Weight	112.41
Boiling Point	765 ºC
Melting Point	321 ºC
Vapor Pressure	1 mm Hg at 394 ºC

Production and Uses

Cadmium metal and cadmium salts have been used in a number of different products over the years. Cadmium is used as an anticorrosive coating on steel, used in steel alloys, used in silver solders and in welding (Occupational Health and Safety Administration (OSHA), 1992). Cadmium is used extensively in electrode material in Ni-Cd batteries, in solar cells, and in other electronic devices (ATSDR, 1999). Cadmium has also been used as a pigment in paint, glass, plastics and ceramics. Cadmium is used to stabilize PVC and was used in the past as a fungicide.

Sources

Cadmium is widely distributed in the earth's crust with an average concentration of 0.1 mg/kg (International Programme on Chemical Safety (IPCS), 1992). Because cadmium occurs at low concentrations, ores that contain cadmium are not mined for their cadmium content because it is not profitable (OSHA, 1992). Cadmium is recovered as a by-product of ore mined for other metals such as lead and zinc. Zinc ores contain cadmium and therefore zinc smelters release small amounts of cadmium into the air. Cadmium is also released in wastewater from ore processing facilities. ATSDR (1999) reported 3 kilograms of cadmium for every ton of zinc that is produced. Contamination of irrigation water in Japan resulted from the release of cadmium-laden wastewater from mining operations (Nogawa *et al*., 1989).

Despite their low cadmium content, the combustion of large quantities of coal and the large-scale production of cement constitute important sources of cadmium release into the environment. Municipal incinerators also release considerable amounts of cadmium because of the disposal of cadmium-containing products such as plastics and Ni-Cd batteries. Cadmium is also a contaminant in sewage sludge, which has been used as a soil amendment for farm fields and sold for use in residential settings.

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Air

Low levels of cadmium have been detected in particulates collected at various California locations. Statewide average cadmium levels in air are shown in Table 2.

Table 2. Cadmium Levels (ng/m^3) in Ambient Air in California[a]

Site Name	Year	Average	Std Dev	Maximum
California (statewide)	1990	0.65	1.75	37.6
California (statewide)	1991	0.62	1.06	15
California (statewide)	1993	0.362	0.345	4.7
California (statewide)	1994	0.39	0.586	11
California (statewide)	1995	0.366	0.399	5
California (statewide)	1996	0.252	0.226	1.9

[a] California Air Resources Board (ARB) (2004).

Soil

The cadmium levels in soil are generally quite low but can become elevated due to disposal of cadmium wastes or application of cadmium-laden irrigation waters. The application of sewage sludge to land or the application of phosphate fertilizers containing cadmium results in significant transfer of cadmium to soil (ATSDR, 1999). The U.S. EPA estimated that about 31 percent of sewage sludge produced annually in the United States is disposed of by application to land (ATSDR, 1999).

Water

Drinking water is a relatively minor source of human exposure to cadmium (IPCS 1992; Berglund *et al*., 1998; Kjellstrom, 1979). For example, cadmium was not detected in the drinking water of San Francisco or San Diego in 2003 (San Francisco Public Utilities Commission, 2003; City of San Diego Water Report, 2004). A median level of 0.01 µg/L was observed in the drinking water of Seattle, Washington (Sharrett *et al.*, 1982). Cadmium intake from drinking water has been reported as usually less

than 1 µg/day (IPCS, 1992). However, the detection limit for the purpose of reporting (DLR) for California municipal utilities is 1 µg/L (CDHS, 2005a), so average California consumption from this pathway would be difficult to calculate. Relatively few instances of drinking water contamination above the California MCL of 5 µg/L have been reported in California, including 23 sources reported over the last 10 years (CDHS, 2005b).

Food

Cadmium is taken up into food crops grown with cadmium-laden irrigation water. High cadmium exposure resulted from consumption of rice grown with irrigation water contaminated with Cd from mining wastes in Japan. This exposure resulted in the occurrence of Itai-Itai disease (Nogawa *et al*., 1979; Friberg *et al*., 1974).

Cadmium is a normal constituent of food crops. Levels of cadmium in food crops in the United States are shown in Table 3. These data reflect typical cadmium levels in agricultural soils and should not be considered to be biased to areas of high cadmium contamination of soil.

Table 3. Cadmium Concentrations in Major Crops in the United States[a]

Crop	Sample size	Cadmium concentration (mg/kg wet weight)		
		Median	Minimum	Maximum
Rice	166	0.0045	< 0.001	0.23
Peanuts	320	0.060	0.010	0.59
Soybeans	322	0.041	0.002	1.11
Wheat	288	0.030	< 0.0017	0.207
Potatoes	297	0.028	0.002	0.18
Carrots	207	0.017	0.002	0.13
Onions	230	0.009	0.001	0.054
Lettuce	150	0.017	0.001	0.160
Spinach	104	0.061	0.012	0.20
Tomatoes	231	0.014	0.002	0.048

[a] From IPCS, 1992, which was adapted from Wolnik *et al.*, 1983, 1985.

The cadmium levels in organ meats (liver and kidney) and shellfish can be quite elevated, and result in substantial cadmium exposure. Women who ate shellfish once a week had substantially higher cadmium intake than non shellfish-consumers (Vahter *et al.*, 1996). The California mussel watch program reported upper bound estimates of cadmium levels (based on 1977-1997 data) of 2 mg/kg wet weight in *Mytilus californianus*, 1.3 mg/kg wet weight in *Mytilus edulis*, and 7 mg/kg wet weight in *Corbicula fluminea* (State Water Resources Control Board, 2000). The U.S. FDA has

developed dietary intake estimates for cadmium based on its total diet studies. Cadmium intake estimates were 0.14 to 0.15 µg/kg in adult males and 0.13 to 0.14 µg/kg in adult females based on the Food and Drug Administration's Total Diet Study (IPCS, 2004).

Other Sources

Cadmium is readily taken up by tobacco plants. One cigarette typically contains 1-2 µg of cadmium, although there is considerable variation in the amount of cadmium found in cigarettes (Elinder *et al.*, 1983). The amount of cadmium in the mainstream smoke of a cigarette is estimated to be around 10 percent of the amount in the cigarette (Elinder *et al.*, 1983). Consequently, smokers appear to receive substantially greater exposure to cadmium than non-smokers. The U.S. EPA estimated that smoking two packs of cigarettes a day results in cadmium exposure of 4-6 ug/day by the inhalation route (U.S. EPA, 1986). Smoking has been estimated to double the body burden of cadmium (Bernard and Lauwerys, 1984). Elinder *et al.* (1976) found that smokers had about twice the levels of cadmium in the renal cortex compared to non-smokers. Kjellstrom (1979) estimated that smoking accounted for nearly half of the body burden of cadmium and half of the urinary cadmium content.

Exposure

Based on the aforementioned studies, estimates of exposure to cadmium from various sources are as follows:

Source	Cadmium daily intake (µg/day)
Food	10
Air	0.01
Water	0.02 to 2
Smoking	4-6

METABOLISM AND PHARMACOKINETICS

Absorption

Inhalation route. Because cadmium is a relatively non-volatile substance, exposure to airborne cadmium occurs due to the inhalation of cadmium-laden particulates. The amount of cadmium absorbed is governed by particle size, mucociliary clearance from the lung and the chemical form of cadmium (Jarup *et al.*, 1998). Estimates of the absorption of inhaled cadmium range from 10 to 50 percent (Jarup *et al.*, 1998; Elinder *et al.*, 1976), and up to 90 percent from the deep lung (Oberdorster, 1990). Cigarettes have been estimated to provide a sizable source of daily exposure of smokers to cadmium, roughly equivalent to the amount of exposure that occurs through the diet (Elinder *et al.*, 1983; IPCS, 1992).

Oral route. A small proportion of total cadmium is absorbed by the oral route. Estimates are in the range of 1 to 10 percent. Berglund and associates observed that the quantity of cadmium collected in the feces was almost identical (98 to 100 percent) to the quantity measured in the diet of 57 non-smoking women (Berglund *et al.*, 1994). Radiolabeled $CdCl_2$ was administered in a porridge of rolled oats and milk to 14 volunteers (McLellan *et al.*, 1978). Labeled trivalent chromium, which is poorly absorbed, was also administered to the volunteers to help identify when the unabsorbed portion of the oral dose of cadmium was cleared from the GI tract. After the labeled chromium was no longer detected in the body, approximately 5 percent of the administered dose of cadmium was detected in the volunteers.

Radiolabeled cadmium was mixed with a calf-kidney suspension and administered to five male human volunteers (Rahola *et al.*, 1972). Approximately 6 percent of the administered dose of radiolabeled cadmium (100 μg) was not recovered in excreta after the rapid elimination of cadmium was completed (which represents excretion of unabsorbed cadmium in the feces). Oral absorption of labeled cadmium ranged from 1 to 7 percent in 12 humans administered cadmium in a beef kidney cortex homogenate **(**Shaikh and Smith, 1980). Less than three percent of the cadmium dose administered in crabmeat to seven subjects was bioavailable (Newton *et al.*, 1984).

The bioavailability of cadmium was investigated in male and female humans with normal or low ferritin levels (Flanagan *et al.*, 1978). Cadmium absorption in males averaged 2.6 percent while the average absorption in females was 7.5 percent. The difference in absorption may be related to serum ferritin levels. Absorption in males and females with low serum ferritin was quite variable, ranging from 2-11 percent, but may have been even greater in a couple of subjects. Absorption of cadmium in males and females with higher ferritin levels was lower and was no greater than 4 percent. These investigators also observed an increase in cadmium absorption in iron-deficient mice compared to iron-normal mice. However, Tsukahara and coworkers did not find any significant differences in the blood or urinary cadmium levels or urinary β_2 or α_1 microglobulin levels in normal or anemic women with low ferritin levels in a very large study in Japan (Tsukahara *et al*., 2002).

Sunflower kernels labeled with a stable cadmium isotope and processed into a buttery spread were administered to 14 women between the ages of 30 and 70 years (Vanderpool and Reeves, 2001). Stool samples were collected for 21 days and excess cadmium (an amount of cadmium recovered in feces greater than the amount in the diet) was detected for four to seven days. Based on dietary intake and fecal excretion of the labeled cadmium, approximately 11 percent of the administered dose was absorbed.

Cadmium was administered in rice for 20 days to 25 female volunteers, aged 20 to 23 years (Kikuchi *et al.*, 2003). A diet low in cadmium was administered for the first 11 days followed by a high cadmium diet for one or three days; the volunteers were then returned to the low cadmium diet. When a high cadmium diet was administered for one day, the amount of cadmium recovered in the feces over the next seven days was approximately 70 percent of the amount consumed in the diet over the same time period. When the high cadmium diet was administered for three days, the amount of

cadmium in the feces over the next seven days was 78 percent of that consumed in the diet. At the end of the study, more cadmium was still being recovered in the feces than the amount in the diet. This observation is consistent with the aforementioned studies in which excess cadmium was recovered in the feces for up to 11 days, and could explain why absorption in this study appeared to be somewhat higher than in other studies.

Cadmium absorption and retention was studied in eight healthy young children that were administered a "normal diet" (Alexander *et al.*, 1974). The children's ages ranged from a few months to eight years, with half the children less than 2.25 years of age. Cadmium levels were measured in samples of the diet, feces, and urine and cadmium absorption and retention were determined.

Cadmium absorption defined as the amount of cadmium in the diet less the amount of cadmium recovered in the feces was quite high. Approximately 55 percent of cadmium in the diet appeared to be absorbed. However, cadmium retention, defined as the amount of cadmium in the diet minus the amount in the urine, was negative as substantially more cadmium was recovered in the urine than what was in the diet (on average 154 percent of that in the diet). These findings may indicate that cadmium does not accumulate in the body of young children, despite the higher apparent absorption, compared to adults.

Iron status was linked to the absorption of cadmium by Berglund *et al.* (1994). Serum ferritin levels (a measure of iron status) were correlation to blood cadmium levels (a measure of recent exposure to cadmium). Consistent with the above findings is that blood cadmium and urine levels tend to be higher in women than in men (Jarup *et al.*, 1998). Women tend to have a lower iron status.

Comparable to findings in humans, only a few percent of orally administered cadmium was retained in animals. Oral absorption was determined to be approximately 2 to 3 percent or less in rats (Decker *et al.*, 1957; Moore *et al.*, 1973; Ragan, 1977; Muller *et al.*, 1986; Schafer *et al.*, 1990) and 5 to 6 percent in monkeys (Suzuki and Taguchi, 1980). Absorption of cadmium in newborn piglets averaged 2 percent from water and 1 percent from formula **(**Eklund *et al.*, 2004).

The absorption of cadmium did not appear to be substantially influenced by the presence of food (Ruoff *et al.*, 1994). However, in other studies, dietary levels of calcium (Washko and Cousins, 1976), iron, or zinc appear to influence the amount of cadmium that is orally absorbed (Bunn and Matrone, 1966; Ragan, 1977; Fox *et al.*, 1979; Schafer *et al.*, 1990).

Based on the studies of Vanderpool and Reeves, 2001 and Flanagan *et al.*, 1978 of oral absorption of cadmium in women and individuals with low ferritin levels, oral absorption of cadmium in women, approximately 10 percent, appears to be higher than in men. This value of oral absorption will be employed in the derivation of the PHG.

Dermal route. Wester and associates investigated *in vitro* percutaneous absorption of cadmium applied to human cadaver skin maintained in a flow-through Franz-type cell (Wester *et al.*, 1992). Less than 1 percent of the applied dose of radiolabeled cadmium

chloride (116 ppb in water, 5 μL/cm^2) was recovered in the perfusate after 16 hours. This is consistent with studies of dermal absorption of other metal salts.

Distribution

Studies of cadmium levels in human cadaver tissues revealed that the kidney and liver contain the highest levels of cadmium. Studies in Japan in 15 male and 15 female cadavers (cause of deaths mainly accidents) revealed that females had higher cadmium levels than males and that the levels in kidney were higher than in the liver (Sumino *et al.*, 1975). The cadmium content of the liver and kidney represented roughly two thirds of the total body burden of cadmium. Assay of cadmium levels in tissues from autopsies of U.S. accident victims revealed average cadmium levels of 21 ppm in kidney; 1.2 ppm in liver; 0.067 ppm in muscle, 0.58 ppm in pancreas, and 0.04 ppm in fat (Kowal *et al.*, 1979).

Cadmium levels change with age. A number of studies have observed that cadmium body burden and cadmium levels in the liver, muscle and kidney are very low at birth and then increase with age, accumulating mainly in the kidney. Livingston measured cadmium levels in samples of renal cortex obtained from adults and infant cadavers (deaths mostly from accidents and unrelated to cadmium exposure). Mean cadmium levels in infants were 0.1 μg/g dry renal cortex compared to 104 μg/g in adults (Livingston, 1972). Cadmium levels in the organs of fetus, newborn, and young children were an order of magnitude lower than in adult females (Cherry, 1981). Cadmium levels in blood obtained from the umbilical cord were lower than maternal cadmium blood levels (Baglan *et al.*, 1974). The placenta appears to act as a barrier to cadmium transport into the developing fetus (Roels *et al.*, 1978).

Hammer and coworkers measured cadmium levels in the liver and kidney from male and female cadavers (Hammer *et al.*, 1973). These investigators found that cadmium levels in the kidney increased with age until age 50-60 and then declined during the subsequent decades. Interestingly, these investigators observed higher levels of cadmium in the kidney of males compared to females. Smokers had higher cadmium concentrations in the kidney compared to non-smokers.

Whole kidney cadmium levels were determined in 314 deceased persons (sudden deaths unrelated to kidney toxicity) in the province of Quebec, Canada (Benedetti *et al.*, 1999). Mean cadmium levels in the kidney increased with age in both male and females until age 50 to 60, whereupon levels began to decrease. The mean cadmium level in the whole kidney (all ages) was 17.6 μg/g and levels in males were not significantly different than in females in this study. Smokers had a much higher level of cadmium in the kidney than non-smokers and ex-smokers. Levels in the liver increased rapidly until age 20 and then leveled off.

Using a whole body neutron activation technique to measure cadmium levels *in vivo*, Ellis and coworkers also observed higher levels of cadmium in the kidney and urine of male smokers compared to male non-smokers (Ellis *et al.*, 1979). The mean body burden of cadmium associated with dietary exposure (non-smokers, age 52) was

estimated to be 19 mg. The additional body burden of cadmium associated with smoking was 16 mg.

Orlowski and associates measured cadmium in the renal cortex of 60 subjects (40 men, 20 women) who died from various causes (cardiovascular disease, accidents and injuries, etc.) in a copper mining area of Poland (Orlowski *et al.*, 1996). Cadmium in the renal cortex increased with age until around age 50 and then decreased in an age-dependent manner. Cadmium levels in the kidney of smokers were approximately two-fold higher than levels in non-smokers.

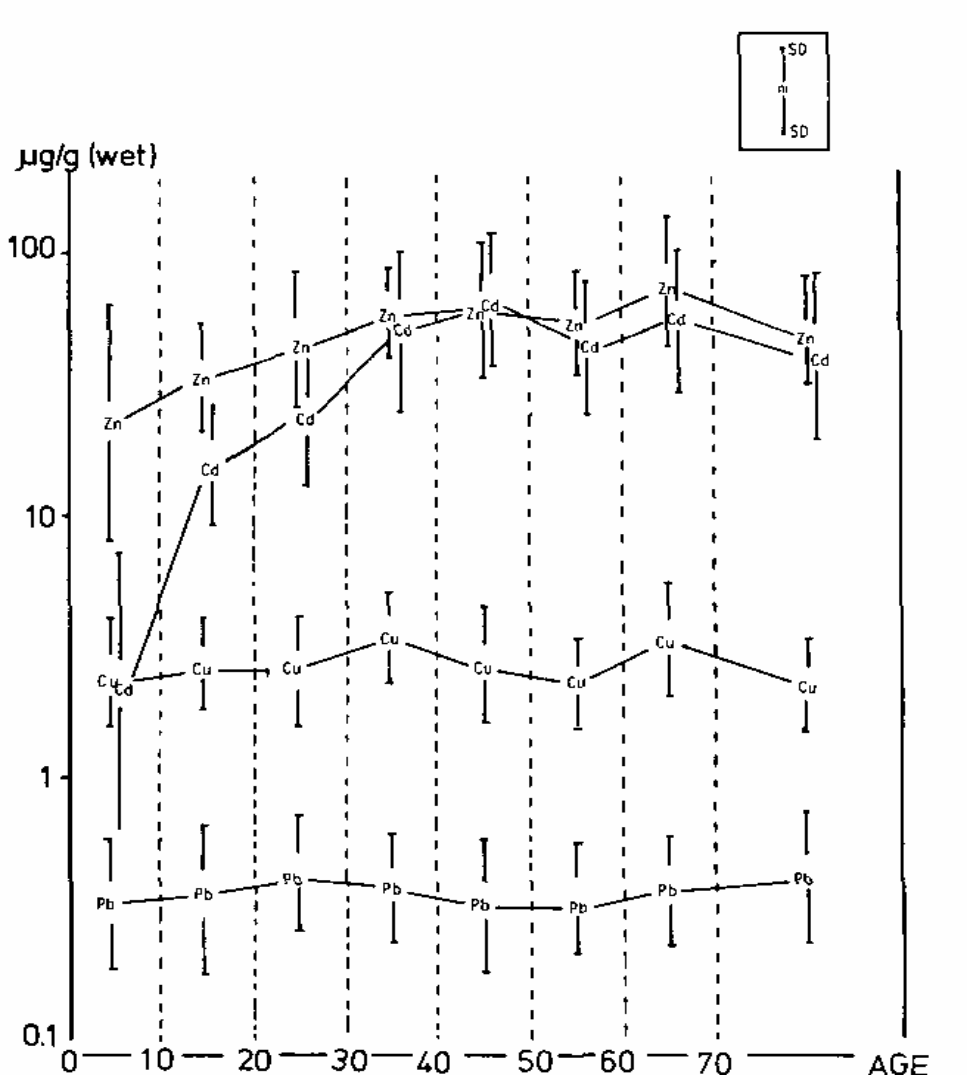
Salmela and coworkers measured cadmium levels in various organs obtained from autopsies of 86 persons who died in acute traumatic accidents (Salmela *et al.*, 1983). These individuals had no evidence of any chronic diseases and were from areas that were not considered to be polluted by cadmium. Cadmium levels in renal cortex peaked around age 30 to 39 and then decreased slightly in the older age groups. The body burden of cadmium and the cumulative total in the organs (organ concentration times the organ weight) also rose sharply between the ages of 5 and 30, then leveled off at approximately 8 mg. Most of the body burden of cadmium (85 percent) was contained in the kidney and liver.

