

H *Health effects of cadmium exposure – a review of the literature and a risk estimate*

*by Lars Järup (editor),^{1,2} Marika Berglund,² Carl Gustaf Elinder,³
Gunnar Nordberg,⁴ Marie Vahter²*

¹ Department of Environmental Health, Norrbacka, Karolinska Hospital,
S-171 76 Stockholm, Sweden

² Institute of Environmental Medicine, Karolinska Institutet,
Box 210, S-171 77 Stockholm, Sweden

³ Department of Renal Medicine, Huddinge University
Hospital and Karolinska Institutet,
S-141 86 Huddinge, Sweden

⁴ Department of Occupational and Environmental Medicine,
Umeå University, S-901 87 Umeå, Sweden

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Preface

The initiative to produce this report was taken by the Swedish National Chemicals Inspectorate. The report should contribute to the undertaking of the EC Commission to review existing EC provisions on the substances for which Sweden has been granted transitional provisions, implying that Sweden may maintain more stringent regulations on cadmium until the end of 1998. Thus the report emphasizes Swedish conditions, in particular regarding the exposure situation.

Although the various chapters were written by separate authors, as stated in the heading of each chapter, they have repeatedly been reviewed and discussed by the entire group. The Risk Characterization chapter as well as the Summary are joint efforts and reflect the consensus of the group.

The authors

Dedication to Professor Emeritus Lars Friberg

This document, which is an assessment of the risks of health effects after long-term exposure to cadmium, is dedicated to our common tutor and source of inspiration Professor Emeritus Lars Friberg at the Karolinska Institutet in Stockholm.

Almost exactly 50 years ago, Lars Friberg started his research on the health effects of cadmium. At that time, he was a young, recently graduated physician. In contrast to most other physicians and researchers at that time, Lars Friberg realized that health care is not merely the treatment of diseases, but also very much a matter of prevention. Furthermore, he realized that risk assessment and prevention must be based on knowledge about exposure, dose-effect, and dose-response relationships. In other words, it is essential to know what kind of substances people are exposed to, at what levels, and what the health effects are. Shortly after the Second World War, the occupational health clinic, where Lars Friberg was working (in addition to the National Institute of Occupational Health), was approached by some workers from a nickel-cadmium battery plant in southern Sweden. The workers complained about deteriorated and poor health. Lars Friberg set out to examine this complaint in great detail, and some years later, in 1950, the results were presented in his classical thesis report: *Health Hazards in the Manufacture of Alkaline Accumulators with Special Reference to Chronic Cadmium Poisoning*. In fact, the health effects due to cadmium exposure, identified and described by Lars Friberg in his thesis, still hold true and are essentially the same as those we discuss in the present risk assessment document.

The thesis of Lars Friberg was the starting point of a long and very productive research program at the Department of Environmental Hygiene at the Karolinska Institutet, which Lars Friberg chaired for more than three decades, and at the Institute of Environmental Medicine. However, the interest of Lars Friberg was much wider than merely cadmium. Exposure to, and health effects from, several other metals and environmental pollutants were delineated. In his capacity as a senior researcher, Lars Friberg inspired a great number of students to carry out research in environmental medicine. An impressive number of scientific reports and several extensive review books were produced by him and his collaborators. Several of his disciples later became professors in occupational or environmental medicine or both at different universities and institutes in Sweden or took up other important positions in national or international agencies.

Lars Friberg has continued to carry out high quality research at the Karolinska Institutet, where he still is active, and is committed to unraveling the health consequences and hazards of cadmium exposure. The principles and practices that we have used in our own research and in this document have all directly or indirectly been taught to us by Lars Friberg. The fact that cadmium research in Sweden still has significant merits is very much because of Lars Friberg, and he is the main person to acknowledge. As so many times before, Lars Friberg has reviewed this document and provided us with many very pertinent and valuable comments.

Thus we would like to dedicate this cadmium risk assessment document to our dear friend, tutor and mentor, Professor Emeritus Lars Friberg. Without his pioneering and successful research on cadmium, You, dear reader, would certainly not have this monograph in hand.

The authors

Abbreviations

AAS	atomic absorption spectrophotometry
B-Cd	cadmium in blood (blood cadmium)
Cd	cadmium
Cd-MT	cadmium bound to metallothionein (cadmium-metallothionein)
Cr-EDTA	⁵¹ human-ethylenediaminetetraacetic acid
D-Cd	dietary cadmium intake
DNA	deoxyribonucleic acid
EC	European communities
EEC	European Economic Community
EU	European Union
GFR	glomerular filtration rate
HEAL	human exposure assessment location (WHO)
IARC	International Agency for Research on Cancer
MT	metallothionein
NAG	N-acetyl- β -D-glucosaminidase
PPC-10	population critical level of 10%
Protein HC	human complex-forming glycoprotein
PtH	parathyroid hormone
PTWI	provisional tolerable weekly intake
RBP	retinol binding protein
RIA	radioimmunoassay
RR	relative risk
RRT	renal replacement therapy
SMR	standardized mortality ratio
U-Cd	cadmium in urine (urinary cadmium)
UNEP	United Nations Environmental Programme
WHO	World Health Organization
95% CI	95% confidence interval

Conversions

1 μ g cadmium = 8.9 nmol cadmium

1 μ g cadmium/g creatinine $\cong$ 1 nmol cadmium/mmol creatinine

Summary

This report provides a review of the cadmium exposure situation in Sweden and updates the information on health risk assessment according to recent studies on the health effects of cadmium. The report focuses on the health effects of low cadmium doses and the identification of high-risk groups.

The diet is the main source of cadmium exposure in the Swedish nonsmoking general population. The average daily dietary intake is about 15 µg/day, but there are great individual variations due to differences in energy intake and dietary habits. It has been shown that a high fiber diet and a diet rich in shellfish increase the dietary cadmium intake substantially. Cadmium concentrations in agricultural soil and wheat have increased continuously during the last century. At present, soil cadmium concentrations increase by about 0.2% per year. Cadmium accumulates in the kidneys. Human kidney concentrations of cadmium have increased several fold during the last century. Cadmium in pig kidney has been shown to have increased by about 2% per year from 1984–1992. There is no tendency towards decreasing cadmium exposure among the general nonsmoking population.

The absorption of cadmium in the lungs is 10–50%, while the absorption in the gastrointestinal tract is only a few percent. Smokers have about 4–5 times higher blood cadmium concentrations (about 1.5 µg/l), and twice as high kidney cortex cadmium concentrations (about 20–30 µg/g wet weight) as nonsmokers. Similarly, the blood cadmium concentrations are substantially elevated in persons with low body iron stores, indicating increased gastrointestinal absorption. About 10–40% of Swedish women of child-bearing age are reported to have empty iron stores (S-ferritin <12 µg/l). In general, women have higher concentrations of cadmium in blood, urine, and kidney than men. The population groups at highest risk are probably smokers, women with low body iron stores, and people habitually eating a diet rich in cadmium.

According to current knowledge, renal tubular damage is probably the critical health effect of cadmium exposure, both in the general population and in occupationally exposed workers. Tubular damage may develop at much lower levels than previously estimated, as shown in this report. Data from several recent reports from different countries indicate that an average urinary cadmium excretion of 2.5 µg/g creatinine is related to an excess prevalence of renal tubular damage of 4%. An average urinary excretion of 2.5 µg/g creatinine corresponds to an average concentration of cadmium in renal cortex of 50 µg/g, which would be the result of long-term (decades) intake of 50 µg per day.

When the critical concentrations for adverse effects due to cadmium accumulation are being evaluated, it is crucial to consider both the individual variation in kidney cadmium concentrations and the variations in sensitivity within the general population. Even if the population average kidney concentration is relatively low for the general population, a certain proportion will have values exceeding the concentration where renal tubular damage can occur. It can be estimated that, at the present average daily intake of cadmium in Sweden, about 1% of women with low body iron stores and smokers may experience adverse renal effects related to cadmium. If the average daily intake of cadmium would increase to 30 µg/day, about 1% of the entire population would have cadmium-induced tubular damage. In risk groups, for example, women with low iron stores, the percentage would be higher, up to 5%.

Both human and animal studies indicate that skeletal damage (osteoporosis) may be a critical effect of cadmium exposure. We conclude, however, that the present evidence is not sufficient to permit such a conclusion for humans. We would like to stress, however, that osteoporosis is a very important public health problem worldwide, but especially in the Scandinavian countries. Studies assessing the potential role of cadmium as a risk factor for osteoporosis are already in progress. The results from these studies may lead to a reevaluation of the critical effects of cadmium exposure. It should also be noted that women have a much greater risk of developing osteoporosis. Since women are also at greater risk of achieving a high cadmium dose, they may be particularly at risk for cadmium-induced osteoporosis.

The International Agency for Research on Cancer concluded in 1993 that there was sufficient evidence to classify cadmium as a human carcinogen (category I). As the World Health Organization earlier pointed out, however, the human evidence was based on relatively few studies, including a limited number of lung cancer cases, and that the control of confounding was insufficient. Recent reevaluation of these studies, as well as new data from a Swedish cohort, indicate that a classification of cadmium as a "probable human carcinogen, group 2A" would be more appropriate. This conclusion is also in agreement with the existing classification of some cadmium compounds in EC countries in the European Union (carcinogen category 2; annex 1 to directive 67/548/EEC).

Although an increased risk for cardiovascular disease was found in a Japanese population with evidence of tubular damage, there is presently not sufficient evidence for cadmium as a risk factor for cardiovascular disease.

Studies on experimental animals have indicated that a single high dose of cadmium can give rise to necrosis of the testicles. Long-term, low-dose exposure to cadmium did not give rise to this effect, but may cause changes in male sex hormone levels in animals. Such effects have not been shown to occur in humans, but very few studies have been done on this topic. The available evidence does not allow any conclusions to be drawn about the effects on the male reproductive system at protracted low exposures.

Elevated levels of cadmium in babies of smoking mothers have been associated with decreased birthweight. Since decreased birthweight was not observed in babies of mothers occupationally exposed to cadmium, the causal relationship is uncertain. However, pathological changes have been induced in human placentas perfused with cadmium after delivery. Since experimental animal studies have shown that cadmium may give rise to several adverse effects in ovaries and placentas and also to teratogenic and developmental effects, there is a need

for more studies on humans. The present human evidence is not sufficient to consider female reproductive and developmental effects as critical effects in humans.

In conclusion, recent data indicate that adverse health effects from cadmium exposure may develop in about 1% of the adult general population at an average daily intake of 30 µg over a life-span. In high-risk groups the percentage will be even higher (up to 5%). This intake is already exceeded by some population groups in Europe, and the margin is very narrow for large groups. Therefore, measures should be taken to reduce cadmium exposure in the general population to minimize the risk of adverse health effects. At an average daily intake of 70 µg/day [corresponding to the present PTWI (provisional tolerable weekly intake)], 7% of the adult general population would be expected to develop cadmium-induced kidney lesions. For high-risk groups the percentage would be even higher (up to 17%). Thus, in our opinion, the current PTWI is unacceptable and needs to be lowered.

Introduction

The aim of the present report is to review the cadmium exposure situation in Sweden and to update the health risk assessment on the basis of recent studies on the health effects of cadmium. The report focuses on health effects of low cadmium doses and the identification of high-risk groups.

The following 4 important previous publications have been used as the starting cornerstones of the present report: *Cadmium and Health*, volumes I and II, by Friberg et al (1, 2), the proceedings from an IARC conference on cadmium in the human environment (3), the IARC monograph on the carcinogenicity of cadmium (4), and the WHO environmental health criteria report on cadmium (5, 6). In these documents it is concluded that the kidney is the critical organ for both the general population and occupationally exposed populations. IARC has concluded that there is sufficient evidence to classify cadmium as a human carcinogen. WHO is consistently

more cautious and recognizes that cadmium may contribute to cancer of the lung but that the studies on which such conclusions are based are difficult to interpret because of possible confounding factors.

Food is the major source of cadmium exposure in the general population. According to the WHO document, average daily intakes vary considerably, from about 10 to 40 µg in nonpolluted areas to several hundreds of micrograms in cadmium-polluted regions. WHO further states that it has been estimated that signs of renal tubular damage occur in humans with a life-long daily intake of about 140–260 µg of cadmium, or a cumulative intake of about 2000 mg. New data challenging the previous risk assessments have become available in recent years, in particular regarding early renal effects from cadmium in the general population. Pertinent recent studies are cited and commented upon in this report.

Exposure and dose

by Marika Berglund & Marie Vahter

Occupational exposure

The main route of cadmium exposure in the occupational setting is via the respiratory system. Air concentrations of cadmium fumes or dust vary considerably between different industries, such as smelters, pigment plants and battery factories. (For a review, see reference 7.) In many countries, improvements in industrial hygiene have led to continuous decreases in cadmium levels in workroom air, and current levels in Sweden are typically at or below the existing Swedish occupational exposure limits (0.05 and 0.01 mg/m³ for total dust and respirable dust, respectively).

Environmental exposure

The diet is the most important source of cadmium exposure in the general nonsmoking population of Sweden (8), as in most other countries (5). Both natural and anthropogenic sources of cadmium, including industrial emissions and the application of fertilizer and sewage sludge to farm land, may lead to the contamination of soils and to increased cadmium uptake by crops and vegetables grown for human consumption. Airborne cadmium will also add to the cadmium content in wild plants, berries, fungi, and wild animals, which altogether add to human exposure via the oral route. Even if the emission of cadmium from point sources has decreased during the last few years, there are still considerable amounts of cadmium in various products and constructions. This cadmium may eventually enter the human exposure pathway.

The uptake process of soil cadmium by plants is enhanced at low pH (6, 9, 10). Especially, cadmium uptake by potatoes and carrots is sensitive to changes in pH (11). Thus decreasing soil pH due to environmental acidification, a recognized problem in Sweden, may further increase the cadmium content in the human exposure pathway.

When human exposure to environmental cadmium is evaluated, it is important to consider all routes of exposure, as well as factors which affect the exposure level and dose, for example, life-style factors such as smoking, food consumption, and nutritional factors that may affect cadmium uptake.

Exposure to cadmium in air

Cadmium concentrations in ambient air are generally low. In rural areas of Sweden, an annual mean air cad-

mium concentration of 0.9 ng/m³ and, in Stockholm, weekly mean concentrations of about 5 ng/m³ have been reported (12). In studies of integrated personal exposure to cadmium, carried out in Stockholm, Zagreb, Beijing and Yokohama as part of the WHO/UNEP HEAL program, cadmium in the breathing-zone air of about 15 women in each study area was measured with personal air samplers over a period of 7 consecutive days. Only about 1% of the total cadmium uptake, corresponding to inhalation of about 10 ng/day and absorption of 5 ng/day (assuming 50% absorption in the lungs) could be attributed to inhalation for the women in Stockholm (8). Similar results (1–4%) were obtained in the other study areas (13).

Smoking

Smoking is an important source of cadmium exposure. One cigarette contains about 1–2 µg of cadmium (14). An average of about 10% is inhaled during smoking (15). If it is assumed that about 50% of the cadmium inhaled via cigarette smoke is absorbed (16), it can be estimated that a person smoking 20 cigarettes a day will absorb about 1 µg of cadmium. In addition, biological monitoring of cadmium in the general population has shown that cigarette smoking often causes a significant increase in the B-Cd concentration, the extent of which may vary considerably (eg, with the type of tobacco). In Sweden, the B-Cd concentrations in smokers are 4–5 times higher than in nonsmokers, while the kidney cadmium concentrations are about 2–3 times higher than in nonsmokers (16–19). However, there are considerable interindividual variations.

