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## Cadmium Exposure and Nephropathy in a 28-Year-Old Female Metals Worker

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A 28-year-old female presented for evaluation of left flank pain and polyuria after having been exposed to cadmium in the jewelry manufacturing industry for approximately 3 years. This patient possessed both elevated 24-hr urinary  $\beta_2$ -microglobulin and elevated blood cadmium levels. Approximately 6 months after initial presentation, the patient resigned from her job due to shortness of breath, chest pain, and anxiety. Exposure to cadmium in the jewelry industry is a significant source of occupational cadmium exposure. Other occupational sources include the manufacture of nickel-cadmium batteries, metal plating, zinc and lead refining, smelting of cadmium and lead, and production of plastics. Cadmium is also an environmental pollutant that accumulates in leafy vegetables and plants, including tobacco. Major toxicities anticipated from cadmium exposure involve the renal, pulmonary, and, to a lesser extent, gastrointestinal systems. These include the development of renal proximal tubular dysfunction, glomerular damage with progressive renal disease, and respiratory symptoms including pneumonitis and emphysema. Low-level cadmium exposure has also been associated with increased urinary calcium excretion and direct bone toxicity, effects that recent research suggests may result in the development of osteoporosis. The body burden of cadmium, over half of which may reside in the kidneys, is most often measured through the use of urinary cadmium levels. Blood cadmium measurements generally reflect current or recent exposure and are especially useful in cases with a short exposure period and only minimal accumulation of cadmium in the kidneys. Both  $\beta_2$ -microglobulin and  $\alpha_1$ -microglobulin serve as organ-specific, early-effect biomarkers of tubular proteinuria and thus play a role in identifying early signs of cadmium-induced renal damage in those with potential exposures. In addition to ensuring workplace compliance with Occupational Safety and Health Administration-mandated monitoring and screening measures, it is prudent for those with cadmium exposure to maintain adequate intake of both iron and calcium, appropriate measures even in the absence of exposure. **Key words:** cadmium, kidney disease, occupational disease, osteoporosis. *Environ Health Perspect* 110:1261–1266 (2002). [Online 29 October 2002] <http://ehpnet1.niehs.nih.gov/docs/2002/110p1261-1266wittman/abstract.html>

The patient was a 28-year-old white female who was referred to an academic occupational/environmental medicine center (the “center”) in April 2000 for evaluation of cadmium exposure. She had been working for 3 years as an employee of a metals shop that specialized in producing materials used in the jewelry manufacturing industry. Her specific job duties involved taking precious metals (gold, silver, etc.) and mixing them with a portion of solid cadmium with a metal stick. She would then melt the metal-cadmium mixture. Once it hardened, the patient would blast the alloy with liquid nitrogen, add brighteners and other chemicals, and sift the powdered mixture to produce a gold solder past product. She described being exposed to the metal mixture during various stages in the process in solid, fume, and powdered forms. She wore eye protection, but was not required to wear nor was

provided with respiratory protection, gloves, or other garment protection. The patient recalled that, after work, her nasal passages were frequently coated with brown waxy soot.

In August of 1999, the patient began to notice left flank pain and increased frequency of urination. She was treated for an upper respiratory infection but continued to notice persistence in her symptoms. Two months later, a supervisor visiting from another company warned her that she was not wearing proper protective equipment and that, among the metals she was being exposed to, cadmium and copper were particularly dangerous. The patient reported this to her primary physician, who then ordered blood cadmium and copper levels. Her blood cadmium and copper levels were 19.2  $\mu\text{g/L}$  and 1.88  $\mu\text{g/mL}$ , respectively (normal levels of < 5.0  $\mu\text{g/L}$  and 0.75–1.45  $\mu\text{g/mL}$ , respectively). She alerted her company,

which reassigned her to a position free of direct work with cadmium. A renal ultrasound in November 1999 was within normal limits. Repeat blood cadmium in late November 1999 showed a level of 26  $\mu\text{g/L}$ . Her 24-hr urinary  $\beta_2$ -microglobulin level was 0.16  $\text{mg/L}$  (normal < 0.12  $\text{mg/L}$ ). Subsequent testing (Figure 1) showed blood cadmium and urinary  $\beta_2$ -microglobulin levels that fluctuated at high or high normal levels before declining.

