2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO CADMIUM IN THE UNITED STATES

Cadmium occurs in the earth's crust at a concentration of 0.1–0.5 ppm and is commonly associated with zinc, lead, and copper ores. It is also a natural constituent of ocean water with average levels between <5 and 110 ng/L, with higher levels reported near coastal areas and in marine phosphates and phosphorites. The cadmium concentration of natural surface water and groundwater is usually <1 μg/L. Surface soil concentrations will depend on several factors such as its mobility, natural geochemistry, and magnitude of contamination from sources such as fertilizers and atmospheric deposition. Natural emissions of cadmium to the environment can result from volcanic eruptions, forest fires, generation of sea salt aerosols, or other natural phenomena.

In the environment, cadmium exists in only one oxidation state (+2) and does not undergo oxidation-reduction reactions. In surface water and groundwater, cadmium can exist as the hydrated ion or as ionic complexes with other inorganic or organic substances. Soluble forms of cadmium can migrate in water. Insoluble forms of cadmium will settle and adsorb to sediments. Cadmium's fate in soil depends on several factors such as pH of the soil and the availability of organic matter. Generally, cadmium will bind strongly to organic matter and this will, for the most part, immobilize it. However, cadmium's behavior in soil will vary depending on the environmental conditions. It is not likely that cadmium will undergo significant transformation in the atmosphere. It will exist in particulate form and sometimes vapor form (emitted from high temperature processes) where it will undergo atmospheric transport and eventually deposit onto soils and surface waters.

Non-ferrous metal mining and refining, manufacture and application of phosphate fertilizers, fossil fuel combustion, and waste incineration and disposal are the main anthropogenic sources of cadmium in the environment. Except for those who live near cadmium-emitting industries, inhalation of cadmium in the ambient air may occur, but is not a major source of exposure. Water sources near cadmium-emitting industries, both with historic and current operations, have shown a marked elevation of cadmium in water sediments and aquatic organisms. Concentrations of cadmium in these polluted waters have ranged from <1.0 to 77 μg/L. For the U.S. population, cadmium exposure through the drinking water supply is of minor concern. Cadmium from polluted soil and water can accumulate in plants and organisms, thus entering the food supply.

In the United States, the largest source of cadmium exposure for nonsmoking adults and children is through dietary intake. The estimated daily intakes of cadmium in nonsmoking adult males and females living in the United States are 0.35 and 0.30 μg Cd/kg/day, respectively. Females generally absorb greater amounts of cadmium in the gastrointestinal tract. In general, leafy vegetables such as lettuce and spinach and staples such as potatoes and grains contain relatively high values of cadmium. Peanuts, soybeans, and sunflower seeds have naturally high levels of cadmium. People who regularly consume shellfish and organ meats (liver and kidney) have increased cadmium exposure.

Mean values of cadmium in the blood and urine of the U.S. population were reported in the National Health and Nutrition Examination Survey (NHANES) 1999–2002. Blood cadmium reflects both recent and cumulative exposures and urinary cadmium reflects cadmium exposure and the concentration of cadmium in the kidneys. The 20 years or older age group had geometric mean levels of blood and urine cadmium that were slightly higher than the younger age groups (0.468 and 0.273–0.281 μg/L in blood and urine, respectively). Females (0.421 μg/L, blood; 0.187–0.219 μg/L urine) had slightly higher blood and urine cadmium levels than males (0.403 μg/L, blood; 0.199–0.201 μg/L, urine).

Smoking greatly increases exposure to cadmium, as tobacco leaves naturally accumulate high amounts of cadmium. It has been estimated that tobacco smokers are exposed to 1.7 μg cadmium per cigarette, and about 10% is inhaled when smoked. A geometric mean blood cadmium level for a heavy smoker has been reported as high as 1.58 μg/L, compared to the estimated national mean of 0.47 μg/L for all adults. Nonsmokers may also be exposed to cadmium in cigarettes via second-hand smoke.

2.2 SUMMARY OF HEALTH EFFECTS

Since the early 1950s, when the hazards of occupational cadmium exposure were recognized, a large amount of information has been generated concerning the toxic effects of cadmium exposure in humans and laboratory animals. Toxicological properties of cadmium are similar for the several different salts and oxides of cadmium that have been investigated, although differences in absorption and distribution lead to different effect levels. For inhalation exposure, particle size and solubility in biological fluids (in contrast to solubility in water) appear to be the more important determinants of the toxicokinetics. For oral exposure, most experimental studies have used soluble cadmium, which exists as the Cd^{+2} ion regardless of the initial salt. Absorption appears to be similar for cadmium ion and cadmium complexed with proteins in food, except for a few specific types of foods such as Bluff oysters and seal meat. Also, poorly soluble cadmium pigments may be absorbed to a lesser extent than soluble cadmium ion. For the

general population, dietary exposure to cadmium is the most likely route of exposure. There is an extensive database on the toxicity of cadmium in environmentally exposed populations and in cadmium workers; however, most of these studies were focused on the presumed sensitive targets. These sensitive targets of cadmium toxicity are the kidney and bone following oral exposure and kidney and lung following inhalation exposure. Studies in animals support the identification of these sensitive targets and provide some suggestive evidence that the developing organisms may also be a sensitive target. There is also evidence to suggest that cadmium is a human carcinogen. Other effects that have been observed in humans and/or animals include reproductive toxicity, hepatic effects, hematological effects, and immunological effects.

The earliest indication of kidney damage in humans is an increased excretion of low molecular weight proteins, particularly β2-microglobulin, human complex forming glycoprotein (pHC) (also referred to as α1-microglobulin), and retinol binding protein; increased urinary levels of intracellular enzymes such as N-acetyl-β-glucosaminidase (NAG); and increased excretion of calcium and metallothione. Numerous studies of cadmium workers and populations living in areas with low, moderate, or high cadmium pollution have found significant associations between urinary cadmium levels and biomarker levels or significant increases in the prevalence of abnormal biomarker levels. At higher exposure levels, decreases in glomerular filtration rate, increased risk of renal replacement therapy (dialysis or kidney transplantation), and significant increases in the risk of deaths from renal disease have been observed. The sensitivity of the kidney to cadmium is related to its distribution in the body and *de novo* synthesis of metallothionein in the kidney. In the blood, cadmium is bound to metallothionein and is readily filtered at the glomerulus and reabsorbed in the proximal tubule. Within the tubular cells, the metallothionein is degraded in lysosomes and free cadmium is released; the synthesis of endogenous metallothionein by the tubular cells is then stimulated. However, when the total cadmium content in the renal cortex reaches between 50 and 300 μg/g wet weight, the amount of cadmium not bound to metallothionein becomes sufficiently high to cause tubular damage. Free cadmium ions may inactivate metal-dependent enzymes, activate calmodulin, and/or damage cell membranes through activation of oxygen species. Because the toxicity of cadmium is dependent on its concentration in the kidney, adverse effects in humans are typically not observed after shorter durations.

Acute inhalation exposure to cadmium at concentrations above about 5 mg/m^3 may cause destruction of lung epithelial cells, resulting in pulmonary edema, tracheobronchitis, and pneumonitis in both humans and animals. A single, high-level cadmium exposure can result in long-term impairment of lung function. At the cellular level, catalase, superoxide dismutase, non-protein sulfhydryl, glucose-6-phosphate

dehydrogenase, and glutathione peroxidase are decreased in response to cadmium lung insults. The respiratory response to cadmium is similar to the response seen with other agents that produce oxidative damage. There typically is an alveolar pneumocyte type 2 cell hyperplasia in response to type 1 cell damage and necrosis. Longer-term inhalation exposure at lower levels also leads to decreased lung function and emphysema in cadmium workers. Some tolerance to cadmium-induced lung irritation develops in exposed humans and animals, and respiratory function may recover after cessation of cadmium exposure. Another effect of long-term inhalation cadmium exposure is damage to the olfactory function and nasal epithelium. Lung damage has also been seen in a few studies of oral cadmium exposure in rats, but the lung effects are likely to be related to liver or kidney damage and subsequent changes in cellular metabolism.

Prolonged inhalation or ingestion exposure of humans to cadmium at levels causing renal dysfunction can lead to painful and debilitating bone disease in individuals with risk factors such as poor nutrition; the occurrence of these bone effects in elderly Japanese women exposed to high levels of cadmium in rice and water was referred to as Itai-Itai disease. Decreases in bone mineral density, increases in the risk of fractures, and increases in the risk of osteoporosis have also been observed in populations living in cadmium polluted areas or in cadmium nonpolluted areas. Similar effects have also been observed in young rats orally exposed to cadmium. Animal data strongly suggest that cadmium exposure results in increases in bone turnover and decreases in mineralization during the period of rapid bone growth. Although animal studies suggest that these effects are due to direct damage to the bone, it is likely that renal damage resulting in the loss of calcium and phosphate and alteration in renal metabolism of vitamin D would compound these effects.

There are few human data on developmental effects from exposure to cadmium. Some studies indicate that maternal cadmium exposure may cause decreased birth weight in humans, but most of these studies are of limited use because of weaknesses in the study design and lack of control for confounding factors. A number of other studies did not find a significant relationship between maternal cadmium levels and newborn body weight. In animals, cadmium has been shown to be a developmental toxin by the inhalation, oral, and parenteral routes. Decreased fetal weight, skeletal malformations, and delayed ossification are produced by relatively high maternal doses (1–20 mg/kg/day) due to placental toxicity, interference with fetal metabolism, and damage to the maternal liver. Neurodevelopmental effects have been observed at lower doses. Impaired performance on neurobehavioral tests were observed in the offspring of rats exposed to 0.02 mg/m^3 or ≥0.04 mg/kg/day.