Satarug *et al.* (2002) analyzed cadmium levels in lung, liver, kidney cortex and urine from 61 males and females who died from accidental causes. The level of cadmium in males and females were stratified based on lung cadmium levels (high levels were from smokers, low levels from non-smokers and moderate levels, a mixture of smokers and non-smokers). The renal cortex cadmium level rose sharply and then leveled off after age 41 to 50. Cadmium levels in the kidney of individuals with lower lung cadmium levels were considerably lower than levels in the kidney from the other two groups. Urinary cadmium levels were correlated with levels in renal cortex and lung. Cadmium levels in the kidney of females were higher than the levels in males.

Salzman and associates measured cadmium levels in various tissues in human cadavers (from deaths that resulted mainly from trauma) and used these findings to estimate cadmium body burden (Saltzman *et al.*, 1990). The renal cortex and medulla had the highest levels of cadmium, mean levels of 29 and 15 ppm in males and 16 and 7 ppm in females, respectively. Mean total body burden in males and females (21 males and 5 females) was approximately 13.6 mg at age 50 years with 9.4 mg in the liver, kidney, pancreas and thyroid (69 percent of total body burden). No correlation was found between blood levels and body burden of cadmium in this study.

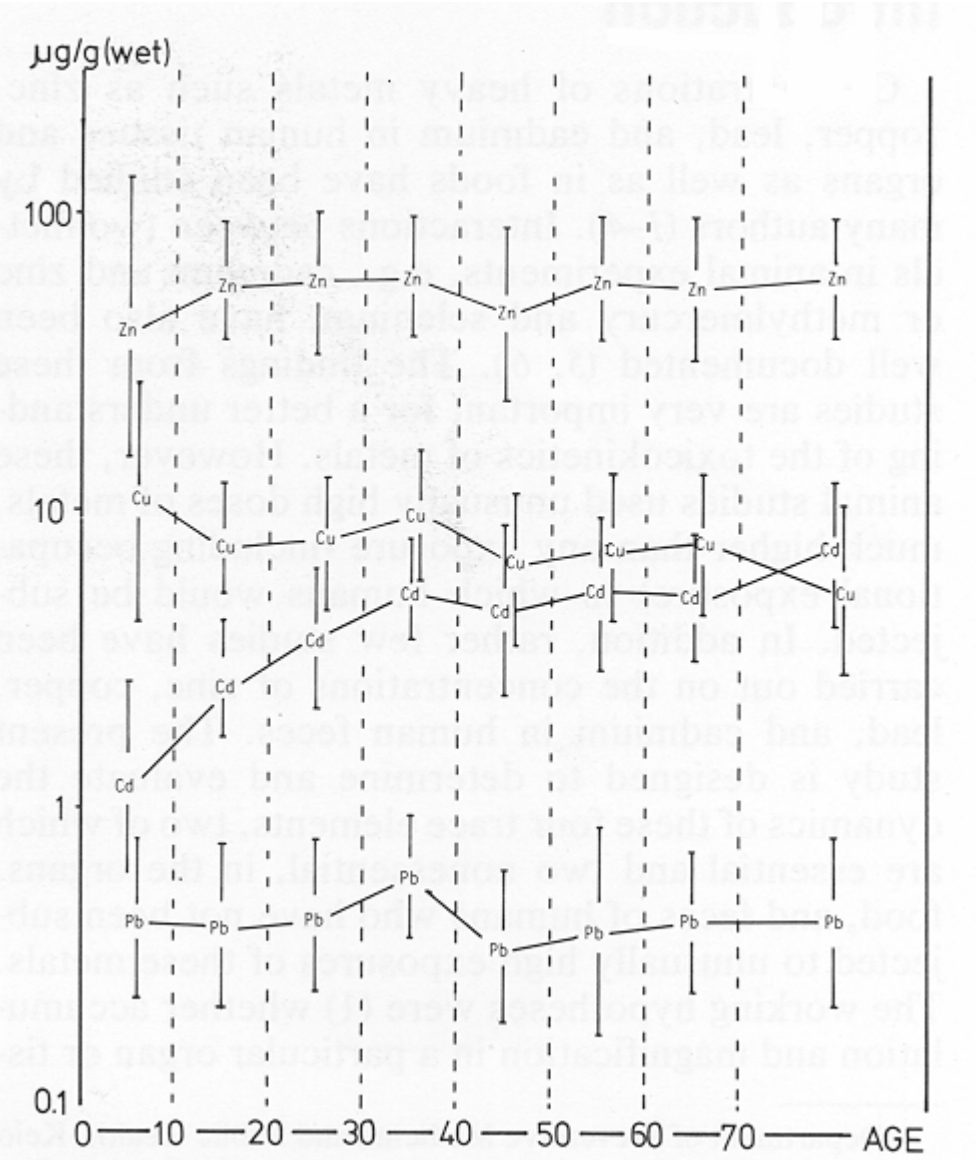
Cadmium levels were determined in kidney cortex from human males and females that were victims of sudden death (no evidence of chronic diseases or chemical poisoning) (Tsuchiya and Iwao, 1978). Cadmium levels increased markedly during the first decades of life in both males and females and then leveled off between the ages of 40 and 50 (Figure 1). The mean level in the renal cortex peaked at 68 ppm and then declined in successive decades, falling to 40 ppm in individuals age 70 or greater. Cadmium levels in the liver increased with age throughout the lifetime; the increase was not nearly as dramatic as was observed in the kidney. Levels in the liver were in the range of 3 to 5 ppm over most of the lifetime (Figure 2).

Figure 1. Concentrations of metals, including cadmium, in the human renal cortex (male and female)[a]



[a]from Tsuchiya and Iwao, 1978 (Figure 1)

Figure 2. Concentrations of metals, including cadmium, in the human liver (male and female)[a]

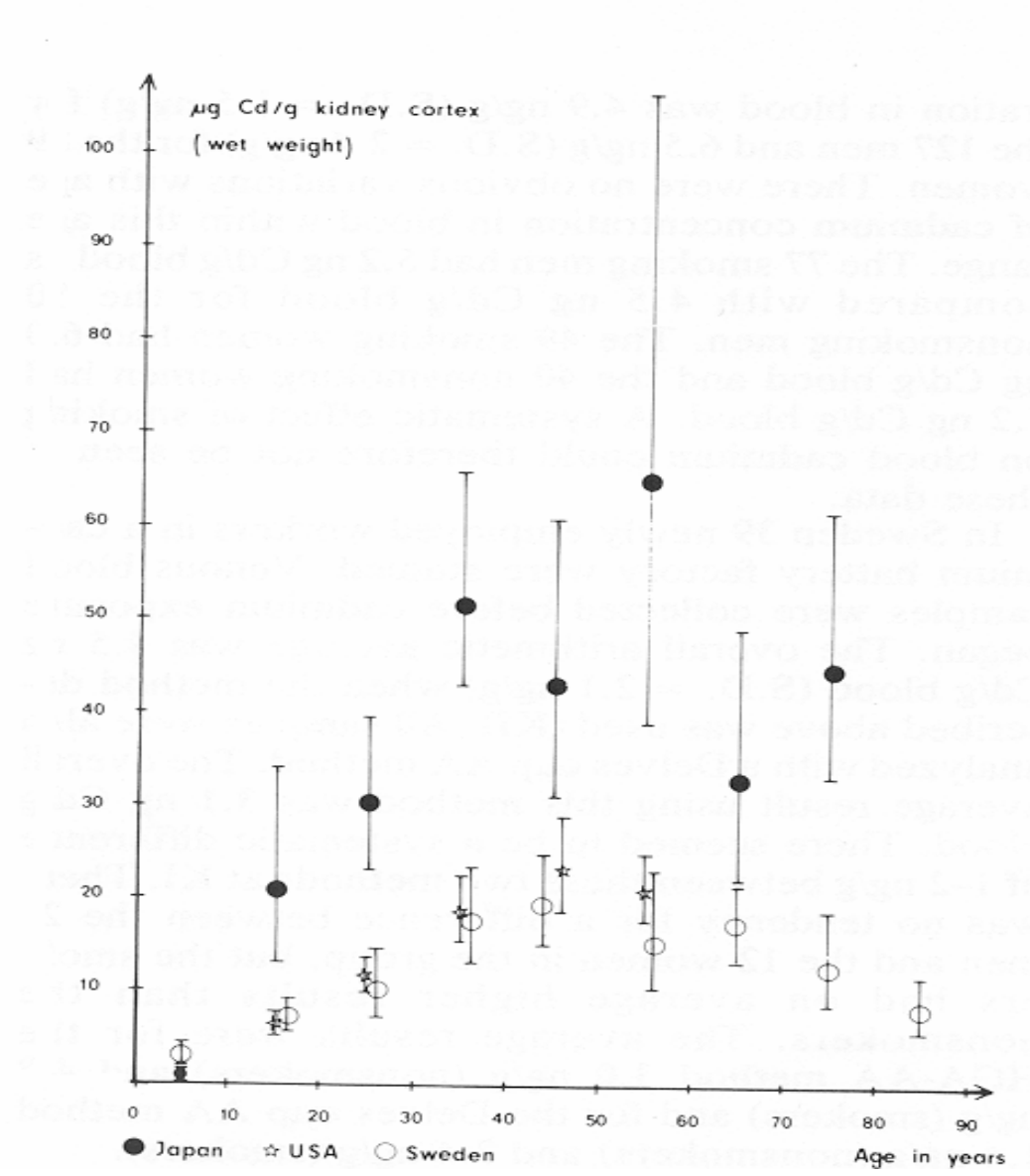


[a]from Tsuchiya and Iwao, 1978 (Figure 2)

In a large study, cadmium levels were measured in samples of human tissues (liver, kidney, muscle and pancreas), urine and feces (Kjellstrom, 1979) from cases of sudden and accidental death. The cadmium levels in the feces, kidney cortex and urine were higher in Japan than in the United States and Sweden, indicating higher levels of exposure to cadmium in the Japanese diet (Figures 3 and 4). The cadmium level in the kidney (Figure 3) increased with age, peaking around age 40 to 50 in all three countries (Kjellstrom, 1979). Renal cadmium levels then declined in successive decades of life. The pattern of change in urinary cadmium levels (Figure 4) mirrored

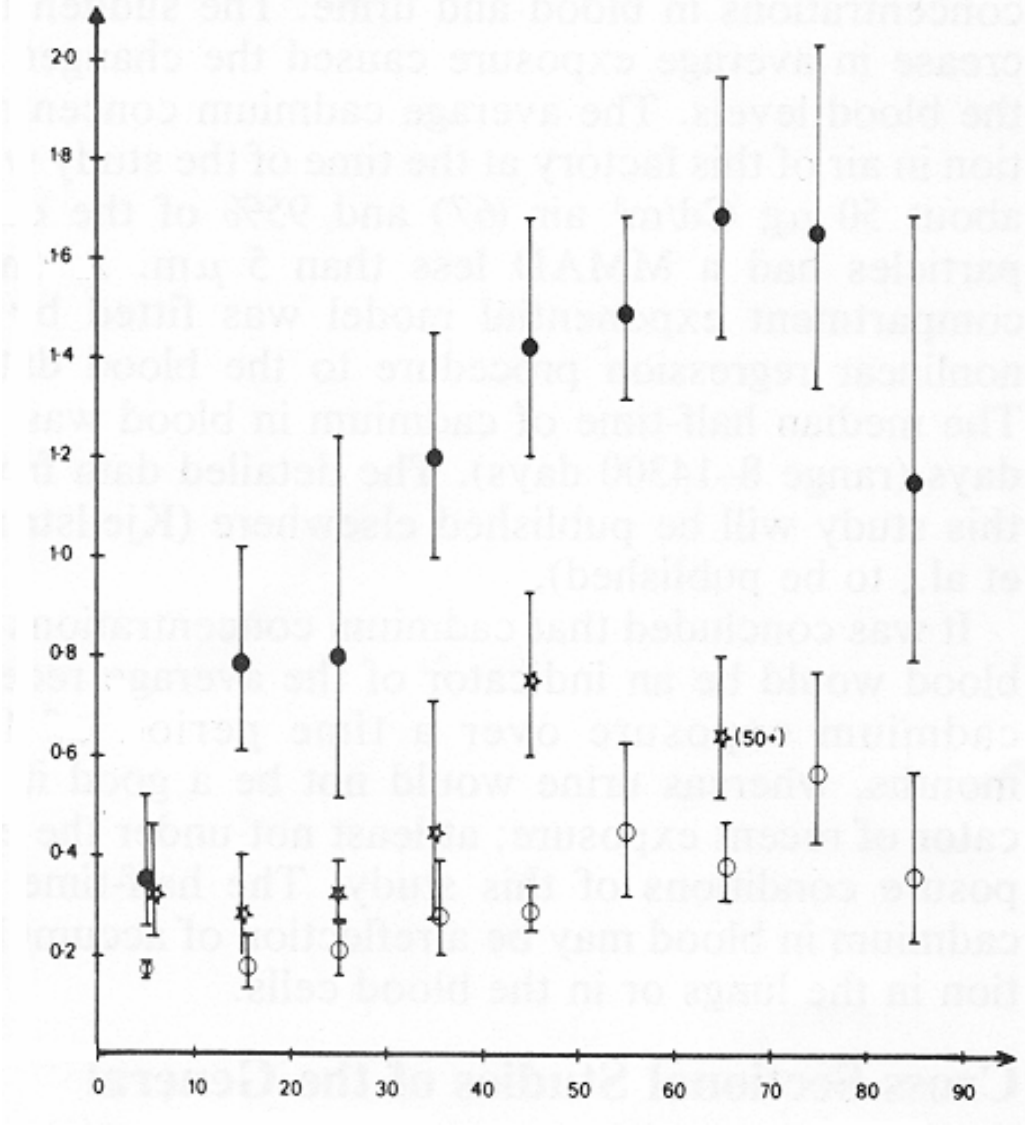
that observed in the kidney and the total body burden of cadmium as estimated using cadmium content of the kidney, liver, pancreas and muscle. These findings indicate that urinary cadmium levels reflect the levels of cadmium in the body. The cadmium level in the feces from smokers was only slightly higher than from non-smokers, but urinary cadmium levels were higher in smokers, indicating that excess absorbed cadmium from cigarettes is eliminated primarily in the urine.

Figure 3. Concentration of cadmium in the human renal cortex (males)[a]



[a]from Kjellstrom, 1979 (Figure 13)

Figure 4. Concentration of cadmium in human urine (males)[a]



[a] from Kjellstrom, 1979 (Figure 17)

Blood levels of cadmium appear to reflect recent (months) exposure to the metal. Blood levels of newly exposed workers increased within a few months of beginning exposure (Kjellstrom, 1979; Kjellstrom and Nordberg, 1978; Lauwerys *et al.*, 1979; Lauwerys *et al.*, 1976). When cadmium exposure was reduced, blood levels tended to decrease rapidly (Kjellstorm, 1979). Blood cadmium levels did not continue to increase with duration of employment (unlike urinary cadmium levels) prompting Lauwerys and coworkers to suggest that blood levels reflect recent exposure to cadmium (Lauwerys *et al.*, 1976).

However, other investigators observed that in addition to recent exposure, blood cadmium levels also appear to be influenced by the body burden of cadmium (Berglund *et al.*, 1994; Jarup *et al.*, 1998). Blood levels remained elevated in workers with long-term cadmium exposure for years after the termination of exposure (Friberg *et al.*, 1974; Jarup *et al.*, 1983). Jarup and associates reported that blood cadmium levels were still elevated in workers fifteen years after exposure ceased (Jarup *et al.*, 1983, 1998).

Metallothionein

Metallothioneins are a class of low molecular weight proteins (6,000 daltons) that contain a number of cysteine residues that bind metals. Metallothioneins are synthesized in the liver, kidney and other tissues and appear to play a very important role in the toxicokinetics of cadmium as well as the mechanism of cadmium toxicity to the kidney. The following is a summary of the work of many investigators (e.g. Squibb *et al.*, 1982, 1984; Fowler and Nordberg, 1978; Cherian *et al.*, 1976; also see reviews of Jarup *et al.*, 1998; ATSDR, 1999) on the role of metallothionein in cadmium metabolism and cadmium's renal toxicity.

Following oral exposure to cadmium, the metal is transported in the blood in erythrocytes or bound to large molecular weight proteins (Nordberg, 1972; Jarup *et al.*, 1998). Other studies indicate that cadmium binds to a metallothionein(s) in the intestinal mucosa and the cadmium-metallothionein complex is then transported in the blood (Ohta and Cherian, 1991; Groten *et al.*, 1991). Cadmium is taken up by liver cells, where it binds to metallothionein. Cadmium bound to metallothionein in the liver is slowly released back into the plasma; because of the small size of the cadmium-metallothionein complex, it passes freely through the glomerulus and into the renal tubule.

Cadmium bound to metallothionein is efficiently taken up in the proximate tubule by pinocytosis. Within renal tubular cells, the pinocytosis vacuoles fuse with lysosomes, which degrade the metallothionein, thereby freeing the cadmium. The cadmium combines with newly synthesized metallothionein produced by the tubular cell and accumulates (is stored) in the kidney for decades. Metallothionein is inducible in the liver and kidney by cadmium and other metals. Studies have shown that exposure to low levels of cadmium induces metallothionein production, allowing greater storage in the kidney and liver and reducing the acute toxicity of the metal (Nordberg *et al.*, 1971).

Cadmium continues to accumulate in the kidney until metallothionein levels are exceeded. Once metallothionein levels are no longer sufficient to bind all cadmium in the tubular cell, damage to the kidney tubule is believed to occur from the unbound cadmium. The damaged tubule is no longer able to sequester all the cadmium in the urine, and therefore increased levels of cadmium are observed in the urine and reduced cadmium levels are observed in the kidney. When this occurs, the urinary cadmium level is more influenced by recent exposure to cadmium because the kidney is no longer able to efficiently accumulate and store cadmium.