The patient developed symptoms of shortness of breath, chest pain, and anxiety and resigned from her job in January 2000. Her physical examination at the center showed a blood pressure of 124/80 and no remarkable findings with respect to her cardiovascular, pulmonary, skin, oral, gastrointestinal, or neurologic systems. A chest X ray and spirometry were within normal limits. A repeat 24-hr urinary  $\beta_2$ -microglobulin level was 0.07  $\text{mg/L}$ .

### Case Discussion

This patient, a premenopausal, nonsmoking female, was clearly exposed occupationally to cadmium and had evidence of having accumulated a significant cadmium body burden as well as a transient cadmium-related nephropathy. Over a 3-year period during which she executed tasks that placed her at risk for both oral and respiratory exposures to a number of metals, including cadmium, without adequate personal protective equipment, the patient performed mixing, a close-contact manual process that required frequent handling of powder and paste, as well as melting and blasting, both temperature-driven,

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We thank K. Cassidy, who coordinated the data extraction for this case.

This work was supported by an Education and Research Center grant from the National Institute for Occupational Safety and Health to the Harvard School of Public Health and by National Institute of Environmental Health Sciences Center grant ES00002.

Received 28 May 2002; accepted 10 September 2002.

fume-generating processes involving cadmium and other metals. The patient's own description of brown soot habitually coating her nasal passages after her shift conveys a sense of the degree of these exposures.

**Occupational sources of cadmium.** Previous cases of cadmium overexposure in the jewelry-making industry have been reported. Baker et al. (1979) described cadmium intoxication secondary to cadmium oxide exposure in jewelry brazers and solderers. The symptom profile of those affected matched that of the patient and included the presence, at a significant level, of dysuria (painful or difficult urination), polyuria (copious and hence frequent urination), dyspnea (shortness of breath, difficult or labored breathing), chest pain, irritability, fatigue, headache, and dizziness (Baker et al. 1979).

In general, the use of cadmium in a variety of industries has steadily climbed over the last 40 years, but actual occupational exposures have declined markedly over the last 20 years following the adoption of more stringent exposure limits in most industrialized nations (Penney 1993). Nonetheless, it has been estimated that approximately 512,000 workers in the United States are in environments each year where a cadmium exposure may occur (ATSDR 1999). Table 1 provides a summary of available information on the range of occupations with exposures to cadmium, presented in relative order of potential exposure, from highest to lowest.

**Environmental sources of cadmium.** Cadmium is a ubiquitous environmental pollutant (Staessen et al. 1999) that has no known biological function in humans. Cadmium occurs in nature as a natural component of rock and sediment, soil and dust, air and water, and plant and animal tissues (Pinot 2000). Of the estimated 25,000–30,000 tons of cadmium released into the environment each year, approximately one-half is liberated from the weathering of rocks into river and ocean water. Forest fires and volcanoes also release some cadmium into the air (ATSDR 1999). Anthropogenic cadmium resulting from the industrial production of batteries, plastics, alloys, and synthetic materials is released into the environment in the form of atmospheric emissions (70%), liquid effluents,

sludges, and solid waste (Pinot 2000). The release of cadmium due to human activities is estimated at 4,000–13,000 tons/year, with mining and the burning of fossil fuel serving as the major contributors (ATSDR 1999). Polluted industrial sites are continuous sources of environmental cadmium; leaching of cadmium into groundwater and distribution of metal-loaded soil particles by lateral wind erosion are two primary mechanisms (Staessen et al. 1999).

Cadmium itself tends to accumulate in leafy vegetables and plants, including tobacco, that are grown on contaminated soils rather than in seed or root crops (Pinot 2000). As a result, even individuals who do not encounter cadmium in the workplace are at risk of exposure. Levels of such exposures have been rising, as reflected by a study in France demonstrating a 10-fold rise in the concentration of cadmium in human bones during the 20th century (Jaworowski et al. 1985; Staessen and Lauwerys 1993). In the United States and Europe, the average uptake via ingestion in unpolluted areas has been estimated to be from 10–25 µg/day (Pinot 2000). High fiber diets and a diet rich in shellfish increase the dietary intake substantially, although absorption may not increase proportionally.