The results of occupational exposure studies examining the possible association between cadmium exposure and an increased risk of lung cancer are inconsistent, with some studies finding significant increases in lung cancer deaths and other studies not finding increases. Interpretation of the results of many of the studies is complicated by inadequate controls for confounding factors such as co-exposure with other metal carcinogens and smoking, small number of lung cancer deaths, and the lack of significant relationships between cadmium exposure and duration. For prostate cancer, initial studies in European workers indicated an elevation in prostate cancer, but subsequent investigations found either no increases in prostate cancer or increases that were not statistically significant. Strong evidence from animal studies exists that cadmium inhalation can cause lung cancer, but only in rats. Most oral studies in laboratory animals have not found significant increases in cancer incidence. The Department of Health and Human Services concluded that there were sufficient human and animal data to conclude that cadmium is a known human carcinogen; likewise, IARC classified cadmium as carcinogenic to humans (Group 1). The EPA has classified cadmium as a probable human carcinogen by inhalation (Group B1), based on its assessment of limited evidence of an increase in lung cancer in humans and sufficient evidence of lung cancer in rats.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for cadmium. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990d), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

The database on the toxicity of cadmium in humans and animals following inhalation or oral exposure is extensive. Target organs are similar among species and, in general, toxicokinetic properties after oral and inhalation exposures are similar. Most of the human data involve chronic inhalation exposure of workers or chronic dietary exposure of the general population or populations living in cadmium-polluted areas. Several approaches for characterizing cadmium exposure have been used in these studies. Occupational exposure studies have used current air concentrations or have estimated cumulative exposure based on historical and current monitoring data. Some epidemiology studies have estimated cumulative intake based on the levels of cadmium in rice, in populations where rice has been the dominant source of oral exposure to cadmium. However, most studies (particularly oral studies) have used urinary cadmium levels as a biomarker of exposure. As discussed in greater detail in Section 3.8.1, urinary cadmium levels correlate with cadmium body burden and cadmium concentration in kidney (a critical target organ for chronic exposure). The relationship between renal and urinary cadmium appears to be nearly linear at chronic intakes and kidney burdens that do not produce nephrotoxicity (i.e., elimination half-time is independent of dose). However, at high kidney cadmium burdens, associated with renal damage (>50 μg Cd/g cortex), the elimination half-time increases with increasing severity of renal damage. Linearity in the dose-urinary excretion relationship also does not appear to apply following an acute high exposure to cadmium. The Nordberg-Kjellström model (described in detail in Section 3.4.5.3) is a multicompartment pharmacokinetic model that can be used to estimate cadmium intakes (inhalation and oral exposure) associated with a given urinary cadmium level and/or kidney cadmium burden. The model has been extensively evaluated for predicting dose-kidney-urinary cadmium relationships within the linear range of the dose-urinary cadmium relationship.

Inhalation MRLs

Acute-duration Inhalation MRL

- An MRL of $3x10^{-5}$ mg Cd/m^3 (0.03 μg Cd/m^3) has been derived for acute-duration inhalation exposure (<14 days) to cadmium.

The acute toxicity of airborne cadmium, particularly cadmium oxide fumes, was first recognized in the early 1920s and there have been numerous case reports of cadmium workers dying after brief exposures to presumably high concentrations of cadmium fumes (European Chemicals Bureau 2007). The initial symptoms, similar to those observed in metal fume fever, are usually mild but rapidly progress to severe pulmonary edema and chemical pneumonitis. Persistent respiratory effects (often lasting years after the

exposure) have been reported in workers surviving these initial effects. There are limited monitoring data for these human reports; however, Elinder (1986b) estimated that an 8-hour exposure to 1–5 mg/m^3 would be immediately dangerous.

Animal studies support the findings in humans that acute exposure to cadmium results in lung damage. Single exposures to approximately 1–10 mg Cd/m^3 as cadmium chloride or cadmium oxide resulted in interstitial pneumonitis, diffuse alveolitis with hemorrhage, focal interstitial thickening, and edema (Boudreau et al. 1989; Buckley and Bassett 1987b; Bus et al. 1978; Grose et al. 1987; Hart 1986; Henderson et al. 1979; Palmer et al. 1986). Repeated exposure to 6.1 mg Cd/m^3 1 hour/day for 5, 10, or 15 days resulted in emphysema in rats (Snider et al. 1973). Lower concentrations of 0.4–0.5 mg Cd/m^3 as cadmium oxide for 2–3 hours (Buckley and Bassett 1987b; Grose et al. 1987) or 0.17 mg Cd/m^3 as cadmium chloride 6 hours/day for 10 days (Klimisch 1993) resulted in mild hypercellularity and increases in lung weight. Alveolar histiocytic infiltration and focal inflammation and minimal fibrosis in alveolar septa were observed in rats exposed to 0.088 mg Cd/m^3 as cadmium oxide 6.2 hours/day, 5 days/week for 2 weeks (NTP 1995); in similarly exposed mice, histiocytic infiltration was observed at 0.088 mg Cd/m^3 (NTP 1995). At similar concentrations (0.19 or 0.88 mg Cd/m^3as cadmium chloride), decreases in humoral immune response were observed in mice exposed for 1–2 hours (Graham et al. 1978; Krzystyniak et al. 1987). Other effects that have been reported in animals acutely exposed to cadmium include erosion of the stomach, decreased body weight gain, and tremors in rats exposed to 132 mg Cd/m^3 as cadmium carbonate for 2 hours (Rusch et al. 1986) and weight loss and reduced activity in rats exposed to 112 mg Cd/m^3 as cadmium oxide for 2 hours (Rusch et al. 1986).

The NTP (1995) study was selected as the basis of an acute duration inhalation MRL. In this study, groups of five male and five female F344 rats were exposed to 0, 0.1, 0.3, 1, 3, or 10 mg cadmium oxide/m^3 (0, 0.088, 0.26, 0.88, 2.6, or 8.8 mg Cd/m^3) 6.2 hours/day, 5 days/week for 2 weeks. The mean median aerodynamic diameter (MMAD) of the cadmium oxide particles was 1.5 μm with a geometric standard deviation of 1.6–1.8. The animals were observed twice daily and weighed on days 1, 8, and at termination. Other parameters used to assess toxicity included organ weights (heart, kidney, liver, lungs, spleen, testis, and thymus) and histopathological examination (gross lesions, heart, kidney, liver, lungs, tracheobronchial lymph nodes, and nasal cavity and turbinates). All rats in the 8.8 mg Cd/m^3 group died by day 6; no other deaths occurred. A slight decrease in terminal body weights was observed at 2.6 mg Cd/m^3; however, the body weights were within 10% of control weights. Significant increases in relative and absolute lung weights were observed at 0.26 (males only), 0.88, and 2.6 mg Cd/m^3. Histological alterations were limited to the respiratory tract and consisted of alveolar histiocytic infiltrate and focal

inflammation and minimal fibrosis in alveolar septa at ≥0.088 mg Cd/m^3, necrosis of the epithelium lining alveolar ducts at ≥0.26 mg Cd/m^3, tracheobronchiolar lymph node inflammation at ≥0.88 mg Cd/m^3, degeneration of the nasal olfactory epithelium at 0.88 mg Cd/m^3, and inflammation and metaplasia of the nasal respiratory epithelium at 2.6 mg Cd/m^3.

The lowest-observed-adverse-effect level (LOAEL) of 0.088 mg Cd/m^3 was selected as the point of departure for derivation of the MRL; benchmark dose analysis was considered; however, the data were not suitable for benchmark dose analysis because the data do not provide sufficient information about the shape of the dose-response relationship below the 100% response level. The $LOAEL_{HEC}$ was calculated using the equations below.

$$LOAEL_{HEC} = LOAEL_{ADJ} \times RDDR$$

The duration-adjusted LOAEL ($LOAEL_{ADJ}$) was calculated as follows:

$$LOAEL_{ADJ} = 0.088 \text{ mg Cd/m}^3 \times 6.2 \text{ hours}/24 \text{ hours} \times 5 \text{ days}/7 \text{ days}$$
$$LOAEL_{ADJ} = 0.016 \text{ mg Cd/m}^3$$

The regional deposited dose ratio (RDDR) for the pulmonary region of 0.617 was calculated with EPA's RDDR calculator (EPA 1994a) using the final body weight of 0.194 kg for the male rats exposed to 0.088 mg Cd/m^3, the reported MMAD of 1.5 μm and the midpoint of the reported range of geometric standard deviations (1.7).

$$LOAEL_{HEC} = 0.016 \text{ mg Cd/m}^3 \times 0.617$$
$$LOAEL_{HEC} = 0.01 \text{ mg Cd/m}^3$$

The $LOAEL_{HEC}$ was divided by an uncertainty factor of 300 (10 for the use of a LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments, and 10 for human variability) resulting in an acute-duration inhalation MRL of 3×10^{-5} mg Cd/m^3 (0.03 μg Cd/m^3).

Intermediate-duration Inhalation MRL

There are no studies examining the intermediate-duration toxicity of inhaled cadmium in humans; however, numerous animal studies have identified several targets of cadmium toxicity. Increases in the number of bronchioalveolar macrophages, alveolar histiocytic infiltration, degeneration or metaplasia in

the larynx, and proliferations have been observed in rats and mice exposed to 0.022 mg Cd/m^3 as cadmium oxide or cadmium chloride (Glaser et al. 1986; NTP 1995; Prigge 1978a). At higher concentrations (>0.88 mg Cd/m^3), marked inflammation and fibrosis was observed in lungs of rats (Kutzman et al. 1986; NTP 1995). In general, these studies did not identify no-observed-adverse-effect levels (NOAELs) for lung effects. The NTP (1995) study also found significant increases in the incidence of inflammation of the nasal respiratory epithelium in rats exposed to 0.22 mg Cd/m^3 and degeneration of the nasal olfactory epithelium in mice exposed to 0.088 mg Cd/m^3. The NTP (1995) study did not find any histological alterations in non-respiratory tract tissues, alterations in urinalysis parameters, or changes in blood pressure (rats only) in rats or mice. Prigge (1978a, 1978b) reported increases in hemoglobin and hematocrit levels in rats continuously exposed to ≥0.052 mg Cd/m^3; however, this effect was not observed in the NTP (1995) studies. Reproductive effects (increased duration of estrous cycle and decreased spermatid counts) have also been observed at higher concentrations (0.88–1 mg Cd/m^3) (Baranski and Sitarek 1987; NTP 1995).