The distribution of cadmium in experimental animals is similar to that observed in humans. Most administered cadmium is distributed to the kidneys and liver. Intravenous injection of radiolabeled $CdCl_2$ into the tail vein of mice resulted in high concentrations of cadmium in the liver and kidneys 24 hours, 90 and 180 days post-injection (Shibata, 1974). Intravenous injection of radiolabeled $CdCl_2$ in mice resulted in elevated cadmium levels in the kidneys and liver after 44 days (Nordberg and Nishiyama, 1972). After 112 days, cadmium levels were substantially lower in the liver, while levels in the kidneys remained elevated (Nordberg and Nishiyama, 1972).

The concentration of cadmium in the liver and kidneys of rats after three weeks of oral exposure to cadmium were comparable, but the levels of cadmium appeared to be higher in the kidney after 6, 12 and 24 weeks of exposure (Kotsonis and Klaassen, 1978). Oral administration of a single dose of cadmium to rats resulted in elevated cadmium levels in the liver and kidneys after two days (Kotsonis and Klaassen, 1977). Fourteen days post-administration; cadmium levels in the liver were unchanged from levels on day two, while cadmium levels in the kidneys were substantially higher than levels two days post-administration.

Excretion

Cadmium is stored in the kidneys and liver and very little is eliminated from the body until renal toxicity occurs. Thereupon, renal excretion increases and levels of cadmium diminish in the liver and in particular in the kidney. Following its oral administration, large quantities of cadmium are found in the feces (90-95 percent or greater) because only a small fraction is absorbed (Shaikh and Smith, 1980; McLellan *et al.*, 1978; Flanagan *et al.*, 1978). Orally administered labeled cadmium is detected in the feces for days or weeks (not for just one day) (Shaikh and Smith, 1980; McLellan *et al.*, 1978; Flanagan *et al.*, 1978; Kikuchi *et al.*, 2003). This may be due to the metal binding to or being taken up by mucosal cells, which are then sloughed off. Twenty-five days after cadmium was administered to monkeys, Suzuki and Taguchi (1980) recovered 3 percent of an oral dose of cadmium in the GI tract wall.

Smokers receive a much larger dose of cadmium than non-smokers, as reflected in higher blood cadmium levels (Kjellstrom 1979) and a higher body burden (Ellis *et al.*, 1979). Fecal elimination of cadmium did not appear to be related to body burden in a study in Sweden and the United States, while urinary excretion of cadmium was consistent with the increased body burden (Kjellstrom, 1979). Fecal elimination of cadmium was only slighter higher in smokers, indicating little fecal elimination of inhaled cadmium (Johnson *et al*., 1977 as reviewed by Kjellstrom, 1979). Urinary excretion of cadmium was double that in non-smokers (Elinder *et al.*, 1978; Ellis *et al.*, 1979).

Studies in the rat revealed substantial biliary elimination of cadmium (Klaassen and Kotsonis, 1977). Administration of cadmium to rats by intravenous injection resulted in 10 percent of the dose recovered in the feces after 24 hours and 5 percent in the subsequent 24 hours. Less than 0.5 percent of the administered dose was recovered in the urine after seven days. The amount of cadmium recovered in the bile was dose-dependent, with markedly increased recovery at higher doses. The authors speculate

that at lower doses cadmium is bound to metallothionein and is less available to move into the canaliculus. In dogs, very little of the injected cadmium was recovered in bile. Recovery of cadmium in the bile of rabbits was only slightly greater than in dogs.

Substantial biliary excretion of cadmium was also observed in rats administered cadmium by subcutaneous injection (Elinder and Pannone, 1979). Unlike the findings of Klaassen and Kotsonis (1977), the elimination rate did not increase at a higher dose.

Urine cadmium levels in humans are normally quite low because of the almost complete reabsorption of cadmium in the proximate kidney tubule. An observed increase in urinary cadmium levels with duration of employment (in workers with no evidence of kidney lesions) prompted Lauwerys and associates to suggest that urinary cadmium levels reflect cadmium body burden (Lauwerys *et al.*, 1976). Roels and coworkers measured cadmium levels *in vivo* in the livers, kidneys, and urine of a sizable worker population (309 male workers) in zinc-cadmium plants, including some that were exposed to cadmium and some that did not appear to receive any significant occupational exposure to cadmium (Roels *et al.*, 1981). Some of the workers exhibited signs of renal toxicity (elevated levels of proteins in the urine) while other workers did not. The investigators observed a linear relationship between the level of cadmium in kidney and urine in workers that did not exhibit cadmium toxicity, but not in workers that exhibited renal toxicity. The body burden of cadmium, defined as twice the amount detected in the liver and kidneys, was also correlated with urinary levels in workers that did not exhibit renal dysfunction.

Kinetics

Cadmium appears to have a very long residence time in the body, although this may vary by age. Because of its long residency, it is exceedingly difficult to measure the half-life of cadmium in humans. McClellan and coworkers were able to measure the level of radiolabeled cadmium in one of 14 individuals who ingested radiolabeled cadmium because this individual retained a high portion of the administered dose (10 percent) (McLellan *et al.*, 1978). The half-life of cadmium in this individual was estimated to be approximately 100 days. Rahola and associates followed the whole body retention of cadmium in one individual who was administered labeled Cd mixed with a calf-liver suspension (Rahola *et al.*, 1972). The authors indicated it was "not possible to give an exact value of biological half-time." They estimated the shortest possible biological half-life of 130 days and the longest "is infinity."

Whole–body retention was determined in one male subject given labeled cadmium in a kidney cortex preparation, using whole body scanning techniques (Shaikh and Smith, 1980). The percent of initial dose retained in the body was monitored for 800 days post-administration. The change in cadmium levels after the initial rapid decline was very slight. The investigators indicated a terminal half-life of 26 years but also note that the data are consistent with an infinite half-life as well.

Taguchi and Suzuki (1981) administered labeled cadmium chloride to male and female mice by subcutaneous or intraperitoneal injection and measured the percent of cadmium retained in the mouse at various post-administration times. Retention

estimates were based on amount of radioactivity not recovered in the feces (essentially no radioactivity was recovered in the urine). These investigators observed a final or terminal half-life ranging from 255 to 630 days, depending on the age of the mouse (older mice had a longer cadmium half-life). They reported that subcutaneous or intraperitoneal injection yielded similar terminal half-lives. The half-life in females was considerable longer than was observed in males (terminal half-life of 349 days for females versus 220 days in males). The cadmium half-life in mice was quite long, approximately a 35 percent or greater portion of the mouse lifetime (two years).

Male rats were administered labeled cadmium chloride by four different exposure routes and the whole body retention of radioactivity was determined at various times (Moore *et al.*, 1973). Retention of radioactive cadmium was markedly influenced by the administration route. Injection and inhalation resulted in higher retention than the oral route; only a few percent of the oral dose was absorbed. The change in whole body radiation with time was very similar for all routes beginning ten days after cadmium was administered. The biological half-life ranged from 173 to 252 days, with the oral and inhalation routes yielding half-life estimates of 200 days, about 30 percent of the rat lifetime.

The effect of dose on cadmium retention was investigated in mice orally administered the metal (Engstrom and Nordberg, 1979). The high dose group had a markedly higher percent of administered dose that was absorbed and a much longer half-life (236 days) than the lower dose groups (66 to 81 days). The increased half-life may be due to a cadmium-mediated increase in the synthesis of metallothionein (Kotsonis and Klaassen, 1978), particularly in the liver. This may have increased the metal's net absorption as well as prolonging the retention in the mouse.

Toxicokinetic Models

Several models have been employed to describe the toxicokinetics of cadmium in humans (Tsuchiya and Sugita, 1971; Friberg *et al.*, 1974; Nordberg and Kjellstrom, 1979; Diamond *et al.*, 2003; Choudhury *et al*., 2001; and others are discussed in ATSDR, 1999). Tsuchiya and Sugita (1971) used a mathematical model to estimate the biological half-life of cadmium in humans. Based on first order kinetics, the authors estimated the urinary half-life of cadmium associated with an accumulated level of cadmium in the body (body burden) after 50 years as follows:

$$X = I * k (1-e^{-kt})$$

where:

I = intake (μg/yr);

X = body burden (μg);

k = rate of elimination (yr^{-1}) or $0.693/ T_{1/2}$;

t = time (years).

Autopsy findings were used to estimate a cadmium body burden of 30 mg in individuals 40 to 50 years old. The model was employed to predict the expected urinary half-life of cadmium associated with various daily exposure rates (the metric used was the absorbed dose of cadmium). Using this model, given a specified daily rate of cadmium intake (I), a half-life ($T_{1/2}$) can be predicted that would be necessary to achieve a cadmium body burden (X) of 30 mg after 50 years of exposure. Table 3 presents the predicted half-lives associated with a range of absorbed daily doses of cadmium (Tsuchiya and Sugita, 1971).

Table 3. Estimated Cadmium Half-life Associated with Various Daily Intakes[a]

Daily Intake[b] (µg/day)	Predicted Half-Life (yr)
2	85
4	16
6	10
8	7
10	6

[a]Tsuchiya and Sugita (1971). Half-life necessary to achieve an average body burden of 30 mg after 50 years of exposure at the indicated daily intake.
[b]Absorbed dose.

Physiologically Based Pharmacokinetic Modeling

One widely used model is the physiologically based pharmacokinetic model of Nordberg and Kellstrom (1979). This eight-compartment model addresses both inhalation and oral exposure to cadmium, its movement from the lung to the stomach by mucociliary clearance, as well as its excretion into the urine, bile and into the feces due to the sloughing off of intestinal mucosa. The model includes separate compartments for liver and kidney, three separate blood compartments, and a miscellaneous tissue compartment. Differential equations are employed to describe the movement of cadmium into and out of the compartments. Twenty-two different coefficients, some that are a function of age, are employed in the model. Unfortunately, little or no data were available for many of these coefficients.

To obtain reasonable values for the coefficients, ranges were first identified based on "data from the literature and general considerations regarding various pathways." The authors then settled on coefficients "that gave the best fit of calculated and observed values for cadmium concentration in various compartments on the basis of trials with calculation of various alternatives." Data from humans exposed to cadmium due to smoking, long-term occupational exposure, or environmental exposure were employed to evaluate the various coefficients and the model itself. The investigators indicated that three separate blood compartments were needed as well as a very low rate of biliary excretion to yield good predictions consistent with the empirical observations.

PHYSIOLOGICAL/NUTRITIONAL ROLE

There is no known physiological or nutritional role for cadmium.

TOXICOLOGY

Toxicological Effects in Animals and Plants

Toxic effects observed in animals tend to mirror what is observed in humans.

Acute Toxicity

The oral acute LD_{50} of cadmium in rats and mice ranged from 100 to 3,000 mg/kg (ATSDR, 1999). The inhalation of cadmium oxide fumes resulted in the death of rats, mice, rabbits, guinea pigs and dogs (review by ATSDR, 1999). Death occurred after a large single inhalation exposure or when the animals were exposed to lower level of cadmium from several days to two weeks.

Subchronic Toxicity

Subchronic inhalation exposure of animals to cadmium resulted in respiratory injury that is consistent with what has been observed in humans. Effects in the lung including interstitial pneumonitis, hemorrhage, edema, hyperplasia and fibrosis have been observed in rats, hamsters, and rabbits (reviewed by ATSDR, 1999). Adverse effects associated with subchronic oral exposure to cadmium in rats include necrosis of the renal tubules and hepatocytes, intestinal hemorrhage, ulcers and anemia (ATSDR, 1999).

Genetic Toxicity

The genotoxicity of cadmium has been studied in humans, animals and *in vitro* genotoxicity bioassays. Another review of these studies is not needed, given the availability of reviews by California DHS (1986), IARC (1993), and more recently by Pinot *et al.* (2000). While genotoxicity has been observed in certain studies of humans (chromosomal aberrations) exposed to cadmium and in certain *in vitro* bioassays, the findings are mixed and there are conflicting results. The genotoxicity studies do not provide compelling evidence that cadmium acts mainly due to genotoxic effects; genotoxicity appears to be just one of the mechanisms of action that may contribute to cadmium toxicity.

Developmental and Reproductive Toxicity

OEHHA previously conducted a comprehensive evaluation of the developmental and reproductive toxicity of cadmium (OEHHA, 1996, 2001). The metal was listed as "known to the State to cause reproductive toxicity" effective May 1, 1997. A

maximum allowable daily level (MADL) of 4.1 µg/day was established using methodology required by regulation (Title 22, California Code of Regulations, Sections 12801 and 12803). OEHHA determined that the most consistent reproductive or developmental effect of cadmium in animals was reduced fetal weight or birth weight and alterations in locomotor behavior. While cadmium also caused maternal toxicity in many of these studies, effects in offspring did not appear to be necessarily due to maternal toxicity. A summary of the results of various developmental studies in which cadmium was administered orally, taken from the recent review by OEHHA (Table 2 in the review), is provided below.

Table 4. Development Effects of Cadmium in Animal Studies[a]

Reference	Study Design	Reported effects[b]
Food		
Machemer and Lorke, 1981	rat, in feed, gestation days 6-15 0, 30, 100 ppm	Transitory reduction in maternal weight gain at 100 ppm. No effects on implantation, viability, litter size, fetal weight, malformations or ossification of skeletal elements.
Pond and Walker, 1975	rat, in feed, gestation 0, 200 ppm	Birthweight and maternal weight gain reduced at 200 ppm. No changes in litter size or increase in malformations
Whelton *et al*., 1988	mice, in feed, throughout 6, 42 day rounds of gestation-lactation 0.25, 5.0, 50.0 ppm	No significant effect on maternal survival. At 50 ppm, 15% decrease in litter size at birth, and 25% decrease in pre-weaning weight gain.
Gavage		
Baranski *et al*., 1982	rat, gavage, gestation days 7-16 0, 2, 4, 8, 12, 20, 40 mg/kg-d	Maternal death at 40 mg/kg, maternal weight gain reduced at all doses. Fetal weight reduced at 8, 12, 20, 40 mg/kg-d. Early and late resorptions increased at 40 mg/kg-d. Malformations increased at 20 and 40 mg/kg. Delayed ossification at all doses.
Baranski, 1983	rat, gavage, 5 weeks plus gestation, 5 d/wk 0, 0.04, 0.4, 4 mg/kg-d	No effect on maternal or fetal viability, or on fetal weight.
Baranski *et al*., 1985	rat, gavage, gestation days 7-16 2, 12, 40 mg/kg-d	Maternal death at 40 mg/kg-d. Decreased maternal weight gain at all doses. Decreased fetal weights at 12 and 40 mg/kg-d. Decreased viability and major malformations at 40 mg/kg-d. Retarded ossification at all doses.

Reference	Study Design	Reported effects[b]
Cornwall *et al*., 1984	rat, gavage, gestation days 6-18 0, 25 mg/kg-d	No effect on resorption frequency or fetal weight.
Machemer and Lorke, 1981	rat, gavage, gestation days 6-15 0, 1.8, 6.1, 18.4, 61.3 mg/kg-d	Maternal weight gain reduced at 6.1, 18.4, 61.3 mg/kg-d. Maternal mortality 60% at 61.3 mg/kg-d, no pregnancies at this dose. Malformations increased at 18.4, 61.3 mg/kg-d. Fetal weight decreased at 18.4 mg/kg-d.
Scharpf *et al*., 1972	rat, gavage, gestation days 6-19 0, 20, 40, 60, 80 mg/kg-d	Maternal death increased at 60 and 80 mg/kg/d. Fetal viability not affected at 20 or 40 mg/kg-d, decreased at 60 or 80 mg/kg-d. Decreased fetal weight only at 80 mg/kg-d. External and internal anomalies increased at all doses.
Seidenberg *et al*., 1986	mice, gavage, gestation days 8 - 12 340 mg/kg-d	No maternal death. No change in number of live pups, but an increase in number of dead pups on pnd 1. Decreased birth weights.
Simmons *et al*., 1984	rat, gavage, gestation days 6-18 0, 10, 25, 50 mg/kg-d	Maternal mortality: 4/9 at 50 mg/kg-d. Two litters surviving this dose had reduced viability on pnd 1. Fetal weight not decreased at any dose on gd 19. Some 25 mg/kg-d litters allowed to deliver; pup weights decreased on pnd 1, 5, 10, 20. No effects on litter size, resorption frequency, or implantation frequency.
Sutou *et al*., 1980a,b	rat, gavage, males and females 6-9 weeks prior to mating, plus females during gestation 0, 0.1, 1.0, 10 mg/kg-d	Decreased implants and live fetuses, and increased resorptions at 10 mg/kg/d. Fetal weight and maternal weight gain decreased at 10 mg/kg/d. Increased placental weights.
Water		
Wardell *et al*., 1982	rat, gavage, gestation days 6-18 0, 25, 50, 75, 100 mg/kg-d	Maternal deaths increased at 75 and 100 mg/kg-d. All fetuses resorbed at these doses. Fetal weight, length, and tibial length decreased at 50, 75 mg/kg-d. Malformations not increased at any dose.
Ahokas *et al*., 1980	rat, water, gestation days 1-21 0, 1, 10, 100 ppm	Fetal weight decreased at 100 ppm. No change in litter size at any exposure. Maternal weight reduced at 10, 100 ppm.
Ali *et al*., 1986	rat, water, gestation 0, 4.2, 8.4 ppm	Birthweight decreased at 8.4 ppm. No changes in maternal weight gain, litter size, or malformation frequency at any exposure level.

Reference	Study Design	Reported effects[b]
Baranski, 1987	rat, water, gestation days 1-20 0, 60, 180 ppm	Fetal weight reduced at 60, 180 ppm. Maternal weight gain reduced at 60, 180 ppm. No change in litter size, fetal death, resorption frequency, or frequency of preimplantation loss at any exposure.
Cooper *et al*., 1978	rat, water, 90 d plus gestation 0, 4.3, 8.6, 17.2, 34.4 ppm	No effect on birthweight or postnatal growth at 4.3 or 8.6 ppm. At 17.2 and 34.4 ppm, birthweights and postnatal weight gain reduced.
Hastings *et al*., 1978	rat, water, 90 d plus gestation 0, 17.2 ppm	Birthweight decreased at 17.2 ppm. No change in maternal weight gain or litter size at any exposure.
Kelman *et al*, 1978	rat, water, gestation 0, 10, 25 ppm	No changes in litter size or malformation frequency
Sasser *et al*., 1985	rat, water, gestation 0, 50, 100 ppm	No maternal death, no change in maternal weight gain. No effect on litter size, no malformations, no effect on fetal weights.
Saxena *et al*., 1986	rat, water, gestation 0, 100 ppm	Fetal weight and maternal weight gain decreased at 100 ppm. No change in litter size or malformation frequency at any exposure.
Sorell and Graziano, 1990	rat, water, gestation days 6-20 0, 5, 50, 100 ppm	Fetal weight decreased at 100 ppm. Maternal weight gain reduced at 50, 100 ppm. No change in litter size or malformation frequency at any exposure.
Sowa and Steibert, 1985	rat, water, gestation days 1-20 0, 50 ppm	Maternal weight gain reduced at 50 ppm. No change in litter size, fetal weight, or malformation frequency at any exposure.
Sowa *et al*., 1982	rat, water, 30 d; 30 d + gestation; gestation 0, 100 ppm	No change in fetal weight or litter size at any exposure.
Steibert *et al*., 1984	rat, water, 5 months plus gestation 0, 50 ppm	Fetal weight and maternal weight gain reduced at 50 ppm. Reduced numbers of renal nephrons in offspring.
Webster, 1978	mouse, water, gestation 0, 10, 20, 40 ppm	Fetal weight decreased at 10, 40 ppm. Maternal weight gain said to be decreased at 40 ppm, but not clear if this was statistically significant. No change in litter size at any exposure.
Webster, 1979a,b	mouse, water, gestation 0, 40 ppm	Fetal weight decreased at 40 ppm. No change in litter size at any exposure.