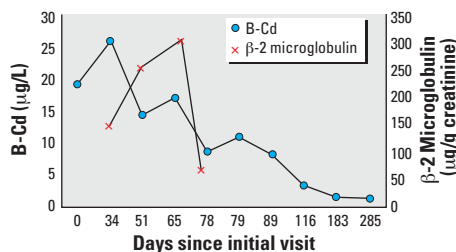
Even though the gastrointestinal absorption of cadmium is only a few percent, the absorption of cadmium in the lungs is 10–50%. As a consequence, cigarette smoking is a major route for nonoccupational lung exposure. One cigarette contains about 1–2 µg of cadmium, roughly 10% of which is inhaled; based upon a 50% absorption rate, a person who smokes 20 cigarettes (1 pack) per day will absorb about 1–3 µg of cadmium. Smokers, on average, have 4–5 times higher (~1.5 µg/L) blood cadmium (B-Cd) levels than nonsmokers. Interestingly, despite the high cadmium content of cigarette smoke, there is little evidence for significant exposure

from passive smoking (ATSDR 1999; Elinder et al. 1983; Ikeda et al. 1999).

**Biologic testing.** Due to the close relationship between the cadmium concentration in the urine and the kidney, urinary cadmium (U-Cd) has been used as an estimate of the body burden of cadmium (Järup et al. 1997). This is sensible because after long-term exposure, the kidneys may contain more than half of the body burden of cadmium (Börjesson et al. 2001). In cases of renal tubular damage, however, the use of U-Cd for estimating dose may be problematic, because although the urinary excretion of cadmium is initially increased after renal injury, at a later stage, urinary excretion of cadmium decreases once overall kidney cadmium burden declines (Järup et al. 1998b, 2000; Moon et al. 1999).

In currently exposed workers, U-Cd is considered to be more reflective of the total body burden than B-Cd (Penney 1993). Nonetheless, B-Cd levels are generally regarded as a reflection of current or recent exposure and are especially useful in cases with a short exposure period and only minimal accumulation of cadmium in the kidneys (Järup et al. 1998b; Moon et al. 1999). B-Cd levels, however, readily fluctuate due to recent exposures, including smoking (Järup et al. 1997).

Elevations in B-Cd levels can be measured within weeks after an acute exposure, as they were in the case of our patient. If exposure continues, B-Cd remains relatively stable and can be used as a time-averaged estimate of dose; within a few months, the B-Cd reaches a concentration that corresponds to the intensity of the exposure (Järup et al. 1998b, 2000). Following the cessation of exposure, the decay of B-Cd can be described by the sum of two exponential functions. A fast component, with an initial half-life of about 2 months (Börjesson et al. 2001), 2–3 months (Järup et al. 1998b), or 3–4 months (Järup et al. 1997), reflects recent exposure. A slow



**Figure 1.** Biologic exposure measurements for the patient.

**Table 1.** Industries and job tasks associated with cadmium exposure.

Industry-associated exposure	Job task
Nickel-cadmium battery manufacturing	Plate-making, impregnation, assembly
Zinc refining/ cadmium smelting	Multiple stages of cadmium production
Plastics: cadmium-containing pigment production	Crushing, milling, wet system processes
Plastics: dry color formulating	Material handling, mixing, grinding, cleaning
Plastics, PVC: cadmium-based stabilizer production	Drying, crushing, blending, oxide charging
Metal plating: automotive, electronic, aerospace, marine (35% of all worldwide cadmium use)	Mechanical plating or electroplating
Alloy production with copper, zinc, lead, silver, tin	Melting, casting
Lead smelting and refining	Material handling, casting, refining, furnace operation
Iron and steel production	Welding, furnace/cupola operation, maintenance
Coal-fired electrical utilities, waste incineration	Inspection, maintenance, malfunction of boilers/ovens
General industry (occupational history should include queries on these tasks)	Chemical mixers, electroplaters, furnace operators/ molders, kiln/kettle operators, heat-treaters, equipment cleaners, metal machine operators, painters, maintenance workers, mechanics, welders, brazers, solderers
Other occupations	Jewelry producers, ceramists, artists, theater crafts