In spite of the high cadmium content of cigarette smoke, there is little exposure from passive smoking. Thus no significant effect on B-Cd concentrations could be detected in children exposed to environmental tobacco smoke (20).

Drinking water

In general, cadmium in drinking water does not contribute much to the total intake of cadmium. Most people in Sweden consume drinking water from public supplies with very low cadmium concentrations (<0.05 µg/l). The threshold limit for cadmium in drinking water is 5 µg/l (21). The cadmium concentration in ground water increases with decreasing pH. Recently, the metal exposure of people living and working in areas with different degrees of acid precipitation, and consuming water only from private wells, was investigated (18). The cadmium

concentrations in water ranged from <0.01 to 1.6 µg/l (<0.09 to 14 nmol/l) and were found to increase with decreasing pH (range 4.7–8.2). No association between water cadmium content and B-Cd concentrations could be detected. However, the cadmium concentrations in water were relatively low, resulting in a low cadmium intake from water, compared with that from the diet. Since the acidification of the environment is an ongoing process in Sweden, leading to a still lower pH of the ground water in certain areas, it is essential to include metals in drinking water in health-related environmental monitoring programs.

Dietary intake

The diet is the main source of cadmium exposure in the general nonsmoking population. Cadmium is present in virtually all foods, but the concentrations vary to a great extent, depending on the type of food (22). Thus there are great individual variations in the dietary intake of cadmium due to differences in dietary habits. For instance, it has been estimated that 10% of the population consumes twice the average quantity of a particular food class and 2.5% consumes 3 times the average (23). The amount of food consumed per day also varies to a great extent between persons, and in relation to age and gender. Thus women usually have a lower daily intake of cadmium because of a lower energy intake than men. Therefore, when the data on dietary intake of cadmium from different studies are compared, it is essential to consider the energy intake. In the following discussion,

the daily intake of cadmium is expressed as micrograms of cadmium per 10 MJ, whenever possible. The daily energy requirement is about 9 MJ for moderately active women and 12 MJ for men (24). There is very little information on the daily dietary intake of cadmium in various subgroups of the general Swedish population. The few data that have been reported are given in table 1. [For further discussion, see the section on the dietary intake of cadmium under Trends in Human Cadmium Exposure, page 15.]

It should be noted that dietary cadmium intake is log-normally distributed, with a small fraction of the population ingesting much more cadmium than the average. Thus, as can be seen from table 1, the arithmetic mean values are higher than the median values. Therefore median values, or geometric mean values, should be used for comparisons between groups.

Recently, it was shown that nonsmoking Swedish women eating diets rich in cereals and root vegetables (rich in fiber) or shellfish (at least once a week) had a higher intake of cadmium than women eating a mixed diet (30, 31). The duplicate diets of women (N = 34) consuming a mixed diet over 4 consecutive days contained an average of 14 (range 7.8–38) µg/10 MJ for individual 4-day averages, while those of women (N = 23) on a high fiber diet had a 30% higher cadmium content (median 17, range 6.6–45 µg/10 MJ), and those of women (N = 17) on a diet rich in shellfish had twice as high a cadmium content, 29 (range 9–76) µg/10 MJ. The overall range of cadmium content of the single daily duplicate diets (N = 296) was 2–175 µg/day.

Table 1. Dietary intake in the Swedish general population.

Reference	Studied parameter	Dietary intake					
		µg Cd/day			µg Cd/10MJ		
		Mean	Range	Median	Mean	Range	Median
Wester, 1974 (25)	Duplicate diets for 10 days for 4 subjects	10	.	.	.	.	.
Kjellström et al, 1978 (26)	Feces collected over 3 consecutive days by 60 men (14–59 years)	18	.	.	.	.	.
Kjellström et al, 1978 (26)	Feces collected over 3 consecutive days by 10 women (20–29 years)	15	.	.	.	.	.
Schütz, 1979, personal communication	28 daily duplicate diets, 15 elderly women	10	4–29	9	16 13	.	.
Schütz, 1979, personal communication	21 daily duplicate diets, 9 elderly men	13	6–35	11	16 14	.	.
Slorach et al, 1983 (27)	A typical Swedish weekly diet, N = 7 prepared daily diets	10	6–15	9	8	5–13	8
Becker & Kumpulainen, 1991 (28)	Market basket study of 60 food items				.	10–11	10
Vahter et al, 1991 (8); Vahter et al, 1990 (29)	15 women, daily duplicate diets for 7 days each	8.5	5.7–14	8.1	11	7.7–16	9.6
Berglund et al, 1994 (30)	34 women, daily duplicate diets for 4 days	11	5.7–26	10	15	7.8–38	14
Berglund et al, 1994 (30)	23 women, daily duplicate diets for 4 days, vegetarian diets	16	5.5–38	13	21	6.6–45	17
Vahter et al, 1996 (31)	17 women, daily duplicate diets for 4 days, shellfish diets	28	9.0–70	22	36	9–76	29

Feces can be used as an indicator of dietary cadmium intake (or total oral intake), since the average gastrointestinal uptake is only a few percent (5). In a study of fecal elimination (48-h sampling) of cadmium by 16 subjects, who changed from a mixed diet to a lacto-vegetarian diet, the median daily fecal elimination of cadmium was 15 µg/10 MJ during the mixed-diet period and 18 µg/10 MJ during the vegetarian diet period, giving further evidence for a higher intake of cadmium from vegetarian food (32). This result is in very good agreement with the data obtained on fecal cadmium in the aforementioned study on nonsmoking women consuming mixed diets (30). The median fecal cadmium was 98% of the dietary cadmium in the mixed diet group; this result offers verification for the dietary intake data.

Biological indicators of exposure and dose

For quite some time biological monitoring has been used to evaluate the exposure to cadmium and the risk of the adverse health effects caused by such exposure. Biological monitoring measures the total exposure from different sources and takes into account the inter- and intraindividual variations in uptake due to differences in metabolism and physical activity. However, the results of the biological monitoring of cadmium are complicated to interpret. It is essential to consider the toxicokinetics of cadmium in relation to biological monitoring and the evaluation of exposure and absorbed dose. Other factors that need to be considered include age, duration and approximate intensity of elevated exposure, and time elapsed since cessation of elevated exposure.

Cadmium kinetics

The uptake of cadmium following inhalation is of the order of 10–50%, depending mainly on the particle size and the chemical form of cadmium (5). The absorption of cadmium from the gastrointestinal tract is much lower, on the order of one or a few percent (5, 30). Experimental studies have shown that after a single, fairly high dose absorbed cadmium is bound to high molecular-weight proteins in the blood and transported to the liver, where it is bound to MT and then redistributed to various tissues and organs (33). The Cd-MT complex, in contrast to cadmium bound to albumin, is filtered in the glomerulus and reabsorbed in the kidney tubuli. After reabsorption, cadmium is accumulated in the kidney cortex with a half-time of 10–30 years.

There is increasing evidence for the kinetics of cadmium being dose-dependent, possibly also route-dependent. Recent research indicates that the ingested dietary cadmium (long-term low-dose exposure) taken up by the mucosal cells is primarily bound to MT directly in the mucosa (34–37). One part may be sequestered for sev-

eral days, after which it is eliminated in feces by desquamation of the mucosal cells. The absorbed Cd-MT complex is transported in the blood mainly to the kidneys (36). Thus there may be a difference in the kinetics of cadmium dependent on the route and level of exposure. There is a need for further data on the low-dose kinetics of cadmium.

The gastrointestinal absorption of cadmium may be influenced by nutritional factors. Experimental animal data indicate that a low intake of calcium, iron, zinc, and copper may increase the intestinal absorption of cadmium (33, 38). In humans, iron status has been shown to influence its absorption in the gastrointestinal tract (30, 39). In one study on the intake and uptake of cadmium in women with preference for vegetarian or mixed diets, reduced body iron stores (serum ferritin) were highly associated with higher B-Cd concentrations (30). The B-Cd concentration was mainly correlated with the U-Cd (reflecting body burden) and serum ferritin, which explained almost 60% of the variation in the B-Cd concentrations. In fact, no woman with adequate iron stores (serum ferritin >30 µg/l) had a B-Cd level above 0.3 µg/l.

Animal experiments have indicated that the absorption of cadmium is inhibited by fiber, phytate, and lignin (40–43). A high dietary intake of fiber may thus result in a lower rate of intestinal absorption of cadmium. This possibility may explain why the fairly high intake of cadmium with vegetarian diets is not reflected in a corresponding increase in the B-Cd concentration (30).

Cadmium in blood

Cadmium is localized mainly in the red cells of blood. The concentration in plasma or serum is low and difficult to determine. In nonsmoking, nonoccupationally exposed persons, the B-Cd levels are usually between 0.1 and 0.8 µg/l, while, in smokers, the concentrations are often considerably higher, about 1–4 µg/l (table 2). There is a close relationship between the number of cigarettes smoked per day and the concentration of B-Cd.

B-Cd generally reflects current exposure. During occupational exposure, the B-Cd level increases relatively rapidly. Blood analyses can help identify persons with particularly high exposure, and preventive measures can be taken to decrease exposure before kidney damage occurs. After some months of exposure, the B-Cd reaches a concentration that corresponds to the intensity of the exposure. If the exposure is discontinued, the B-Cd concentration decreases fairly rapidly. The initial half-time is 2 to 3 months (53, 54). However, cadmium accumulated in the body will influence the B-Cd concentration. Therefore, following the cessation of exposure, the B-Cd concentration will not decrease to the preexposure level. In fact, for some time after an elevated exposure has ceased, the B-Cd may serve as a good estimate of the

Table 2. Cadmium concentrations (medians or geometric means) in blood (B-Cd) and urine (U-Cd) in the general Swedish population. (Ni = nickel)

Reference	Study population	B-Cd (µg/l)		U-Cd (µg/g creatinine)	
		Nonsmokers	Smokers	Nonsmokers	Smokers
Elinder et al, 1978 (44)	Adults, Stockholm, 40—49 years of age Women (N = 10) Men (N = 16)	.	.	0.33 0.21	— —
Vahter, 1982 (17)	Urban adults, Stockholm, Women (N = 64) Men (N = 62)	0.3 0.2	1.5 1.8	.	.
Elinder et al, 1978 (45); Jawaid et al, 1983 (46)	Adults, Stockholm and Västerås (about 400 blood samples and 40 urine samples) Women Men	0.3 0.2	1.4 1.6	0.4 0.2	0.5 0.5
Vahter et al, 1991 (8)	Women (N = 15), Stockholm	0.3	—	.	.
Jakobsson Lagerkvist et al, 1993 (47)	Pregnant women (N = 96 nonsmokers, including former smokers, and 53 smokers), northern Sweden	0.5 0.2	1.3 —	.	.
Berglund et al, 1994 (30)	Women (N = 34), west coast of Sweden	0.2	—	0.15	—
Hanberg et al, 1995 (48)	Women (N = 55 nonsmokers and 21 smokers), Örebro, 19—50 years of age	0.2	0.8	.	.
Bensryd et al, 1994 (18)	Male farmers (N = 237) southern Sweden	0.2	1.3	.	.
Basun et al, 1994 (49)	Elderly men and women (N = 12, smokers), Stockholm	0.46	1.1	.	.
Järup et al, 1995 (50)	Men (N = 11) living within 500 m of a Ni/Cd plant	.	.	0.9	—
Järup et al, 1995 (50)	Adults living within 1 km of a Ni/Cd plant Women (N = 21) Men (N = 28)	.	.	0.3 0.6	— —
Järup et al, 1995 (50)	Men (N = 35) 24—68 years of age, including smokers	.	.	0.2	.
Baecklund et al, 1996 (51)	Middle-aged and elderly, general population (N = 330 nonsmokers and 35 smokers) Women Men	0.35 0.25	1.4 1.2	.	.
Nordberg et al, 1996 (52)	Elderly men and women (N = 124 nonsmokers and 21 smokers) (84 years of age) in Stockholm	0.41	0.63	.	.

accumulated body burden of cadmium, or the concentration in the kidneys. An examination of cadmium-exposed workers more than 15 years after the cessation of exposure showed that the B-Cd levels were still clearly elevated and related to signs of tubular damage (55). Interestingly, the association between U-Cd and tubular damage was less evident, probably due to the fact that cadmium was lost from the kidneys in cases of tubular damage. [See the section on urinary cadmium beginning on page 13.]

In the general population, B-Cd is also largely influenced by the body burden of cadmium. In one study on the influence on B-Cd concentrations from various dietary sources, there was no significant association between the B-Cd concentrations and duplicate diets, while

body burden (U-Cd) and serum ferritin (measure of body iron stores) were the main determining factors for B-Cd (30).

The influence of accumulated cadmium on the B-Cd concentration leads to an increase in B-Cd with age (30, 45). As shown in table 2, elderly people have higher B-Cd concentrations than younger adults. Furthermore, the B-Cd concentrations are usually much lower in children than in adults, in the range <0.1—0.5 µg/l (table 3). In a study of B-Cd concentrations in middle-aged and elderly people, an increase in B-Cd with age was observed for nonsmoking men, but not for nonsmoking women, possibly as a consequence of a higher intestinal absorption due to inadequate iron status before menopause than after menopause (51).

In general, women have higher B-Cd concentrations than men (table 2). In the aforementioned study on elderly people (51), women 50–55 years of age had higher B-Cd levels (0.5 µg/l) than men of the same age (0.3 µg/l). The difference was probably related to an increased absorption of dietary cadmium in women with low iron status before menopause.

In table 2, the B-Cd concentrations in pregnant women, living in northern Sweden (in nonsmokers and ex-smokers at gestational week 10) were higher than those obtained in other studies (47). It is not known whether this finding is related to pregnancy. There was a tendency towards increasing B-Cd concentrations in nonsmokers and ex-smokers during pregnancy, reaching 7 nmol/l (0.78 µg/l) at delivery. An opposite tendency was reported for smokers, probably due to reduced smoking during pregnancy. In a later report by the same authors, it was stated that there was a statistically significant increase in B-Cd only in former smokers (60).

One possible reason for an increase in the B-Cd concentration during pregnancy is an increase in the gastrointestinal absorption of cadmium due to the depletion of body iron stores that commonly occurs during the third trimester (61). In nonpregnant women depleted iron stores are associated with markedly increased B-Cd concentrations (30). An increase in B-Cd during pregnancy may also be related to a mobilization of cadmium from liver to blood, as indicated by studies on rats, and to higher plasma cadmium levels (and MT levels) in pregnant rats than in nonpregnant rats (62, 63). The basal level of MT was increased already at day 8 of pregnancy in rats given no cadmium treatment (64).

Urinary cadmium

The U-Cd concentration is mainly influenced by the body burden, and U-Cd is proportional to the concentration in the kidneys. In general, nonsmokers have U-Cd concentrations of 0.02–0.7 µg/g creatinine, and their cadmium levels slowly increase with age in parallel with the accumulation of cadmium in the kidney (30, 31). Some examples of U-Cd concentrations in the Swedish general population are given in table 2. Smokers and people living in contaminated areas have higher values. Smokers have concentrations that are about twice as high as those of nonsmokers (65). Measurements of U-Cd in nonoccupationally exposed nonsmokers living in urban areas of Sweden (46) showed higher concentrations in women than in men. This finding may partly be due to differences in the urinary excretion of creatinine, it being about 1.8 g/day for men and 1.2 for women (24).