The studies by Baranski (1984, 1985) provide suggestive evidence that the developing organism is also a sensitive target of cadmium toxicity. Significant alterations in performance on neurobehavioral tests were observed in the offspring of rats exposed to 0.02 mg Cd/m^3 as cadmium oxide 5 hours/day, 5 days/week for 5 months prior to mating, during a 3-week mating period, and during gestation days 1–20. No other studies examined neurodevelopmental end points following inhalation exposure. However, the identification of neurodevelopmental effects as a sensitive target of cadmium toxicity is supported by several intermediate-duration animal studies finding neurodevelopmental effects including alterations in motor activity and delays in the development of sensory motor coordination reflexes (Ali et al. 1986; Baranski 1985; Desi et al. 1998; Nagymajtenyi et al. 1997). Other developmental effects observed in the inhalation studies included decreases in fetal body weight in the fetuses of rats exposed to 1.7 or 0.581 mg Cd/m^3 (NTP 1995; Prigge 1978b) and mice exposed to 0.4 mg Cd/m^3 (NTP 1995).

Based on the available animal data, the LOAEL of 0.022 mg Cd/m^3 for lung and larynx effects in mice (NTP 1995) and the LOAEL of 0.02 mg Cd/m^3 for neurodevelopmental effects (Baranski 1984, 1985) were evaluated as possible points of departure for the intermediate-duration inhalation MRL for cadmium. The LOAEL of 0.022 mg Cd/m^3 identified in the NTP (1995) mouse study was considered as the point of departure for the MRL because the NTP study provided more study details and information on particle size distribution. Because an MRL based on this LOAEL ($LOAEL_{HEC}$ of 1 μg Cd/m^3) would be lower than the chronic-duration inhalation MRL based on human data, an intermediate-duration inhalation MRL was not derived.

Chronic-duration Inhalation MRL

- An MRL of 0.01 μg Cd/m^3 has been derived for chronic-duration inhalation exposure (≥1 year) to cadmium.

Numerous studies examining the toxicity of cadmium in workers have identified the respiratory tract and the kidney as sensitive targets of toxicity. A variety of respiratory tract effects have been observed in cadmium workers including respiratory symptoms (e.g., dyspnea, coughing, wheezing), emphysema, and impaired lung function. However, many of these studies did not control for smoking, and thus, the role of cadmium in the induction of these effects is difficult to determine. Impaired lung function was reported in several studies that controlled for smoking (Chan et al. 1988; Cortona et al. 1992; Davison et al. 1988; Smith et al. 1976); other studies have not found significant alterations (Edling et al. 1986). The observed alterations included an increase in residual volume in workers exposed to air concentrations of cadmium fumes ranging from 0.008 (in 1990) to 1.53 mg/m^3 (in 1975) (mean urinary cadmium level in the workers was 4.3 μg/L) (Cortona et al. 1992); alterations in several lung function parameters (e.g., forced expiratory volume, transfer factor, transfer coefficient) in workers exposed to 0.034–0.156 mg/m^3 (Davison et al. 1988); and decreased force vital capacity in workers exposed to >0.2 mg/m^3 (Smith et al. 1976). Additionally, Chan et al. (1988) found significant improvements in several parameters of lung function of workers following reduction or cessation of cadmium exposure.

The renal toxicity of cadmium in workers chronically exposed to high levels of cadmium is well established. Observed effects include tubular proteinuria (increased excretion of low molecular weight proteins), decreased resorption of other solutes (increased excretion of enzymes such as NAG, amino acids, glucose, calcium, inorganic phosphate), evidence of increased glomerular permeability (increased excretion of albumin), increased kidney stone formation, and decreased glomerular filtration rate (GFR). The earliest sign of cadmium-induced kidney damage is an increase in urinary levels of low molecular weight proteins (particularly, β2-microglobulin, retinol binding protein, and pHC) in cadmium workers, as compared to levels found in a reference group of workers or the general population (Bernard et al. 1990; Chen et al. 2006a, 2006b; Chia et al. 1992; Elinder et al. 1985a; Falck et al. 1983; Jakubowski et al. 1987, 1992; Järup and Elinder 1994; Järup et al. 1988; Shaikh et al. 1987; Toffoletto et al. 1992; Verschoor et al. 1987). Although increases in the excretion of low molecular weight proteins are not diagnostic of renal damage (Bernard et al. 1997; Järup et al. 1998b), tubular proteinuria is considered an adverse effect because it is an early change in a sequence of events which ultimately may result in compromised renal function (Bernard et al. 1997). Most investigators consider a 10% cadmium-

associated increase in the prevalence of abnormal levels of renal biomarkers (urinary β2-microglobulin, retinol binding protein, pHC) to be indicative of cadmium-induced renal disease in the population. However, there is less consensus on the low molecular protein level regarded as elevated or abnormal (cut-off point).

Several biomarkers of tubular damage have been used in occupational exposure studies; these include β2-microglobulin, retinol binding protein, NAG, and pHC. Of these biomarkers, which differ in their sensitivities to detect tubular damage, β2-microglobulin is the most widely used in occupational exposure studies. In healthy humans, urinary β2-microglobulin levels are <300 μg/24 hours (approximately 300 μg/g creatinine). Four studies have estimated the prevalence of abnormal urinary β2-microglobulin levels among cadmium workers using cut-off levels of 187–380 μg/g creatinine (Chen et al. 2006a; Elinder et al. 1985a; Jakubowski et al. 1987; Järup and Elinder 1994). The prevalence of abnormal urinary β2-microglobin levels was 10% among workers with urinary cadmium levels of 1.5 (≥60 years of age) or 5 (<60 years of age) μg/g creatinine (β2-microglobulin cut-off level of 220 μg/g creatinine) (Järup and Elinder 1994), 25% among workers with urinary cadmium levels of 2–5 μg/g creatinine (cut-off level of 300 μg/g creatinine) (Elinder et al. 1985a), 40% among workers with urinary cadmium levels of 5–10 μg/g creatinine (cut-off level of 187 μg/g creatinine) (Chen et al. 2006a), and 10% among workers with urinary cadmium levels of 10–15 μg/g creatinine (cut-off level of 380 μg/g creatinine (Jakubowski et al. 1987). A 10% prevalence of abnormal β2-microglobulin levels (cut-off level of 300 μg/g creatinine) was also observed in workers with a cumulative blood cadmium level of 300 μg-years/L (30 years of 10 μg/L) (Jakubowski et al. 1992) or blood cadmium level of 5.6 μg/L (cumulative exposure of 691 μg-years/m^3) (Järup et al. 1988).

Most of the studies reporting respiratory effects expressed cadmium exposure as air concentrations; however, these air concentrations may not be indicative of cadmium exposure over time. For example, in the Cortona et al. (1992) study, cadmium levels of 0.030 mg/m^3 were measured in 1990 in one foundry; in 1976, the cadmium levels in this foundry were 1.53 mg/m^3. Cortona et al. (1992) also reported cadmium body burden data; the mean urinary cadmium level in the workers was 4.3 μg/L (roughly equivalent to 4 μg/g creatinine). Renal effects have been observed at similar cadmium burdens. Most studies have reported renal effects in workers with urinary cadmium levels of ≥5 μg/g creatinine; Järup and Elinder (1994) found an increased prevalence of low molecular weight proteinuria in workers ≥60 years of age with mean urinary cadmium of 1.5 μg/g creatinine. The air concentration that would result in this urinary cadmium level would be considered a LOAEL. However, cadmium in the workplace air was not the only source of cadmium. The workers were also exposed to other sources of cadmium (e.g., cadmium in the

diet); both sources contributed to the renal cadmium burden. Thus, in order to calculate a chronic-duration inhalation MRL from the LOAEL identified in the Järup and Elinder (1994) study, the workers' other sources of cadmium need to be taken into consideration; this information was not reported in the study.

An alternative approach would be to use environmental exposure studies to establish a point of departure for the urinary cadmium-renal response relationship and pharmacokinetic models (ICRP 1994; Kjellström and Nordberg 1978) to predict cadmium air concentrations. As described in greater detail in the chronic oral MRL section, a meta-analysis of available environmental exposure studies was conducted to estimate an internal dose (urinary cadmium expressed as μg/g creatinine) corresponding to a 10% excess risk of low molecular weight proteinuria (urinary cadmium dose, UCD_{10}). For the inhalation MRL, the meta-analysis also included dose-response data from three occupational exposure studies (Chen et al. 2006a, 2006b; Järup and Elinder 1994; Roels et al. 1993). Analysis of the environmental exposure studies resulted in an estimation of a urinary cadmium level that would result in a 10% increase in the prevalence of β2-microglobulin proteinuria (1.34 μg/g creatinine); the 95% lower confidence limit on this value was 0.5 μg/g creatinine. The UCD_{10} values from the occupational exposure studies were 7.50 μg/g creatinine for the European cohorts (Järup and Elinder 1994; Roels et al. 1993) and 4.58 μg/g creatinine for the Chinese cohort (Chen et al. 2006a, 2006b). Because the dose-response analysis using the European environmental exposure studies provided the lowest UCD_{10}, it was selected for derivation of the chronic-duration inhalation MRL; the 95% lower confidence limit on this value ($UCDL_{10}$) of 0.5 μg/g creatinine was used as the point of departure for the MRL.

Deposition and clearance of inhaled cadmium oxide and cadmium sulfide particles were modeled using the ICRP Human Respiratory Tract Model (ICRP 1994). The ICRP model simulates deposition, retention, and absorption of inhaled cadmium particles of specific aerodynamic diameters, when specific parameters for cadmium clearance are used in the model (ICRP 1980). Cadmium-specific parameters represent categories of solubility and dissolution kinetics in the respiratory tract (e.g., slow, S; moderate, M; or fast, F). Cadmium compounds are classified as follows: oxides and hydroxides, S; sulfides, halides and nitrates, M; all other, including chloride salts, F.

Inhalation exposures ($\mu g/m^3$) to cadmium oxide or cadmium sulfide aerosols having particle diameters of 1, 5, or 10 μg (AMAD) were simulated using the ICRP model. Predicted mass transfers of cadmium from the respiratory tract to the gastrointestinal tract (i.e., mucocilliary transport) and to blood (i.e., absorption) were used as inputs to the gastrointestinal and blood compartments of the Nordberg-Kjellström

pharmacokinetic model (Kjellström and Nordberg 1978) to simulate the kidney and urinary cadmium levels that correspond to a given inhalation exposure.