Data from Penney (1993).

component, with a half-life of several decades, reflects long-term exposure (Börjesson et al. 2001) and, much like U-Cd, can reflect the body burden several years after the end of exposure (Järup et al. 1998a, 2000). This indicates that both B-Cd and U-Cd are valid as indicators of long-term environmental exposure of the general population to cadmium. Several studies have supported this assumption and the close correlation between B-Cd and U-Cd in such circumstances (Liu et al. 2001; Moon et al. 1999; Roels et al. 1993). In fact, many years after an exposure, B-Cd is likely better than U-Cd as an indicator of previous exposure because if tubular damage has occurred, U-Cd measurements may be difficult to interpret (Börjesson et al. 2001; Ikeda et al. 1999; Järup et al. 2000). The distributions of B-Cd and U-Cd values seen in the general U.S. population are shown in Tables 2 and 3.

The Occupational Safety and Health Administration's (OSHA) revised limits for workplace biomonitoring of cadmium have been in operation since 1 January 1999. Based on blood testing for cadmium and urine monitoring for cadmium and  $\beta_2$ -microglobulin, OSHA has created three levels of exposure that are described in Table 4. Medical removal is mandatory for Category C designations, although with respect to  $\beta_2$ -microglobulin,

medical removal is mandatory only when  $\beta_2$ -microglobulin > 750  $\mu\text{g/g}$  creatinine and either U-Cd > 3  $\mu\text{g Cd/g}$  creatinine or B-Cd > 5  $\mu\text{g/L}$  whole blood. Return to work is permissible when Category A biomonitoring criteria have been met and the actions described in Table 5 have been completed.

Recent studies have indicated that elevated protein HC ( $\alpha_1$ -microglobulin) is an earlier and more sensitive indicator of cadmium-induced renal damage than  $\beta_2$ -microglobulin (Alfvén et al. 2000; Hunder et al. 2001; Ikeda et al. 1999; Järup and Elinder 1993; Järup et al. 2000). Given its stability in the low pH of urine, in contrast to  $\beta_2$ -microglobulin, protein HC appears to be a more practical marker of renal tubular damage. Within the past decade, investigators (Järup et al. 2000; Jaworowski et al. 1985; Staessen et al. 1999) have found similar protein HC reference values (95% cutoff points) for determining the presence of tubular proteinuria, namely 0.6 mg protein HC/mmol creatinine for women and 0.8 mg protein HC/mmol creatinine for men. Currently, however, there are no firmly established protein HC reference cutoff values for tubular dysfunction, and as such, despite the promise seen with protein HC use, a  $\beta_2$ -microglobulin level > 300  $\mu\text{g/g}$  creatinine will continue to maintain its acceptance as a reliable indicator of functional damage to the proximal

convoluted tubules in the kidneys (Järup et al. 2000; Moon et al. 1999).

Our patient possessed a significant body burden of cadmium. Her peak B-Cd measurement was 26  $\mu\text{g/L}$ , considerably above the OSHA Category C limit of 10  $\mu\text{g/L}$  and significantly above the cadmium levels in the general population. This B-Cd level mandated medical removal until biomonitoring revealed that Category A criteria were fulfilled (Table 4).

**Renal effects.** The patient's urinary level of  $\beta_2$ -microglobulin also exceeded reference values. This elevation in  $\beta_2$ -microglobulin provides evidence that she had developed a proximal tubule defect, it increases her likelihood for maintaining an element of renal tubular dysfunction, and depending on the degree and chronicity of her exposure, it also increases her risk for developing glomerular damage and progressive renal disease.

In total, approximately one-third of the cadmium absorbed in the body is stored in the kidneys, where it persists with a biologic half-life of approximately 10–30 years. Immediately after gastrointestinal or pulmonary absorption, cadmium circulates in the blood mainly bound to albumin and other high molecular weight proteins. These complexes are largely absorbed in the liver, and the uptake of cadmium by the kidney is limited. In chronic exposure or in situations long after a single exposure, however, much of the plasma cadmium is bound to metallothionein (MT). Due to its small molecular size, cadmium–MT, in contrast to the cadmium–albumin complex, is efficiently filtered through the glomerular membrane and reabsorbed by renal tubular cells through pinocytosis. The cadmium–MT complex is then metabolized within lysosomes and cadmium ion is released (Järup et al. 1998b).