There is a close relationship between the cadmium concentrations in urine and kidneys. If one assumes a linear relationship between cadmium in urine and kidneys, which, however, may not always be totally correct, a U-Cd of 5 µg/g creatinine corresponds to a concentra-

Table 3. Cadmium concentrations (medians or geometric means) in the blood (B-Cd) of Swedish children.

Reference	Study population	B-Cd (µg/l)
Unpublished data, Berglund et al, 1994	Urban male and female children (N = 90), about 4 years of age	≤ 0.11
Berglund et al, 1994 (56)	Male and female children (N = 71), 1–5 years of age smelter area	0.24
Berglund et al, 1995 (57)	Male and female children (N = 72), 1–5 years of age, mining and control area	0.04
Willers et al, 1988 (20)	Children, 4–11 years old, southern Sweden	
	Girls (N = 50)	0.14
	Boys (N = 55)	0.13
Willers et al, 1992 (58)	Male and female children (N = 77), 7–10 years of age, southern Sweden	0.08
Granvik et al, 1988 (59)	Male and female teenagers (N = 418), about 14–15 years of age, urban and rural areas	≤ 0.2

tion of about 100 mg/kg in the kidneys, while 2.5 µg/g in urine corresponds to about 50 mg/kg in the kidneys. However, soon after an incident of high exposure to cadmium, for example, after unintentional exposure to cadmium fumes, the urinary excretion of cadmium may temporarily increase substantially without reflecting an increase in body burden. During long-term occupational exposure, the U-Cd concentration increases slowly and in proportion to the accumulated amount in the body (66).

In cases of tubular kidney damage, the normal reabsorption of Cd-MT decreases, and the U-Cd increases (33). Thus, paradoxically, when the cadmium accumulation damages the kidney, the excretion of cadmium increases, and the cadmium concentration in the kidneys gradually decreases. In the long run, the concentrations of cadmium in both the kidney and urine decrease, while the tubular damage remains.

It should be noted that most studies using U-Cd as the dose estimate are cross-sectional. Before the dose-response relationship can be assessed correctly, U-Cd should ideally be analyzed at the time of the development of the tubular damage. Such assessment is rarely feasible, however, and, when persons with cadmium-induced tubular damage are examined a long time after the appearance of tubular dysfunction, the dose-response curve shifts to the left. For example, Järup et al (55) have reported that a 10% prevalence of β₂-microglobulinuria was seen at a U-Cd level of about 6.5 µg/g creatinine in 1984, as compared with 3.5 µg/g creatinine when the same group of workers was examined 10 years later. On the other hand, cases studied shortly after the onset of kidney damage may, as already mentioned, have elevated U-Cd due to kidney damage, the result being an overestimation of the kidney concentration. In this case, the dose-response curve shifts to the right.

Cadmium in kidneys

Cadmium is accumulated mainly in the liver and kidneys, and, in general, the highest concentrations are found in the renal cortex (14). The cadmium concentration in the kidneys increases with age up to about 50–60 years, after which it decreases (5, 17). However, there are great individual variations among people from the same area and of the same age group (65). The cadmium concentrations in the kidneys are not normally distributed, but are instead positively skewed (16). Therefore, a small shift to the right of the average cadmium concentration in the kidney results in a proportionally much larger increase in the fraction of persons with an increased risk for renal tubular damage, as shown in figure 1.

Concentrations of cadmium in kidney cortex ($\mu\text{g/g}$ wet weight) can be measured in samples obtained at autopsy or in vivo by X-ray fluorescence or by neutron activation analysis. The latter methods are not yet sensitive enough to enable the evaluation of relationships with other biological indicator data, such as U-Cd (68), and further research in this area is urgently needed. The in vivo methods offer several advantages over the analysis of autopsy samples, especially concerning the selection of study populations and the possibilities of following persons over time. The autopsy cases chosen are often "victims of sudden and accidental death" so that the effects of long-term diseases on kidney cadmium can be avoided. These cases are not representative of the general population.

The average kidney cortex concentration (geometric mean) of cadmium was $11 \mu\text{g/g}$ wet weight for the non-smokers and $23 \mu\text{g/g}$ wet weight for the smokers among 292 persons (victims of sudden and accidental death) autopsied in Stockholm in 1973–1974 between the ages of 40 and 60 years (16). About 10% had cadmium concentrations above $50 \mu\text{g/g}$ wet weight. Interestingly, the

women had considerably higher cadmium concentrations than the men — about $23 \mu\text{g/g}$ wet weight for the women, 40–60 years of age, compared with about $17 \mu\text{g/g}$ wet weight for the men, in spite of a probably higher smoking rate among the men.

In 20 men, aged 30–59 years and autopsied in Stockholm in 1983, the median kidney cortex concentration was 17 (range whole kidney 2.8–39) $\mu\text{g/g}$ wet weight (69). No information on smoking was given. The average cadmium concentration in kidney biopsies from 29 patients with clinical findings that motivated a diagnostic percutaneous kidney biopsy or a history of possible cadmium exposure or both was 13 (range 0.6–45) $\mu\text{g/g}$ wet weight (70). In a reference group of 22 autopsies, the mean cadmium concentration was 8.7 (range 2.9–22) $\mu\text{g/g}$ wet weight. No information on smoking was given.

A more recent study of cadmium concentrations in kidney cortex measured in vivo by X-ray fluorescence analysis in the general urban population of southern Sweden showed a median concentration of 8 $\mu\text{g/g}$ for non-smokers ($N = 10$, 26–60 years of age) and 28 $\mu\text{g/g}$ for smokers ($N = 10$, 27–65 years of age) (19). It should be noted that 11 of 20 of the analytical results were below or at the detection limit. The same method has also been used to determine cadmium concentrations in the kidneys of workers with limited cadmium exposure in a secondary smelter (71). Active workers (mean age 49 years) had a mean concentration of 24 $\mu\text{g/g}$, whereas retired workers (mean age 71 years) had a mean level of 12 $\mu\text{g/g}$, and the referents (mean age 47 years) had a corresponding value of 10 $\mu\text{g/g}$. Smoking had a major impact on the kidney concentrations of cadmium, but individual smoking data were not given.

A recent study on metal concentrations in tissue in second trimester fetuses and infants (deceased before 3 months of age) showed median kidney cadmium concentrations of about 2 ng/g wet weight in both age groups (72). Thus the kidney concentrations increased about 5000 times from birth to adult age.

Cadmium in placenta

In contrast to many other metals, cadmium accumulates in the placenta (73, 74). Even fairly low concentrations of cadmium may impair the physiological function of the placenta, in particular the zinc homeostasis (75). This impairment may have serious consequences since zinc is essential for the growth and development of the fetus. These effects are further discussed in the section on reproductive and developmental effects, which begins on page 37. The zinc content of the Swedish diet is fairly low, and about 10% of the women of child-bearing age do not meet the recommended daily intake for this metal (76). The requirement for zinc increases during pregnancy, and the low dietary intake is often reflected in de-

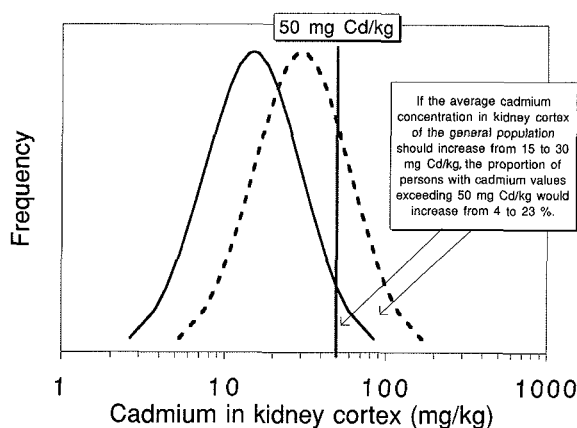


Figure 1. Schematic presentation of the frequency distribution of different cadmium concentrations.

creasing serum zinc concentrations during the course of pregnancy (77, 78). Like zinc and copper, cadmium is bound to MT in the placenta. While the placenta functions as a partial barrier for cadmium between maternal and fetal blood, zinc and copper are easily transported over to the fetus (79). Little is known about the mechanisms for the selective transport of these metals.

In Sweden, placenta cadmium concentrations of 20 and 36 ng/g dry weight have been reported for non-smokers and smokers, respectively (74). The usefulness of samples of human placenta in monitoring exposure to cadmium in the human population was discussed by Lagerkvist et al (60). Because of the variation in concentrations between different lobuli, homogenized samples were analyzed. There were no significant differences in the concentrations of cadmium in the placentas of women from a smelter area ($N = 49$) and women from a reference area ($N = 53$) in northern Sweden. The geometric mean concentrations were 5.0, 3.6, and 2.6 ng/g wet weight for smokers, ex-smokers, and nonsmokers, respectively. The placenta cadmium concentrations were 4 times higher than in maternal blood and 6 times higher than in umbilical cord blood. Berlin et al (73) showed that placental cadmium concentrations in female nickel-cadmium battery workers ($N = 27$) correlated positively with maternal B-Cd. The mean placenta cadmium concentration was 21 ng/g wet weight.

Trends in human cadmium exposure

During the 20th century, cadmium production, cadmium consumption, and cadmium emissions to the atmospheric, aquatic and terrestrial environment have increased dramatically. Only limited amounts of cadmium in products are re-cycled. Cadmium-containing products are frequently dumped together with household waste and thereby contaminate the environment, especially if the waste is burned. Thus it seems likely that human exposure to cadmium has increased in modern times.

Cadmium in crops or wheat

In Sweden, the cadmium content in wheat increased by approximately 100% (more than doubled) during the period 1918–1980 (80, 81). During the same period, the cadmium content of agricultural land increased by 30% (82). At present, the cadmium content in agricultural land increases by about 0.2% a year, despite reduced or restricted input of cadmium from phosphate fertilizers and reduced atmospheric deposition of cadmium (82). Soil cadmium content and soil pH are the main factors determining the plant uptake of cadmium (6, 9). In Denmark, Tjell et al (83) estimated that cadmium input from phosphate fertilizers and atmospheric deposition will

cause an annual increase of 0.6% in the cadmium levels of soil in Denmark. The corresponding increase in the cadmium concentration of crops would lead to a predicted 70% increase in the dietary cadmium intake in 100 years.

Dietary intake of cadmium

Cadmium is present in most foodstuffs, and the diet is the most significant source of cadmium exposure among nonsmokers (5). A comparison of the few studies available on dietary cadmium intake in Sweden during the past 25 years is given in figure 2. It should be noted that different methods were used in the various studies and that some of the studies included very few daily diet samples. These differences could explain part of the differences between the findings of the studies. Thus it is not possible to perform a statistical analysis of any trends in the dietary intake of cadmium. Due to the limited data available, more research should be carried out on the dietary intake of cadmium, especially studies based on duplicate diets (84).

In the first study of duplicate diets (85), the cadmium levels of 49 duplicate diets collected by 15 elderly women and 9 elderly men were analyzed by flame AAS. The mean concentration of cadmium in the daily diets was 16 $\mu\text{g}/10 \text{ MJ}$. The median values were 13 $\mu\text{g}/10 \text{ MJ}$ for the women and 14 $\mu\text{g}/10 \text{ MJ}$ for the men (Schütz, personal communication). The total range for the 49 diets

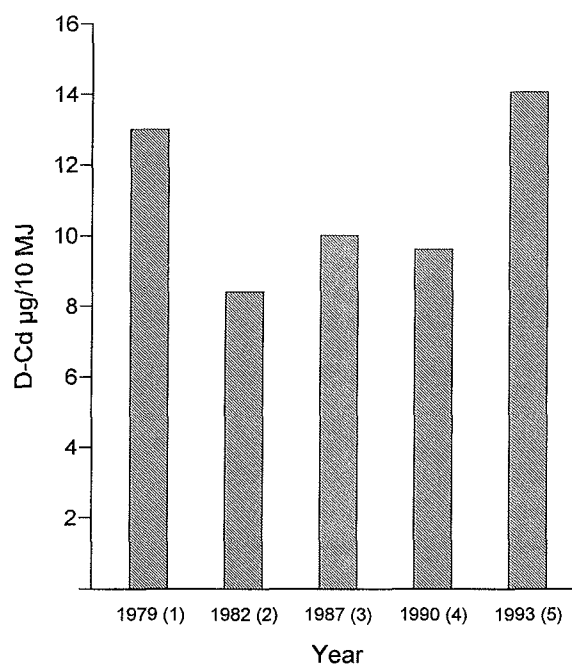


Figure 2. Comparison of studies on dietary cadmium intake (D-Cd) (mg/10 MJ) in Sweden. 1 = Schütz (85), 2 = Slorach et al (27), 3 = Becker & Kumpulainen (28), 4 = Vahter et al (8, 29), 5 = Berglund et al (30).

was 4–29 µg/day. In the second study (27), 7 duplicate diets (a typical Swedish weekly diet) were prepared and analyzed by flame AAS. The median cadmium concentration of the daily diets was 8 (range 5–13) µg/10 MJ (or 6–15 µg/day). The third study (28) was a market basket study. Four market baskets, each containing 60 food items representing a typical diet, were purchased in 4 major cities and analyzed by electrothermal AAS. The median or mean cadmium content of the market baskets corresponded to a daily intake of 10 (range 10–11) µg/10 MJ. In the study by Vahter et al (8, 29), 7 daily duplicate diets, collected by 15 women (a total of 105 duplicate daily diets), were analyzed by graphite furnace AAS. The median daily intake was 9.6 (range 7.7–16) µg Cd/10 MJ (or 5.7–14 µg/day). The total range for the 105 daily diets was 2–56 µg/day. In the latest study (30), 4 subsequent daily duplicate diets collected by 34 women consuming a mixed diet (a total of 136 daily diets) were analyzed by flame AAS or graphite furnace AAS. The median daily intake was 14 (range 7.8–38) µg/10 MJ (or 5.7–26 g/day). The total range for the 136 daily diets was 2.0–47 µg/day. There is also an early study on the dietary intake of cadmium, estimated from 10 duplicate diets of 4 subjects (25). Only a mean value of 10 µg/day was given.

Regression analysis of cadmium concentrations in pig kidneys (N = 1051) (from the control analyses made by the Swedish National Food Administration in 1984–1992) showed that the cadmium concentration increased by about 2% per year (86). The overall median concentration was 0.09 µg/g fresh weight.

It should be noted that dietary cadmium intake is log-normally distributed. Therefore, a small increase in the average daily intake of cadmium will result in a proportionally much larger increase in the fraction of the population having the highest intake. On the basis of the studies on the cadmium intake of Swedish women (30, 31), it can be calculated that an increase in the median daily intake by a factor of 2 (ie, from 15 to 30 µg/day) would correspond to an increase in the 95th percentile, from about 20 to 60 µg/day.

Blood and urinary cadmium levels

There is no indication of an increasing trend in human B-Cd or U-Cd concentrations (table 2). However, it should be noted that the analytical detection limit has decreased considerably with time. Since the concentrations in nonsmokers in the general population have been close to the detection limit, an increase in B-Cd and U-Cd concentrations may well have been covered by the increase in analytical sensitivity that had made it possible to detect lower concentrations. Thus the fact that the reported values have not decreased significantly with time is probably indicative of an increase in the actual concentrations.

Cadmium in kidneys

Comparisons between the cadmium content in human kidneys preserved at anatomical museums in Sweden and in kidney samples obtained in recent decades indicate a several-fold increase during the last century, about 300% (87). Drasch (88) compared the cadmium concentrations in pathological-anatomic specimens (N = 61) from 1897 to 1939 with modern autopsy material (N = 207) from 1980 and found that the cadmium concentration in kidney cortex had increased by a factor of 47.