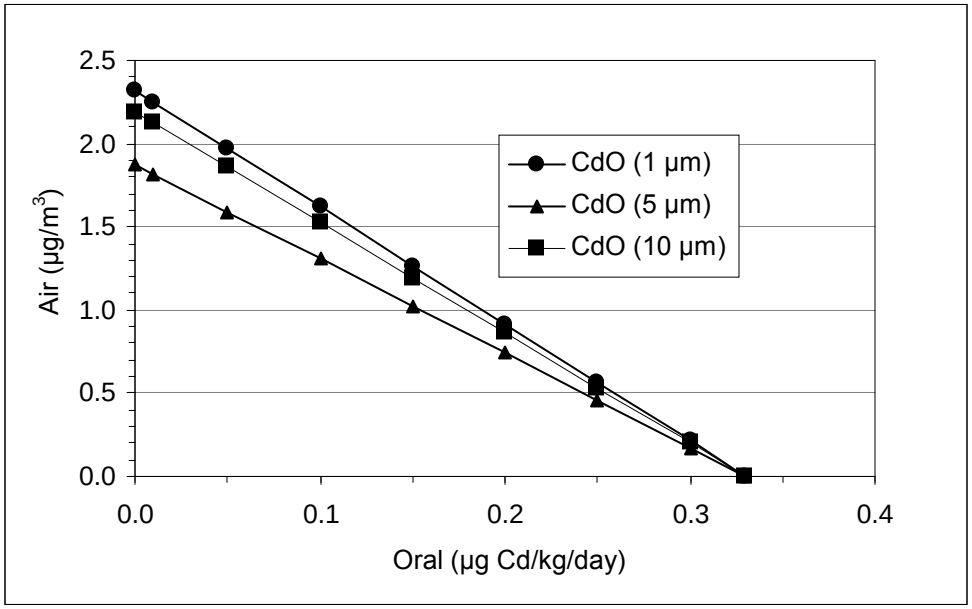
As illustrated in Figure 2-1, an airborne cadmium concentration of 1.8–2.4 μg/m^3 as cadmium oxide or 1.2–1.4 μg/m^3 as cadmium sulfide would result in a urinary cadmium level of 0.5 μg/g creatinine, assuming that there was no dietary source of cadmium. This assumption is not accurate because the diet is a significant contributor to the cadmium body burden. Thus, inhalation exposures were combined with ingestion intakes to estimate an internal dose in terms of urinary cadmium. The age-weighted average intakes of cadmium in non smoking males and females in the United States are 0.35 and 0.30 μg Cd/kg/day, respectively (0.32 μg/kg/day for males and females combined) (estimated from data in Choudhury et al. 2001). Based on the relationship predicted between chronic inhalation exposures to cadmium sulfide (activity median aerodynamic diameter [AMAD]=1 μm) and oral intakes that yield the same urinary cadmium level (Figure 2-1), exposure to an airborne cadmium concentration of 0.1 μg/m^3 and a dietary intake of 0.3 μg/kg/day would result in a urinary cadmium level of 0.5 μg/g creatinine. Dividing this cadmium air concentration (0.1 μg Cd/m^3) by an uncertainty factor of 3 for human variability and a modifying factor of 3 results in chronic-duration inhalation MRL of 0.01 μg Cd/m^3. The uncertainty factor of 3 for human variability was used to account for the possible increased sensitivity of diabetics (Åkesson et al. 2005; Buchet et al. 1990) and the modifying factor of 3 was used to account for the lack of adequate human data, which could be used to compare the relative sensitivities of the respiratory tract and kidneys. Although based on exposure to cadmium sulfide, the MRL would be protective of exposure to cadmium oxide; the pharmacokinetic models predict that exposure to 0.1 μg/m^3 as cadmium oxide (AMAD=1 μm) in combination with a dietary intake of 0.3 μg/kg/day would result in a urinary cadmium level of 0.4 μg/g creatinine.

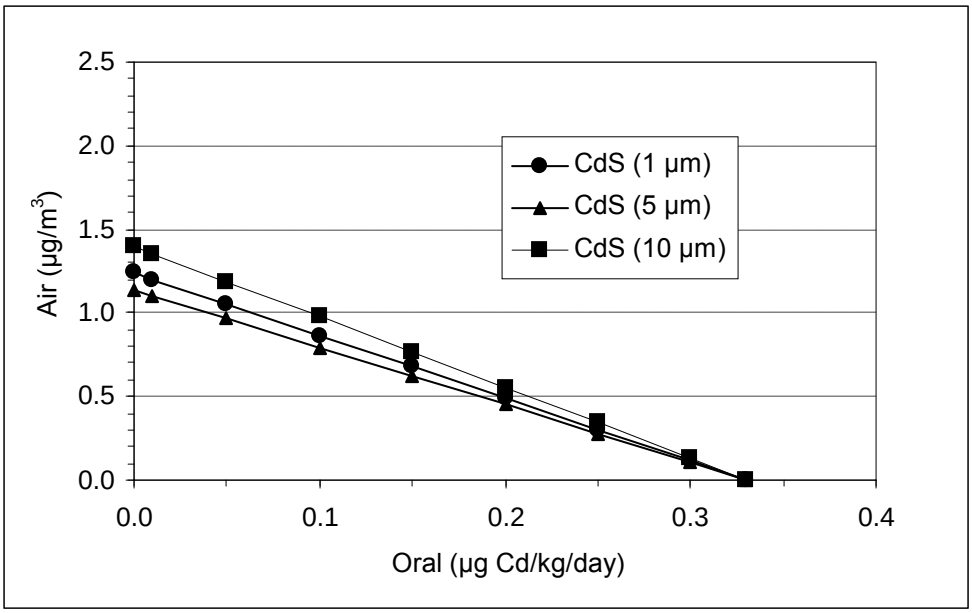
Oral MRLs

Acute-duration Oral MRL

There are no reliable studies on the acute toxicity of cadmium in humans; animal studies have identified several targets of toxicity. High exposures (>10 mg Cd/kg/day) to cadmium chloride administered via gavage or drinking water resulted in increases in hematological (increased hemoglobin, hematocrit, and erythrocytes, anemia), liver (focal necrosis and degeneration), kidney (focal necrosis of tubular epithelium), intestine (necrosis, hemorrhage, ulcers), stomach (gastritis, necrosis), neurological (decreased motor activity), and testicular (atrophy and necrosis, loss of spermatogenic elements) effects

Figure 2-1. Combined Chronic Oral Cadmium Intakes (µg/kg/day) and Inhalation Cadmium Exposures (µg/m^3) that Achieve a Urinary Cadmium Excretion of 0.5 µg/g Creatinine at Age 55 Years Predicted by the Cadmium Pharmacokinetic Model and the International Commission on Radiological Protection (ICRP) Human Respiratory Tract Model*





*The upper panel shows simulations of inhalation exposures to cadmium oxide (AMAD=1, 5, or 10 µm); the lower panel shows simulations of inhalation cadmium sulfide aerosols.

and decreases in body weight in rats and mice (Andersen et al. 1988; Basinger et al. 1988; Bomhard et al. 1987; Borzelleca et al. 1989; Dixon et al. 1976; Kotsonis and Klaassen 1977; Machemer and Lorke 1981; Sakata et al. 1988; Shimizu and Morita 1990). The NOAELs for these effects ranged from 1.12 to 65.6 mg Cd/kg/day.

Developmental effects have been observed at lower cadmium doses. Delayed ossification of the sternum and ribs was observed in the offspring of rats administered 2 mg Cd/kg/day via gavage on gestation days 7–16; at 40 mg Cd/kg/day, fused lower limbs, decreased number of live fetuses, and increased resorptions were observed (Baranski 1985). A significant increase in malformations was observed in the offspring of rats administered 18.39 mg Cd/kg/day on gestation days 6–15 (Machemer and Lorke 1981); no developmental effects were observed in the offspring of rats administered 12.5 mg Cd/kg/day via drinking water on gestation days 6–15 (Machemer and Lorke 1981).

Although the Baranski (1985) study identified the lowest LOAEL (2 mg Cd/kg/day) following acute-duration exposure, this study was not considered suitable for derivation of an MRL. The investigators noted that "a retarded process of ossification of the sternum and ribs was observed after exposure to cadmium at any of the doses used." However, the data were not shown and the statistical significance of the finding was not reported. Additionally, an intermediate-duration study conducted earlier by this investigator (Baranski et al. 1983) did not find delays in ossification in the offspring of rats administered up to 4 mg Cd/kg/day for 5 weeks prior to mating, during the 3-week mating period, and throughout gestation.

Intermediate-duration Oral MRL

- An MRL of 0.5 µg Cd/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to cadmium.

There are limited data on the toxicity of cadmium in humans following intermediate-duration exposure. Numerous animal studies have examined the systemic, immunological, neurological, reproductive, and developmental toxicity of cadmium. The most sensitive systemic effect following intermediate-duration oral exposure to cadmium appears to be damage to growing bone. Exposure to 0.2 mg Cd/kg/day as cadmium chloride in drinking water for 3–12 months resulted in decreases in bone mineral density, impaired mechanical strength of the lumbar spine, tibia, and femur bones, increased bone turnover, and increased incidence of deformed or fractured lumbar spine bone in young female rats (3 weeks of age at study initiation) (Brzóska and Moniuszko-Jakoniuk 2005d; Brzóska et al. 2004b, 2005a, 2005b, 2005c);

similar findings were observed in young male rats exposed to 0.5 mg Cd/kg/day for up to 12 months (Brzóska and Moniuszko-Jakoniuk 2005a, 2005b). Decreases in bone strength were also observed in young rats exposed to 0.8 mg Cd/kg/day as cadmium chloride in drinking water for 4 weeks (Ogoshi et al. 1989); however, no skeletal effects were observed in adult or elderly female rats exposed to doses >20 mg Cd/kg/day for 4 weeks (Ogoshi et al. 1989). Decreases in bone calcium were observed in mice undergoing repeated pregnancy/lactation periods (Bhattacharyya et al. 1988b) or ovariectomized mice (Bhaattacharyya et al. 1988c); these changes were not observed in groups not under physiological stress.

Renal effects have been observed at higher doses than the skeletal effects. Vesiculation of the proximal tubules was observed in rats exposed to 1.18 mg Cd/kg/day as cadmium chloride in drinking water for 40 weeks (Gatta et al. 1989). At approximately 3–8 mg Cd/kg/day, proteinuria, tubular necrosis, and decreased renal clearance were observed in rats (Cha 1987; Itokawa et al. 1974; Kawamura et al. 1978; Kotsonis and Klaassen 1978; Prigge 1978a). Liver necrosis and anemia (Cha 1987; Groten et al. 1990; Kawamura et al. 1978) were observed at similar cadmium doses.