Cadmium-induced renal injury initially presents as tubular proteinuria that can be quantified through the measurement of the urinary excretion of low molecular weight proteins such as  $\beta_2$ -microglobulin, retinol binding protein and protein HC and enzymes such as N-acetyl- $\beta$ -glucosaminidase. With continued cadmium exposure, this tubular dysfunction progresses, and ultimately glomerular damage characterized by a decreased glomerular filtration rate may emerge (Elinder et al. 1983; Pinot 2000). Several studies have documented that in almost all cases, this cadmium-induced tubular proteinuria and damage is irreversible even if exposure ends (Järup et al. 1998a, 1998b, 2000; Järup and Elinder 1993). In a recent study detailing a 5-year follow-up of a subpopulation chosen for its high urinary cadmium levels, Hotz et al. (1999) concluded that in environmentally exposed populations, tubular effects were not associated with progressive deterioration in renal function after

**Table 2.** Selected percentiles of blood cadmium concentrations ( $\mu\text{g/L}$ ) for the U.S. population.

	Sample size	Percentile (95% confidence interval)				
		10th	25th	50th	75th	90th
Total, $\geq 1$ of age	3,189	< LOD <sup>a</sup>	< LOD	0.3 (0.2–0.3)	0.5 (0.4–0.6)	0.9 (0.7–1.1)
Sex						
Male	1,594	< LOD	< LOD	< LOD	0.5 (0.4–0.6)	0.9 (0.8–1.1)
Female	1,595	< LOD	< LOD	0.3 (0.2–0.3)	0.5 (0.4–0.6)	0.9 (0.7–1.2)
Race/ethnicity						
Black, non-Hispanic	693	< LOD	< LOD	< LOD	0.5 (0.4–0.6)	0.9 (0.7–1.2)
Mexican American	1,289	< LOD	< LOD	0.3 (0.2–0.4)	0.5 (0.4–0.5)	0.7 (0.6–1.0)
White, non-Hispanic <sup>b</sup>	1,207	< LOD	< LOD	0.3 (0.2–0.3)	0.5 (0.4–0.6)	0.9 (0.7–1.1)
Age group						
1–19 years	1,541	< LOD	< LOD	< LOD	< LOD (0.3–1.0)	0.4
$\geq 20$ years	1,648	< LOD	< LOD	0.3 (0.3–0.4)	0.6 (0.5–0.7)	1.0 (0.8–1.3)

LOD, limit of detection. Data from the National Health and Nutrition Examination Survey (CDC 1999).

<sup>a</sup>LOD = 0.3  $\mu\text{g/L}$  blood. <sup>b</sup>Includes other race/ethnic groups.

**Table 3.** Selected percentiles of urine concentrations and creatinine-adjusted levels of cadmium in the U.S. population  $\geq 6$  years of age.

	Sample size	GM (95% CI)	Percentile (95% confidence interval)				
			10th	25th	50th	75th	90th
U-Cd ( $\mu\text{g/L}$ of urine)	1,007	0.32 (0.30–0.33)	0.10 (0.08–0.12)	0.18 (0.15–0.19)	0.33 (0.29–0.35)	0.57 (0.52–0.62)	0.95 (0.85–1.04)
Cadmium ( $\mu\text{g/g}$ of creatinine)	1,007	0.29 (0.27–0.31)	0.11 (0.10–0.13)	0.17 (0.15–0.19)	0.27 (0.26–0.30)	0.46 (0.43–0.50)	0.74 (0.66–0.79)

GM, geometric mean. Data from the National Health and Nutrition Examination Survey (CDC 1999).



the implementation of exposure reduction measures. In the case of ongoing low-level environmental exposure, however, cadmium does appear to be a determinant for the development of end-stage renal disease (Hellström et al. 2001).