It is difficult to obtain a clear picture of the possible trends related to kidney cadmium concentrations based on the few more recent studies in Sweden because of the influence of smoking, age, gender, and occupational exposure. However, a few studies on cadmium concentrations in kidney samples from autopsy cases and in vivo measurements of cadmium in kidneys are under way.

Cadmium in human bone tissue

To assess trends in bone cadmium, a few studies have been undertaken on deceased people. In a study of bone samples of 14 North American natives from the 15th century, the cadmium concentration in inner bone was assessed by graphite furnace AAS (89). The bone samples were selected according to their overall integrity, and highly fractured bones and bones showing excessive diagenetic alteration (physiochemical changes that occurred during and after burial in sediments) were excluded. After adjustment for postmortem contamination, the average concentration of cadmium in inner bones was found to be 0.032 (SD 0.013) µg/g dry weight, as compared with a concentration of 1.8 µg/g in bones of modern people. Thus bone cadmium concentrations have increased approximately 50 times in 600 years. Furthermore, the authors stated that the historic cadmium concentration may be too high due to residual contamination effects.

In another study from France, it was concluded that the concentrations of cadmium in human bones have increased about 10 times in the 20th century (90).

Concluding remarks

It has been clearly demonstrated that cadmium concentrations in agricultural soil, wheat, and human kidneys have increased significantly during the last century. Although there is no clear evidence of a further increase in the concentrations of cadmium in diets, blood, urine, and human kidneys, there is a tendency towards an increase for each medium. Taken together, it seems likely that the human exposure to cadmium continues to increase. This assumption is supported by the reported ongoing increases in concentrations of cadmium in soil and pig kidney.

Risk groups and risk factors for high exposure or dose

Risk groups for high cadmium exposure in the general population can be identified as follows: (i) people living in contaminated areas, (ii) smokers, (iii) people having a higher intake of cadmium due to dietary habits, (iv) people having a higher uptake due to nutritional factors, and (v) women.

Environmental exposure

People living in cadmium-contaminated areas have higher urinary cadmium concentrations (5). The total uptake of cadmium depends on the nature of the cadmium contamination (ie, whether food, water, and air levels are elevated).

In 1982, 75 persons living in the vicinity of a large lead smelter in northern Sweden (Rönnskärsverken), who consumed large quantities of locally grown vegetables, were examined with regard to their exposure and accumulation of cadmium and lead by measurements of these metals in blood and urine (91). Among the nonsmoking women, urinary cadmium excretion was twice as high (average concentration = 1 µg/g creatinine) as that of nonsmoking women living in the middle region of Sweden.

The body burden of cadmium (reflected by urinary cadmium) and signs of tubular damage were studied in a rural population (N = 62 nonsmoking 28- to 88-year-old adults) nonoccupationally exposed and living near a closed nickel-cadmium battery plant (92). People living within a vicinity of 500 m from the plant had higher median urinary cadmium concentrations than those living further away, but within 1 km of the plant and also higher concentrations than a reference group (table 2).

Smoking

As has already been mentioned, smoking is an important source of cadmium exposure. Figure 3 shows the concentrations of B-Cd in nonsmokers and smokers in different countries (17). In Sweden, smokers have, in general, 4–5 times higher B-Cd concentrations than nonsmokers. The concentrations in the kidneys, which reflect life-long exposure, as well as the risk for kidney damage, are about 2–3 times higher for smokers than for nonsmokers (16, 19).

Dietary habits

People who frequently eat food with a high cadmium content receive a higher dose of cadmium. However, due to modifying factors for cadmium absorption, the absorbed dose is not always proportional to the dietary intake of cadmium. Because of the comparatively high concentrations of cadmium in vegetables and roots, people eating a vegetarian diet have a higher intake of cad-

mium than people eating a mixed diet (30). However, due to the low bioavailability of cadmium in fiber-rich diets, the absorption is often not proportional to the dietary content of cadmium. On the other hand, the fibers may also inhibit the absorption of iron and lead to reduced iron stores and an increased absorption of cadmium.

Certain seafoods, in particular shellfish, also contain elevated cadmium concentrations. Women eating shellfish at least once a week had twice as high an intake of cadmium as women eating a mixed diet (31). The cadmium concentrations in blood and urine, adjusted for differences in iron stores, were also higher in the women with a preference for the shellfish diet. Oyster fishermen in New Zealand had clearly elevated B-Cd concentrations, with group averages of 1.9–3.7 µg/l among non-smoking fishermen, when compared with the 0.9 µg/l concentration for people not eating oysters (93).

Nutritional factors

The absorption of cadmium in the gastrointestinal tract is relatively low, of the order of a few percent. However, there is substantial individual variation (39) that may be due to interindividual variation in absorption rates or to dietary factors influencing absorption.

Although experimental data indicate that also the intake of calcium, copper, and zinc may influence the absorption of cadmium, there are no data for human subjects. However, iron status has been shown to influence the gastrointestinal absorption of cadmium both in experimental animals and in humans. In one study on intake and the uptake of cadmium in women with a preference for vegetarian or mixed diets, reduced body

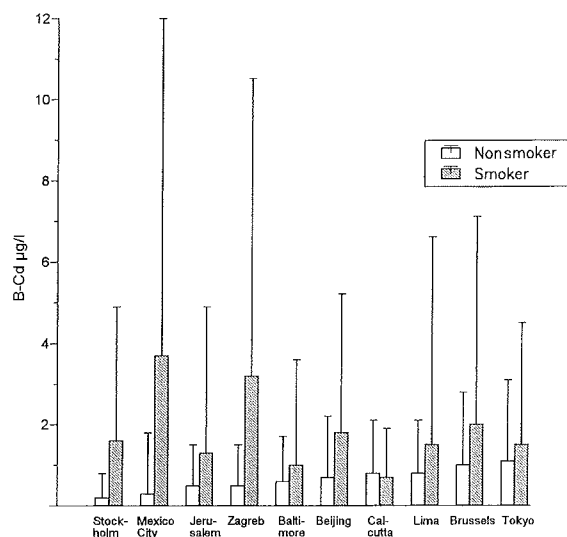


Figure 3. Concentrations of cadmium in the blood (B-Cd) of nonsmokers and smokers in different countries (median values and 90 percentiles) (17).

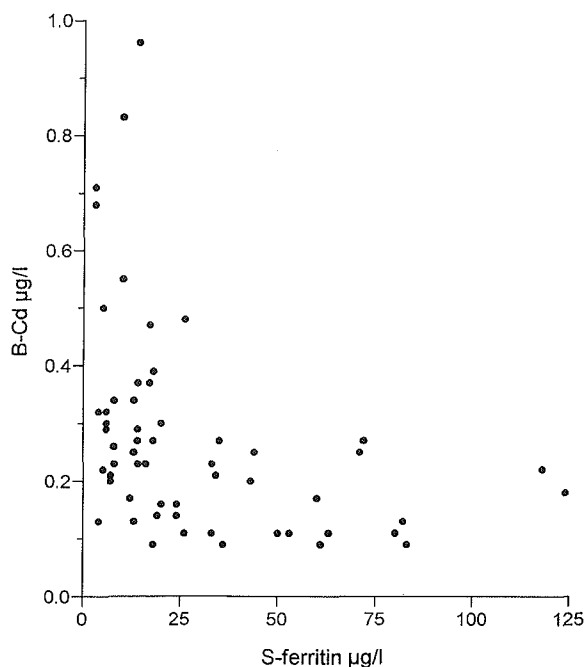


Figure 4. Blood cadmium (B-Cd) concentrations versus serum ferritin (S-ferritin) concentrations in Swedish women (30).

iron stores (serum ferritin) were highly associated with higher B-Cd concentrations (30). The B-Cd concentrations were mainly correlated with U-Cd (reflecting body burden) and serum ferritin, this correlation explained almost 60% of the variation in the B-Cd concentrations. No woman with adequate iron stores (serum ferritin >30 µg/l) had a B-Cd level above 0.3 µg/l, while those with depleted iron stores (serum ferritin <15 µg/l) had concentrations up to 0.8 µg/l.

Women

In general, women show higher concentrations of cadmium in blood, urine, and kidney than men. The reason for

this phenomenon is not known. Possibly, it is related to differences in the kinetics of cadmium. Reduced iron stores, which lead to increased absorption of dietary cadmium, are common for Swedish women. In fact, 10–40% of Swedish women of child-bearing age are reported to have empty iron stores (30, 94–97). In actual numbers, this would correspond to 175 000 to 700 000 women in Sweden. However, it seems likely that cadmium absorption, in parallel with iron absorption, increases before the stores are empty. Thus probably of the order of 1 million women have increased B-Cd concentrations, by about a factor of 2, due to low iron stores, as indicated by the relation between serum ferritin and B-Cd shown in figure 4. Furthermore, during pregnancy, the iron stores commonly decrease considerably. In a study of pregnant women in Stockholm (N = 146), 58% of the women had empty iron stores (serum ferritin ≤12 µg/l) at the end of pregnancy (61). Thus women constitute a risk group with regard to exposure to environmental cadmium. This conclusion is also evident from studies showing higher concentrations of cadmium in blood, urine, and kidney in women than in men. (See the section of biological indicators of exposure and dose beginning on page 11.)

Smoking adds to the body burden of cadmium, smokers having 2–3 times higher cadmium concentrations in their kidneys. In Sweden 22% of the men and 24% of the women are smokers. In 1963, 49% of the men and 23% of the women were smokers. Thus there are no indications of decreasing cigarette smoking among women. Among women, smoking is the most common (30%) in the age group 25–44 years. It can be estimated that, in Sweden, about 250 000 smoking women with low iron stores are likely to have 4–6 times the kidney cadmium concentrations of nonsmokers with adequate iron stores. In fact, in the study by Elinder et al (16), most of the persons with kidney cadmium concentrations exceeding 50 µg/g were women.

Kidneys

by Carl Gustaf Elinder & Gunnar Nordberg

Environmental exposure and the kidneys

The kidneys have a central, albeit unobtrusive, role in human health, and life is not possible without renal function. In the case of chronic and total renal failure, RRT is necessary in the form of dialysis and kidney transplantation. The prevalence of RRT is steadily increasing all

over the world, in most countries at an annual increase rate of about 5%. In western Europe, Japan, and the United States the prevalence of RRT varies between 300 to 1000 per million. The main reason for the continuing increase in RRT is an increased survival rate, thanks to the treatment. Before dialysis and kidney transplantation were introduced, all patients with end-stage renal disease

died. However, RRT is also increasing because more and more patients can be feasibly treated, and thus are accepted for treatment. The peak prevalence for dialysis treatment in, for example, Sweden is in the age group 70–75 years.

RRT is however very expensive for society or the insurance system and complicated and tedious for the patient. For example, the annual cost for hemodialysis in Sweden is of the order of USD 50 000 per patient. Preventing renal disease and failure is, therefore, very important.

Knowledge about the causes of renal diseases is limited. Diabetes, arteriosclerosis, and various types of autoimmune and hereditary diseases are important causes, but in many cases the etiology remains unknown. Certain drugs and chemicals, such as phenacetine and ethylene glycol, are known to elicit acute and chronic failure. Several chemicals (eg, polychlorinated volatile hydrocarbons) and metals (eg, cadmium, mercury, lead and chromium) can also exert more insidious nephrotoxic effects. A review of toxic nephropathies has been provided by WHO (98).

Normal kidney function and the early diagnosis of damage from toxic substances

Normal function of the kidneys. The kidneys play an essential role in the regulation of the fluid and electrolyte balance in the body, and in the control of blood pressure. Several potentially toxic substances, both exogenous (entering the body from the outside) and endogenous (produced in the body), are efficiently eliminated via the kidneys. The kidney capacity to purify the blood is considerable. In the adult, the filtration of blood through millions of glomeruli results in the production of approximately 125 ml of primary urine every minute, which corresponds to a production of 180 l/day. Primary urine consists of an ultrafiltrate of plasma. In the renal tubules the tubular cells usually reabsorb more than 99.9% of the substances (amino acids, small proteins, sugar, etc), salts, and fluid that the body needs to retain. The substances that are not reabsorbed are collected in the urine and excreted from the body. In some cases the kidneys may also actively excrete substances such as some drugs and toxins, and the purification of the blood thus becomes even more efficient.

The kidneys also have important endocrine functions. They produce hormones which regulate the blood pressure and a hormone which stimulates the production of red blood cells in the bone marrow (erythropoietin). Another hormone from the kidneys is calcitriol. It is produced in the kidneys from vitamin D activated in the liver. It stimulates the absorption of calcium from the intestinal tract and the normal mineralization of the bone and exerts negative feedback for the production of parathyroid hormone secretion.

Different types of renal damage. The most serious renal conditions are those which affect the GFR, which is the total amount of plasma filtered through the glomeruli per unit of time. The GFR is at its maximum when a person is around the age of 25 years, when it is approximately 125 ml/min. It then decreases gradually with advancing age. The GFR does not usually fall below 40 ml/min, even in elderly but otherwise healthy persons, and this rate is sufficient for obtaining an adequate purification of the blood and body fluids. The kidneys normally have a considerable reserve capacity. During various types of disease processes in the kidneys, the GFR can fall rapidly, for example, in some types of kidney inflammation (glomerulonephritides), or slowly, for example, in diabetic nephropathy or in some chronic inflammations of the kidneys. Symptoms of uremic toxicity, or uremia, do not usually appear until the GFR has fallen below 15 ml/min. Uremic symptoms, such as nausea, vomiting, weight loss, and anorexia, are caused by the body accumulating toxic substances that would normally be excreted in the urine.

Other types of glomerular lesions lead to excessive protein leakage. Normally only plasma substances with a molecular weight of less than 50 000 are filtered through the glomerulus to form primary urine. The glomerulus acts as a filter used for brewing coffee, where the coffee flavor should be filtered through, but the coffee grounds (analogous to blood cells and large proteins) should be retained in the filter. Heavy proteinuria, with the appearance of comparatively large plasma molecules such as albumin and immunoglobulins in the urine, reveals a glomerular lesion with increased permeability. A patient with a nephrotic syndrome loses several grams of proteins every day, and this level of loss can result in a protein deficiency in the plasma, with subsequent general swelling (edema) and weight gain. Even a moderately increased excretion of albumin, microalbuminuria, may suggest a glomerular lesion, which may progress and eventually affect the GFR. In recent years it has been shown that diabetic patients with microalbuminuria have an increased risk of developing severe renal insufficiency with a greatly reduced GFR later in life. In the type of kidney inflammation called glomerulonephritis, the glomerulus itself is inflamed and both blood cells and proteins are filtered through the glomerulus and appear in the urine (hematuria and proteinuria). This process can be compared to a torn paper filter.

In tubular lesions, the normal capacity of the tubular cells to reabsorb substances from the primary urine is reduced.