Immunological effects have been observed in studies of monkeys, rats, and mice. The observed effects include increases in cell-mediated immune response in monkeys exposed to 5 mg Cd/kg/day as cadmium chloride in the diet for 10 weeks (Chopra et al. 1984), decreased humoral immune response in mice exposed to 2.8 mg Cd/kg/day as cadmium chloride in drinking water for 3 weeks (Blakley 1985), and greater susceptibility to lymphocytic leukemia virus in mice exposed to 1.9 mg Cd/kg/day as cadmium chloride in drinking water for 280 days (Blakley 1986).

Neurological effects observed in rats include decreases in motor activity at 3.1 or 9 mg Cd/kg/day (Kotsonis and Klaassen 1978; Nation et al. 1990) and increased passive avoidance at 5 mg Cd/kg/day (Nation et al. 1984). Reproductive effects (necrosis and atrophy of seminiferous tubules, decreased sperm count and motility) were observed in rats exposed to 8–12 mg Cd/kg/day (Cha 1987; Saxena et al. 1989).

A number of developmental effects have been observed in the offspring of rats exposed to cadmium during gestation and lactation. Decreases in glomerular filtration rates and increases in urinary fractional excretion of phosphate, magnesium, potassium, sodium, and calcium were observed in 60-day-old offspring of rats administered via gavage 0.5 mg Cd/kg/day on gestation days 1–21 (Jacquillet et al. 2007). Neurodevelopmental alterations have also been observed at the low maternal doses. Delays in the development of sensory motor coordination reflexes and increased motor activity were observed at 0.706 mg Cd/kg/day (gestation days 1–21) (Ali et al. 1986), decreased motor activity at 0.04 mg

Cd/kg/day (5–8 weeks of pre-gestation exposure, gestation days 1–21) (Baranski et al. 1983), decreased ambulation and rearing activity and altered ECG at 14 mg Cd/kg/day (gestation days 5–15, lactation days 2–28, postnatal days 1–56) (Desi et al. 1998) or 7 mg Cd/kg/day (F_2 and F_3 generations) (Nagymajtenyi et al. 1997) have been observed. Decreases in pup body weight were observed at ≥5 mg Cd/kg/day (Baranski 1987; Gupta et al. 1993; Kostial et al. 1993; Pond and Walker 1975) and decreases in fetal body weight or birth weight were observed at ≥2.4 mg Cd/kg/day (Petering et al. 1979; Sorell and Graziano 1990; Webster 1978; Sutou et al. 1980). Another commonly reported developmental effect was alterations in hematocrit levels or anemia in the offspring of animals exposed to ≥1.5 mg Cd/kg/day (Baranski 1987; Kelman et al. 1978; Webster 1978). Increases in the occurrence of malformations or anomalies is limited to a study by Sutou et al. (1980), which reported a significant delay in ossification in rats exposed to 10 mg Cd/kg/day.

The animal studies identify several sensitive targets of toxicity following intermediate-duration exposure to cadmium; these include skeletal mineralization in young female rats exposed for at least 3 months to 0.2 mg Cd/kg/day (Brzóska and Moniuszko-Jakoniuk 2005d; Brzóska et al. 2004b, 2005a, 2005b, 2005c), decreased glomerular filtration in young rats exposed during gestation to maternal doses of 0.5 mg Cd/kg/day (Jacquillet et al. 2007), and neurodevelopmental effects following gestational exposure to 0.04 mg Cd/kg/day (Baranski et al. 1983). Although the Baranski et al. (1983) study reported the lowest LOAEL, it was not selected as the principal study for derivation of an intermediate-duration MRL. For locomotor activity, a significant decrease in activity was observed in female offspring exposed to 0.04, 0.4, and 4 mg Cd/kg/day, as compared to controls; however, no significant differences were found between the cadmium groups despite the 100-fold difference in doses. Locomotor activity was also decreased in males exposed to 0.4 or 4 mg Cd/kg/day. For the rotorod test, a significant decrease in the length of time the rat stayed on the rotorod was observed in males exposed to 0.04 and 0.4 mg Cd/kg/day, but not to 4 mg Cd/kg/day and in females exposed to 0.4 and 4 mg Cd/kg/day; no differences between the cadmium groups were observed in the males and females. The results were not well described and the investigators did not explain the lack of dose-response of the effects or the discrepancy between genders.

The skeletal effects observed in young rats exposed to cadmium during the period of rapid skeletal growth and mineralization was selected as the critical effect. The Brzóska and associate study (Brzóska and Moniuszko-Jakoniuk 2005d; Brzóska et al. 2005a, 2005c) was selected as the principal study. In this study, groups of 40 3-week-old female Wistar rats were exposed to 0, 1, 5, or 50 mg Cd/L as cadmium chloride in drinking water for 12 months. The investigators noted that cadmium intakes were 0.059–0.219, 0.236–1.005, and 2.247–9.649 mg Cd/kg/day in the 1, 5, and 50 mg/L groups, respectively. Using

cadmium intake data presented in a figure, cadmium intakes of 0.2, 0.5, and 4 mg Cd/kg/day were estimated. Bone mineral density, bone mineral concentration, and mineralization area of the lumbar spine, femur, and total skeleton (bone mineral density only) were assessed after 3, 6, 9, or 12 months of exposure. The mechanical properties of the femur and tibia were evaluated after 12 months of exposure. Markers for bone resorption (urinary and serum levels of C-terminal cross-linking telopeptide of type I collagen [CTX]) and bone formation (serum osteocalcin, total alkaline phosphatase, and cortical bone and trabecular bone alkaline phosphatase), and serum and urinary levels of calcium were also measured at 3, 6, 9, and 12 months.

No significant alterations in body weight gain or food and water consumption were observed. Significant decreases in total skeletal bone mineral density was observed at ≥0.2 mg Cd/kg/day; the decrease was significant after 3 months in the 4 mg Cd/kg/day group, after 6 months in the 0.5 mg Cd/kg/day group, and after 9 months in the 0.2 mg Cd/kg/day group. Significant decreases in whole tibia and diaphysis bone mineral density were observed at ≥0.2 mg Cd/kg/day after 12 months of exposure. At 0.2 mg Cd/kg/day, bone mineral density was decreased at the proximal and distal ends of the femur after 6 months of exposure; diaphysis bone mineral density was not affected. At 0.5 mg Cd/kg/day, bone mineral density was decreased at the femur proximal and distal ends after 3 months of exposure and diaphysis bone mineral density after 6 months of exposure. At 4 mg Cd/kg/day decreases in femoral proximal, distal, and diaphysis bone mineral density were decreased after 3 months of exposure. Similarly, bone mineral density was significantly decreased in the lumbar spine in the 0.2 and 0.5 mg Cd/kg/day groups beginning at 6 months and at 3 months in the 4 mg Cd/kg/day group. Significant decreases in the mineralization area were observed in the femur and lumbar spine of rats exposed to 4 mg Cd/kg/day; lumbar spine bone mineral area was also affected at 0.5 mg Cd/kg/day. Significant decreases in tibia weight and length were observed at 4 mg Cd/kg/day. In tests of the mechanical properties of the tibia diaphysis, significant alterations in ultimate load, yield load, and displacement at load were observed at ≥0.2 mg Cd/kg/day; work to fracture was also significantly altered at 4 mg Cd/kg/day. In the mechanical properties compression tests of the tibia, significant alterations were observed in ultimate load, ultimate load, and stiffness at 0.2 mg Cd/kg/day; displacement at yield and work to fracture at ≥0.5 mg Cd/kg/day; and displacement at ultimate at 4 mg Cd/kg/day. Multiple regression analysis showed that the the cadmium-induced weakness in bone mechanical properties of the tibia was primarily due to its effects on bone composition, particularly the non-organic components, organic components, and the ratio of ash weight to organic weight. The mechanical properties of the femur were strongly influenced by the bone mineral density (at the whole bone and diaphysis). A significant decrease in femur length was observed at 6 months of exposure to ≥0.2 mg Cd/kg/day; however, decreases in length

were not observed at other time points in the 0.2 or 0.5 mg Cd/kg/day groups. Femur weight was significantly decreased at 4 mg Cd/kg/day. In tests of mechanical properties of the femur (neck and distal portions), decreases in yield load, ultimate load, displacement at ultimate, work to fracture (neck only), and stiffness (distal only) were observed at ≥0.2 mg Cd/kg/day. For the femoral diaphysis, significant alterations were observed for yield load, displacement at yield, and stiffness at ≥0.2 mg Cd/kg/day. Significant decreases in osteocalcin concentrations were observed in all cadmium groups during the first 6 months of exposure, but not during the last 6 months. Decreases in total alkaline phosphatase levels at 4 mg Cd/kg/day, trabecular bone alkaline phosphatase at 0.2 mg Cd/kg/day, and cortical bone alkaline phosphatase at 4 mg Cd/kg/day were observed. CTX was decreased at ≥0.2 mg Cd/kg/day. Total urinary calcium and fractional excretion of calcium were increased at ≥0.2 mg Cd/kg/day.

At the lowest dose tested, 0.2 mg Cd/kg/day, a number of skeletal alterations were observed including decreases in bone mineral density in the lumbar spine, femur, and tibia, alterations in the mechanical properties of the femur and tibia, decreases in osteocalcin levels, decreases in trabecular bone alkaline phosphatase, and decreases in CTX. Of these skeletal end points, the decrease in bone mineral density was selected as the critical effect because Brzóska et al. (2005a, 2005c) demonstrated that the bone mineral density was a stronger predictor of femur and tibia strength and the risk of fractures. As discussed in greater detail in Appendix A, available continuous models in the EPA Benchmark Dose Software (version 1.4.1c) were fit to data for changes in bone mineral density of the femur and lumbar spine in female rats resulting from exposure to cadmium in the drinking water for 6, 9, or 12 months (Brzóska and Moniuszko-Jakoniuk 2005d). The benchmark dose (BMD) and the 95% lower confidence limit (BMDL) is an estimate of the doses associated with a change of 1 standard deviation from the control. The $BMDL_{sd1}$ derived from the best fitting models for each dataset ranged from 0.05 to 0.17 mg Cd/kg/day. The $BMDL_{sd1}$ of 0.05 mg Cd/kg/day estimated from the 9-month lumbar spine data set was selected as the point of departure for the MRL. In young female rats, the process of intense bone formation occurs during the first 7 months of life (the first 6 months of exposure in this study); thereafter, the increase in bone mineral density slows. In the lumbar spine of the control group, the changes in bone mineral density at 3–6 months, 6–9 months, and 9–12 months were 15, 4, and 1%, respectively. Thus, the 9-month data may best reflect the effect of cadmium on bone mineral density during the period of rapid skeletal growth. The lumbar spine data was selected over the femur data set because trabecular bone, which is abundant in the spine, appears to be more susceptible to cadmium toxicity than cortical bone. The $BMDL_{sd1}$ was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) resulting in an intermediate-duration oral MRL of 0.5 μg Cd/kg/day.