During the past decade, several studies have shown that urinary cadmium concentrations of 2–4 nmol/mmol creatinine are associated with tubular proteinuria in both occupationally and environmentally exposed populations (Järup et al. 2000). A meta-analysis of data from these and other studies indicated that a urinary cadmium level of 2.5 µg/g creatinine is associated with a 4% excess prevalence of renal tubular damage. Based on these results, it can be estimated that in order to prevent tubular damage that can progress to clinical disease, cadmium levels should be kept < 2.5 µg/g creatinine in the urine and < 50 mg/kg in the kidney cortex (Järup et al. 1998b).

Over the long term this tubular damage can also affect the excretion of calcium. In workers occupationally exposed to cadmium, an increased prevalence of kidney stones has been documented and likely relates to the increased urinary excretion of calcium (Elinder et al. 1985; Ikeda et al. 1999; Järup et al. 1998a). One review noted a lifetime prevalence rate of 18–44% in those with occupational cadmium exposure compared to a rate < 5% in control populations (Borak 1992; OSHA 1993).

**Respiratory effects.** Other manifestations of cadmium toxicity that were not apparent in the patient include those characteristic of both acute and chronic exposure. Metal fume fever is most commonly described in workers exposed to metal oxide fumes during welding or soldering zinc- or cadmium-containing metals. Symptoms, which appear within 3–10 hr after exposure, initially include throat irritation with an associated metallic taste, followed within hours by a nonproductive persistent cough, fever, chills, malaise, and myalgias in the back and limbs. Nausea, vomiting, and headache may occasionally complete the symptom profile. These signs and symptoms peak roughly 18 hr postexposure and normally resolve completely within a few days (Balmes and Scannell 1997; OSHA 1993).

Higher dose cadmium fume inhalation may lead to a more advanced and prolonged pulmonary response ranging from tracheo-bronchitis to pneumonitis to pulmonary edema. Initial symptoms may mimic metal fume fever, but these then progress within hours to days to include severe dyspnea with wheezing, cyanosis, tachycardia, pleuritic chest pain, abdominal pain, diarrhea, hemoptysis, and life-threatening noncardiogenic pulmonary edema. Even a few hours of exposure to 2–3 mg/m<sup>3</sup> can have fatal results, and

those who survive may have impaired lung function years after a single episode. Respiratory effects may also occur as a result of high exposures to cadmium dust, but these are usually less severe than those caused by cadmium fumes (ATSDR 1999; Hotz et al. 1999; OSHA 1993).

A number of morbidity studies have documented that longer-term inhalation exposure to levels of cadmium below that which causes acute disease can lead to shortness of breath, obstructive patterns of lung function with decreases in forced vital capacity, bronchitis, and emphysema. Survivors of cadmium-related pneumonitis appear to be particularly vulnerable, and there is evidence that cadmium may accelerate the development of emphysema in smokers (Penney 1993). In both humans and animals, mild to moderate pulmonary fibrosis has been documented with chronic inhalation exposure to cadmium oxide and cadmium sulfide (ATSDR 1999).

**Gastrointestinal effects.** Cadmium ingestion can also be associated with severe nausea, persistent vomiting, salivation with choking, abdominal cramps, diarrhea, vertigo, and loss of consciousness. This symptom profile has been mainly observed in those acutely exposed to high levels of cadmium in food or beverages. Gastrointestinal sequelae may also result from mucous membrane deposition and subsequent ingestion of large cadmium dust particles. Smoking in a cadmium-contaminated workplace may also increase exposure through the oral route (ATSDR 1999; Hotz et al. 1999; OSHA 1993).

**Skeletal effects.** Exposure to cadmium can have both indirect and direct effects on bone loss. Cadmium-induced bone damage may be mediated through the dysfunction of renal tubular cells caused by increased cadmium

concentration in the kidneys. Within the renal tubular cells, cadmium reduces the normal activation of vitamin D<sub>3</sub> to the hormone 1,25-dihydroxy-calcitriol; this in turn impedes calcium absorption from the duodenum and active reabsorption of calcium in the distal convoluted tubule (Järup et al. 1998b; Staessen and Lauwerys 1993). Cadmium-induced tubular dysfunction also leads to urinary losses of calcium and phosphate and subsequent decreases in serum calcium. Increased secretion of parathyroid hormone then may lead to calcium and phosphate mobilization from bone, impaired bone mineralization, and hence osteoporosis and osteomalacia (Berglund et al. 2000).