Early diagnosis of renal damage and impairment of renal function. The glomerular function, GFR, can be measured very accurately by different methods. In clinical practice the most commonly used methods measure how

quickly an injected foreign substance is cleared from the blood stream via the kidneys. The GFR is calculated from the slope of the elimination curve and when the result is interpreted, factors such as the age, height and bodyweight of the person must be taken into account. The substances used for injection are usually very small amounts of radioactively labeled Cr-EDTA or the contrast medium Iohexol®. One simple and widely used method for making a rough estimation of the GFR is to measure creatinine in plasma or serum. Creatinine is a low molecular-weight nitrogen-containing substance that is produced continuously in the body, mainly from the metabolism in muscle. Creatinine is filtered through the glomerulus and normally efficiently excreted in the urine. In renal insufficiency, the excretion via the urine is decreased and the concentration of creatinine in the blood increases. The normal serum concentration of creatinine (70–120 µmol/l) varies between persons, and it is affected by, among other things, the muscle mass and diet of the person. The concentration of creatinine does not usually increase until the GFR has been reduced to approximately half its normal value. Thus it is a sign of relatively advanced renal impairment.

An increased permeability of the glomerulus is easily detected by the presence of an increased amount of proteins or blood cells in the urine. Measuring albumin is especially useful. A 24-hour excretion of albumin in the urine in excess of 50 mg is pathological, but it does not necessarily indicate renal disease and does not always lead to a deterioration of the GFR. As in diabetes, microalbuminuria can be present in different glomerulonephritides, but it can also be found in perfectly healthy persons who, for instance, have orthostatic proteinuria.

Investigations to detect the presence of cells and albumin in the urine is commonly used in occupational medicine, with the aim to detect early glomerular damage. (See, eg, reference 98.) Studies, some of which were carried out in Sweden, suggest that it may be possible to use microalbuminuria for the very early detection of glomerular damage in persons who have been occupationally exposed to organic solvents. An increased excretion of albumin has also been reported in workers exposed to mercury.

There are several sensitive methods for determining the tubular function of the kidneys. Analysis of low-molecular plasma proteins, such as β_2 -microglobulin, RBP, or tubular intracellular enzymes (eg, NAG) are used to detect early tubular damage. In recent years many more early urinary indicators of tubular effects have been identified (99). However, when these tubular markers are analyzed it is important to remember that increased levels of proteins or enzymes are not diagnostic of renal damage caused by heavy metals. The concentration of β_2 -microglobulin in urine is increased, for instance, in

fever, urinary tract infections, and some other mild infections.

Cadmium exposure and the kidneys

It is well established that occupational and environmental exposure to cadmium can cause kidney injury. One of the first signs of the renal lesion is tubular damage characterized by an increased excretion of proteins such as β_2 -microglobulin with low molecular weight (2, 5, 100). In several areas of Japan, cadmium pollution of soil and subsequent human exposure via rice have caused endemic outbreaks of renal tubular disease (2, 5). Likewise, Belgian, Chinese, and German populations have been identified that have attained high cadmium body burdens and renal tubular damage from environmental cadmium exposure (101–104). Several of the more recent studies are summarized in the following discussion.

Research on health effects from cadmium has focused for a long time on tubular injury, which from a health point of view may have limited importance, as tubular proteinuria in itself does not give rise to any subjective symptoms or disease. Glomerular damage with a decreased filtration rate (GFR) may however also develop in occupationally exposed workers and in persons environmentally exposed to cadmium. Uremia was a common cause of death among Japanese farmers suffering from Itai-Itai disease, and end-stage renal disease has been observed by formerly heavily exposed workers. An increased overall mortality among residents with cadmium-induced renal damage has been reported for cadmium-polluted areas of Japan. Thus the important long-term prognosis of cadmium-induced renal damage has also been addressed in this section.

It has been claimed, on very shaky grounds, that cadmium-induced proteinuria is reversible (105). This is however not the case. It has repeatedly been shown that cadmium-induced tubular proteinuria *is not reversible* in almost all cases (55, 106–108).

Tubular damage

Friberg (109) was the first to observe proteinuria among cadmium-exposed workers. Butler & Flynn (110), in 1958, revealed that the proteinuria was of a tubular type. In severe cases of cadmium-induced nephrotoxicity, several signs of tubular damage are evident, for example, renal glucosuria, aminoaciduria, hyperphosphaturia, hypercalcuria, polyuria due to decreased concentration capacity, and a deteriorated ability to handle an acid (ammonium chloride) load (2, 5).

In recent years, several highly sensitive indicators of tubular damage have been developed and used in epide-

miologic studies of cadmium-exposed groups (99, 100, 111). In particular, the urinary excretion of β_2 -microglobulin, a low-molecular plasma protein with a molecular weight of 12 000, which can easily be determined with RIA methods, has frequently been used. The concentration of β_2 -microglobulin in plasma is usually around 2 mg/l. β_2 -Microglobulin is normally freely filtered through the glomerulus into primary urine. Under normal circumstances the proximal tubulus reabsorbs almost all the 360 mg of β_2 -microglobulin ($2 \text{ mg/l} \times 180$ of primary urine), and the normal urinary excretion of β_2 -microglobulin is less than 0.3 mg/24 h. This level of reabsorption implies that the amount of β_2 -microglobulin normally eliminated in urine comprises less than 0.1% of the filtered load, or, alternatively, that the tubular reabsorption capacity is 99.9% or more. A relatively small drop in the tubular reabsorptive capacity, from say 99.9% to 99.0% will bring about a 10-fold increase in the β_2 -microglobulin excretion in urine (5). Indeed, epidemiologists have a sensitive tool in ascertaining subtle renal effects of cadmium. An important drawback with the use of β_2 -microglobulin is, however, that the protein is unstable in the urine at low pH (<5.6). Such a low pH is not uncommon in random human urine samples, and it necessitates the collection of a second urine sample from the same person (100). Alternatively, all participating subjects could be asked to ingest a small amount of bicarbonate the night before the urine collection to ensure that all urine samples have a pH of ≥ 5.6 . Such a request is, however, not always feasible. There are several other equally sensitive, or even more sensitive, indicators of tubular damage [eg, RBP, apolipoprotein, human complex-forming glycoprotein (protein HC or α_1 -microglobulin), and Clara cell protein] which are not affected by a low pH in the urine, and they are all plasma proteins filtered through the glomerulus.

Other urinary markers that have been used to detect early kidney dysfunction are, for example, intracellular enzymes (proteins indicative of subtle tubulotoxic effects), NAG, an enzyme localized in lysosomes of the tubular cells, and human intestinal alkaline phosphatase (99, 100, 112). In particular, the urinary excretion of NAG seems to be very sensitive, and it does not show any threshold below which no associations are found between urine U-Cd and the urinary excretion of NAG. NAG exists as 2 different iso-enzymes, A and B. NAG-A is secreted into the urine by exocytosis, whereas NAG-B is released from the tubular cell membranes. NAG-B in urine is more or less linearly related to U-Cd (113).

Glomerular damage

Already in 1950 it was observed that cadmium-exposed workers also have a decreased GFR, measured by inulin

clearance, in addition to proteinuria (109). This finding has later been confirmed in studies of occupationally exposed workers (92, 107, 114–116), as well as among environmentally exposed Japanese farmers (117, 118). Roels et al (116) measured the GFR reserve capacity of 87 cadmium-exposed workers and 92 referents. Subjects with microproteinuria displayed a significantly decreased GFR, calculated from the creatinine clearance, but there was no evidence that cadmium accumulation had affected the functional reserve capacity of the glomerulus. Järup et al (92) examined solderers with previous heavy cadmium exposure and showed an association between the degree of tubular damage, or the cadmium dose, and a decrease in the age-adjusted GFR. (See figure 5.)

Cadmium-exposed workers sometimes show slightly increased urinary excretion of transferrin, albumin, and other high molecular-weight plasma proteins. The interpretation of this occurrence has been debated. It may indicate primary glomerular damage with increased permeability of larger proteins, such as albumin, or the albuminuria may be secondary to the decreased tubular reabsorption of the small amount of albumin normally filtered through the glomerulus (2, 119). Although competitive reabsorption of filtered plasma proteins may explain part of the albuminuria seen in workers with cadmium-induced tubular damage, Bernard and his collaborators in Belgium have shown that glomerular damage with increased permeability to high molecular-weight proteins may occur in humans independent of tubular damage (100). However, there are much more quantitative data available on cadmium-induced tubular proteinuria, which, therefore, is used in risk assessment.

Kidney stones

An increased prevalence of kidney stones in workers occupationally exposed to cadmium has been noted by

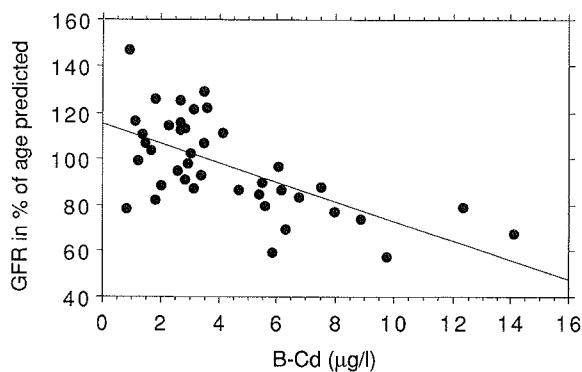


Figure 5. Glomerular filtration rate (GFR) as the percentage of reference age-adjusted values as a function of B-Cd in solderers previously exposed to cadmium.

several investigators (2, 5, 67). This increased rate of occurrence is possibly related to the increased urinary excretion of calcium, secondary to tubular damage (120). The dose-response relation between cumulative cadmium exposure and the age-adjusted cumulative incidence of renal calculi in a group of cadmium-exposed battery workers is shown in figure 6 (121).

Vitamin D

As discussed in the section beginning on page 31 of this document, cadmium may also affect bone. One important causative link is probably via the kidneys. Vitamin D is activated in the kidney to calcitriol (1,25 dihydroxy-vitamin D), which functions as a hormone with an important role in the absorption of calcium from the gut and in the calcification of bone. Calcitriol also possesses a negative feedback for the synthesis of parathyroid hormone. From two of the cadmium-polluted areas in Japan, the Jinzu and Kakehashi river basins, Aoshima & Kasuya (118) and Tsuritani et al (122) have reported a significant association between cadmium-induced renal damage, detected as β_2 -microglobulinuria or increased serum creatinine, and lowered plasma concentrations of calcitriol.

Dose-response relationship for the development of renal effects and prognosis

The relationship between exposure to cadmium and the prevalence of renal effects has been examined in a large number of studies. The long-term, or accumulated, exposure to cadmium is, however, not always easy to assess. Ideally, one would like to know the actual concentration of cadmium in the kidney cortex of each examined subject. Even if *in vivo* methods are available nowadays, it is not practically feasible to measure cadmium concen-

trations in the kidneys of large groups of persons. Thus such methods have rarely been attempted, mainly because of the practical problems and financial constraints. Another reason, perhaps even more important, is that the accuracy of the *in vivo* methods are not good enough for reliable individual dose assessment (68). Therefore, most epidemiologic studies of the health effects of cadmium exposure have relied on calculated cumulative doses based on food intake or workroom air concentrations or on biological monitoring, that is to say, on the measurement of B-Cd or U-Cd. In particular, U-Cd has proved to be useful. See further the section on biological indicators of exposure and dose beginning on page 11.

On the basis of cross-sectional studies of occupationally exposed workers, it was suggested in the 1970s that a urinary concentration of 10 $\mu\text{g/g}$ creatinine (10 nmol/mmol creatinine) would be a safe level, below which kidney damage would rarely develop (123). Roughly, this level corresponds to a kidney cortex concentration of 200 mg/kg, which has long been considered to be the "critical level" at which kidney damage is first seen. Because of the interindividual variation in susceptibility to cadmium, it was stated in a WHO document (5) that about 10% of persons with a cadmium level of 200 mg/kg in their kidney cortex and about 50% of persons with a cadmium concentration of 300 mg/kg in their kidneys would have renal tubular proteinuria.

However, recent reports, which are discussed in this section, indicate that this is a serious underestimation of the risk and an overestimate of the "critical concentration" of cadmium in the urine and kidney.

In the following presentation of the different reports, it is distinguished between studies on occupationally and environmentally exposed groups. In general, occupationally exposed groups are comprised of young or middle-aged men, whereas the general population also includes high-risk groups, such as women and elderly persons. Thus it is not surprising that effects in the form of kidney tubular damage are observed at lower levels of cadmium exposure in the general population than in industrial groups.

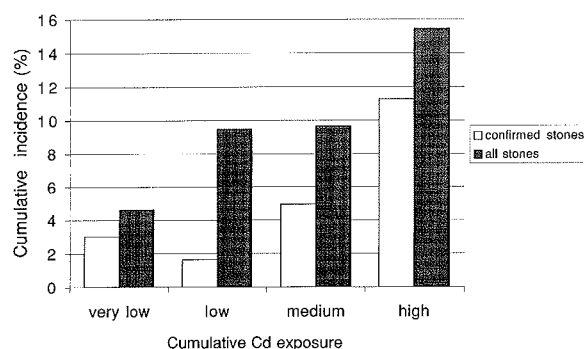


Figure 6. Cumulative incidence of kidney stones in relation to the estimated cumulative inhalative exposure of cadmium among cadmium-battery workers in Sweden.

Environmental exposure to cadmium and renal effects

Dose-response analysis

An important and frequently cited study of the effects of cadmium in the general population, the Cadmibel study, indicated that a significant proportion of a population, environmentally exposed to cadmium in Belgium displayed evidence of cadmium-induced renal damage already at U-Cd concentrations exceeding 2–3 $\mu\text{g/g}$ creatinine (100, 101). Altogether, 1699 persons between the

ages of 20 and 80 years were examined. Cadmium exposure was assessed from measurements of U-Cd excretion during 24 hours. Urinary excretion of RBP, β_2 -microglobulin, NAG, amino acids, and calcium served as early indicators of renal effects. After adjustment for possible confounders, such as age, significant associations were found between urine cadmium on one hand and all renal effect parameters on the other. When the examined population was divided into 4 equally sized groups, according to the urinary excretion of cadmium (<0.5 , $0.5\text{--}<0.9$, $0.9\text{--}<1.4$, and ≥ 1.4 $\mu\text{g}/24$ h) the prevalence of "elevated" RBP, β_2 -microglobulin, and NAG increased stepwise from about 3% to 8–10%. Although a cross-sectional study like this does not prove causality, the data are extremely interesting. The findings in the Cadmibel study does, in fact, agree with what has later been observed by others, and therefore it supports the hypothesis of a causal association.

In 1994, another extensive study on the renal effects of cadmium was published from Belgium (124). This time urine and blood samples from 703 randomly selected residents in 6 cadmium-polluted districts and 4 nonpolluted districts were analyzed. The urinary excretion of cadmium, β_2 -microglobulin, RBP, and NAG was significantly higher in the polluted districts. The mean cadmium excretion was, however, not very different (0.81 and 0.66 $\mu\text{g}/\text{g}$ creatinine in the polluted and nonpolluted districts, respectively). Significant associations were also found within the whole group between U-Cd and the urinary excretion of β_2 -microglobulin and NAG. In addition, significant rank correlations were noted between soil cadmium and U-Cd and GFR when calculated from serum creatinine, age, and gender.

From Germany, Jung et al (103) reported data on another population with possible environmental cadmium exposure. The investigation was primarily aimed at examining early kidney effects in 62 battery workers occupationally exposed to cadmium ("exposed group"), but it also included 36 persons working in a nearby plant, located 1.5 km from the cadmium plant and not considered to be occupationally exposed ("risk group"), as well as 73 persons living and working far away from the pollution source ("reference group"). Several significant associations were found between U-Cd and various renal effect parameters (eg, total protein, α_1 -microglobulin, RBP and NAG in urine). The prevalences of elevated α_1 -microglobulin, RBP and NAG in urine were significantly elevated both in the occupationally exposed group (18–32%) and in the risk group (11–22%). The average urinary excretion of cadmium in the exposed and risk groups was 9.8 and 5.4 $\mu\text{g}/\text{g}$ creatinine, respectively. If the risk group was indeed not occupationally exposed in some way or another, these data show that there is also heavy environmental exposure for European populations.