Reference	Study Design	Reported effects[b]
Webster, 1988	mouse, water, 1 month plus gestation 0, 0.0015, 0.24, 40 ppm	Fetal weight decreased at 40 ppm. No change in litter size at any exposure. All fetuses externally normal, except for anemic appearance at highest concentration.
Xu *et al*., 1993	mouse, water, males and females 2 months, plus gestation and lactation for females 0, 30, 75 ppm	No change in birthweight, litter size, or postnatal viability at any exposure.

[a]from OEHHA, 1996.
[b]Effects reported to be statistically significant at $p \leq 0.05$ or, if statistical significance was not reported, incidence data are provided.

Given OEHHA's previous review of the reproductive and development studies, the following discussion of the reproductive and developmental effects of cadmium in animals is limited to the study of Ali and coworkers, the key animal study used to develop the MADL (Ali *et al.*, 1986).

Pregnant Wistar rats were exposed to cadmium acetate, 4.2 or 8.4 μg/mL (the equivalent of 0.706 and 1.21 mg/kg-day, respectively) in drinking water for the duration of gestation. The mean body weights of pups were significantly decreased in both dose groups on postnatal days 5, 10 and 20 compared to control, although there were no differences in the body weight of the treated and control dams during gestation. There were also significant differences in the development of spontaneous locomotor activity, swimming behavior and reflexes (development of aversion response) in pups that were exposed to cadmium *in utero.* Because adverse effects were observed at both administered doses, 0.706 mg/kg-day was determined to represent a LOAEL in this study.

Immunotoxicity

Cadmium has been observed to produce a wide range of immunological effects in animal studies, some of which appear to represent suppression, and others that appear to represent stimulation of immune responses (reviewed by ATSDR 1999). Cadmium has been observed to suppress humoral immunity (Graham *et al.*, 1978) and to be cytotoxic to splenic lymphocytes (Krzystyniak *et al.*, 1987). Cadmium has been shown to increase mortality to virally-induced leukemia, suggesting that immunosuppression is a possible mechanism of action regarding cadmium's tumorigenic effects (Blakley, 1985). On the other hand, cadmium administration has resulted in increased resistance to viral infection and an increase in cell-mediated immunity (Chopra *et al.*, 1984; Exon, 1986).

Neurotoxicity

While there is little evidence of cadmium exposure resulting in neurotoxicity in humans, studies in animals have revealed a range of effects including decreased motor activity, muscle weakness and atrophy, and neuropathies (reviewed in ATSDR, 1999). These effects were observed following high exposure levels.

Renal Toxicity

The observation of renal toxicity in workers in a battery manufacturing facility (Friberg, 1950) triggered numerous studies on the effects of cadmium in animals (reviewed by ATSDR, 1999; IPCS, 1992). As in humans, renal toxicity is observed in animals chronically exposed to cadmium. Animal studies are particularly useful because direct measurement of cadmium levels in the kidney in individuals displaying renal toxicity is difficult in humans, and the data were at first limited to samples from autopsies from accident victims. These data are not particularly useful in identifying the level of cadmium in the kidney at which toxicity begins to occur. Studies in animals that can control cadmium intake and monitor urinary excretion of pertinent biomarkers or other indicators of renal toxicity have been useful in identifying the cadmium level in the kidney associated with onset of renal toxicity. Table 5, which provides a comprehensive summary of these studies, is from the IPCS (1992) report.

Carcinogenicity

Oral exposure - Rats were administered 0, 25, 50, 100 or 200 ppm of cadmium in the diet for 77 weeks (Waalkes and Rehm, 1992). The effect of zinc deficiency induced by restricting zinc to 7 ppm in the diet was also evaluated in this study (Table 6). No statistically significant increase in tumors was observed in rats on a normal diet (analysis by OEHHA; Fischer's Exact Test and Cochran-Armitage, $p < 0.05$). The leukemia increase was not statistically significant in any of the dose groups compared to control in the zinc deficient animals (OEHHA analysis by Fischer's Exact, $p < 0.05$). However, a trend test indicated a dose-related increase in leukemia in the zinc deficient rats (OEHHA analysis by Cochran-Armitage, $p < 0.05$). An increase in the incidence of testes interstitial cell tumors was observed in the high cadmium dose group in rats receiving normal dietary zinc levels, 6 of 27 compared to 1 of 28 in the zinc-deficient control group (no normal control group reported), but the increase was not statistically significant (OEHHA analysis by Fischer's Exact, $p < 0.05$).

Table 5. Effect of Cadmium on the Kidney and the Associated Cadmium Levels in Animals (from IPCS, 1992)

Species, route of administration	Exposure level	Duration (months)	Average cadmium level in kidney cortex (mg/kg wet weight)	Renal changes	Reference
Mouse, sc	0.25 mg/kg-d 0.50 mg/kg-d	6 6	110-170 [a] 170 [a]	No effect Tubular proteins in urine	Nordberg & Piscator, 1972
Rat, ip	0.75 mg/kg-d 0.75 mg/kg-d	3 4	200 [a] 300 [a]	No effect Histological changes in 60% of animals	Bonnell *et al*., 1960
Rat, sc	0.65 mg/kg-d	3	200	Histological changes	Goyer *et al.*, 1984
Rat, drinking water	10 mg/L 50 mg/L 100 mg/L 200 mg/L	8.5 8.5 8.5 8.5	11 [a] 35 [a] 90 [a] 145[a]	No histological changes Slight histological changes Histological changes Histological changes	Kawai *et al.*, 1976
Rat, drinking water	200 mg/L	11	200	Total and low molecular weight proteinuria	Bernard *et al.*, 1981
Rat, drinking water	50 mg/L	3	100[a]	Decreased insulin and PAH clearance; histological changes	Kawamura *et al.*, 1978
Rat, drinking water	50 mg/L	2.5	235	Slight histological changes in proximal tubules	Axelsson & Piscator, 1966a; Axelsson *et al.*, 1968
Rabbit, sc	2.5 mg/kg-d 2.5 mg/kg-d	2.5 4	235 460	Slight histological changes in proximal tubules More severe histological changes, reduced alkaline phosphatase in renal cortex, total proteinuria	Axelsson & Piscator, 1966a; Axelsson *et al.*, 1968

Species, route of administration	Exposure level	Duration (months)	Average cadmium level in kidney cortex (mg/kg wet weight)	Renal changes	Reference
Rabbit, sc	0.5 mg/kg-d 0.5 mg/kg-d	1 2.5	120 300	β2-microglobulin Total proteinuria	Nomiyama *et al.*, 1982b
Rabbit, sc	0.5 mg/kg-d	0.7	200	proteinuria, glucosuria, and aminoaciduria; decrease in C_{IN} and Tm_{PAH}	Nomiyama & Nomiyama, 1982
Rabbit, sc	1.5 mg/kg-d	1	50-200	decreased tubular readsorption	Nomiyama, 1973a; Nomiyama *et al.*, 1978a
Rabbit, sc	0.5 mg/kg-d	2	160[a]	slight histological changes	Kawai *et al.*, 1976
Rabbit, drinking water	160 mg/L	6	170[a]	extensive fibrosis; pronounced changes	Stowe *et al.,* 1972
Rabbit, drinking water	50 mg/L 200 mg/L	10 10	58 200	Slight tubular atrophy Severe interstitial and tubular fibrosis	Kawai *et al.*, 1976
Rabbit, diet	300 ppm	4 10	200 300	Aminoaciduria, enzymuria Proteinuria, glucosuria	Nomiyama *et al.*, 1975
Horse, diet	No cadmium added	Lifelong (up to 240)	75	Renal tubular interstitial changes and fibrosis in 25% of animals	Elinder *et al.*, 1981a,b
Bird, sc	0.16 mg/kg-d		20 [b]	Histological changes	Nicholson & Osborn, 1983

[a] These values are whole kidney concentrations; about 0.8 times kidney cortex values, on average.

[b] Denotes concentrations (wet weight) calculated as 0.2 times dry weight concentrations.

Table 6. Incidence of Leukemia in Normal and Zinc-Deficient Rats[a]

Zinc dietary level (ppm)	Rats at risk	Cadmium dose (ppm in diet)	Rats with leukemia
7	27	0	2
7	26	25	1
7	26	50	3
7	25	100	5
7	25	200	7
60	28	0	1
60	27	25	4
60	24	50	5
60	24	100	5
60	27	200	1

[a] from Waalkes and Rehm, 1992.

The effect of 50 ppm cadmium administered in the diet on the incidence of spontaneously-occurring liver tumors in C3H and C57BL/6 male mice was investigated by Nishiyama *et al.* (2003). Liver tumors were significantly reduced in C3H mice receiving cadmium compared to control and no effect was evident on the incidence of tumors in the C57BL/6 mouse. Cadmium was administered in the diet (0, 1, 3, 10, 50) of male and female Wistar rats for two years (Loser, 1980 as reported in U.S. EPA, 1986). No increase was observed in any specific tumors.

Other exposure routes - Exposure of male rats to a cadmium aerosol (12.5, 25 or 50 $\mu g/m^3$) for 23 hours/day, seven days/week for 18 months resulted in a dose-dependent increase in lung carcinomas (15.4, 52.6 and 71.4 percent respectively) (Takenaka *et al.*, 1983, as reported in U.S. EPA, 1986; IARC, 1993).

IARC (1993) has reviewed a number of studies in which cadmium was instilled in the lung or injected into experimental animals. In several studies, the injection of cadmium in rats produced localized sarcoma. Injection into the peritoneal cavity resulted in malignant tumors, and subcutaneous injection in mice and rats resulted in interstitial testicular tumors.

Toxicological Effects in Humans

Adverse effects associated with human exposures to cadmium are well known and have been characterized in both occupational and residential settings. In occupational settings, exposure is primarily to cadmium oxide and occurs through the inhalation route. Renal toxicity, as reported by Friberg in 1950 in a battery manufacturing plant, has been corroborated in a number of subsequent studies (Friberg, 1950; see reviews by ATSDR,

1999; IPCS, 1992; Jarup *et al*., 1998). Epidemiologic studies have also demonstrated an increase in lung cancer associated with inhalation exposure to cadmium in the workplace.

Notable human toxicity in residential settings was associated with ingestion of contaminated rice irrigated with cadmium-contaminated water in Japan and China. Effects on the skeleton and musculature were observed as well as renal toxicity. Recently, as renal toxicity has been detected at lower levels of exposure, investigators have raised concerns that renal toxicity may be occurring in individuals exposed to typical levels of cadmium in the diet in combination with exposure to cadmium from inhalation of cigarette smoke.

Acute Toxicity

The inhalation of high levels of cadmium fumes in occupational settings resulted in fatalities (reviewed by ATSDR, 1999). Symptoms that were observed include severe pulmonary edema, pneumonitis, and then death due to respiratory failure.

Subchronic Toxicity

Other less severe respiratory effects have been observed in workers exposed subchronically to lower levels of cadmium via inhalation. Changes in pulmonary function were observed, such as decreased forced volume capacity (FVC) and mild to moderate interstitial fibrosis observed in chest X-rays (ATSDR, 1999). A dose-dependent excess in death due to bronchitis has been observed in worker exposure to cadmium (Smith *et al*., 1976; Davison *et al.,* 1988; and Armstrong and Kazantzins, 1983; as reviewed by ATSDR, 1999). Other studies did not reveal impairment of pulmonary function or effects on pulmonary function tests (ATSDR, 1999).

Developmental and Reproductive Toxicity

Jarup *et al.* (1998) and ATSDR (1999) reviewed studies that investigated the relationship between cadmium exposure and reproductive effects in humans. No link could be found between exposure to cadmium and reproductive effects. While there is evidence of reproductive effects associated with smoking (low birth weight), it is unclear if the effects are due to the increased exposure to cadmium or to the myriad of other chemicals that occur in mainstream cigarette smoke.

OEHHA (1996) reviewed the evidence of developmental and reproductive effects in humans associated with exposure to cadmium and concluded, "The nature of workplace, environmental and consumer exposure to Cd make it difficult to isolate the effects of Cd on human populations from other, potentially confounding, factors." "While the interpretation of human epidemiological studies is complicated by the difficulty of controlling for confounding exposures, particularly cigarette smoke and Pb, the overall evidence from human studies is consistent with that from experimental animals."

Renal Toxicity

Several reviews describe the adverse effects of cadmium in humans associated with chronic exposure (IPCS, 1992; Jarup *et al.*, 1998; Friberg, 1984). Long-term, low-level cadmium exposure in humans is associated with effects mainly on the kidney. While higher exposure levels have been associated with adverse effects on the skeleton and the lungs, the following discussion focuses on the kidney because it appears to be the site of the most sensitive non-carcinogenic toxic endpoint.

Occupational exposure to cadmium was first linked to adverse effects on the kidney in the 1950s (Friberg, 1950; Butler and Flynn, 1958). Renal toxicity due to environmental exposures to cadmium has been observed in studies in Japan, China and Europe. Cadmium damages both the glomerulus and the proximate renal tubule. Damage to the glomerulus is characterized by the leakage of large proteins into the urine, decreased glomerular filtration rate (GFR), uremia and ultimately kidney failure.

Adverse effects on the proximate tubule are characterized by increases in the urine levels of a variety of tubular proteins (Jarup *et al.*, 1998). Tubular proteins are small proteins that occur in the plasma that are not filtered out by the glomerulus, and therefore pass into the renal tubule. In a healthy kidney, tubular proteins are efficiently reabsorbed by the renal proximal tubule. The levels of tubular proteins begin to increase in the urine, often markedly, when the tubule is damaged because they are not being reabsorbed in this segment of the kidney. Increased levels of urinary tubular proteins are a very sensitive indicator of tubular damage.

An increase in tubular proteins, in itself, does not necessarily represent a disease symptom (Jarup *et al.*, 1998). However, continued exposure to cadmium will result in more severe renal toxicity, and studies indicate that the effects may become more severe with time even if exposure is stopped. Other studies indicate that termination of exposure does not appear to result in recovery from renal toxicity. Therefore, increased levels of tubular proteins, an early sign of onset of renal toxicity, should not be considered innocuous.

Increased urinary levels of tubular proteins such as β_2 microglobulin, α_1 microglobulin, retinol binding protein (RBP), and N-acetyl-β-glucosaminidase (NAG) indicate damage to the proximate tubule (Bernard and Lauwerys, 1991). The most commonly used biomarker is β_2 microglobulin, a protein that is normally freely filtered through the glomerulus and then almost completely reabsorbed in the proximal tubule. Because in the healthy kidney over 99.9 percent of β_2 microglobulin that is filtered is reabsorbed, tubule damage that results in a drop of one percent in β_2 microglobulin reabsorption can lead to an increase in urinary levels of 10 fold or more (Jarup *et al.*, 1998).

Unfortunately, there are several problems with using β_2 microglobulin as a biomarker of renal toxicity. 1) β_2 microglobulin is labile in an acid environment and therefore can rapidly degrade in acidic urine. 2) The level of β_2 microglobulin in urine increases with age and therefore, increased levels in urine are not necessarily due to chemically-induced tubular damage. 3) Investigators have employed various criteria as to when levels of β_2 microglobulin are considered "elevated."

Effects on the renal tubule and glomerulus

Urinary excretion of NAG, RBP and β_2 microglobulin and cadmium was measured during a 24-hour period in a large study (Cadmibel study) of over 1,600 persons in Belgium (Buchet *et al.*, 1990). While persons that were occupationally exposed were excluded from the study, the study included subjects who were from cadmium-contaminated areas, and others from uncontaminated areas. The subjects were stratified into four groups based on the amount of urinary cadmium excretion over 24 hours. The mean urinary excretion of RBP, NAG and β_2 microglobulin increased with the amount of urinary excretion of cadmium, but not with the blood cadmium level. Higher cadmium body burdens were observed in women and in smokers. The investigators suggest that when cadmium excretion is below 2 μg in 24 hours, the risk of renal effects remains low. The investigators estimate that a cadmium excretion rate of 2 μg in 24 hours corresponds to a mean renal cortex concentration of about 50 ppm, which they estimate would be reached with a daily cadmium intake of 1 μg/kg body weight after 50 years.

Buchet *et al.* (1980) investigated the renal function of workers exposed to cadmium in the workplace. The study comprised 148 workers at two cadmium smelters and a control group of workers judged not exposed to cadmium and with urinary levels below 2 μg Cd/g creatinine. The investigators observed increased urinary levels of protein, IgG, alkaline phosphatase and β_2 microglobulin in worker exposed to cadmium compared to the control group. When the findings were stratified by the level of cadmium in urine, an increase in prevalence of some signs of renal dysfunction was observed in the 2 to 9.9 μg Cd/g creatinine group (increased urinary orosomucoid levels; alkaline phosphatase and P-galactosidase) compared to workers with less than 2 μg Cd/g creatinine. Increases in urinary levels of β_2 microglobulin began to be evident in workers with urinary cadmium levels greater than 10 μg Cd/g creatinine. The prevalence of signs of abnormal renal function became more notable with increasing urinary cadmium level.

Renal tubular function was investigated in 97 workers from a nickel-cadmium battery factory and a control population of 122 workers with no known occupational exposure to cadmium (Chia *et al.*, 1992). The levels of cadmium, NAG, β_2 microglobulin and α_1 microglobulin (more stable in urine than β_2 microglobulin) were determined in spot urine samples. The average cadmium exposure length in this study of 3.3 years was relatively short. Workers from the battery plant had higher urinary cadmium levels than control workers (mean levels of 4.4 versus 1.2 μg Cd/g creatinine). Urinary α_1 microglobulin but not β_2 microglobulin and NAG were elevated in workers from the battery plant. Both NAG and α_1 microglobulin were elevated in workers with urinary cadmium levels above 5.0 μg Cd/g creatinine.

Cadmium released from a smelter in China resulted in the contamination of rice and the subsequent exposure of a human population (Nordberg *et al.*, 1997). Urinary levels of cadmium and β_2 microglobulin were measured (note, urinary levels of cadmium do not appear to be normalized to creatinine). Stratifying the population according to urinary cadmium resulted in elevated β_2 microglobulin in 51 percent of the population with urinary cadmium levels greater than 20 μg/L. Less than 5 percent of the population had elevated β_2 microglobulin with urinary cadmium levels < 2 μg/L. Elevated urinary albumin was observed in 19 percent of individuals in the >20 μg/L cadmium stratum and less than 5 percent in the < 2 μg/L cadmium stratum.

Various indicators of renal toxicity were measured in workers, some of whom were occupationally exposed to cadmium, in a large collaborative study in Europe (Fels *et al.*, 1994). The subjects were stratified into three cadmium exposure categories with mean urinary cadmium levels of 0.65, 2.35 and 11.47 μg/g creatinine. Spot urine samples were analyzed for various biomarkers indicative of tubular toxicity or effects on the glomerulus. Two biomarkers of tubular toxicity were increased in the intermediate exposure group (the brush border antigens HF5 and BBA), while more than half of the biomarkers indicative of tubular toxicity (including α_1 microglobulin, RBP and NAG activity) were increased in the subjects in the high exposure group.