Chronic-duration Oral MRL

- An MRL of 0.1 μg/kg/day has been derived for chronic-duration oral exposure (≥1 year) to cadmium.

The database examining the chronic toxicity of cadmium following oral exposure is extensive. Although there are some chronic studies in animals, the majority of the studies in the chronic database examine the relationship between urinary cadmium levels (or cumulative cadmium intake) and adverse health effects in the general population or in populations living in cadmium polluted areas. A variety of health effects have been observed including increased blood pressure, skeletal defects (osteoporosis, increased bone fractures, decreased bone mineral density), kidney dysfunction, and alterations in reproductive hormone levels. These environmental exposure studies strongly support the identification of bone and kidney as the most sensitive targets of chronic cadmium toxicity.

Bone effects, particularly osteomalacia and/or osteoporosis and increased bone fractures, were first reported in Japanese women living in areas with heavy cadmium contamination. Chronic cadmium exposure has been shown to play a role in this disorder, referred to as Itai-Itai disease; however, other factors such as multiple pregnancies, poor nutrition (low calories, calcium, protein, vitamin D, and iron intakes), and low zinc levels in food also play important roles in the etiology. Although a conclusive role of cadmium in Itai-Itai has not been established, several other studies have found bone defects. Observed bone effects include increased risk of bone fractures in post-menopausal women with urinary cadmium levels of >1 μg/day (approximately >0.7 μg Cd/g creatinine; Staessen et al. 1999), individuals (>50 years of age) with urinary cadmium levels of >2 μg/g creatinine (Alfvén et al. 2004), and men and women (>40 years of age) with urinary cadmium levels of 9.20 and 12.86 μg/g creatinine, respectively (Wang et al. 2003); increased risk of osteoporosis in men (>60 years of age) with urinary cadmium levels of ≥1.5 μg/g creatinine (Alfvén et al. 2000), in males and females with urinary cadmium levels of ≥10 μg/g creatinine (Jin et al. 2004b), and in males and females (>40 years of age) with urinary cadmium levels of 9.20 and 12.86 μg/g creatinine, respectively (Wang et al. 2003); and decreased bone mineral density in women with urinary cadmium levels of >0.6 μg/g creatinine (Schutte et al. 2008) and post-menopausal women with urinary cadmium levels of >20 μg/g creatinine (Nordberg et al. 2002).

Evidence of renal dysfunction in environmentally exposed populations include increases in deaths from renal dysfunction in residents living in cadmium polluted areas of Japan (Arisawa et al. 2001, 2007b; Iwata et al. 1991a, 1991b; Matsuda et al. 2002; Nakagawa et al. 1993; Nishijo et al. 1995, 2004a, 2006), increases in renal replacement therapy which is indicative of severe renal dysfunction (Hellström et al.

2001), and increases in the excretion of biomarkers of renal dysfunction in association with increased cadmium intake, increased renal cadmium concentrations, increased blood cadmium levels, and/or increased urinary cadmium concentrations (Buchet et al. 1990; Cai et al. 1990, 1992, 1998, 2001; Hayano et al. 1996; Horiguchi et al. 2004; Ishizaki et al. 1989; Izuno et al. 2000; Järup et al. 2000; Jin et al. 2002, 2004a, 2004c; Kawada et al. 1992; Kido and Nogawa 1993; Kobayashi et al. 2002a; Monzawa et al. 1998; Nakadaira and Nishi 2003; Nakashima et al. 1997; Nogawa et al. 1989; Noonan et al. 2002; Nordberg et al. 1997; Olsson et al. 2002; Oo et al. 2000; Osawa et al. 2001; Roels et al. 1981b; Suwazono et al. 2006; Teeyakasem et al. 2007; Trzcinka-Ochocka et al. 2004; Uno et al. 2005; Yamanaka et al. 1998; Wu et al. 2001). The urinary excretion of several biomarkers have been shown to increase due to cadmium-related alterations in kidney function; these biomarkers include low molecular weight proteins (e.g., β2-microglobulin, pHC, retinol binding protein), intracellular tubular enzymes (e.g., NAG), amino acids, high molecular weight proteins (e.g., albumin), metallothionein, and electrolytes (e.g., potassium, sodium, calcium). Although the more severe renal effects have been observed in populations living in highly contaminated areas (e.g., decreased glomerular filtration rate), alterations in the above biomarkers have been observed in areas not considered to be cadmium polluted. Alterations in these biomarker levels appear to be the most sensitive indicator of cadmium toxicity. Many of the studies examining biomarkers have reported significant correlations between urinary cadmium levels and biomarker levels. However, these correlations do not provide insight into exposure levels associated with renal dysfunction. In this MRL analysis, attention was given to dose-response studies examining the derived quantitative relationships between cadmium exposure and the prevalence of abnormal biomarker levels. As discussed in the inhalation MRL section, a 10% increase in the prevalence of abnormal biomarker levels (particularly β2-microglobulin, pHC, or retinol binding protein) in association with increasing cadmium exposure is generally considered to be indicative of cadmium-associated renal dysfunction in populations. However, when examining the prevalence of abnormal levels, careful consideration should be given to the response criterion (cut-off level) used in the study. A wide range of cut-off levels have been used in the environmental exposure studies. For β2-microglobulin, the most commonly used biomarker, the cut-off values ranged from 283 to 1,129 μg/g creatinine. A summary of environmental studies finding significant dose-response associations between urinary cadmium (or cumulative cadmium intake) and the prevalence of abnormal levels of urinary biomarkers of renal dysfunction is presented in Table 2-1. The adverse effect levels range from urinary cadmium levels of 1 μg/g creatinine (Järup et al. 2000) to 9.51 μg/g creatinine (Jin et al. 2004a).

Table 2-1. Summary of Human Studies Finding Dose-Response Relationships Between Biomarkers of Renal Dysfunction and Cadmium Exposure

Population	Effect biomarker	Response criterion	Adverse effect level (urinary cadmium)	Reference
General population (Japan)	Total prt β2M NAG	157.4 µg/g creat. (M) 158.5 µg/g creat. (F) 507 µg/g creat. (M) 400 µg/g creat. (F) 8.2 µg/g creat. (M) 8.5 µg/g creat. (F)	2.4 µg/g creat.[a]	Suwazono et al. 2006
General population (Belgium)	β2M RBP NAG amino acid calcium	283 µg/24 hours 338 µg/24 hours 3-6 IU/24 hours 357 mg α-N/24 hours 4-9 mmol/24 hours	1.92 µg/g creat.[b]	Buchet et al. 1990
Residents in cadmium-polluted area (China)	β2M	355 µg/g creat. (M <45 years) >2,500 µg/g creat. (M ≥45 years) 500 µg/g creat. (F)	4–7.99 µg/g creat.[c]	Cai et al. 1998
Residents in cadmium-polluted area (China)	β2M RBP albumin	300 µg/g creat. 300 µg/g creat. 15 mg/g creat.	≥5 µg/g creat.	Jin et al. 2002
Residents in cadmium-polluted area (China)	β2M NAG albumin	800 µg/g creat. 15 U/g creat. 20 mg/g creat.	9.51 µg/g creat.	Jin et al. 2004a
Residents in cadmium-polluted area (China)	β2M	800 µg/g creat.	2–4 µg/g creat.[c]	Nordberg et al. 1997
Residents in cadmium-polluted area (Japan)	β2M	1,000 µg/g creat.	6.9 µg/g creat.	Cai et al. 2001
Residents in cadmium-polluted area (Japan)	β2M	1,000 µg/g creat. (M,F)	Cadmium intake: 150 µg/day	Nogawa et al. 1989; Kido and Nogawa 1993
Residents in cadmium-polluted area (Japan)	β2M	1,129 µg/g creat. (M) 1,059 µg/g creat. (F)	4–4.9 µg/g creat.[c]	Ishizaki et al. 1989; Hayano et al. 1996

Table 2-1. Summary of Human Studies Finding Dose-Response Relationships Between Biomarkers of Renal Dysfunction and Cadmium Exposure

Population	Effect biomarker	Response criterion	Adverse effect level (urinary cadmium)	Reference
Residents in cadmium-polluted area (Thailand)	β2M	400 µg/g creat.	6–10 µg/g creat.	Teeyakasem et al. 2007
Residents in cadmium-polluted area (includes occupationally exposed subjects (Sweden)	pHC	7.1 mg/g creat. (M) 5.3 mg/g creat. (F)	1 µg/g creat.[d]	Järup et al. 2000

[a]Mean urinary cadmium level
[b]>10% prevalence of abnormal β2-microglobulin, retinal binding protein, amino acid, and calcium values at 3.05, 2.87, 2.74, 4.29, or 1.92 µg/24 hours, respectively.
[c]Urinary cadmium level associated with an approximate doubling of prevalence of abnormal β2-microglobulin levels
[d]The European Chemicals Bureau (2007) recalculated this value (using raw data from Järup et al. 2000) to account for differences in age of the reference population and study population; based on these recalculations, a doubling of the probability of abnormal pHC values would occur at 2.62 µg/g creatinine for the total population and a 0.5 µg/g creatinine for the environmentally exposed population.

AAP = alanine aminopeptidase; β2M = β2-microglobulin; creat. = creatinine; F = female; M = male; NAG = N-acetyl-β-glucosaminidase; pHC = human complex-forming glycoprotein, also referred to as α1M; RBP = retinol binding protein

The adverse effect levels for renal effects were similar to those observed for skeletal effects. Because the renal effects database is stronger, it was used for derivation of a chronic-duration oral MRL for cadmium. Several approaches were considered for derivation of the MRL: (1) NOAEL/LOAEL approach using a single environmental exposure study finding an increased prevalence of abnormal renal effect biomarker levels, (2) selection of a point of departure from a published benchmark dose analysis, or (3) selection of a point of departure based on an analysis of the dose-response functions from a number of environmental exposure studies.