Järup et al (92) examined 72 persons living in the vicinity of a closed cadmium polluting industry in southern Sweden. Those living within 500 m of the plant had significantly elevated U-Cd (average around 1 $\mu\text{g}/\text{g}$ creatinine) and also displayed a high prevalence of elevated NAG in urine. (See also table 2 under Exposure and Dose.)

If these data, and the ones from the Cadmibel Study (101), are taken at face value, it seems apparent that early and subtle renal effects in the general population are induced already at the present levels of environmental exposure to cadmium in many areas of the industrialized world. The early signs of renal effects are detected in large groups already at U-Cd levels in the range of 0.5–2 $\mu\text{g}/\text{g}$ creatinine, corresponding to a renal cortex concentration of 10 to 40 mg/kg, that is to say, in the range where close to 50% of the adult Swedish population belongs.

Nogawa et al (125), in a summarizing report on the polluted Jinzu river basin in Japan, presented data on the association between U-Cd and the prevalence of kidney damage. Altogether 542 inhabitants over 20 years of age were examined. The prevalence of marked β_2 -microglobulinuria (≥ 5 mg/l) increased more or less on a linear basis from a few percent in the lowest exposure group, who had a U-Cd concentration of 3.8 $\mu\text{g}/\text{g}$ creatinine, to more than 50% in the high exposure groups, having U-Cd exceeding 40 $\mu\text{g}/\text{g}$ creatinine. Threshold limits for the U-Cd of the men and women were calculated to be 3.2 and 5.2 $\mu\text{g}/\text{g}$ creatinine, respectively. It should be noted that this cohort included a large proportion of elderly people and that the cut-off point of urinary β_2 -microglobulin was set about 10 times higher than what is typical because the detection limit for β_2 -microglobulin was high at that time.

In several studies (126) Nogawa has shown that a close association exists between the cumulative intake of cadmium from food, in particular from rice, the body burden of cadmium, the U-Cd, and the occurrence of renal effects. According to these studies, a lifelong intake of about 2 g of cadmium would, in Japanese subjects, bring about a U-Cd value of the order of 4 to 5 $\mu\text{g}/\text{day}$, which would elicit a significant rise in the prevalence of tubular damage. A lifelong intake of 2 g would correspond to a daily average intake of 80 μg of cadmium over 60 years. Recent studies, however, indicate that the threshold for renal effects is lower than 4 to 5 $\mu\text{g}/\text{day}$, and thus, as a consequence, it is also lower than the acceptable daily intake.

In 1982, a health examination was carried out on about 200 persons over 50 years of age in 4 cadmium-polluted areas of the Izuhara and Tsushima Islands, Japan (127). Urinary excretion of β_2 -microglobulin and α_1 -microglobulin (urinary protein HC) was determined to assess renal damage. Compared with what is usually

observed in nonoccupationally exposed persons in Sweden and Europe, the U-Cd concentration was about 5 times higher; the median U-Cd concentration was 6.6 (range 1.9–36.7) $\mu\text{g/g}$ creatinine. There was a close association between the effect parameters β_2 -microglobulin and α_1 -microglobulin in urine. Both correlated strongly with U-Cd. In this group of people, with a history of prolonged exposure to cadmium from rice, there was no evidence of a threshold; the urinary excretion of β_2 -microglobulin and α_1 -microglobulin in urine increased on a linear basis down to the lowest U-Cd levels, which were in the range of 2–10 $\mu\text{g/g}$. Many of the examined subjects, particularly women, displayed signs of more generalized renal damage with increased urinary excretion of total protein, phosphate, and uric acid and an increased serum concentration of urea and creatinine, indicating glomerular damage as well. A 10-year follow-up of the same population was carried out by Iwata et al (108). As a result of prefecture actions, for example, by replacing the soil in polluted rice fields with nonpolluted soil, the average daily exposure to cadmium from food was calculated to have dropped from around 200 $\mu\text{g/day}$ in 1969 to between 53 and 106 $\mu\text{g/day}$ in 1983. It was possible to reexamine 48 persons. There was no evidence that the cadmium-induced renal lesions were reversible. On the contrary, the tubular damage had, in most cases, been aggravated, in spite of the fact that oral exposure and U-Cd had decreased, the latter from 8.5 in 1982 to 6.0 $\mu\text{g/g}$ in 1989. Elderly persons in particular appeared to be at risk. Likewise, studies on cadmium-exposed inhabitants of the Kakehashi river basin have shown that β_2 -microglobulinuria is usually not reversible, it may even be aggravated (128). Furthermore, serum creatinine, indicative of more severe glomerular damage, tended to increase in most of the examined subjects (129).

Important observations on severe cadmium pollution and subsequent health effects have recently become available from China (104). The pollution source was a cadmium smelter, and human exposure took place via contaminated rice. The mean cadmium concentration in the most polluted area was 3.7 $\mu\text{g/g}$ rice, which is very high, also compared with what has been reported from the most severely polluted areas of Japan. In order to assess exposure and possible renal effects, urine was collected from 3 groups, each consisting of about 250 persons over 35 years of age, a reference group, and medium- and high-exposure groups. The average U-Cd concentrations, β_2 -microglobulin, and albumin increased from 0.33 $\mu\text{g/l}$, 0.14 mg/g creatinine and 3.8 mg/g creatinine, respectively, in the reference group to 10.7 $\mu\text{g/l}$, 0.53 mg/g creatinine and 9.0 mg/g creatinine, respectively, in the most heavily exposed group. When the whole population was stratified according to U-Cd, the prevalence of elevated β_2 -microglobulin and albumin

in urine increased stepwise from 4.9% in the subgroup with a U-Cd of $<2 \mu\text{g/l}$ to 51% for elevated urinary β_2 -microglobulin and 18% for urinary albumin among the subjects with U-Cd values of $>20 \mu\text{g/l}$.

Long-term prognosis

A recent study on inhabitants of the cadmium-polluted Kakehashi river basin in Japan (130) has reported worrisome results regarding the long-term prognosis of persons with cadmium-induced renal damage. Survival among 3178 inhabitants of a cadmium-contaminated area, who had been examined with regard to their kidney function during 1981–1982, was followed for 10 years. The 1981–1982 examination revealed that 16.8% of the examined group had urinary β_2 -microglobulin levels exceeding 1 mg/g creatinine. Total urinary protein excretion was elevated in 6.3%, urinary amino acids in 5.7% and urinary glucose in 10.9%. These renal effects had already been clearly shown to be related to environmental cadmium exposure from contaminated rice in several earlier studies and reports (131, 132).

As all the examined persons were over 50 years of age already in the early 1980s, considerable mortality had occurred ($N=296$). SMR values were calculated for those with and those without signs of cadmium-induced kidney damage. The total SMR was significantly below the national average for the group as a whole, but significantly increased for those with signs of cadmium-induced kidney damage. For the men with increased β_2 -microglobulin in their urine the SMR was 130, and for the women it was 146. The corresponding SMR values for men and women with increased urinary total protein and amino acids were 190 and 185 for the men and 188 and 142 for the women, respectively. Likewise, when the mortality of subjects with signs of cadmium-induced renal damage was compared with that of subjects without such signs, in Cox proportional hazard models, the increased risk for death was of the order of 1.4 to 2.0. The strongest association was found for total urinary protein excretion (table 4). This finding is reasonable, as it is a sign of more severe renal damage than urinary β_2 -microglobulin is. Nevertheless, for the women, the urinary β_2 -microglobulin level was an independent risk factor for death.

In a similar manner, Iwata et al (133) reported on the mortality experienced by 230 residents in another cadmium-polluted area of Japan, in Akita, who were at first examined during a health survey in 1975–1977. At that time 70 had clearly elevated levels of urinary β_2 -microglobulin, above 1 mg/g creatinine. In 1990, the vital status was checked. All told, 51 of the 160 subjects (32%) without β_2 -microglobulinuria had died as compared with 37 of 70 persons (53%) with β_2 -microglobulinuria — a significant difference. In addition, among the inhabitants with β_2 -microglobulinuria in a cadmium-

Table 4. Cox hazard ratio for mortality among inhabitants of the cadmium-polluted Kakehashi river basin of Japan, with and without signs of cadmium-induced renal damage.

Group	Number of	Percentage of all	Number of deaths	Hazard ratio ^a	P-value
All men	1424	100	296		
β_2 -microglobulin (≥ 1 mg/g)	205	14.4	99	1.4	< 0.05
Protein (≥ 100 mg/g)	88	6.2	47	2.0	< 0.001
Amino acid (≥ 0.3 mg/g)	29	2.0	14	1.8	< 0.05
All women	1754	100	278		
β_2 -microglobulin (≥ 1 mg/g)	329	18.8	136	1.8	< 0.001
Protein (≥ 100 mg/g)	112	6.4	63	1.9	< 0.001
Amino acid (≥ 0.3 mg/g)	151	8.6	44	1.4	< 0.05

^a The hazard ratio compares the mortality of persons with tubular damage with those without [derived from Nishiyo et al (130)]

polluted area on Sasu Island, in southern Japan, an increased overall mortality was observed (134). The mortality of 256 subjects (men and women combined) with urinary β_2 -microglobulinuria below the used threshold of 1 mg/g creatinine was below the expected (22 observed versus 31 expected), whereas the mortality among those with a urinary β_2 -microglobulinuria above 1 mg/g creatinine was elevated (40 observed versus 26 expected).

These important reports from 3 different areas of Japan provide strong support for the assumption that cadmium-induced renal damage is neither benign nor without clinical relevance. Subjects with signs of cadmium-induced renal damage have a roughly 40–80% increased annual mortality risk. Unfortunately there are, as yet, no data on the causes of death, but one would in particular anticipate an increased risk for end-stage renal disease as the cause, or contributing cause, of death. In this context it is noteworthy that the prevalence of RRT in Japan, where the cadmium pollution problems are the most severe, is about 2–4 times higher than in Europe (135). The reason for the very high prevalence and incidence of RRT in Japan, in comparison with other industrialized countries, is not known, but the possibility that cadmium may have a pertinent role should not be disregarded.

Occupational exposure to cadmium and renal effects

Dose-response analysis

Verschoor et al (136) reported their findings from an examination of 27 male workers with a “low level” of cadmium exposure giving rise to U-Cd levels in the range of 10–410 nmol Cd/l. The men were divided into 3 subgroups based on their urinary excretion of cadmium (<30, 30–<50, and ≥ 50 nmol Cd/l). The average uri-

nary levels of β_2 -microglobulin and NAG increased in each subgroup and therefore indicated that early renal effects were distinguished already in the U-Cd range of <50 nmol/l.

From Singapore, Chia et al reported their results of the examination of 92 workers in a nickel-cadmium battery factory (137). The prevalences of elevated β_2 -microglobulin, α_1 -microglobulin, and NAG in urine were clearly higher in the cadmium-exposed group than in a group of 122 unexposed referents. Within the exposed group, the prevalences of elevated urinary levels of α_1 -microglobulin and NAG were evident already at U-Cd levels above a few micrograms of cadmium per gram of creatinine.

An American study of workers occupationally exposed to cadmium reported a response of 10% tubular proteinuria at U-Cd concentrations of 5–7 μ g/g creatinine (138). Results from Swedish battery workers (139) followed the American findings and therefore suggested a critical level of around 3 nmol/mmol creatinine, below which significant renal effects in the form of tubular proteinuria can rarely be detected. Depending on age, the prevalence of β_2 -microglobulinuria was 5% to 15% at U-Cd levels above 3 nmol/mmol creatinine.

Age influences the dose-response relationship, elderly persons being more susceptible (139). In an examination of Swedish battery workers, a 10% prevalence of tubular proteinuria already at 1.5 nmol/mmol creatinine was found in an older age group, whereas this response level was reached at 5 nmol/mmol creatinine in a younger age group. (See figure 7.) The higher prevalence in older people could be explained by degenerative changes that occur in the renal tubuli from aging and that give rise to an increased sensitivity to cadmium and an acceleration of cadmium-induced renal tubular damage.

Age may constitute an important confounder when the long-term health effects of cadmium accumulation in the kidneys is being examined. Kidney function normal-

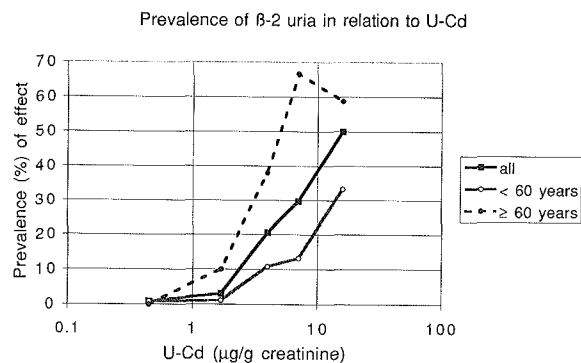


Figure 7. Prevalence of tubular β_2 -microglobulinuria (β_2 -uria) in relation to the U-Cd of cadmium-exposed battery workers.

ly deteriorates with age, independent of cadmium exposure. This deterioration is the most evident for GFR, but possibly, at least to some extent, aging affects tubular function as well. The effect of aging on the normal urinary excretion of β_2 -microglobulin appears, however, to be limited, and an increased prevalence of urinary β_2 -microglobulin in the general population is not due to aging only (140). In some of the more recent studies on the renal effects of cadmium [eg, the Cadmibel studies (100, 101)], the age factor has been accounted for in the statistical analysis.

The Commission of the European Community has supported a European collaborative study (99) aimed at identifying early indicators of cadmium toxicity, in particular renal toxicity. Altogether, 172 subjects with different occupational exposure provided blood and urine samples. These samples were analyzed for a large number of early indicators of renal effects, 4 in serum and 26 in urine. The examined group was divided into 3 exposure categories according to the U-Cd (<1.5, 1.5–5, and >5 $\mu\text{g/g}$ creatinine). More than half of the urinary effect parameters were increased in the subjects with moderate and high U-Cd. Among the most sensitive indicators of nephrotoxicity were α_1 -microglobulin, NAG, thromboxane β_2 , and RBP.

Long-term prognosis

Twenty-three workers with previous exposure to cadmium and tubular damage were reexamined 5 years after the cessation of exposure. Not surprisingly, B-Cd, which, to great extent, reflects current exposure, decreased, whereas U-Cd, which primarily mirrors the kidney or body burden of cadmium, was not significantly changed. More important was the observation that tubular proteinuria was irreversible and, in particular, that the GFR, assessed by the serum creatinine and β_2 -microglobulin concentrations, deteriorated faster with increasing age than were predicted (106, 107). Similar observations were made by Järup & Elinder (141) when the GFR was

measured in 16 workers in 1983, and again in 1986 by a Cr-EDTA clearance technique. The data suggested that the GFR of workers with previous (before 1978) heavy exposure to cadmium, as reflected by a high B-Cd level, deteriorated more rapidly than it did in a reference group. Furthermore, there was a significant association between B-Cd, reflecting the cumulative dose, or the β_2 -microglobulinuria, and a reduction in GFR (92).