No increases in the levels of biomarkers that are indicative of glomerular toxicity were observed in the intermediate exposure group, while the levels of three biomarkers (thromboxane B_2, transferrin and high molecular weight proteins) were increased in the urine in the high dose group. Increased levels of three biomarkers that are indicative of glomerular toxicity in the high dose group were slight, indicating slight changes in glomerular barrier function.

Renal dysfunction was evaluated based on the occurrence of proteinuria in 60 workers exposed to cadmium–containing solders (Elinder *et al.*, 1985a). Spot urine samples were collected and analyzed for cadmium and β_2 microglobulin content. In workers with urinary cadmium levels below 2.1 μg/g creatinine, only one of 14 workers had β_2 microglobulin greater than 300 μg/g creatinine. Three of 12 workers with urinary cadmium levels between 2 and 5 μg/g creatinine had β_2 microglobulin levels that exceeded 300 μg/g creatinine, while 6 of 18 workers with urinary cadmium between 5 and 10 μg/g creatinine had urinary β_2 microglobulin levels in excess of 300 μg/g creatinine.

A variety of biomarkers that are indicative of early renal toxicity were investigated in 50 workers exposed to cadmium and 50 matched referents (Roels *et al.*, 1993). Workers who were exposed, on average, for 11.3 years had urinary cadmium levels of 5.4 μg/g creatinine, compared to 0.7 μg/g creatinine in the referent group. Urinary levels of biomarkers such as transferrin, NAG, and BBA were significantly increased in worker exposed to cadmium compared to the control population. When urinary cadmium levels were stratified into three levels, <2, 2-10 and >10 μg/g creatinine, workers with the highest urinary cadmium levels had elevated levels of the usual markers of tubular toxicity such as NAG, RBP and β_2 microglobulin. Interestingly, in this study the investigators observed elevated levels of certain large urinary proteins (transferrin, albumin) in addition to elevated levels of NAG and BBA at relatively low levels of urinary cadmium (around 4 μg/g creatinine). The levels of RBP and β_2 microglobulin were not elevated until urinary cadmium level exceeded 10 μg/g creatinine.

Urine β_2 microglobulin and cadmium levels were analyzed in 342 farmers in China who were exposed to cadmium contaminated rice due to the contamination of irrigation water (Cai *et al.*, 1998). Urinary levels of cadmium were stratified into four groups. Elevated β_2 microglobulin was identified as >355 μg/g creatinine in males younger than 45 years; > 2,500 μg/g creatinine in males older than 45 year; and > 500 μg/g creatinine in females (all ages). The prevalence of males exhibiting elevated β_2 microglobulin increased with the cadmium level in urine. Nineteen percent of males with urinary cadmium levels between 4 and 8 μg/g creatinine had elevated urinary β_2 microglobulin levels compared

to 10 percent of males with urinary cadmium levels below 4 μg/g creatinine. Only females with urinary cadmium greater than 16 μg/g creatinine appeared to have elevated urinary β_2 microglobulin levels.

Kidney tubular dysfunction was evaluated based on urinary NAG activity in a population (29 men and 43 women) that resided in the vicinity of a cadmium plant in Sweden (Jarup *et al.*, 1995)**.** Individuals who were occupationally exposed to cadmium were excluded from this study. A strong relationship was detected between the levels of NAG and cadmium in the urine. The prevalence of tubular dysfunction (defined as NAG > 0.5 U/mmol creatinine) was 40 percent with urinary cadmium levels > 0.5 μg/g creatinine and 5 percent with urinary cadmium levels < 0.5 μg/g creatinine.

The effect of low-level exposure to cadmium on renal tubular function was assessed in males and females that resided in a polluted area and an unpolluted area in Japan (Nakadaira and Nishi, 2003). While mean urinary cadmium levels were significantly different, they were very low in males from the polluted and control areas (2.7 and 1.1 μg/g creatinine respectively). No significant increases in urinary NAG, β_2 microglobulin or α_1 microglobulin levels were observed in males from the polluted area. Levels of cadmium in the urine in females were also low but significantly increased in women who resided in the polluted area compared to the control area, 4.7 μg/g creatinine and 1.7 μg/g creatinine respectively. Only the level of α_1 microglobulin was significantly increased in the urine of women from the polluted area.

Nephrotoxicity was investigated in 58 male workers exposed to cadmium at a non-ferrous smelter (Bernard *et al.*, 1990). A matched referent population that was not exposed to cadmium in the workplace was also evaluated. Urinary levels of β_2 microglobulin, NAG and RBP were measured to detected signs of tubular dysfunction while urinary levels of albumin and transferrin were measured to investigate effects on the glomerulus. The study findings were stratified into four urinary cadmium ranges. No significant increases were observed in any of the parameters until urinary cadmium levels exceeded 10 μg/g creatinine. Interestingly, increased mean levels of albumin and transferrin (which were not reported as statistically significant) but not β_2 microglobulin, NAG or RBP were observed in the 5-10 μg/g creatinine stratum. The investigators indicated that in this study, effects on the glomerulus might be occurring at urinary cadmium levels associated with tubular dysfunction.

Jarup and associates investigated adverse effects on the glomerulus and renal tubule in 46 workers exposed to cadmium solder (Jarup *et al.*, 1995). While the first signs of renal dysfunction relate to the proximal tubule, the more important clinical finding was a change in the glomerular filtration rate (GFR). A decrease in GFR was correlated with an increase in the β_2 microglobulin levels in the urine and the level of cadmium in the blood (indicator of recent exposure to cadmium). Various parameters of renal function were stratified into three groups based on β_2 microglobulin clearance (a measure of tubular function). GFR was significantly decreased and urinary levels of α_1 microglobulin and NAG were significantly increased in individuals with increased β_2 microglobulin clearance (decreased tubular function).

The relationship between various indicators of kidney dysfunction and urinary cadmium levels was studied in nine hamlets that were heavily polluted by cadmium in Japan

(Nogawa *et al.*, 1979). These villages were characterized by the occurrence of Itai-Itai disease. Most of the population of these villages (293 male and 335 females) over age 20 was enrolled in the study. The findings of the study were stratified by urinary cadmium level (0-4.9, 5-9.9 10-14.9, 15-19.9, 20-24.9, 25-29.9, 30-39.9 and > 40 µg/g creatinine for females, and similar groupings except the highest stratum in males (Table 7).

The prevalence of elevated levels of urinary biomarkers that are indicative of renal toxicity increased with urinary cadmium levels in both males and females. Abnormal urinary biomarker levels indicating tubular toxicity (β_2 microglobulin and RBP) were observed when urinary cadmium levels were greater than 5 µg/g creatinine. Urinary cadmium levels greater than 15 µg/g creatinine were associated with elevated levels of urinary protein with glucose that are indicative of damage to the glomerulus.

Table 7. Prevalence of Abnormal[a] Urinary Findings in Human Males and Females[b]

Urine cadmium (µg/g creatinine)	β_2 microglobulin > 5 mg/L[a] Prevalence (%)		RBP > 4 mg/L[a] Prevalence (%)		Proteinuria with glucosuria Protein > 50 mg/L[a] Prevalence (%)	
	Males	Females	Males	Females	Males	Females
0-4.9	0	3.9	0	0	0	0
5-9.9	16.7	2.8	8.3	0	2.1	0
10-14.9	46.7	22.2	20.0	8.3	4.5	2.8
15-19.9	76.0	27	36.0	10.8	12.0	5.4
20-24.9	69.4	51.1	51.0	33.3	22.9	20.5
25-29.9	95.2	70.0	71.4	46.7	19.0	24.1
30-39.9		79.5		53.8		24.3
>40		85.1		70.2		34.0
>30	93.1		82.8		57.1	

[a]abnormal findings indicated in the table are from the investigators.
[b]from Nogawa *et al.*, 1979.

Low Cadmium Exposure Levels

The relationship between seemingly background cadmium exposure levels (individuals not occupationally exposed or not living in a contaminated area) and renal toxicity in humans was investigated by Ezaki *et al.* (2003). In a very large Japanese study that included 10,000 women, Ezaki and coworkers observed statistically significant increases in urinary β_2 microglobulin and α_1 microglobulin at urinary cadmium levels just above the detection limit (below 1 µg/g creatinine) (Ezaki *et al.*, 2003). The urinary levels of β_2 microglobulin and α_1 microglobulin were quite low and not necessarily indicative of renal toxicity (e.g., around 100 µg/g creatinine for β_2 microglobulin). In the same

population, urinary levels of β_2 microglobulin and α_1 microglobulin were also related to increased urinary levels of calcium, magnesium and zinc (Ezaki *et al.*, 2003). These findings suggest that the increase in all these urinary constituents may reflect minimal renal dysfunction, and cadmium may not be the causative agent. Marked increases in β_2 microglobulin and α_1 microglobulin did not occur in this population until urinary cadmium levels exceeded 10 to 12 μg Cd/g creatinine (Ikeda *et al.*, 2003).

Signs of renal toxicity were investigated in two communities in Pennsylvania, one which was impacted by past smelting activity (zinc smelter) and one that was approximately 10 miles from the defunct smelter (Noonan *et al.*, 2002). Both populations were characterized by very low urinary cadmium levels (means of 0.14 and 0.12 μg/g creatinine for the smelter and control communities, respectively) so the results from both areas were combined. A positive association was observed between urinary cadmium levels and NAG and alanine aminopeptidase activity, but not urinary β_2 microglobulin or albumin levels. Urinary cadmium levels were stratified into five categories (< 0.25, 0.25-0.49, 0.5-0.74, 0.75-0.99, ≥ 1 μg/g creatinine). The levels of NAG and alanine aminopeptidase activity were significantly different in the highest group (cadmium ≥ 1 μg/g creatinine) compared to the lowest urinary cadmium group (< 0.25 μg/g creatinine).

The renal effects of cadmium were investigated in men and women from two areas in Japan that were not considered to be polluted by cadmium (Oo *et al*., 2000). Mean urinary cadmium levels were 2.2 μg/L in males and 2.5 μg/L in females in area 1, and 2.3 μg/L in males and 3.9 μg/L in females in area 2. These investigators observed a significant association between urinary cadmium levels and two indicators of renal dysfunction, urinary β_2-microglobulin and NAG levels.

Yamanaka and coworkers investigated the association between indicators of renal dysfunction and cadmium exposure in areas in Japan that were not polluted by cadmium (Yamanaka *et al.,* 1998). Urinary cadmium levels averaged 1.3 μg/g creatinine in men and 1.3 μg/g creatinine in women. These investigators observed a significant correlation between urinary cadmium levels and three indicators of renal dysfunction: levels of urinary protein, β_2-microglobulin, and NAG.

Long-term prognosis

Twenty-three male workers previously exposed to cadmium at non-ferrous smelters for, on average, nearly 25 years were examined over five years for signs of renal dysfunction, beginning six years after their removal from cadmium exposure (Roels *et al.*, 1989). The workers had been removed from Cd exposure because of elevated urinary β_2 microglobulin or RBP levels. While the Cd levels in the urine and serum decreased, β_2 microglobulin, RBP and albumin levels were increased over the five years of the study. Serum β_2 microglobulin and creatinine levels increased, indicating a decrease in the glomerular filtration rate. Workers in the control group (no exposure to Cd) did not exhibit a significant change the mean levels of serum β_2 microglobulin or creatinine. These finding are disturbing because they suggest that the damage to the kidney progresses even though exposure to cadmium was terminated.

Arisawa and coworkers conducted a follow-up study ten years after an earlier study to detect possible long-term health consequences of cadmium exposure (Arisawa *et al.*,

2001). The follow-up study evaluated 275 subjects environmentally exposed to cadmium. Cadmium exposure at the time of follow-up had decreased because of a soil cleanup around the time of the original study. The death rate in males and females with high urinary β_2 microglobulin (> 1000 μg/g creatinine) was significantly higher (about twice) than the reference population. While there appeared to be an increase in mortality in males (but not females) with urinary cadmium above 10 μg/g creatinine compared to the group with urinary cadmium levels below 10 μg/g creatinine, the increase was not statistically significant. No detectable increases in cancer incidence were observed in this small population exposed to high cadmium levels.

A small follow-up study was conducted in nine of 12 cadmium workers 16 years after an initial study (Kazantzis, 1979). After the original study, cadmium oxide and metal production was halted and heavy cadmium exposure no longer occurred. In the original study, only one of 12 subjects had toxicity related to the kidney but eight of the workers exhibited tubular proteinuria. In the follow-up study, more severe findings were reported in all the subjects, including osteoporosis, osteomalacia, hypercaluria, glycosuria and other signs of more severe renal dysfunction.

The possible contribution of cadmium exposure to end-stage renal disease was investigated in Sweden in men and women exposed to cadmium in the workplace or because they resided near a battery plant (Hellstrom *et al*., 2001). No direct exposure measurements were used. Exposure categories were based on the distances of the residences from the plant (as a surrogate for exposure; plant workers were placed in the high exposure group). In both men and women, increased occurrence of end stage renal disease was linked to the apparent amount of exposure to cadmium.

Overall Evaluation of Cadmium Renal Toxicity

Evidence that cadmium is nephrotoxic to humans has been mounting for over 50 years. Cadmium accumulates in the kidney and has a very long half-life. Therefore, it may be decades before low-level exposure to cadmium is manifested by renal toxicity. Numerous studies have linked cadmium exposure to damage in both the proximal tubule and the glomerulus. Adverse effects on the tubule generally appear earlier. Various biomarkers have been employed to identify the onset of damage to tubule and glomerulus. These biomarkers are useful not only to identify when damage occurs but also to identify exposure level(s) associated with the onset of kidney damage.

Biomarkers that have been used to identify kidney damage are detected in the urine of all individuals, not just those who have sustained kidney damage. The biomarker levels associated with kidney damage are elevated compared to "normal" levels, but elevated levels are also linked to other factors such as aging. Precisely when urinary biomarkers are considered elevated or abnormal is open to interpretation; different investigators employ somewhat different criteria for when the level of a particular biomarker is considered abnormal. For example, urinary β_2 microglobulin levels greater than 300 μg/g creatinine are often used to define abnormal for this biomarker. Others consider this biomarker elevated if there is a statistically significant increase compared to control.

In addition to increased levels of certain urinary proteins, increased urinary cadmium levels can also be a consequence of renal damage. When no tubular effects are evident,

age-related increases in cadmium levels in the kidney and the urine (reflecting levels in the kidney) are observed. However, at about age 50, cadmium levels in the kidney peak and then begin to decrease. The decrease may be due to onset of compromised tubular function with age (perhaps only in a portion of the population). Renal dysfunction associated with high exposure to cadmium is also reflected by reduced cadmium levels in the kidney and elevated urinary cadmium levels. Under both circumstances, the ability of the kidney to store cadmium may be compromised.

Several recent studies have linked increased urinary cadmium levels with increases in urinary tubular proteins in populations exposed to seemingly background cadmium levels. The correlation is observed at very low levels of urinary cadmium. Whether the low cadmium level is the cause of the increase in tubular proteins or is a consequence of renal damage unrelated to cadmium that compromises cadmium storage is unclear. Renal damage reflected by an increase in tubular proteins in these studies may cause the release of a number of substances from tubular cells. Because cadmium is accumulated in the kidney, increased cadmium levels in the urine may be a sensitive biomarker of tubular damage (analogous to tubular proteins) that is not caused by cadmium.

Bernard and associates investigated the issue of causality by measuring urinary cadmium levels and tubular protein levels in pregnant women (Bernard *et al.*, 1992). While tubular protein levels were modestly "elevated," the investigators did not observe a correlation between urinary cadmium and tubular protein levels. This prompted their conclusion that tubular dysfunction is not necessarily associated with increased urinary cadmium excretion. However, it should be noted that levels of tubular proteins in this study were below levels typically used to identify renal dysfunction. The urinary cadmium levels (mean of 0.6 μg/g creatinine) were also quite low and consistent with a younger age group (mean 29 years) and the lack of much cadmium exposure. Studies that have correlated urinary cadmium with urinary protein levels have typically been conducted in older populations, which often were exposed to significant sources of cadmium and had more time to accumulate cadmium. Thus the inability of Bernard and associates to observe elevated urinary cadmium levels may be due to the lower cadmium level in the renal cortex in this population.

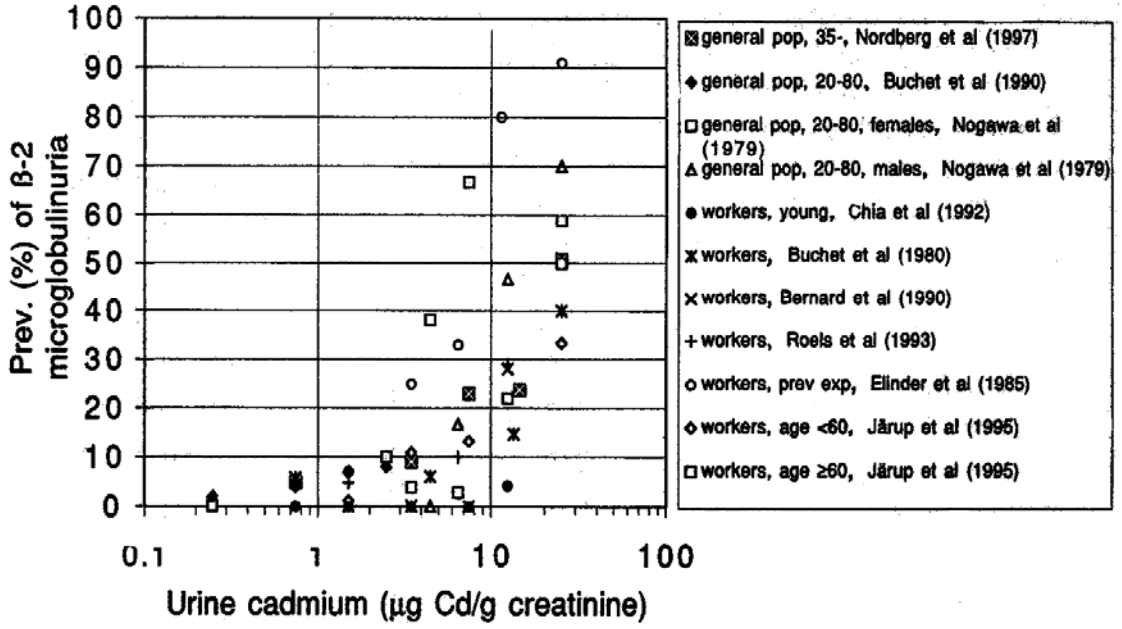
Jarup and coworkers assembled the findings of a number of studies that describe the dose-response relationship between urinary cadmium levels and the prevalence of abnormal levels of β_2 microglobulin (Figure 5) and NAG (Figure 6) in the examined populations (Jarup *et al.*, 1998). These figures indicate urinary cadmium levels in excess of 1 to 3 μg/g creatinine are associated with an increased prevalence of an "abnormal" or "elevated" level of the given biomarker.

An expanded assembly of dose-response data that incorporates the findings of more studies and more biomarkers of renal toxicity is shown in Tables 8 and 9. Table 8 contains findings of studies in which the investigators classified the level of urinary biomarker as normal or abnormal; the incidences of abnormal values are shown in the table. OEHHA categorized the prevalence of abnormal values as "background levels" or "above background levels" (indicating evidence of renal dysfunction) to aid in understanding when renal toxicity appears to be manifested. Table 9 shows findings in which the investigators presented the mean levels of the urinary biomarker(s). OEHHA

categorized the mean value as "normal" or "abnormal" (indicating evidence of renal dysfunction) to aid in understanding when renal toxicity appears to be manifested.