In the first approach, all studies in which individual internal doses for subjects were estimated based on urinary cadmium were considered. The Järup et al. (2000) study is selected as the principal study because it identified the lowest adverse effect level (Table 2-1). In this study, 1,021 individuals living near a nickel-cadmium battery factory (n=799) or employed at the factory (n=222) were examined. The mean urinary cadmium concentrations were 0.81 μg/g creatinine in men and 0.65 μg/g creatinine in women. A significant association was found between urinary cadmium concentrations and urinary pHC levels, after adjustment for age; the association remained statistically significant after removal of the cadmium workers from the analysis. The investigators estimated that a urinary cadmium level of 1 μg/g creatinine would be associated with a 10% increase in the prevalence of abnormal pHC levels above background prevalence (approximately a 10% added risk). However, the European Chemicals Bureau (2007) recalculated the probability of HC proteinuria because the reference population and the study population were not matched for age (40 versus 53 years, respectively). They estimated that the probability of HC proteinuria (13%) would be twice as high as the reference population at a urinary cadmium concentration of 0.5 μg/g creatinine.

The second approach involves the evaluation of five published benchmark dose analyses. The benchmark doses and the lower 95% confidence interval of the benchmark dose (BMDL) for low molecular weight proteinuria are presented in Table 2-2 (benchmark doses and BMDLs for all effect parameters are presented in Table 3-8 in the toxicological profile). The BMDL values corresponding to a 10% increase in the prevalence of low molecular weight proteinuria above background (excess risk) ranged from 0.7 μg/g creatinine (Uno et al. 2005) to 9.9 μg/g creatinine (Kobayashi et al. 2006). Both studies examined populations living in non-cadmium polluted areas of Japan and used β2-microglobulin as the effect biomarker. The large difference in cut-off values (233 versus 784 μg/g creatinine) likely contributed to the order of magnitude difference in BMDLs. The $BMDL_{10}$ of 0.7 μg/g creatinine is supported by the Suwazono et al. (2006) benchmark dose analysis, which found a similar $BMDL_{10}$ (0.81 μg/g creatinine) using pHC as the effect biomarker. The Uno et al. (2005) study examined 410 men

Table 2-2. Selected Benchmark Dose Estimations of Urinary Cadmium Levels Associated with Increases in the Prevalence of Low Molecular Weight Proteinuria

Study population	Effect biomarker	Response criterion	BMD model	5% BMR		10% BMR		Reference
				BMD	BMDL	BMD	BMDL	
General population (Sweden)	pHC	6.8 mg/g creat. (95% cut-off)[a]		0.63 (F)	0.49 (F)	1.05 (F)	0.81 (F)	Suwazono et al. 2006
Residents in cadmium-polluted and non-polluted areas (Japan)	β2M	507 µg/g creat. (M) 400 µg/g creat. (F) (84% cut-off)[b]	Quantal linear model	1.5 (M) 1.4 (F)	1.2 (M) 1.1 (F)	3.1 (M) 2.9 (F)	2.5 (M) 2.3 (F)	Shimizu et al. 2006
		994 µg/g creat. (M) 784 µg/g creat. (F) (95% cut-off)[c]		2.3 (M) 1.7 (F)	1.8 (M) 1.4 (F)	4.7 (M) 3.5 (F)	3.7 (M) 2.9 (F)	
General population (Japan)	β2M	507 µg/g creat. (M) 400 µg/g creat. (F) (84% cut-off)[d]	Log-logistic model	2.9 (M) 3.8 (F)	2.4 (M) 3.3 (F)	5.0 (M) 6.6 (F)	4.0 (M) 5.5 (F)	Kobayashi et al. 2006
		994 µg/g creat. (M) 784 µg/g creat. (F) (95% cut-off)[e]		6.4 (M) 8.7 (F)	4.5 (M) 7.3 (F)	10.2 (M) 12.0 (F)	7.1 (M) 9.9 (F)	
General population (Japan)	β2M	233 µg/g creat. (M) 274 µg/g creat. (F) (84% cut-off)[f]	Quantal linear model	0.5 (M) 0.9 (F)	0.4 (M) 0.8 (F)	1.0 (M) 1.8 (F)	0.7 (M) 1.3 (F)	Uno et al. 2005
Residents in cadmium highly, or moderately polluted area (China)	β2M	800 µg/g creat. (95% cut-off)[g]	Quantal linear logistic regression model	5.86 (M) 9.98 (F)	4.74 (M) 8.47 (F)			Jin et al. 2004b
	RBP	0.300 mg/g creat. (95% cut-off)[g]		5.99 (M) 9.03 (F)	4.87 (M) 7.63 (F)			

[a]95th percentile of effect biomarkers on the "hypothetical" control distribution at a urinary cadmium level of zero.
[b]84% upper limit values from a group of 424 males and 1,611 females who did not smoke and lived in three different cadmium nonpolluted areas.
[c]95% upper limit values from a group of 424 males and 1,611 females who did not smoke and lived in three different cadmium nonpolluted areas.
[d]84% upper limit value of the target population of people who have not smoked.
[e]95% upper limit value of the target population of people who have not smoked.
[f]84% upper limit value of the target population.
[g]95% upper limit value from a control group 98 males and 155 females living in a cadmium nonpolluted area.

BMD = benchmark dose; BMDL = benchmark dose low; BMR = benchmark response; β2M = β2-microglobulin; creat. = creatinine; F = female; M = male; NAG = *N*-acetyl-β-D-glucosaminidase; NAG-B = *N*-acetyl-β-D-glucosaminidase's isoform B; RBP = retinol binding protein

and 418 women (aged 40–59 years) living in three areas of Japan without any known environmental cadmium pollution. Mean urinary cadmium concentrations were 1.3 and 1.6 μg/g creatinine in men and women, respectively. Cut-off levels for β2-microglobulin were 233 and 274 μg/g creatinine in males and females; these values represent the 84% upper limit values calculated from the target population assuming a log normal distribution.

The third approach involved a meta-analysis of selected environmental exposure dose-response studies. Studies were selected for inclusion in this analysis based on the following qualitative criteria: (1) the study measured urinary cadmium as indicator of internal dose; (2) the study measured reliable indicators of low molecular weight (LMW) proteinuria; (3) a dose-response relationship was reported in sufficient detail so that the dose-response function could be reproduced independently; (4) the study was of reasonable size to have provided statistical strength to the estimates of dose-response model parameters (i.e., most studies selected included several hundred to several thousand subjects); and (5) major co-variables that might affect the dose-response relationship (e.g., age, gender) were measured or constrained by design and included in the dose-response analysis. No attempt was made to weight selected studies for quality, statistical power, or statistical uncertainty in dose-response parameters. Studies using a cut-off value for β2-microglobulin of ≥1,000 μg/g creatinine were eliminated from the analysis based on the conclusions of Bernard et al. (1997) that urinary β2-microglobulin levels of 1,000–10,000 μg/g creatinine were indicative of irreversible tubular proteinuria, which may lead to an age-related decline in GFR. Additionally, an attempt was made to avoid using multiple analyses of the same study population.

The individual dose-response functions from each study were implemented to arrive at estimates of the internal dose (urinary cadmium expressed as μg/g creatinine) corresponding to probabilities of 10% excess risk of low molecular weight proteinuria (urinary cadmium dose, UCD_{10}). Estimates were derived from the seven environmental exposure studies listed in Table 2-3. When available, male and female data were treated separately; thus, 11 dose-response relationships were analyzed. For studies that did not report the UCD_{10}, the value was estimated by iteration of the reported dose response relationship for varying values of urinary cadmium, until an excess risk of 10% was achieved:

$$ER = \frac{P(d) - P(0)}{1 - P(0)}$$

Table 2-3. Selected Studies of Dose-Response Relationship for Cadmium-Induced Low Molecular Weight Proteinuria

Reference	Population	Number	Effect biomarker	Response criterion	Dose-response model	UCD_{10} (µg/g creat.)
Buchet et al. 1990	General population (Belgium)	1,699 M 2,080 F	β2M	283 µg/24 hours	Logistic[a]	2.51 M 1.44 F
Suwazono et al. 2006	General population (Sweden)	790 F	pHC	3.6 U/g creat.	Logistic	0.81
Järup et al. 2000	Residents in cadmium polluted area (Sweden)	1,465 M,F	pHC	7.1 mg/g creat. M 5.3 mg/g creat. F	Logistic	0.6
Kobayashi et al. 2006	General population (Japan)	1,114 M 1,664 F	β2M	507 µg/g creat. M 400 µg/g creat. F	Log-logistic	5.0 M 6.6 F
Shimizu et al. 2006	Residents in cadmium polluted and non-polluted areas (Japan)	1,865 M 1,527 F	β2M	507 µg/g creat. M 400 µg/g creat. F	Log-logistic	5.1 M 4.2 F
Jin et al. 2004c	Residents in cadmium polluted or non-polluted area (China)	790 M,F	β2M	800 µg/g creat.	Logistic	9.5 M 15.4 F
Wu et al. 2001	Residents in cadmium polluted area (China)	247 M,F	β2M	800 µg/g creat. M 900 µg/g creat. F	Linear[b]	3.75

[a]Digitized from Figure 2 in Lauwerys et al. 1991
[b]Digitized from Figure 2 in Wu et al. 2001

β2M = β2-microglobulin; creat. = creatinine; F = female; M = male; pHC = human complex-forming glycoprotein (also referred to as α1-microglobulin); UCD_{10} = urinary cadmium level corresponding to a probability of 10% excess risk of low molecular weight proteinuria

where ER is the excess risk, P(d) is the probability of low molecular weight proteinuria associated with a given internal (i.e., urinary cadmium) dose, and P(0) is the background probability (i.e., the probability predicted by the dose-response model when urinary cadmium was zero). For studies that reported the dose-response relationship graphically, but did not report the actual dose-response function, a function was derived by least squares fitting based on data from a digitization of the graphic.