Overall evaluation of the risk for renal toxicity from cadmium exposure

It is obvious from the preceding text that cadmium has important nephrotoxic properties, affecting both tubular function and the more clinically important glomerular function. Until the time when the WHO criteria document on cadmium was prepared in the mid-80s most analyses of dose-response from environmental or occupational exposure to cadmium were based either on relatively crude methods to detect the renal damage or on cross-sectional examinations of occupational groups of generally healthy middle-aged male workers. During the last 10 years much more sensitive methods have become available with which to detect renal damage. Large populations (including elderly people and others with a potentially increased susceptibility to cadmium) exposed to relatively low levels of cadmium have also been examined.

Renal damage, associated with low-dose cadmium exposure in humans, is similar in nature to the age-related changes in tubular and glomerular function. There are no specific indicators (except for elevated cadmium concentrations in blood, urine or tissues) that can distinguish age-related changes from cadmium-induced ones. It is, however, possible in epidemiologic studies to distinguish cadmium-related changes from age-related ones by comparing age-standardized groups with different cadmium exposure. With such an approach the effect of cadmium exposure can be demonstrated in a specific age group, even though there may be a considerably higher “background” prevalence of renal tubular damage in older age groups than in younger ones.

In figures 8 and 9 an attempt has been made to summarize more recent studies presenting data on the prevalence of β_2 -microglobulinuria (figure 8) or elevated urinary values of NAG or protein HC (figure 9) in relation to U-Cd, for groups of people. The different studies are not readily comparable, as different cut-off points have been used for what is regarded as “elevated” or “abnormal”. For example, Nogawa et al (125) used a very high cut-off level for diagnosing urinary β_2 -microglobulinuria (≥ 5 mg/l). In addition, exact data on U-Cd were not always available in the reports. It should also be born in

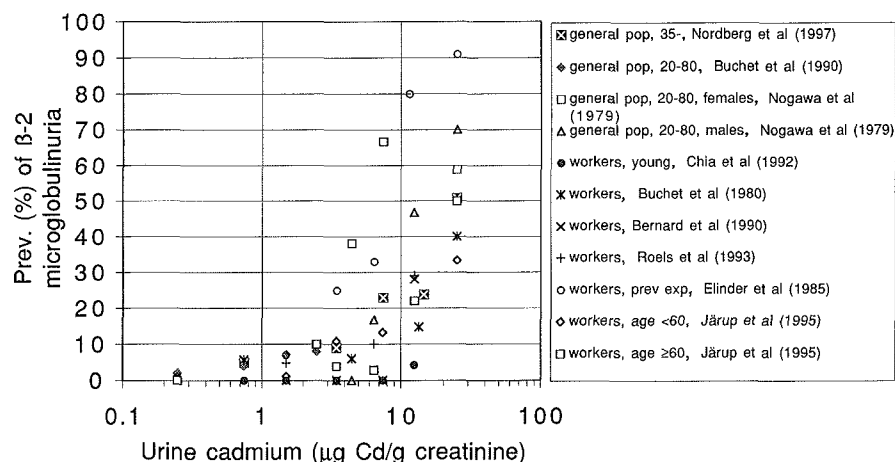
Meta-analysis of elevated U- β -2 in relation to U-Cd

Figure 8. Dose-response data for "elevated" β -2-microglobulin in urine (U- β -2) in relation to U-Cd in some examined populations. (prev = prevalence, pop = population)

Meta-analysis of U-HC & U-NAG

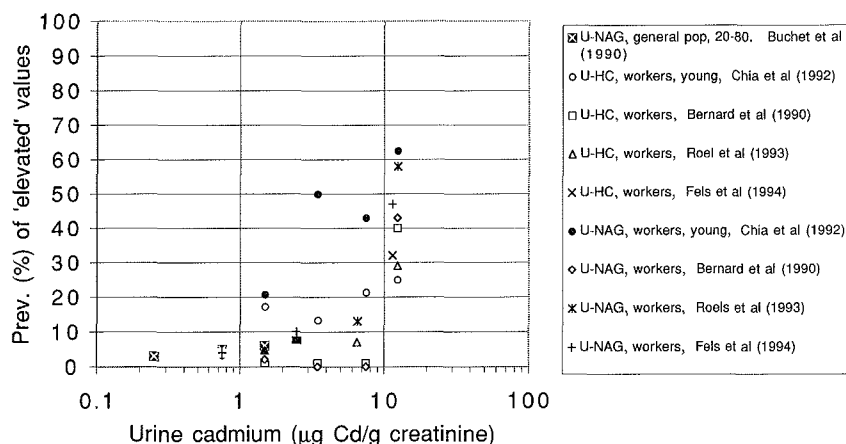


Figure 9. Dose-response data for "elevated" levels of N-acetyl- β -D-glucosaminidase (NAG) and protein HC in urine (U-NAG and U-HC, respectively) in relation to U-Cd in some examined populations. (Prev = prevalence)

mind that the examined groups were very different, varying from young male workers to elderly environmentally exposed women. Taken together, it is nevertheless obvious that the exposure limit of 10 $\mu\text{g/g}$ creatinine, corresponding to a kidney cortex concentration of around 200 mg/kg, that was considered sufficient for U-Cd in the 1980s is no longer adequate.

Friberg et al (2) in the summary of their extensive review on cadmium and health wrote that "At kidney cadmium concentrations of about 180 mg/kg (corresponding to about 9 $\mu\text{g Cd/g}$ creatinine in urine) approximately 10% of the population would have reached their critical concentration [p 253]". This cortical concentration was called PCC-10, a population critical level of 10%. It was emphasized that this estimate was uncertain although based on the best available data at the time. It was concluded that a 1% response in terms of increased β -2-microglobulin in urine would be expected as a result of a daily intake of 50 μg over 45 years. With similar

assumptions concerning the critical concentration of cadmium in renal cortex (10% risk at 200 $\mu\text{g/g}$ in renal cortex), Nordberg & Strangert (142) and Holmberg et al (143) arrived at a similar or slightly lower risk of tubular proteinuria for the general population. They also calculated the expected prevalence of tubular proteinuria in women with low iron status. Long-term intake of 70 μg per day would give rise to a 7% prevalence of proteinuria according to these calculations. The new data reviewed in this document clearly indicate that early renal effects of cadmium are prevalent at lower levels than those known when *Cadmium and Health* (2) was written in the early 1980s. Table 5 summarizes what is evident from figures 8 and 9. According to this table, the lowest level of cadmium in the kidney cortex at which renal effects can be detected in a small percentage of the population is around 50 mg/kg, whereas the PCC-10 would be around 125 mg/kg. It can be estimated from figures 8 and 9 and table 5 that, in order to prevent renal tubular damage that

Table 5. “Best guess” of prevalences of tubular effects in the general population in different intervals of cadmium in kidney cortex, based on all available data published until mid-1997. The studies are presented in the text and in figures 7 and 8. The table also includes the “rule of thumb” relation between kidney and U-Cd in environmentally exposed populations.

Cadmium in kidney cortex (mg/kg)	U-Cd ($\mu\text{g/g}$)	Percentage effect
< 50	< 2.5	0
51–60	2.75	1
61–70	3.25	2
71–80	3.75	3
81–90	4.25	4
91–100	4.75	5
101–110	5.25	6
111–120	5.75	8
121–130	6.25	10
131–140	6.75	12
141–150	7.25	14
151–160	7.75	17
161–170	8.25	20
171–180	8.75	23
181–190	9.25	26
191–200	9.75	30
> 200	> 10.25	> 35

can proceed to clinical disease and perhaps contribute to early death, cadmium levels in the kidneys and in urine should be kept below 50 mg/kg and 2.5 $\mu\text{g/g}$ creatinine, respectively. In view of the fact that large populations in Europe and elsewhere are already close to these levels, actions to decrease human exposure to this metal are well founded (144).

Mechanisms related to the expression of kidney effect

by Gunnar Nordberg

Cadmium can give rise to both tubular and glomerular effects on the kidney, as described in detail in the preceding sections of this text. This section deals with mechanistic information on the importance of understanding how renal damage results from cadmium exposure.

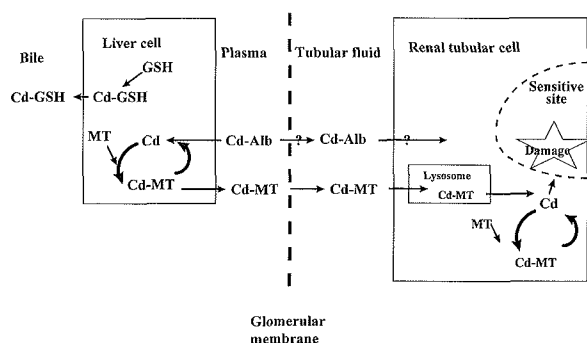


Figure 10. Pathways of cadmium into the kidney. (GSH = glutathione, Alb = albumin)

Toxicokinetic aspects on the transport of cadmium to the kidney

With regard to the transport and distribution of cadmium in mammals, a basic detailed description has been given (33), and the same information constituted the background for the WHO summary of these aspects of cadmium toxicology (5). Conditions influencing the uptake of cadmium via the gastrointestinal tract were reviewed (148). These aspects concerning cadmium kinetics can be summarized as follows: cadmium uptake in the gastrointestinal tract is limited; usually less than 5% (5 %) of ingested cadmium is taken up by the blood. Uptake in the gastrointestinal tract may, to some extent, be related to MT synthesis in the intestines (37). However, in a recent paper (140), higher MT concentrations in tissues of transgenic mice had no appreciable effect on the concentration of cadmium in tissues when compared with the concentrations in controls with normal tissue concentrations of MT.

A scheme illustrating the pathways of cadmium into the kidney is shown in figure 10.

Immediately after uptake from the gastrointestinal tract or the lungs, cadmium is mainly bound to albumin and other larger proteins in blood plasma. There is a pattern with proportionally more of plasma cadmium in a low molecular-weight form (probably mainly bound to MT) when low doses of cadmium are given by the oral route than when large doses are given, particularly if given by injection. There is also a time dependence for plasma binding, with a substantial proportion of plasma cadmium being bound to low molecular-weight plasma proteins at longer time intervals after a single administration.

Cadmium bound to albumin is taken up to a large extent by the liver, where the complex is split and cadmium can cause toxicity to liver cells (at relatively high doses, particularly by injection). Cadmium also induces the synthesis of MT in liver cells, and gradually an increasing proportion of the cadmium in liver is bound to MT. In the early phase after a single administration of cadmium, cadmium in plasma is mainly bound to albumin, and the uptake of cadmium by the kidney is limited.

In previous studies (33) it has been shown that cadmium is excreted in bile mainly bound to glutathione (figure 10). In a recent study (150) further evidence in support of this finding has been provided.

A long time after a single exposure, or in long-term exposure, a considerable proportion of plasma cadmium is bound to MT, probably partly originating from the liver (figure 10). Cd-MT, because of its small molecular size, is efficiently filtered through the glomerular membrane and taken up by renal tubular cells. The uptake of Cd-MT may be more efficient in cells which have previously been exposed to cadmium than in cells which have not (151).

In long-term exposure there is a slow release of Cd-MT from the liver to blood. This transport phenomenon has been confirmed by transplanting cadmium-containing livers to noncadmium-exposed animals and demonstrating the gradual uptake of cadmium in the kidney (152). After the uptake of Cd-MT into renal tubular cells via pinocytosis, MT is metabolized in lysosomes and cadmium ion is released. MT binding in plasma and tissues has thus been considered to be of considerable importance for cadmium distribution after uptake.

In a study of transgenic mice, lacking MT-I and MT-II (MT-null mice), it was found that the elimination of cadmium was much faster than in control mice; this finding confirms the role of MT in the tissue retention of cadmium (149, 153). It was also observed that the renal cadmium concentration continued to increase with time in control mice but not in MT-null mice; this finding confirms the important role of MT in the transport of cadmium to the kidney (154).

Cadmium accumulating in the kidney is probably largely bound to the MT that is synthesized *de novo* (33). This process may be responsible for the long biological half-time of cadmium in the kidney and its accumulation during long-term exposure. It has been estimated that the biological half-time of cadmium in the kidney is on the order of 10 to 30 years in humans. Such a long biological half-time explains why cadmium accumulates constantly up to approximately 50 years of age in humans.

Cellular targets for the cadmium role of membrane damage and protective cadmium-binding proteins

As mentioned, in long-term exposure to cadmium, cadmium continuously accumulates in the liver and kidneys. Cd-MT is transported to renal tubules (figure 10). The first reports on renal damage after the injection of Cd-MT to experimental animals were published by Nordberg et al (154), who interpreted their data as indicative of renal damage occurring subsequent to the dissociation of cadmium from Cd-MT, an occurrence compatible with the view later developed by Fowler & Nordberg (155).

Evidence supporting a hypothesis implying that cellular membranes are the primary targets of cadmium nephrotoxicity after dissociation of the Cd-MT complex has been provided by Nordberg et al (156). Rats with preinduced MT synthesis were compared with control rats with a low cellular MT concentration. Both groups were given a subcutaneous challenge dose of radiolabeled Cd-MT. A considerably larger proportion of the radiolabeled cadmium in the subcellular membrane fraction was bound to high molecular-weight proteins in the control animals than in the ones with MT-induced synthesis. In the latter group, a larger proportion was bound to fractions corresponding to MT and possibly other low molecular-weight proteins in the membrane (156). The animals with preinduced MT synthesis were protected

against the toxic effects of Cd-MT, whereas the control animals later developed nephrotoxic effects. Another observation, which may be of importance when mechanisms of cadmium nephrotoxicity are under consideration, is the early perturbation of calcium metabolism preceding the development of proteinuria after Cd-MT injection (157).

It is also interesting to note that, in studies of the uptake and binding of calcium to membranes isolated from the renal cortex of Cd-MT exposed animals, there is a considerably lower binding and uptake in the exposed animals than in the controls. This is true both in luminal and, particularly, basolateral membrane vesicles (157). There is also evidence that transport mechanisms in brush border membranes exposed to cadmium *in vitro* are affected. (See, for example, reference 158.)

The observations described in the foregoing paragraph were made *in vitro*, in membranes or membrane vesicles obtained from animals in single-dose experiments. In such experiments the disturbances in renal tubular function were reversible. In long-term exposures, or when repeated doses of Cd-MT are given with short intervals (159), irreversible changes in the urinary excretion of calcium and a longer perturbation of protein excretion in urine are seen. These experimental models of cadmium-induced nephropathy reproduce more of the features of human cadmium-induced renal tubular damage than single dose experiments do. Studies by Sudo et al (160) demonstrated renal damage after repeated subcutaneous high doses of cadmium chloride. In these studies it was indicated that cadmium bound to cellular membranes in the kidneys was involved in the manifestation of renal injury.

Apoptotic cell death (161), as well as other cytotoxic changes, have been reported (162). As has already been mentioned, cellular calcium metabolism is perturbed in cadmium-induced renal damage. Since apoptosis may be induced by the perturbation of cellular calcium metabolism, it seems likely that this type of cell death would occur in cadmium toxicity to the kidney. Tanimoto et al (161) observed apoptotic cell death in rats exposed to subchronic cadmium intoxication by repeated subcutaneous injections.

Apoptosis has also been observed in human kidney cell lines. Ishido et al (163) found that there was DNA fragmentation after the exposure of kidney cells to cadmium *in vitro*, and the fragmentation led to apoptotic cell death. Hamada et al (164) found that cells exposed to relatively low concentrations of cadmium chloride displayed apoptosis, particularly when exposed to a cadmium-containing protein complex with characteristics similar to MT. Liu et al (165) described the cytotoxicity of cadmium to renal proximal tubule cells and showed that cells from rats pretreated with zinc were less sensitive to cadmium chloride toxicity, and Blumenthal et al (166)

compared cadmium ions and Cd-MT on cultured kidney tubule cells. They found that Cd²⁺ inhibited the cotransport of Na⁽⁺⁾ glucose while Cd-MT did not.