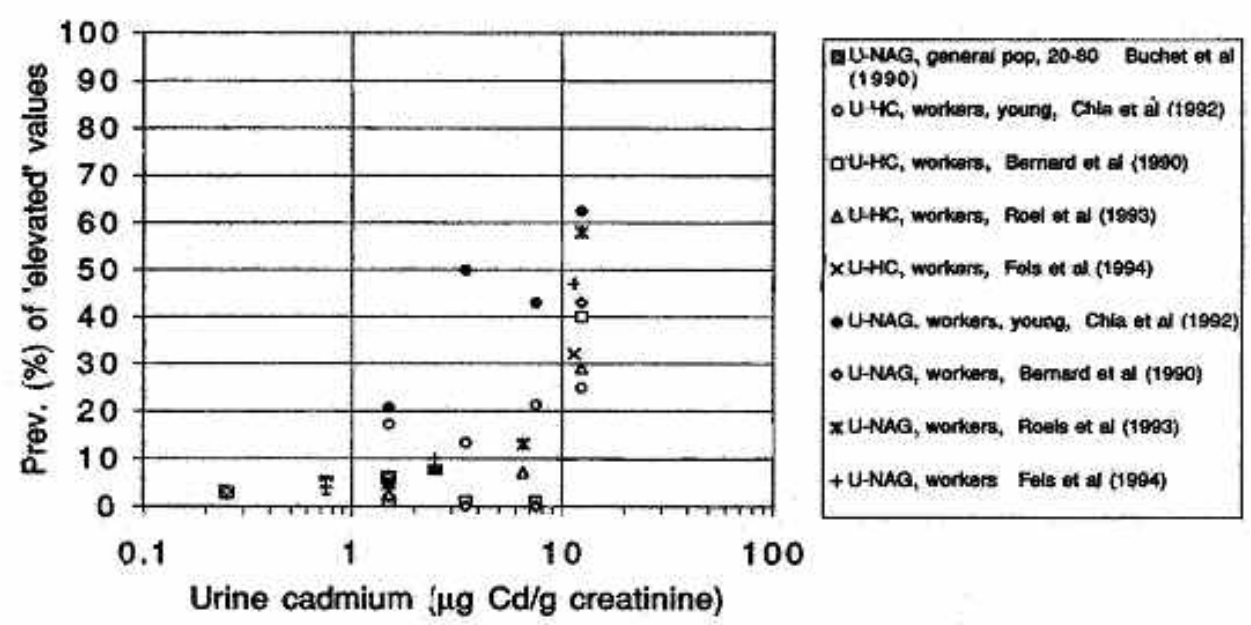
While the data in these tables appears daunting at first, focusing on the individual studies and in particular, on the concentration of urinary cadmium at which the biomarkers begin to indicate renal damage, may be helpful. The studies demonstrate that urinary cadmium levels less than 2 µg/g creatinine were not associated with an increased prevalence of abnormal levels of biomarkers that indicate nephrotoxicity. In a few studies, the grouping of urinary cadmium levels represented levels above and below 2 µg Cd/g creatinine (Noonan *et al.*, 2002; Jarup *et al.*, 1995). Increased biomarker levels were observed in a group that straddled 2 µg Cd/g creatinine, but given the wide range of the Cd level in these studies, it is unclear at what urinary cadmium level the increase in abnormal biomarker(s) began to occur.

Figure 5. Prevalence (Prev) of elevated or abnormal levels of urinary β_2 microglobulin associated with urinary cadmium levels[a]



[a]from Jarup *et al.*, 1998

Figure 6. Prevalence (Prev) of elevated or abnormal levels of NAG and glycoprotein associated with urinary cadmium levels[a]



[a]from Jarup *et al.*, 1998

Table 8. Prevalence of Abnormal Urinary Biomarker Levels Indicative of Renal Dysfunction and Associated Urinary Cadmium Levels

Urinary Cadmium Levels	Urine Biomarker	Background prevalence of abnormal values[a]	In excess of background prevalence of abnormal values[a]
Buchet *et al.*, 1980			
< 2 µg Cd/g creatinine	β_2 microglobulin Alkaline Phosphatase Orosomucoid Protein	<10 percent[b] <10 percent <10 percent <10 percent	
2 - 9.9 µg Cd/g creatinine	B_2 microglobulin Alkaline Phosphatase Orosomucoid Protein	<10 percent <10 percent <20 percent <10 percent	
10 - 19.9 µg Cd/g creatinine	β_2 microglobulin Alkaline Phosphatase Orosomucoid Protein		~15 percent ~20 percent ~15 percent ~15 percent
≥ 20 µg Cd/g	β_2 microglobulin		40 percent

Urinary Cadmium Levels	Urine Biomarker	Background prevalence of abnormal values[a]	In excess of background prevalence of abnormal values[a]
creatinine	Alkaline Phosphatase Orosomucoid Protein		~35 percent ~15 percent ~20 percent
Chia *et al.*, 1992			
< 2 µg/g creatinine	β_2 microglobulin α_1 microglobulin NAG	0 percent 17 percent 21 percent	
2 - 5 µg/g creatinine	β_2 microglobulin α_1 microglobulin NAG	0 percent 13 percent	 50 percent
5 - 10 µg/g creatinine	β_2 microglobulin α_1 microglobulin NAG	0 percent	 21 percent 43 percent
> 10 µg/g creatinine	β_2 microglobulin α_1 microglobulin NAG	4.2 percent	 25 percent 63 percent
Jarup *et al.*, 1995			
< 0.5 µg/g creatinine	NAG	5.4 percent	
≥ 0.5 µg/g creatinine	NAG		40 percent
Cai *et al.*, 1998			
0 - 3.99 µg/g creatinine (males)	β_2 microglobulin	10 percent	
4 - 7.99 µg/g creatinine (males)	β_2 microglobulin		19 percent
8 - 15.99 µg/g creatinine (males)	β_2 microglobulin		27 percent
> 16 µg/g creatinine (males)	β_2 microglobulin		33 percent
0 - 3.99 µg/g creatinine (females)	β_2 microglobulin	20 percent	
4 - 7.99 µg/g creatinine (females)	β_2 microglobulin	18 percent	
8 - 15.99 µg/g creatinine (females)	β_2 microglobulin	21 percent	
> 16 µg/g creatinine (females)	β_2 microglobulin		37 percent

Urinary Cadmium Levels	Urine Biomarker	Background prevalence of abnormal values[a]	In excess of background prevalence of abnormal values[a]
Buchet *et al.*, 1990			
0 - 0.51 µg/24 hr	RBP NAG β_2 microglobulin	<4 percent <4 percent 2 percent	
0.52 - 0.89 µg/24 hr	RBP NAG β_2 microglobulin	4 percent ~4 percent 4 percent	
0.9 - 1.4 µg/24 hr	RBP NAG β_2 microglobulin	 ~6 percent	~8 percent ~6 percent
1.41- 8.00 µg/24 hr	RBP NAG β_2 microglobulin		~8 percent ~8 percent ~8 percent
Nogawa *et al.*, 1979			
Males 0 - 4.9 µg/g creatinine	β_2 microglobulin RBP Urinary Protein	0 percent 0 percent 0 percent	
Females 0 - 4.9 µg/g creatinine	β_2 microglobulin RBP Urinary Protein	3.9 percent. 0 percent 0 percent	
Males 5 - 9.9 µg/g creatinine	β_2 microglobulin RBP Urinary Protein	 2.1 percent	16.7 percent 8.3 percent
Females 5 - 9.9 µg/g creatinine	β_2 microglobulin RBP Urinary Protein	2.8 percent 0 percent 0 percent	
Males 10 - 14.9 µg/g creatinine	β_2 microglobulin RBP Urinary Protein	 4.5 percent	46.7 percent 20.0 percent
Females 10 - 14.9 µg/g creatinine	β_2 microglobulin RBP Urinary Protein	 2.8 percent	22.2 percent 8.3 percent
Males 15 - 19.9 µg/g creatinine	β_2 microglobulin RBP Urinary Protein		76.0 percent 36.0 percent 12.0 percent
Females 15 - 19.9 µg/g creatinine	β_2 microglobulin RBP Urinary Protein	 5.4 percent	27.0 percent 10.8 percent
Elinder *et al.*, 1985a			
≤ 2.1 µg/g creatinine	β_2 microglobulin	7 percent >300 µg/g creatinine 0 percent >900 µg/g creatinine	

Urinary Cadmium Levels	Urine Biomarker	Background prevalence of abnormal values[a]	In excess of background prevalence of abnormal values[a]
2.1 - ≤ 5.1 µg/g creatinine	β_2 microglobulin	0 percent >900 µg/g creatinine	25 percent >300 µg/g creatinine
5.1 - ≤ 10.1 µg/g creatinine	β_2 microglobulin		33 percent >300 µg/g creatinine 11 percent >900 µg/g creatinine
10.1 - ≤ 15.1 µg/g creatinine	β_2 microglobulin		80 percent >300 µg/g creatinine 60 percent >900 µg/g creatinine
≥ 15.1 µg/g creatinine	β_2 microglobulin		91 percent >300 µg/g creatinine 82 percent >900 µg/g creatinine
Bernard *et al.*, 1990			
< 2 µg/g creatinine	β_2 microglobulin NAG RBP Albumin Transferrin	< 5 percent < 5 percent < 5 percent < 5 percent < 5 percent	
2-5 µg/g creatinine	β_2 microglobulin NAG RBP Albumin Transferrin	< 5 percent < 5 percent < 5 percent 15 percent 15 percent	
5-10 µg/g creatinine	β_2 microglobulin NAG RBP Albumin Transferrin	< 5 percent < 5 percent < 5 percent 20 percent ~12 percent	
> 10 µg/g creatinine	β_2 microglobulin NAG RBP Albumin Transferrin		25 percent 40 percent ~32 percent 40 percent 45 percent

Table 9. Urinary Biomarkers That Indicate Renal Dysfunction and Associated Urinary Cadmium Levels

Urinary Cadmium Levels	Urine Biomarker	Normal Values[a]	Abnormal Values
Jarup *et al.*, 1995			
2.2 µg/g creatinine	Clearance - β_2 microglobulin (percent of creatinine clearance) NAG α_1 microglobulin	Normal < 0.1% of creatinine clearance 0.26 U/mmol creatinine 0.6 mg/g creatinine	
4.0 µg/g creatinine	Clearance - β_2 microglobulin (% of creatinine clearance) NAG α_1 microglobulin		Slight increase 0.1 < - ≤ 2.5% of creatinine clearance Significant increase 0.42 U/ mmol creatinine Significant increase 1.9 mg/g creatinine
7.1 µg/g creatinine	Clearance - β_2 microglobulin (% of creatinine clearance) NAG α_1 microglobulin		Substantial increase clearance > 2.5 % of creatinine clearance Significant increase 0.65 U/mmol creatinine Significant increase 5.9 mg/g creatinine
Nakadaira and Nishi, 2003			
1.1 µg/g creatinine (males)	β_2 microglobulin α_1 microglobulin NAG Total protein	117 ug/g creatinine 2.6 mg/g creatinine 4.6 U/g creatinine 40 mg/g creatinine	
2.7 µg/g creatinine (males)	β_2 microglobulin α_1 microglobulin NAG Total protein	102 ug/g creatinine 2.8 mg/g creatinine 4.5 U/g creatinine 37 mg/g creatinine	
1.7 µg/g creatinine (females)	β_2 microglobulin α_1 microglobulin NAG Total protein	171 ug/g creatinine 2.4 mg/g creatinine 5.1 U/g creatinine 44 mg/g creatinine	
4.7 µg/g creatinine (females)	β_2 microglobulin α_1 microglobulin NAG Total protein	183 ug/g creatinine 3.9 mg/g creatinine 6.4 U/g creatinine 53 mg/g creatinine	
Fels *et al.*, 1994			
0.65 µg/g creatinine	Multiple urinary biomarkers	Normal	
2.35 µg/g creatinine	HF5 BBA		Elevated Elevated

Urinary Cadmium Levels	Urine Biomarker	Normal Values[a]	Abnormal Values
11.5 µg/g creatinine	HF5, BBA, NAG, RBP, α_1 microglobulin, thromboxane B_2, transferrin, and large proteins		Elevated for all these constituents
Roels *et al.*, 1993			
< 2 µg/g creatinine	Albumin Transferrin NAG RBP BBA β_2 microglobulin	8.3 mg/L 771 µg/L 1.3 U/L 83 µg/L 3.7 U/L 76 µg/L	
2 ≤ - ≤ 10 µg/g creatinine	Albumin Transferrin NAG RBP BBA β_2 microglobulin	9.1 mg/L 385 µg/L 1.45 U/L 82 µg/L 5.0 U/L 103 µg/L	
> 10 µg/g creatinine	Albumin Transferrin NAG RBP BBA β_2 microglobulin		26.9 mg/L 1112 µg/L 2.59 U/L 165 µg/L 7.1 U/L 163 µg/L
Noonan *et al.*, 2002			
< 0.25 µg/g creatinine	NAG Alanine aminopeptidase	~1 ug/g creatinine ~3.8 U/g creatinine	
0.25 – 0.49 µg/g creatinine	NAG Alanine aminopeptidase	~1 ug/g creatinine ~4 U/g creatinine	
0.5 – 0.74 µg/g creatinine	NAG Alanine aminopeptidase	~1.5 ug/g creatinine ~4 U/g creatinine	
0.75 - 0.99 µg/g creatinine	NAG Alanine aminopeptidase	~1.9 ug/g creatinine ~4.8 U/g creatinine	
≥ 1 µg/g creatinine	NAG Alanine aminopeptidase		~1.8 ug/g creatinine ~5 U/g creatinine

[a]Values in the normal column were judged as representing "background levels" of renal dysfunction. Values in the abnormal column were judged greater than "background levels" of renal dysfunction.

Critical Concentration in Renal Cortex

Cadmium accumulates in the kidney for decades, usually with no apparent toxic effects. Only when cadmium levels reach a "critical concentration" in the kidney is toxicity believed to occur (Friberg *et al.*, 1974; Roels *et al.*, 1983; ATSDR, 1999; Jarup, 2002). Friberg and associates suggested that the toxicity associated with a "critical concentration" in the kidney is a consequence of the occurrence of unbound cadmium as metallothionein-binding capacity in the tubular cell is exceeded (Friberg *et al.*, 1974). The free or unbound cadmium is believed to be responsible for the renal tubule damage. As the tubule cells are damaged, urinary cadmium levels may increase considerably, while cadmium levels in the kidney decrease.

Different approaches have been employed to estimate the critical concentration of cadmium in the renal cortex associated with renal damage. Cadmium levels have been measured in cadavers, but these data are not particularly useful in establishing the cadmium level associated with onset of renal toxicity. Cadmium levels have been measured in the kidney of experimental animals administered cadmium at the time of the onset of proteinuria (reviewed by IPCS, 1992). These data are useful, as they appear to confirm the observations in humans. More recently, methods have been developed to quantify renal cadmium levels in humans *in vivo* (Ellis *et al*., 1979**;** Roels *et al*., 1981). Using these methods allowed investigators to measure cadmium levels in the kidney associated with the appearance of proteinuria or other indicators of renal toxicity. Unfortunately, there appears to be considerable uncertainty in the reliability of the *in vivo* analytical methods (Jarup *et al*., 1998).

Friberg *et al*. (1974) and others proposed that 200 mg/kg appears to be the "critical concentration" of cadmium in the renal cortex. Health-protective criteria were developed based on a critical concentration of 200 mg/kg in the kidney (U.S. EPA, 1986, 2005). As more studies have become available, Buchet *et al*. (1990) and Jarup *et al.* (1998) have noted that toxicity is being detected at lower cadmium levels in the kidney. They indicated that at cadmium levels of 50 mg/kg or more, renal toxicity can be detected in a small percent of the population (Jarup *et al.*, 1998; Buchet *et al.,* 1990).

Jarup and coworker estimated that a cadmium level of 125 mg/kg in the renal cortex is associated with effects in about 10 percent of the population (Jarup *et al.*, 1998). They recommended that cadmium levels in the renal cortex be kept below 50 mg/kg and levels in the urine should be below 2.0 to 2.5 μg/g creatinine (Jarup *et al.*, 1998; Buchet *et al*., 1990). Others also have recently indicated that renal toxicity is occurring at much lower levels than previously believed (Jarup *et al*., 1998, 2002**;** Satarug *et al.*, 2002). Consequently, recommendations regarding safe cadmium exposure levels are being lowered (Satarug *et al.*, 2002, 2003**;** Jarup *et al*., 1998).

Kidney Stones

Increased incidences of kidney stones have been observed in workers exposed to cadmium, particularly in workers that also exhibited proteinuria (Jarup and Elinder, 1993; Jarup *et al.*, 1998). This effect may be secondary to an increase in calcium excretion when there was substantial damage to the renal tubule (Kazantzis, 1979).

Bone

Prolonged exposure of rural Japanese farmers to cadmium, principally through contaminated rice, resulted in the now well-recognized Itai-Itai disease (Jarup, 2002). Itai-Itai disease is characterized by the occurrence of multiple fractures and distortions of skeletal long bones, severe pain and kidney damage. Several toxic mechanisms may contribute to Itai-Itai disease, including disruptions in Vitamin D metabolism, increased urinary excretion of calcium and interference with calcium and phosphate metabolism. Interestingly, skeletal effects are not notable in workers with proteinuria due to cadmium exposure (Jarup *et al.*, 1998). Other large studies in Europe have linked cadmium exposure with increased urinary calcium excretion and increased serum alkaline phosphate activity in women (Buchet *et al*., 1990; Jarup *et al.*, 1998) and men and women (Staessen *et al.*, 1992).

Other Effects

Administration of cadmium, particularly at high doses, has resulted in effects on the liver and GI tract (ATSDR, 1999). Other studies have found hematological and immunological effects. Effects on blood pressure have been reported in a few studies (hypertension), but a number of studies did not find a link (ATSDR, 1999).

Navas-Acien *et al*. (2004, 2005) investigated the relationship between blood and urine cadmium levels and peripheral arterial disease (PAD) using the results of the NHANES III study. They observed a statistically significant increased incidence of PAD in individuals with higher urinary cadmium levels, although the urinary cadmium levels in this study were very low (average of 0.36 μg Cd/L). Urinary levels of antimony and tungsten were also linked to PAD but the levels of other metals (lead, barium cobalt, cesium, molybdenum and thallium) were similar in subjects with and without PAD. While the investigators indicated that various cardiovascular risk factors were considered, the slight increase in urine cadmium might be secondary to slight changes in kidney function that may be related to PAD. Slight damage to the kidney and an associated release of cadmium in the urine would be consistent with the slight increase in urinary cadmium in individuals with PAD (Navas-Acien *et al.*, 2005).

Carcinogenicity

Epidemiological investigations of the carcinogenic activity of cadmium have mainly focused on inhalation exposures in the workplace. Studies were performed at smelters, nickel-cadmium battery plants and other manufacturing facilities that worked with cadmium. The epidemiological evaluations were often complicated because workers were often also exposed to other carcinogenic metals such as nickel and arsenic. In addition, differences in smoking behavior of the exposed and control workers needed to be and was not always fully considered.