There is also increasing evidence that cadmium acts directly on bone tissue. In the past, experimental data indicated that cadmium could affect bone mineralization without clear signs of renal effects (Berglund et al. 2000; Pinot 2000). Now it is more firmly established that cadmium exposure at levels that have not impaired renal function can target bone directly, causing early bone loss by decreasing bone formation and increasing bone resorption (Wilson and Bhattacharyya 1997). Direct effects on osteoblast and osteoclast function have been shown *in vitro* and experimentally in mice (Berglund et al. 2000). *In vitro*, cadmium decreases osteoblastic accumulation of calcium and induces the release of <sup>45</sup>Ca from prelabeled cultured limb bones (Wilson and Bhattacharyya 1997). Cadmium might further interact with bone cells by directly diminishing their ability to mineralize and by inhibiting procollagen C-proteinases and collagen production (Hunder et al. 2001; Staessen and Lauwerys 1993). *In vivo*, cadmium increases or accelerates osteoclast-induced bone resorption (Wilson and Bhattacharyya 1997). Further

**Table 4.** OSHA exposure classification for biologic monitoring of cadmium.

Category	U-Cd (µg/g creatinine)	Urinary β <sub>2</sub> -microglobulin (µg/g creatinine)	B-Cd (µg/L)
A	≤ 3	≤ 300	≤ 5
B	3 < U-Cd ≤ 7	300 < β <sub>2</sub> -microglobulin ≤ 750	5 < B-Cd ≤ 10
C	> 7	> 750	> 10

Data from OSHA (1993).

**Table 5.** OSHA-mandated action based on biomonitoring category.

Action	Category A	Category B	Category C
Biomonitoring	Annually	Semiannually	Quarterly
Medical exam including PFTs, CXR, BUN, creatinine, CBC, U/A	Biennially	Annually	Semiannually
Time frame of medical exam	Within 90 days of receiving biomonitoring results		
Assess within 2 weeks and correct within 30 days	Source of cadmium exposure, work practices, personal hygiene and hygiene facilities, respirator usage, smoking history, engineering controls		
Reassessment			Periodically at intervals ≤ 6 months
Medical removal	Discretionary	Discretionary	Mandatory <sup>a</sup>

Abbreviations: BUN, blood urea nitrogen; CBC, complete blood count; CXR, chest X-ray; PFT, pulmonary function test; U/A, uric acid. Data from OSHA (1993).

<sup>a</sup>Medical removal for category C is mandatory except when both U-Cd and B-Cd are classified as exposure category A.

analysis also revealed that the effect of cadmium on bone might be greatest at the onset of cadmium exposure; as such, intermittent exposures may be required to potentiate a bone effect (Wilson and Bhattacharyya 1997).

It has been well documented among the general population that the urinary excretion of cadmium is positively associated with the urinary excretion of calcium (Bäcklund et al. 1999). In the CadmiBel study, Staessen and colleagues (Staessen et al. 1991a, 1991b, 1993, 1999) showed that after adjustment for confounders, doubling of the urinary cadmium excretion was associated with a 0.25-mmol rise per day in urinary calcium excretion. Similarly, in their cohort of Swedish women, Järup et al (1998b) recently documented a 90% increase in urinary calcium excretion among those whose urinary cadmium concentration was > 1 nmol/mmol creatinine (Staessen and Lauwerys 1993).

In people exposed to low levels of cadmium, urinary calcium excretion thus appears to serve as a biomarker for tubular dysfunction. Aoshima and Kasuya (1991) and Tsuritani et al. (1992) have reported increased urinary  $\beta_2$ -microglobulin, increased serum creatinine, and decreased plasma calcitriol in those with cadmium-induced renal damage (Järup et al. 1998b; Wilson and Bhattacharyya 1997). Most recently, Wu et al. (2001) described a significant and linear dose-response relationship between the prevalence of hypercalciuria and U-Cd excretion, most notably at U-Cd levels > 2  $\mu\text{g/g}$  creatinine. With respect to the clinical relevance of these findings, in a prospective population study, Staessen et al. (1999) documented that a 2-fold increase in cadmium excretion at baseline correlated with a 73% increased risk of fractures in women and with a 60% increased risk of height loss in men (measured as height loss that exceeded the 90th percentile). Similarly, Alfvén et al. (2000) showed that both increased urinary cadmium excretion and renal tubular dysfunction were associated with signs of osteoporosis, as measured by bone mineral density, in men and older women.