Aggregate UCD_{10} estimates and the estimates stratified by location (i.e., Europe, Japan, China) are presented in Figure 2-2. The lowest UCD_{10} (1.34 μg/g creatinine) was estimated from the European database and the 95% lower confidence limit on this UCD_{10} ($UCDL_{10}$) of 0.5 μg/g creatinine was considered as a potential point of departure for the MRL.

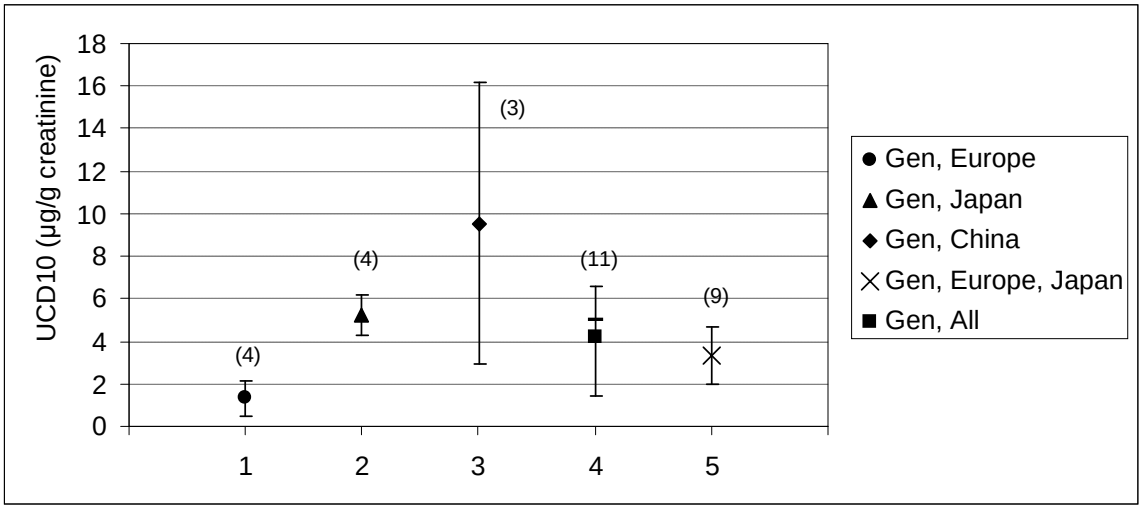
Points of departure selected using the three different approaches are similar: 0.5 μg/g creatinine from the Järup et al. (2000) study (using the European Chemicals Bureau 2007 recalculation), 0.7 μg/g creatinine from the Uno et al. (2005) benchmark dose analysis, and 0.5 μg/g creatinine from the dose-response analysis. The third approach (meta-analysis of environmental exposure studies) was selected for the derivation of the MRL because it uses the whole dose-response curves from several studies rather than data from a single study.

The $UCDL_{10}$ of 0.5 μg/g creatinine was transformed into estimates of chronic cadmium intake (expressed as μg Cd/kg/day) that would result in the $UCDL_{10}$ at age 55 (approximate age of peak cadmium concentration in the renal cortex associated with a constant chronic intake; Figure 2-3). The dose transformations were achieved by simulation using a modification of the Nordberg-Kjellström model (Kjellström and Nordberg 1978). The following modifications (Choudhury et al. 2001; Diamond et al. 2003) were made to the model: (1) the equations describing intercompartmental transfers of cadmium were implemented as differential equations in Advanced Computer Simulation Language (acslXtreme, version 2.4.0.9); (2) growth algorithms for males and females and corresponding organ weights (O'Flaherty 1993) were used to calculate age-specific cadmium concentrations from tissue cadmium masses; (3) the cadmium concentration in renal cortex (RC, μg/g) was calculated as follows:

$$RC = 1.5 \cdot \frac{K}{KW}$$

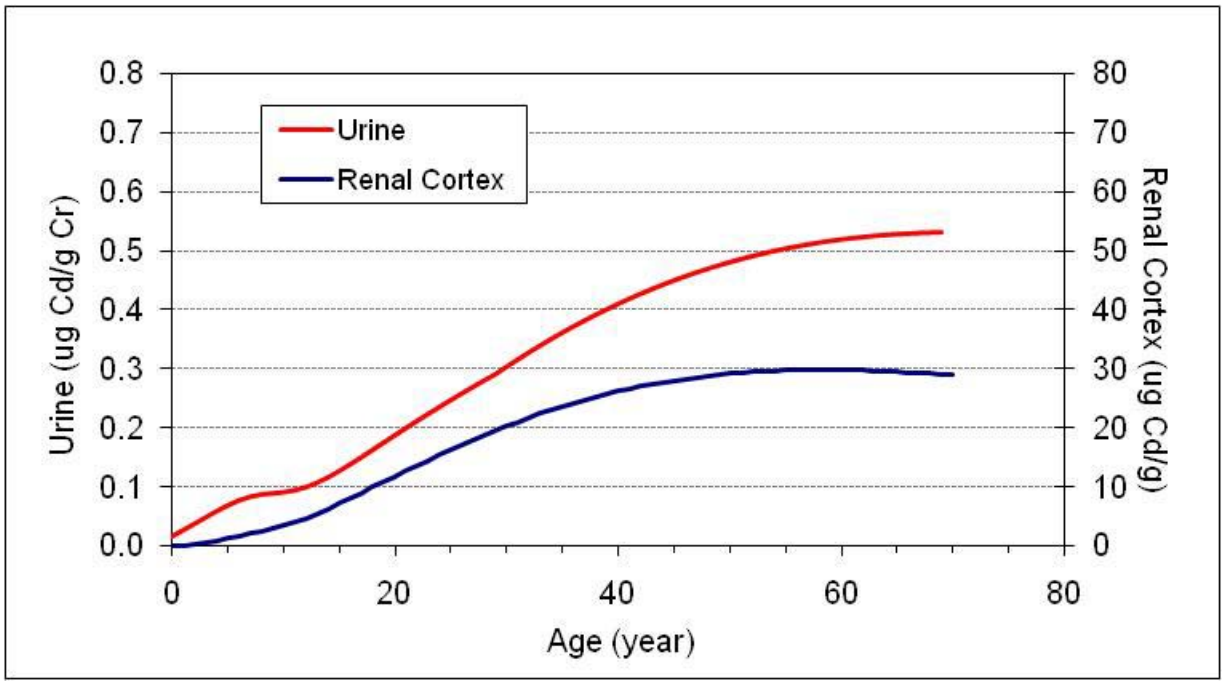
where K is the age-specific renal cadmium burden (μg) and KW is the age-specific kidney wet weight (g) (Friberg et al. 1974).

Figure 2-2. Estimates of the UCD_{10} from Environmental Exposure Dose-Response Studies*



*Estimates of urinary cadmium concentrations (µg/g creatinine) associated with a 10% excess risk of urinary β2-microglobulin (UCD_{10}) using data from European, Japanese, and Chinese studies. For the aggregate of studies (plot #4), the mean (-), median (▪), and 95% confidence intervals (CI) on the median are shown. All other plots show the mean and 95% CI on the mean. Numbers in parenthesis are the number of estimates of the UCD_{10}.

Figure 2-3. Urinary Cadmium (µg/g creatinine) and Renal Cortex Cadmium Concentration (µg/g wet tissue) Predicted by the Cadmium Pharmacokinetic Model*



*Shown is a simulation of peak renal cadmium concentration (at age 55) in females based on a chronic intake of 0.33 µg Cd/kg/day.

(4) the rate of creatinine excretion (e.g., Cr_{ur}, g creatinine/day) was calculated from the relationship between lean body mass (LBM) and Cr_{ur}; and (5) absorption of ingested cadmium was assumed to be 5% in males and 10% in females. The rate of creatinine excretion (e.g., Cr_{ur}, g creatinine/day) was estimated from the relationship between LBM (kg) and Cr_{ur}:

$$LBM = 27.2 \cdot Cr_{ur} + 8.58$$

where the constants 27.2 and 8.58 are the sample size-weighted arithmetic mean of estimates of these variables from eight studies reported in (Forbes and Bruining 1976). Lean body mass was estimated as follows (ICRP 1981):

$$LBM = BW \cdot 0.85, adult\ females$$
$$LBM = BW \cdot 0.88, adult males$$

where the central tendency for adult body weight for males and females were assumed to be 70 and 58 kg for adult European/American males and females, respectively.

Dose units expressed as cadmium intake (μg/kg/day), urinary cadmium excretion (μg/g creatinine), or kidney tissue cadmium (μg/g cortex) were interconverted by iterative pharmacokinetic model simulations of constant intakes for the life-time to age 55 years, the age at which renal cortex cadmium concentrations are predicted to reach their peak when the rate of intake (μg/kg/day) is constant.

The dietary cadmium intakes which would result in urinary cadmium levels of 1.34 and 0.5 μg/g creatinine (UCD_{10} and $UCDL_{10}$) are 0.97 and 0.33 μg/kg/day in females and 2.24 and 0.70 μg/kg/day in males. The dietary concentration associated with the $UCDL_{10}$ in females (0.33 μg/kg/day) was divided by an uncertainty factor of 3 for human variability resulting in a chronic-duration oral MRL of 0.1 μg/kg/day ($1x10^{-4}$ mg Cd/kg/day). The UCD is based on several large-scale environmental exposure studies that likely included sensitive subpopulations; however, there is concern that individuals with diabetes may be especially sensitive to the renal toxicity of cadmium (Åkesson et al. 2005; Buchet et al. 1990) and diabetics were excluded from a number of the human studies, and thus, an uncertainty factor of 3 was used.

The urinary cadmium point of departure used as the basis of the MRL (0.5 μg/g creatinine) is approximately 2-fold higher than the geometric mean urinary cadmium concentrations in the United

States, which is 0.261 µg/g creatinine for adults 20 years and older (CDC 2005). The MRL of 0.1 µg/kg/day is lower than the estimated age-weighted cadmium intake of 0.3 µg/kg/day (estimated from data in Choudhury et al. 2001). Because this intake is derived from the cadmium dietary exposure model which estimates food cadmium concentrations from national survey data and food consumption patterns, it should not be considered a precise value. A better comparison would be between the mean urinary cadmium concentration in adults living in the United States (0.261 µg/g creatinine) and the MRL expressed as a urinary cadmium concentration (0.2 µg/g creatinine).