Two target tissue have been identified, the lung and the prostate. Early reports of increases in prostate cancer in workers exposed to cadmium have not been confirmed by subsequent investigations (IARC, 1993; ATSDR, 1999). Several studies (reviewed by

IARC, 1993; CDHS, 1986) have linked increases in lung cancer in workers with exposure to cadmium. Questions regarding the lack of a dose-response relationship and confounding (smoking behavior or concomitant exposure to arsenic or nickel) were only partially addressed. Because IARC (1993) and IPSC (1992) thoroughly reviewed most of the available key epidemiological studies performed in Europe, the United States and Asia, only a brief description of these studies is presented here.

A series of studies at a nickel-cadmium battery manufacturing plant in the United Kingdom revealed some evidence of an increase in mortality due to lung cancer (Potts 1965). A study in the same plant yielded a statistically significant increase in respiratory cancer mortality (Sorahan and Waterhouse, 1983). In a follow-up study, the data were segregated into early (first employed prior to 1947) and late workers (post 1947, exposure classification in late workers are more likely to be meaningful) (Sorahan, 1987). In the high-dose group, there appeared to be an association between lung cancer mortality and duration of exposure in the early workers but not in the late workers. This finding prompted the investigators to conclude that the increase in risk of respiratory cancer mortality appeared to be unrelated to exposure to cadmium oxide dust.

An increased lung cancer rate was observed in worker at a lead-zinc smelter in the United Kingdom, compared to regional lung cancer rates (Ades and Kazantzis, 1988). The investigators observed an association between increased lung cancer deaths and duration of employment. Studies at a nickel-cadmium battery manufacturing plant in Sweden revealed increased rate ratios for lung cancer incidence or mortality due to lung cancer, but the increase did not appear to be statistically significant (Elinder *et al.*, 1985b). However, lung cancer rates appeared to increase in workers with longer employment duration or with longer latency periods. The latter may reflect higher exposures, as the authors indicate exposures were considerably higher in the plant before 1963.

Several investigators conducted epidemiological studies in workers at a cadmium recovery plant in the United States. Thun and associates observed an increase in deaths due to lung cancer in plant workers compared to rates in U.S. white males (Thun *et al.*, 1985; Stayner *et al.*, 1992). A second analysis of lung cancer in the plant workers using lung cancer mortality rates in white males from Colorado also revealed a significant increase in the relative rate of lung cancer (Thun, 1986). Relative rates were determined in four groups of workers clustered according to cumulative exposure. The relative rates increased with increasing cumulative exposure.

Several recent epidemiological studies conducted after the IARC (1993) and CDHS (1986) reviews attribute or account for the increase in lung cancer observed in cadmium workers to exposure to other carcinogenic metals or to smoking habits (Veruougstraete *et al.*, 2003; ATSDR, 1999). Several recent reviews conclude that there is considerable uncertainty, or the evidence is rather weak, or there is little evidence that cadmium is a human carcinogen (Jarup *et al.*, 1998; ATSDR, 1999; Veruougstraete *et al*., 2003). However, others suggest that the evidence is more compelling. OSHA (1992), commenting on the study of Thun and associates (1985) of workers in Colorado, indicated that "confounding from arsenic exposure and cigarette smoking is not likely to account for the increase in lung cancer risk observed among the cadmium exposed workers." "OSHA agrees with IARC that cadmium is a probable human carcinogen."

Sensitive population

Women tend to have higher levels of cadmium in their blood, urine and kidney than men (Jarup *et al*., 1998; Olsson *et al*., 2002; Kjellstrom, 1979) and appear to be more at risk for adverse effects of cadmium (Kobayashi *et al.*, 2002) given that toxicity is related to the level of cadmium in the kidney. The reason for these differences in cadmium levels is not known but may be due in part to a difference in iron status (lower in women) that leads to an increase in cadmium absorption from the gut (Flanagan *et al.*, 1978; Jarup *et al.*, 1998; Berglund *et al.*, 1994). Approximately 10 percent of an oral cadmium dose was absorbed in iron-deficient subjects (Flanagan *et al.*, 1978; Valberg *et al.*, 1976). However, no significant differences were observed in blood and urinary cadmium levels and the levels of β_2 microglobulin and α_1 microglobulin in urine in anemic women with low ferritin levels compared to controls in a very large recent study (Tsukahara *et al.*, 2002).

The oral uptake of cadmium in iron-deficient rats increased approximately three-fold compared to controls (Schafer *et al.*, 1990). Eight to 13 percent of the administered cadmium dose was retained in iron-deficient rats, depending on the dose administered, compared to 3 percent in the control group.

Smokers have been identified as another sensitive population (Jarup *et al.*, 1998). Median blood levels of cadmium in smokers were substantially higher than in non-smokers in large cities from several different countries. The increase is likely to reflect smokers' marked increase in exposure to cadmium (see Jarup *et al.*, 1998). The cadmium body burden of smokers was almost twice that of non-smokers (Ellis *et al.*, 1979).

Because renal toxicity caused by cadmium appears to result from decades of accumulation, and cadmium level in newborn kidney is very low, children do not appear to be a sensitive population. However, the studies of Alexander and associates indicate that cadmium absorption in young children may be substantiality higher than relative absorption in adults (Alexander *et al*., 1974). Thus early childhood exposure to cadmium may accelerate accumulation in the kidney. However, in the same study, Alexander and coworkers observed that retention of cadmium was negative, i.e., that the amount of cadmium in the urine was greater than the amount in the diet (Alexander *et al*., 1974). These data may indicate that cadmium is not accumulating in the body of young children.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

Numerous studies in humans and experimental animals have demonstrated that exposure to cadmium results in adverse effects on both the proximal tubule and the glomerulus of the kidney. Effects on the renal tubule that are manifested by an increase of certain tubular proteins in the urine occur earlier and at lower exposure levels than effects on the glomerulus. However, increases in tubular proteins are not necessarily manifested by overt signs of disease.

The U.S. Occupational Safety and Health Administration (OSHA) considered this issue as part of its rulemaking regarding cadmium. OSHA conducted a comprehensive review of the available studies on renal toxicity of cadmium, and published testimony by many experts on cadmium's effects on the kidney (OSHA, 1992). There was little dispute that cadmium produces adverse kidney effects. However, it was not completely clear what effects should be considered adverse and how much exposure "causes" an adverse effect. Based on numerous toxicological studies and the testimony of a number of experts, OSHA concluded:

> "Prolonged exposure to cadmium may lead to glomerular proteinuria, glucosuria, aminoaciduria, phosphaturia and hypercalciuria. These conditions are indicated by excess urinary amino acids, glucose, phosphate, or calcium, respectively. Each of these elements is essential to life, and under normal conditions, their excretion is regulated by the kidney. Once low molecular weight proteinuria has developed, however, these elements may dissipate from the body. Loss of glomerular function may also occur, indicated by a decrease in the glomerular filtration rate and an increase in serum creatinine. Severe cadmium-induced renal damage may develop into chronic renal failure and uremia at which point some form of dialysis or kidney operation will be needed.…"
>
> "…OSHA believes that the loss of function of the proximal tubules as indicated by tubular proteinuria, elevated levels of b 2-M in the urine, constitutes material impairment of health.…"
>
> "…It is clear from the record of the rulemaking that despite some controversy, there is general agreement that renal tubular and glomerular lesions represent permanent loss of kidney function reserve and that the lesions are irreversible.... A worker who has only slightly elevated levels of b 2-M in urine may later develop proteinuria, even after cessation of exposures, or the worker may develop more severe forms of renal dysfunction. Such dysfunction is of great concert to OSHA. Renal compromise, described above, meets the definition of material impairment as intended in the OSH Act and as defined in this final standard…"

OEHHA concurs with OSHA's findings.

Numerous studies have linked increased kidney levels of cadmium, particularly in the renal cortex, with occurrence of increasingly severe adverse effects. Once a critical concentration of cadmium is reached in the kidney, renal toxicity (which appears to be irreversible) begins to occur. Increased excretion of specific proteins in the urine, originating from proximal tubules, appears to be a very sensitive indicator of the onset of renal toxicity.

Decades of research have yielded substantial information on the mechanism of cadmium's renal toxicity. However, very little human data are available that identify the cadmium level in the kidney cortex at which renal toxicity begins to occur. A number of studies have correlated the kidney cadmium level with cadmium body burden. Other studies have correlated the urinary cadmium level with kidney cadmium levels and overall body burden. These findings are important because characterizing urinary

cadmium levels associated with the onset of renal toxicity (the appearance of urinary proteins) is a much easier task, and the data are plentiful.

Previous estimates of exposure associated with occurrence of renal toxicity have typically been based on the cadmium level in the renal cortex (a critical concentration) believed to be associated with the renal toxicity. In addition, the level of cadmium in the urine has been employed to limit worker exposure to cadmium to prevent renal toxicity (OSHA, 1992). Given the uncertainty of the critical concentration of cadmium in the renal cortex, OEHHA will rely on the studies that characterized urinary cadmium levels in which no proteinuria was detected.

Regardless of whether cadmium level in the renal cortex or in urine is used to identify when renal toxicity begins to occur, toxicokinetic methods need to be employed to estimate the maximum daily exposure (over four to five decades) that would not result in the critical concentration of cadmium in the renal cortex, or urinary cadmium levels that indicate the onset of renal toxicity. Toxicokinetic methods will be employed to estimate oral cadmium intake that would maintain urinary cadmium below levels associated with appearance of tubular proteins in the urine that are indicative of renal toxicity.

Because cadmium accumulates in the kidney, both long-term low level exposures or shorter-term higher-level exposures to the metal could result in renal toxicity. For the purposes of developing a PHG for cadmium, limiting cadmium intake based on long-term, low-level exposure to cadmium will be protective of shorter-term exposure at the equivalent daily cadmium intake. A short-term exposure would result in less accumulation of cadmium in the kidney.

Cadmium accumulates rapidly in the kidney in the first decades of life and then approaches a plateau around age 40 to 50. Cadmium levels in the kidney then decrease in the final decades of life (Figures 1 and 3). The pattern of cadmium elimination in humans (urinary excretion) which mirrors the level in the kidney (Figure 4) appears to reflect first order kinetics, that is, the rate of elimination is a function of body burden. Several investigators have described a first order toxicokinetic model for the elimination of cadmium in humans (Tsuchiya and Sugita, 1971; Ellis *et al.*, 1979).

Based on first order kinetics, estimating oral intake of cadmium associated with a given rate of urinary excretion necessitates determining the biological half-life of cadmium in humans. Studies in animals and humans have clearly demonstrated a very long cadmium half-life that is a large fraction of the human or animal's lifespan. Estimates of various investigators for cadmium half-life in humans range from 100 days (McLellan *et al*., 1978), 10 years to infinity (essentially no elimination) (Rahola *et al*., 1972) and 26 years to infinity (Shaikh and Smith, 1980).

Unfortunately, few data are useful for the direct estimation of the half-life of cadmium in humans. Typically, to obtain an estimate of half-life, a radiolabeled agent is administered, and excretion is monitored over time. Studies that have measured the change in cadmium levels with time are very limited and were only performed for, at most, several hundred days, and in only a few individuals. Because of the very long cadmium half-life, the results provide a very imprecise estimate of the half-life.

Other investigators have employed other approaches for estimating the cadmium half-life in humans (Ellis *et al.*, 1979). Given first order elimination, an estimate of cadmium half–life can be based on the urinary excretion rate and body burden. Measured levels of cadmium in the kidney and liver, which comprise approximately 50 percent of body burden, are employed to estimate total body burden.

For first order elimination (in which elimination is a function of body burden), the change in body burden with time (dx/dt) is:

$$dx/dt = -k * x + I$$

where:

x = body burden (mg);

k = rate of elimination (yr^{-1}) = $0.693 / T_{1/2;}$

I = absorbed dose of cadmium (mg/year); and

t = time (year).

Available studies in humans indicate that cadmium is eliminated slowly in the urine and perhaps in the feces. In one study, no increase in fecal cadmium levels was apparent in smokers, while urinary levels were substantially increased (Kjellstrom, 1979). Studies in rats but not dogs revealed biliary excretion of cadmium (Klaassen and Kotsonis (1977). Fecal elimination of cadmium in the rat appeared to be dose-dependent, associated with a marked increase in bilary elimination at higher doses, suggesting that at low exposure levels, fecal excretion might be minor.

It is unclear if bilary/fecal elimination in humans is an important pathway, particularly the contribution of this pathway to the overall elimination of cadmium. Given the lack of data on the rate of biliary/fecal elimination in humans, estimates of cadmium half-life will be limited to the urinary pathway. This approach may result in an overestimate of the half-life because a portion of the elimination may not be accounted for. An overestimate of half-life would ultimately result in a lower (more health protective) level, given that the estimate would be based on the cadmium remaining longer in the body than it actually does.

Assuming that most cadmium is eliminated in the urine:

k * x = rate of urinary excretion of cadmium

= urinary volume * Cd concentration in urine

or

k = (urinary volume * Cd concentration in urine) / x

Ellis *et al.* (1979) measured cadmium levels in the urine, liver and kidneys of eight male smokers and 12 male non-smokers. The average age of the nonsmokers and smokers were 52 and 50 respectively, which is the approximate age when the body burden of

cadmium reaches its peak. The terminal half-life for cadmium in non-smokers was 14 years and in smokers was 17 years, based on the findings of Ellis *et al*. (Table 10).

Table 10. Cadmium Half-life Estimates Based on Body Burden and Urinary Excretion Rate[a]

	Smokers (n=12)	Nonsmokers (n=8)
Average urinary levels (mg/L)[a]	0.0027	0.0017
Average urinary excretion (mg/day)[b]	0.00405	0.00255
Average urinary excretion (mg/yr)	1.48	0.93
Mean body burden (mg)[a]	35.5	19.3
k (yr^{-1})[c]	0.042	0.048
$T_{1/2}$ (0.693/k) (yr)	17	14

[a]based on the results of Ellis *et al.*, 1979.
[b]mean urinary cadmium levels * mean urinary flow (1.5 L/day)[a].
[c]urinary excretion (mg/yr) / body burden (mg).

Estimated body burden (x) associated with urinary cadmium levels of 1 µg Cd/g creatinine

The findings of several human studies in men and women (See Figures 5 and 6 and Table 8 and 9) indicate that a urinary cadmium level of 1 µg/g creatinine (0.001 mg/g) would not result in increased excretion of biomarkers (urinary proteins) that are very sensitive indicators of the onset of renal toxicity. The average daily excretion of creatinine in the urine is 1.7 g/day (International Commission on Radiological Protection (ICRP), 1975).

Therefore, the yearly excretion of cadmium (Cd/yr) would be:

Cd/yr = 0.001 mg/g creatinine * 1.7 g creatinine/day x 365 days/year = 0.6 mg Cd/year

Then, urinary cadmium excretion (0.6 mg/year) = k * x

or

x (body burden) = urinary cadmium excretion (0.6 mg/year) / k

Using the value for k (elimination rate constant) for non-smokers from Table 10 above, body burden associated with urinary excretion of 1 µg Cd/g creatinine is:

x (body burden) = 0.6 mg/year / k $(yr)^{-1}$ = 0.6 mg/year / 0.048 $(yr)^{-1}$ = 13 mg

Cadmium intake (I) associated with a body burden of 13 mg at age 52

Solving for I (intake) where I is an absorbed dose,

$dx / dt = I - kx$

$x = I / k * (1-e^{-kt})$ (Tsuchiya and Sugita, 1971)

$13 \text{ mg Cd} = I / k * (1-e^{-kt})$

$I = 13 \text{ mg} \cdot * 0.048 \text{ yr}^{-1} / (1-e^{-(0.048 \text{ yr-1} * 52 \text{ yr})})$

$I = 0.68 \text{ mg/yr}$ or 1.9 μg/day

Oral cadmium intake associated with absorbed dose = 1.9 μg/day

Based on the absorbed fraction in women (believed to be the most sensitive population) of 0.1 (Valberg *et al.*, 1976; Flanagan *et al*., 1978; Rahola *et al*., 1972; Shaikh and Smith, 1980; Vanderpool and Reeves, 2001), total cadmium intake would be estimated as:

1.9 μg/day / 0.1 (absorption) = 19 μg Cd/day

Given a cadmium half-life of approximately 14 years, it is clear that by age 52 (the average age of subjects in the study of Ellis *et al*., 1979), body burden levels are near steady state. With time, both body burden and cadmium levels in the kidney, and therefore urinary levels, should not continue to increase significantly. Also, levels of cadmium in the kidney (regardless of the appearance of renal toxicity) appear to peak between ages 40 and 60. This indicates that the kidney is no longer accumulating cadmium and has become "leaky." Based on this finding, body burden after age 50 associated with a daily intake of 19 μg/day will not continue to increase above the 13 mg predicted to occur at age 52. Thus, urinary levels should remain below 1 μg Cd/g creatinine and renal toxicity should not occur.

Alternative Calculation

A no-effect level for daily cadmium intake can also be derived by assuming a steady state is reached or that body burden is at its maximum. Urinary output of 1 μg Cd/g creatinine had previously been identified as a no adverse effect level in humans.

If I = daily amount of cadmium excreted in urine, at steady state,

$dx/dt = I - kx = 0$ (no net daily change)

I = 1 μg Cd/g creatinine * 1.7 g creatinine/day = 1.7 μg/day

Administered dose = 1.7 μg/day / 0.1 (absorption) = 17 μg/day

where 0.1 is the absorbed fraction in women (Valberg *et al.*, 1976; Flanagan *et al.*, 1978; Rahola *et al.*, 1972; Shaikh and Smith, 1980; Vanderpool and Reeves, 2001).

Theoretically, a daily intake of 17 μg/day would result in a urinary level of 1 μg Cd/g creatinine when steady state occurred. Based on a half- life of 14 years, steady state will be reached at approximately 56 years (approximately four half-lives). Therefore, at a daily intake of 17 μg/day, the urinary cadmium levels by age 52 would be slightly lower than 1 μg Cd/g creatinine because steady state will not have been reached. After age 40-60, cadmium levels in the kidney diminish (independent of toxicity). Therefore, this exposure level would be below a level associated with renal dysfunction.

Carcinogenic Effects

No suitable cancer studies in human or experimental animals were identified in which a dose-response relationship can be developed based on oral exposure to cadmium. The Thun and coworkers study of inhalation exposure of worker to cadmium in a cadmium recovery plant was employed by California and the U.S. EPA to develop a dose-response relationship. The analysis described elsewhere (CDHS, 1986) yielded an inhalation slope factor of 15 $(mg/kg\text{-}day)^{-1}$. Inhalation slope factors for cadmium have also been developed based on the findings of animal studies (CDHS, 1986).

Cadmium is considered a human carcinogen by IARC (1993), OEHHA (2005), and U.S. EPA (2005). The classification is based mainly on studies in which exposure occurred through the inhalation route, but there is little reason to believe that the carcinogenicity is limited solely to inhalation exposure. Because there are no suitable oral studies to develop a dose-response relationship, a potency estimate for the inhalation route could theoretically be employed to estimate an oral potency by taking into consideration differences in toxicokinetics (e.g. absorption) between the two routes. While it is evident that inhalation exposure of workers to cadmium resulted in an increase in lung cancer, it is unclear if an absorbed dose or a specific portion of the inhaled dose was responsible for the increase in lung cancer.