**Other effects.** Cadmium has been classified as a human carcinogen (group I) by the International Agency for the Research on Cancer on the basis of both human and experimental animal data. Several studies of cadmium-exposed workers have shown a small but statistically significant increase in lung cancer, although controversy exists over the degree of excess mortality attributable to the confounding exposures of arsenic or nickel. Cadmium is also suspected to cause prostate cancer in humans, although follow-up studies have been unable to confirm this suspicion (Järup et al. 1998b; OSHA 1993; Tencer et al. 1996; Waalkes 2000). Cadmium exposure has been linked with olfactory impairment, most

notably in those with proteinuria (Penney 1993). Yellowing of the teeth and microcytic hypochromic anemia have been described as well (Hu 2001). Most studies of workers occupationally exposed to cadmium, however, have not found cadmium-related cardiovascular toxicity (ATSDR 1999; Shimbo et al. 2000).

**Modifiers of cadmium absorption.** Studies in Sweden have shown that 10–67% of premenopausal women have low (Berglund et al. 1994) or empty iron stores (Bäcklund et al. 1999) and have identified this as a risk factor for elevated B-Cd levels in those who are either environmentally or occupationally exposed. This is most true among smokers with low iron stores (Bäcklund et al. 1999; Ikeda et al. 1999). Berglund et al. (1994) examined nonsmoking, premenopausal, nonoccupationally exposed women and found that low serum ferritin was correlated with elevated B-Cd in this population as well. Animal studies have supported this finding, indicating that gastrointestinal absorption of cadmium is increased in the setting of low dietary iron, zinc, and calcium (Berglund et al. 1994).

In clinical situations where concerns exist regarding either environmental or occupational cadmium exposure, it would appear to be clinically responsible to ensure adequacy of the patient's iron status, an accepted intervention even in the absence of cadmium exposure. In the case of an ongoing exposure then, dietary supplementation with iron should be implemented to theoretically diminish the degree of cadmium absorption from the intestinal tract. Similarly, healthcare providers should counsel their patients to reduce or eliminate alcohol intake during periods of cadmium exposure because observations also indicate that even short periods of ethanol consumption can increase cadmium absorption from the gastrointestinal tract. This conclusion is further supported by animal data documenting increased blood and tissue cadmium concentrations in rats exposed to both cadmium and ethanol in comparison with cadmium alone (Brzóska et al. 2000).

## Summary and Conclusion

The patient, a 28-year-old nonsmoker with a 3-year history of occupational cadmium exposure, had evidence of a significant cadmium body burden and a transient cadmium-related nephropathy. She met criteria for mandatory medical removal with a B-Cd level > 10  $\mu\text{g/L}$ ; she was subsequently monitored regularly until her B-Cd levels approached 1  $\mu\text{g/L}$ . In the absence of ongoing occupational or environmental cadmium exposure, it is likely that the patient's risk for progressive renal damage is slight; nonetheless, the degree of diminishment of her functional renal reserve is unknown and hence her ability to withstand further renal damage is uncertain.

In the care of patients similar to this one, physicians should follow OSHA guidelines with respect to workplace removal and biologic monitoring. Measurement of urinary protein HC may also serve as a viable and sensitive marker of cadmium-induced renal damage. Subsequent medical follow-up to evaluate for the persistence of renal dysfunction is essential. The healthcare provider should encourage smoking cessation, and pharmacologic intervention may be considered to aid in this process. Measurement of iron stores and continued replacement to ensure their adequacy is recommended, and long-term calcium supplementation with ample hydration is sensible. From a public health standpoint, workplace investigation for companion cases and subsequent workplace and work process modification is imperative to minimize the magnitude of future cadmium exposures.

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