A reasonable estimate is needed of the dose associated with the increase in lung cancer in the Thun study. This necessitates considering particle deposition, clearance from the lung and the amount of cadmium that was absorbed from the particles deposited in the lung. Unfortunately, "no direct data are available on cadmium deposition, retention or absorption in the human lung (ATSDR, 1999)." Detailed characterization of cadmium exposure in the occupational study that underlies the inhalation potency was not undertaken. Studies in animals are not sufficient to address these pharmacokinetic considerations.

With inadequate information on the nature of the inhalation exposure to cadmium, it is unclear how toxicokinetic considerations should be employed to extrapolate a dose-response relationship based on inhalation exposure to characterize the oral cancer potency of cadmium. Because little is known regarding the toxicokinetics of inhaled cadmium nor the mechanism(s) by which inhaled cadmium results in an increase in lung tumors, an extrapolation of the inhalation cancer potency to an oral cancer potency is judged to be inappropriate for development of a PHG.

CALCULATION OF PHG

Noncarcinogenic Effects

For estimation of a health-protective concentration of a chemical in drinking water, an acceptable daily dose of the chemical from all sources will first be calculated. This involves incorporation of appropriate uncertainty estimates in the extrapolation of the critical toxic dose from human or animal studies to the estimation of a lifetime daily dose that is unlikely to result in any toxic effects. For this purpose, the following equation is generally used:

$$\text{ADD} = \frac{\text{NOAEL/LOAEL in mg/kg-day}}{\text{UF}}$$

where,

ADD = an estimate of the maximum daily dose which can be consumed by humans for an entire lifetime without toxic effects;

NOAEL/LOAEL = no-observed-adverse-effect level or lowest-observed-adverse-effect level in the critical study;

UF = uncertainty factor.

Calculation of a public health-protective concentration (C, in mg/L) for a chemical in drinking water uses the following equation for noncarcinogenic endpoints:

$$\text{C} = \frac{\text{ADD mg/kg-day x BW in kg x RSC}}{\text{L/day}}$$

where,

BW = body weight (a default of 70 kg for adult males, 60 kg for adult females, or 25 kg for a child);

RSC = relative source contribution (usually 20 to 80 percent (0.20 to 0.80));

L/day = daily water consumption of an adult (2 L/day) or child (1 L/day).

In selecting the uncertainty factors for chronic effects, it is customary to apply an uncertainty factor in cases where adequate data are not available from full lifetime exposures and data from short-term or subchronic exposures of animals must be used. An uncertainty factor of up to 10 is usually recommended for interspecies extrapolation of effects seen in experimental animals to humans. This factor is used to account for potential differences in the response of humans and animals to a chemical exposure.

Exposed individuals are known to vary in response to toxic chemical and drug exposures as a result of age, disease state, and genetic constitution (e.g., polymorphisms in metabolizing enzymes). An uncertainty factor of up to 10 for human variability is considered prudent based on the exposure of the general population to chemicals in drinking water.

Studies in humans in the 1950s by Friberg and others first demonstrated that cadmium is toxic to the kidney. Numerous subsequent human studies confirmed the renal toxicity of cadmium in men and women. However, women may be more susceptible than men to cadmium toxicity. Women exposed to environmental sources of cadmium appear to exhibit higher cadmium levels in their blood, urine and kidney. Itai-Itai disease, a severe toxic manifestation of environmental exposure to cadmium, occurs principally in women (Fox, 1983; Vahter *et al*., 2002). The increased sensitivity of women to cadmium may be due to lower iron stores, that appear to result in greater absorption of cadmium from the intestine, although other factors could be involved (Fox, 1983; Vahter *et al*., 2002).

Studies in humans have shown that increased levels of certain urinary proteins are sensitive indicators of kidney damage due to cadmium exposure. Studies conducted to evaluate human occupational or environmental exposures to cadmium are very useful in characterizing the exposure level associated with appearance of proteinuria (renal toxicity). Men and women were both represented in the environmental studies, but men were the primary subjects of the occupational studies. The findings of these studies indicate that proteinuria begins to occur in men and women when urine levels exceed 2 μg cadmium/g creatinine.

Using available toxicokinetic information, a daily oral of intake of 19 μg/day was estimated to limit cadmium levels to 1 μg cadmium/g creatinine after 50 years of exposure. Unfortunately, key toxicokinetic data used to estimate cadmium's half-life were obtained from studies that only enrolled men (Ellis *et al*., 1979).

The PHG is based on limiting exposure such that urinary cadmium levels do not exceed 1 μg cadmium/g creatinine, thereby preventing renal toxicity. An uncertainty factor of 5 will be employed in the derivation of the PHG to protect sensitive individuals, notwithstanding that the NOAEL is based on a very sensitive indicator of renal toxicity. The uncertainty factor of 5 principally addresses the uncertainties due to limited information on the toxicokinetics of cadmium, particularly in women.

OEHHA (2005), IARC (2005), and U.S. EPA (2005) have determined that there is sufficient evidence that cadmium is carcinogenic to humans. However, no oral studies in humans or animals were identified that were judged suitable for estimating the oral cancer potency for cadmium. For the purposes of developing a PHG for cadmium, extrapolation of the inhalation potency to the oral route was also judged by OEHHA to be inappropriate. Therefore, an additional uncertainty factor of 10 was judged to be appropriate to account for carcinogenic activity of cadmium. OEHHA has previously applied an additional factor of 10 for other PHGs in situations where either a nonlinear dose extrapolation was applied to a carcinogen or where both linear and nonlinear approaches were used. Therefore, to address cancer risk due to oral exposure to cadmium, an additional 10-fold uncertainty factor will be employed in the derivation of

the PHG. The applicable body weight for the calculation is that for an adult female, the presumed sensitive receptor, or 60 kg.

In this case, an acceptable daily dose is calculated as follows:

$$\text{ADD} = \frac{\text{no-effect level in µg/day}}{\text{BW in kg} \times \text{UF}} = \frac{19\ \text{µg/day}}{60 \times 50} = 0.0063\ \text{µg/kg-day}$$

A relative source contribution of 20 percent was selected for calculation of the PHG. This value was selected because most exposure is attributable to sources other than drinking water (IPCS, 1992; Berglund *et al*., 1998; Kjellstrom, 1979). In addition, exposure to other sources of cadmium is increasing and is becoming a serious issue because a growing portion of the population may be nearing exposure levels that are associated with renal toxicity (Jarup *et al*., 1998; Satarug *et al*., 2003).

Based on data for water consumption by the general population in the Western Region of the U.S. (OEHHA, 2000), a water ingestion amount of 2.0 L/day was assumed. Because cadmium dissolved in water is non-volatile, and because metal salts have low skin penetration, the contributions from inhalation and dermal exposure to cadmium in tap water in the home are negligible.

Using these values, a public health protective concentration for noncarcinogenic effects of cadmium can be calculated as:

$$C = \frac{\text{ADD µg/kg-day x BW in kg x RSC}}{\text{L/day}}$$

$$= \frac{0.0063\ \text{µg/kg-day} \times 60 \times 0.20}{2.0\ \text{L/day}} = 0.038\ \text{µg/L or } 0.04\ \text{µg/L (rounded)}$$

In accordance with this calculation, a PHG of 0.04 µg/L (ppb) is developed for cadmium in drinking water. This value takes into account sensitive subpopulations, which in this case are women. Children are considered to be less susceptible because, at common environmental exposure levels, renal toxicity occurs after decades of cadmium exposure. Cadmium also does not appear to accumulate in the body of children (Alexander *et al*., 1974).

OEHHA identified cadmium as a reproductive toxicant. A LOAEL of 0.701 mg/kg-day was identified based on the findings of Ali *et al*. (1986). A health protective level based on a reproductive toxic endpoint is shown below:

$$C = \frac{700\ \text{µg/kg-day x 60 kg x 0.2}}{1{,}000 \text{ x } 2\ \text{L/day}} = 4.2\ \text{µg/L}$$

The aggregate uncertainty factor of 1,000 corresponds to 10 for extrapolating a LOAEL to a NOAEL, 10 for uncertainty associated with interspecies extrapolation, and 10 for intraspecies variability. An additional uncertainty factor of 10 for carcinogenesis would result in a health protective level of 0.4 μg/L. Therefore the PHG based on renal toxicity (above) also protects against reproductive effects.

Carcinogenic Effects

OEHHA (2005), IARC (1993), and U.S. EPA (2005) have determined that there is sufficient evidence that cadmium is carcinogenic to humans. OEHHA derived an inhalation potency factor based on inhalation studies in humans, but no oral studies in humans or animals were identified that were judged suitable for developing an oral cancer potency for cadmium. No statistically significant increase in tumors was observed in rats administered cadmium orally that had adequate zinc in their diet (Waalkes and Rehm, 1992). A dose-related increase in rats with leukemia was observed in the zinc-deficient rats, but the zinc-deficient rat was judged by OEHHA as not a suitable model for estimating cancer potency in humans.

OEHHA judged it inappropriate to extrapolate a dose-response relationship from an inhalation study to estimate the oral cancer potency of cadmium. Therefore, to address cancer risk due to oral exposure to cadmium, an additional 10-fold uncertainty factor has been employed in the derivation of the PHG from a non-carcinogenic endpoint.

RISK CHARACTERIZATION

The PHG for cadmium of 0.04 μg/L is based on adverse effects in the human kidney following decades of cadmium exposure. Several important issues that were addressed in deriving the PHG are discussed below.

Hazard Identification - The toxic effects of cadmium have been documented for over 50 years. In humans, chronic exposure to cadmium by the inhalation route in the workplace resulted in lung cancer and kidney dysfunction. Chronic oral exposure of humans to cadmium due to environmental contamination resulted in kidney dysfunction and skeletal abnormalities. In animal studies, an adverse effect of cadmium on the kidney has been observed. Reproductive effects have also been detected. Leukemia was observed in rats administered cadmium orally using a zinc-deficient rat model.

While cadmium is associated with several well-characterized adverse effects in human and animals, the kidney appears to be the most sensitive target organ associated with oral exposure to cadmium. Changes in the level of urinary biomarkers that are indicative of damage to the renal tubule were selected as very sensitive sentinels of the onset of renal dysfunction. Although there is sufficient evidence that cadmium is a human carcinogen, insufficient information on carcinogenic potential by the oral route was available to develop a PHG for this effect. An additional uncertainty factor was included in the derivation of the PHG from the non-cancer endpoint to address cadmium's potential oral carcinogenicity.

Dose Response - The development of a health protective criterion for non-carcinogens necessitates identifying an exposure level where toxicity will not occur. Studies of cadmium toxicity in humans have provided various metrics of exposure correlated with the onset of kidney dysfunction. Urinary cadmium levels were identified by OEHHA as the best metric for identifying exposures associated with the onset of renal dysfunction. Urinary cadmium levels appear to be in equilibrium with cadmium levels in the kidney (prior to cadmium-induced renal toxicity) and therefore reflect cadmium levels at the site of toxicity. Because there is little difficulty in measuring urinary cadmium levels, the data are plentiful. The results of a number of studies demonstrated that when urinary cadmium levels are at or below 1 μg/g creatinine there is no evidence of cadmium-related renal toxicity.

An alternative approach to develop the PHG is to rely on estimates of cadmium levels in the renal cortex itself, the site of toxicity, as the appropriate metric for identifying the exposure level associated with renal toxicity. The PHG published in 1999 relied on this type of metric. While there is little difficulty in measuring urinary cadmium levels associated with the levels of urinary biomarkers indicative of renal dysfunction, direct measurement of the concentration of cadmium in the kidney is a different matter. Cadmium levels measured in the kidneys of cadavers are not particularly useful for establishing the exposure level associated with the onset of renal toxicity. Recent studies in which cadmium levels in the kidney were measured *in vivo* using neutron activation or x-ray fluorescence techniques have yielded estimates of cadmium levels around the time of the onset of toxicity. However, the data are relatively sparse and there is a good deal of uncertainty concerning the reliability of these *in vivo* measurements (Jarup *et al.*, 1998; Morgan *et al.,* 1981).

Regardless of whether urinary cadmium levels or kidney cadmium levels are employed as the exposure metric, a daily intake associated with the metric must be estimated. The PHG is derived from a daily cadmium intake based on toxicokinetic studies in humans that demonstrated first order elimination and yielded an estimated terminal half-life of 14 years. With this terminal half-life, a daily oral intake of 19 μg is predicted to yield a urinary cadmium level of 1 μg/g creatinine after 52 years of exposure (when kidney concentrations peak). Maintenance of intake at this level or lower, over a lifetime, is judged to be protective against kidney damage.

Alternatively, the metric of renal cortex cadmium levels could be employed to estimate the daily intake of cadmium that will not result in renal toxicity. This approach was employed to derive the PHG in 1999 (OEHHA, 1999) and the reference dose in the IRIS database (U.S. EPA, 2005). The oral reference dose in IRIS was based on a renal cortex cadmium level of 200 mg/kg (U.S. EPA, 2005). However, recent studies have indicated that adverse effects occur at lower levels. Toxicokinetic models must be employed to estimate the daily intake associated with a cadmium cortex level after decades of exposure. Multicompartmental PBPK models have been employed to estimate daily exposure, but there is a great deal of uncertainty in these models because of limited data on the model parameters.

Given the difficulty and uncertainties of determining the critical concentration of cadmium in the kidney and the uncertainty regarding PBPK modeling used to derive a daily cadmium intake associated with a given cadmium level in the renal cortex, the

derivation of the PHG relies on a different metric, urinary cadmium levels. Using urinary cadmium levels to derive the PHG was judged to be more reliable because measurements of urinary cadmium levels and levels of urinary biomarkers that are indicative of toxicity are plentiful. Also, estimates of daily cadmium intake associated with a given urinary cadmium level rely on standard toxicokinetic methods and toxicokinetic data obtained from human studies and not assumptions regarding the more complex parameters used in a PBPK model.

Toxicokinetic data that were employed to derive the PHG demonstrated that cadmium accumulates in the kidney over decades and that the level of cadmium in the urine reflects the level in the kidney and elsewhere in the body (body burden) prior to damage to the kidney. These data also indicate that cadmium elimination follows first order kinetics, that is, the amount of cadmium in the urine reflects body burden. These data allowed the derivation of a reasonable estimate of the daily cadmium intake associated with a given urinary cadmium level.

Exposure Assessment – Default estimates of drinking water consumption and adult body weight (2 L/day and 70 kg) were employed to develop the health-based criteria to assess oral exposure to cadmium in drinking water. While these are typical conventions employed to estimate exposure, there is uncertainty attendant with their use. The PHG also reflects a relative source contribution of 20 percent of the total exposure coming from drinking water. Studies have shown that drinking water is a minor source of exposure to cadmium (IPCS, 1992; Berglund *et al*., 1998; Kjellstrom, 1979).

Risk Characterization - The various sources of uncertainty attendant in the hazard identification, dose response, and exposure assessment are reflected in the PHG. While a number of studies were useful in characterizing renal toxicity of cadmium in humans, a likely sensitive population, women, were the subjects of many of these studies. Women were not the subjects of a key toxicokinetic study used to derive the PHG (Ellis *et al*., 1979), although there is no evidence to indicate that the half-life of cadmium in women is longer than in men. Therefore, an additional uncertainty factor of 5 was included in the derivation of the PHG to protect this sensitive population.

While cadmium has been identified as a human carcinogen, the available studies are not sufficient to characterize the carcinogenic risk associated with oral exposure to this metal. An additional uncertainty factor of 10 was employed in deriving the PHG to address this source of uncertainty.

As better studies of the toxicity of cadmium and better methods to characterize the dose-response relationship become available, the uncertainties associated with the risk assessment can be reduced.

OTHER REGULATORY STANDARDS

A Public Health Goal (PHG) of 0.07 ppb for cadmium in drinking water was first published in 1999, based on protection against nephrotoxicity from chronic exposure (OEHHA, 1999). This PHG was based on a LOAEL of 1 μg/kg, derived from an epidemiological study in an adult Belgian population (Buchet *et al.*, 1990). The health

endpoint for this LOAEL was renal tubular damage indicated by the appearance in the urine of small proteins (retinol-binding protein, N-acetyl-α-glucosaminidase, and β2-microglobulin) as well as amino acids and calcium. This previous PHG was calculated using an overall uncertainty factor of 100 (10 for protection of sensitive individuals, 3 for extrapolation from a LOAEL to a NOAEL, and 3 to address children's exposure.

The U.S. EPA MCL and MCLG for cadmium is 5 μg/L. U.S. EPA established a reference dose (RfD) for drinking water of 0.5 μg/kg-day (IRIS, 2005). This RfD is based on a no-observed-adverse-effect-level (NOAEL) of 200 μg/g in the renal cortex (Friberg *et al.*, 1974; IRIS, 2005). The RfD incorporates a 10-fold uncertainty factor for protection of sensitive populations, and does not account for potential oral carcinogenicity of cadmium.

Cadmium is listed by the California Air Resources Board as a toxic air contaminant (TAC) (California Administrative Code, Title 17, Section 93000). Data on cadmium emissions must be included in monitoring programs under the air toxics hot spots program. Cadmium levels in California air are regulated to limit cancer risk.

The threshold limit value (TLV) for cadmium dust and salts as cadmium is 0.05 mg/m^3 as a time-weighted average. This level was set to prevent proteinuria, pulmonary edema and emphysema. There is a proposal by the TLV Committee of the American Conference of Government and Industrial Hygienists to lower the TLV to 0.01 mg/m^3 to protect against kidney damage and lung cancer (ACGIH, 1996).

According to section 66699 of the California Health and Safety Code, Title 22, a waste will be classified as a hazardous waste if the soluble threshold limit concentration (STLC) of cadmium exceeds 1.0 μg/mL, or the total threshold limit concentration (TTLC) of cadmium exceeds 100 mg/kg (California Health and Safety Code, section 66699).

There are no standards or action levels for cadmium in individual foods; however, a WHO Committee on Food Additives recommended a provisional maximum tolerable weekly cadmium intake of 400 to 500 μg cadmium from all sources (WHO, 1972). This is equivalent to 60 to 70 μg/day. Adult exposure to cadmium via food has been estimated to range from 4 to 84 μg/day (Hallenbeck, 1984).

The International Agency for Research on Cancer (IARC, 1993) classifies cadmium as a Group 1 carcinogen - a known human carcinogen. U.S. EPA has classified cadmium as a probable human carcinogen by inhalation (Group B1) based on animal and human data (IRIS, 1998). The 10^{-6} cancer risk level for cadmium calculated by U.S. EPA corresponds to an inhalation exposure of 0.012 μg/day. Under the California Toxic Air Contaminant Program, the 10^{-6} cancer risk was taken to be an inhaled dose of 0.0017 μg/day (CDHS, 1986; Collins *et al*., 1992).

In accordance with the California Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65), "cadmium and cadmium compounds" are listed (since October 1, 1987) on the Proposition 65 list as carcinogens (OEHHA, 2005). Cadmium is also listed (since May 1, 1997) as a developmental toxicant, and as a male reproductive toxicant (OEHHA, 2005). The level of cadmium exposure that poses no significant risk of cancer for purposes of Proposition 65 is 0.05 μg/day by inhalation (Title 22, California Code of

Regulations (CCR), Section 12705(b)). However, for purposes of the California Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65), cadmium and cadmium compounds are by regulation declared to "present no significant risk of cancer by the route of ingestion" (Title 22, (CCR), Section 12707(b)). This statutory exclusion does not apply to regulation of drinking water under the California Safe Drinking Water Act (HSC 116365 *et seq*.).

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