Based on available evidence, a model for the mechanism by which cadmium exerts its effect on the renal tubule has been described. (See reference 167 and also figure 10.) It is assumed that the rate of influx of Cd-MT into the renal tubular cell compartment on the one hand, and the rate of de novo synthesis of MT in this compartment on the other, regulates the pool of intracellular “free” cadmium ions that can interact with cellular membrane targets in the tubules. When there is efficient MT synthesis, an influx of Cd-MT into the lysosomes is limited, the free cadmium pool is limited, and no membrane damage occurs. Calcium transport in the cell is normal. When Cd-MT influx into the lysosomal compartment is high and de novo synthesis of MT is deficient, the free cadmium pool is sufficiently large to interact with membrane targets to block calcium transport routes, and there is deficient uptake and transport of calcium through the cell. This deficiency gives rise to increased calcium and protein excretion in urine. It is possible in animal models to inject Cd-MT and induce nephrotoxicity by a high influx of Cd-MT into the renal tubule compartment and therefore overload the sequestering mechanism of the de novo cellular synthesis of MT and, in the most acute models, possibly also bring about a direct toxic effect on the brush border membrane. Such acute toxicity does not occur in human exposure that takes place by oral or inhalation routes, which can only provide a limited flow of Cd-MT.

In exposure situations similar to those occurring in humans, renal toxicity is not expressed until the total tissue concentration of cadmium in the renal cortex reaches between 50 and 300 mg/kg. Cadmium released intracellularly from MT, transported via plasma from other organs in the body, provides only part of the “free” cadmium pool, and another part is derived from the comparatively large amounts of Cd-MT accumulated intracellularly in long-term cadmium exposure. Renal tubular damage in some persons at different total concentrations of cadmium in the kidney may have different explanations, but one important source of such variation may be the variable ability of people to synthesize MT and other protective components. These hypotheses require further confirmation before they can be considered fully established.

Influence of zinc and copper on cadmium nephrotoxicity

Data on the effects of zinc or copper on cadmium toxicity have been summarized by Nordberg (168). In an experiment on rats, Liu et al (169), using a factorial experimental design, showed that proteinuria caused by Cd-

MT injection could be more efficiently reduced by pretreatment with zinc injections than with copper injections while excessive calcium in urine and renal cortex could be more efficiently reduced by injections of copper than of zinc. Cadmium retention was markedly reduced in renal cortex and increased in liver by copper pretreatment, while the urinary excretion of cadmium was significantly lower in these rats (170). The production of MT in liver and renal cortex was induced more efficiently by copper than by zinc. The efficient protective effect of copper against calciuria can thus be explained by both increased MT induction and less accumulation of cadmium in the renal cortex. Renal tubular cells isolated from rats given zinc pretreatment in vivo not only displayed increased MT concentrations, but also increased expression of other low molecular-weight cadmium-binding proteins, namely, heat shock proteins (163). These proteins may serve an important protective role, as MT does. In studies by Liu et al (171) MT-I and MT-II knock-out (MT-null) mice were used to determine the roles of MT in cadmium-induced hepatotoxicity and nephrotoxicity, as well as in zinc-induced protection. The MT-null mice were more sensitive to intraperitoneal hepatotoxicity from cadmium chloride. Zinc pretreatment prevented the hepatotoxicity in the control mice only. MT-null mice were as susceptible as the controls to intravenous Cd-MT nephrotoxicity. Considering the studies by Liu et al (64), in which renal tubular cells from rats treated in vivo with zinc were shown to have an increased level of heat shock proteins in addition to increased MT, the findings by Liu et al (171) may possibly be explained by the induction of protective proteins other than MT by zinc pretreatment of renal tubular cells.

Cadmium-induced renal tubular damage — increased sensitivity in diabetics

Data from animal experiments support the possibility of an increased susceptibility for cadmium nephropathy in diabetics. It is of interest therefore to consider animal models in which the metabolic situation simulates type I and other animal models in which type II diabetes is simulated.

Diabetes induced in animals by the injection of streptozotocin

Streptozotocin-induced diabetes in animals is similar to insulin-dependent diabetes or type I diabetes in humans. In streptozotocin-induced diabetes both an increased resistance and an increased susceptibility to cadmium-induced renal damage have been observed. In a long-term experiment Bernard et al (172) gave cadmium in drink-

ing water (100 ppm over 2.5 months) to rats with streptozotocin-induced diabetes and uninephrectomy and compared them with similar animals without diabetes. The animals with diabetes developed more prominent nephropathy in terms of an increased excretion of albumin, transferrin, and immunoglobulin G compared with the nondiabetic animals. It should be noted that both long-term exposure and uninephrectomy were required in these studies to induce the effects.

In experiments performed during shorter time intervals, an increased resistance was demonstrated against a cadmium concentration of 0.4 mg/kg body weight subcutaneously as Cd-MT (173). In this experiment there was an increased binding of cadmium to MT in the liver in the streptozotocin-injected animals. The animals were studied 24 hours after the injection of Cd-MT, and it was demonstrated that there was an increased binding of cadmium to MT in the liver and that there was a decreased excretion of transferrin, albumin, and total protein in relation to the dose of streptozotocin given. The results indicate that there is an induction of MT by streptozotocin which protects the animals against nephrotoxicity by Cd-MT in the acute phase.

Other animal models for diabetes

Other animal models, like that with Umeå obob obese mice, are similar metabolically to type II diabetes. It was shown by Jin et al (174) that there is an increased susceptibility to the development of proteinuria and calciuria induced by Cd-MT in Umeå obob mice when they are compared with normal mice.

In an experiment by Jin & Frankel (175) there were indications that Cd-MT nephrotoxicity is increased in genetically diabetic hamsters when compared with normal Chinese hamsters. The Chinese hamster develops a subnormal pancreatic insulin release, insulin resistance in the liver, and sometimes hyperinsulinemia. These animals develop diabetic nephropathy with polyuria, polydipsia, albuminuria, increased glycosylation activity in kidney, increased glomerular size, capillary dilation, increased mesangial cell number, thickened glomerular membrane, and reduced number of anionic sites in the glomerular basement membrane. Further studies on this and other animal models are required to elucidate the conditions under which cadmium induces renal damage in diabetics, and also the mechanism through which the damage occurs.

Bone

by Lars Järup

Osteopenia may be caused by both osteomalacia or osteoporosis, the latter being by far the most common. Osteomalacia is characterized by an abnormally high ratio of inadequately mineralized bone matrix to mineralized bone. The most common causes of osteomalacia are impaired vitamin D metabolism and loss of renal tubular phosphate. The most common forms of generalized osteoporosis is senile osteoporosis, which is a gradual loss of skeletal mass with advancing age. Postmenopausal osteoporosis refers to the increased bone loss seen in women after menopause. The pathogenesis is not clear, but it probably involves a combination of decreased bone production and increased resorption.

Accelerated bone loss after menopause has been associated with a decrease in estrogen levels, which not only induces an imbalance at bone remodeling sites, but also can increase the overall rate of bone remodeling. Certain nutritional and life-style factors, such as an inadequate intake of calcium, may contribute to low bone mass independently of estrogen level. Such factors may

therefore further increase a woman's risk of developing postmenopausal osteoporosis. Postmenopausal osteoporosis is more common in white and Asian women than in women of other races. Furthermore, the prevalence of postmenopausal osteoporosis is high in the Nordic countries, particularly in Sweden.

The mechanisms behind cadmium-induced bone damage are not fully clear, but several different possibilities have been suggested (176). One possible mechanism may be the dysfunction of tubular cells as the cadmium concentration increases. The normal activation of vitamin D₃ to the potent hormone 1,25 dihydroxy-calci- triol in the tubular cells may then be reduced and lead to decreasing calcium absorption from the gut and impaired bone mineralization (177).

There is also increasing evidence that cadmium may act independently on bone tissue and that also persons without previous renal lesions may be affected. It has, for example, been suggested that some prostanoids may play a part in the toxicity of cadmium in bone (146).

Effects in humans

Environmental exposure

Prolonged exposure to cadmium may give rise to bone disease, which was first reported from the Jinzu river basin in Japan, where about 150 cases of Itai-Itai (“ouch-ouch”) disease have been recognized (178). Exposure to cadmium was caused by contaminated river water that was used for irrigating rice fields. The Itai-Itai patients were mostly women over 40 years of age who had lived in the endemic area for more than 30 years. The cadmium content in the skeleton of Itai-Itai patients has been found to be several times higher than in unexposed persons. In a study of 46 Itai-Itai patients the average concentration of cadmium in bone was 2.7 µg/g wet weight in men and 1.8 µg/g wet weight in women. The bone cadmium concentrations in referents were 0.3 and 0.6 µg/g wet weight, respectively (179).

Itai-Itai disease is characterized by multiple fractures and distortion of the long bones in the skeleton; these occurrences cause severe pain in the affected persons. The disease exhibits a mixed pattern of osteomalacia and osteoporosis in combination with kidney damage (2).

In the Cadmibel study, the investigators found a positive relationship between U-Cd and both serum alkaline phosphatase activity and the urinary excretion of calcium. The regression coefficients obtained after adjustment for significant covariates indicated that serum alkaline phosphatase and urinary calcium rose by 4% and 0.25 mmol/24 h, respectively, when U-Cd increased 2-fold (180). The findings suggest that calcium metabolism is gradually affected as cadmium accumulates in the body. The authors concluded that the morbidity associated with the latter phenomenon is still unknown. Furthermore, Belgian studies noted that serum alkaline phos-

phatase activity and the urinary excretion of calcium correlated significantly and positively with U-Cd in both men and women (181). It is reasonable to assume that calciuria increases the risk of osteoporosis.

In a recent study involving women in Stockholm (50 to 70 years of age), a significantly increased excretion of urinary calcium was found in women excreting cadmium levels of more than 1 nmol/mmol creatinine versus women with lower U-Cd (figure 11), which is in accordance with the Belgian findings. The mean urinary calcium concentration was 3.2 mmol/l in the subgroup of women with U-Cd levels of less than 1 nmol/mmol creatinine (N=75), whereas women excreting more than 1 nmol/mmol creatinine (N=8) had a mean urinary calcium level of 6.1 mmol/l (P=0.004) (Järup et al, unpublished data).

In a Japanese study, with the objective of evaluating the use of serum bone Gla protein as an indicator of bone damage in cadmium-exposed subjects, the degree of osteopenia in cadmium exposed-subjects was evaluated with a microdensitometry method (182). When compared with unexposed subjects, their levels of serum creatinine and bone Gla protein, U-Cd, and β_2 -microglobulin and B-Cd were higher, while the levels of serum inorganic phosphorus and the microdensitometric indicators were lower in the cadmium-exposed group. When multivariate analysis was applied to the data of the cadmium-exposed subjects, the bone Gla protein level showed a significant association with the microdensitometric indicators among the men. Among the women, both B-Cd and bone Gla protein were significantly associated with the microdensitometric indicators. A gender difference was found in the relationship between bone metabolic markers and osteopenia. The investigators also found significant correlations between B-Cd or U-Cd and serum bone Gla protein for both genders, a result indicating a

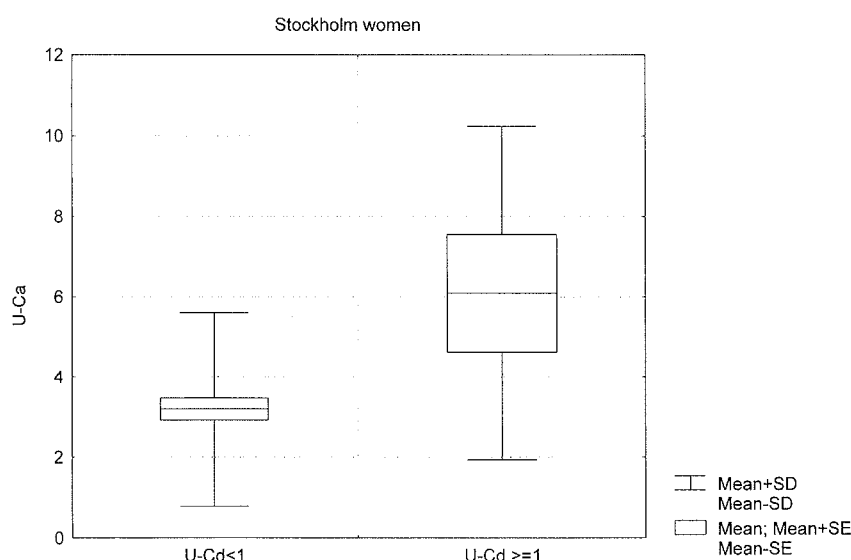


Figure 11. Excretion of urinary calcium (U-Ca) in Stockholm women in relation to the urinary cadmium (U-Cd) concentration.

dose-effect relation between cadmium dose and the degree of bone injury, as estimated by serum bone Gla protein (183).

Increased susceptibility to cadmium-induced bone injury in women

A Japanese investigation evaluated gender-related differences in susceptibility to cadmium-induced bone damage (122). Vitamin D in serum decreased significantly with decreasing creatinine clearance and the percentage of tubular reabsorption of phosphate; it also decreased significantly with increasing serum creatinine and serum β_2 -microglobulin concentrations in the women exposed to cadmium, but not in the men exposed to cadmium. The results suggest that renal damage due to cadmium exposure leads to decreased vitamin D levels in serum and increased serum PTH levels and that the more marked changes in serum vitamin D and PTH in the women may play a role in the development of gender-related differences in cadmium-induced bone injury.

In a recent Japanese study, ultrasound transmission was used to evaluate the bone density of the calcaneus in 17 male and 18 female inhabitants of a cadmium-polluted area and in 23 men and 45 women living in an unpolluted area (184). The authors noted a significant decrease in bone density in the cadmium-exposed women, but not in the men; this finding supports the previous evidence that women are particularly susceptible to bone damage caused by cadmium exposure.

Occupational exposure

A few reports have described bone disorders similar to Itai-Itai disease with concomitant kidney damage in workers heavily exposed to cadmium (120, 185).

To examine the possible role of cadmium as a risk factor for osteoporosis, the bone mineral density was determined in Swedish workers previously exposed to cadmium (Järup et al, unpublished results). Altogether 43 workers who had been exposed to cadmium for at least 5 years before 1978 were included in the study. B-Cd was used as the dose estimate. The bone mineral density of the forearm was assessed with dual-energy X-ray absorptiometry. A reference material matched for age and gender was used to compute Z-scores according to the formula $Z\text{-score} = (X_u - X_m)/SD$, where X_u = measured bone density, X_m = group mean for the same age group, and SD = standard deviation in the reference population. Z-scores are commonly used to assess osteoporosis. The mean forearm Z-score was -0.60 (95% CI -1.08 — -0.12) in the cadmium-exposed group. The decrease in bone mineral density was positively correlated with age ($P=0.008$) and B-Cd ($P=0.043$). Workers with tubular proteinuria had a lower bone mineral density for the forearm ($P=0.034$) and Z-score ($P=0.074$) than the workers without tubular proteinuria, as shown in figure 12.

Thus the results indicate that cadmium may be a risk factor for the development of osteoporosis at lower doses than previously anticipated (Järup et al, unpublished results).

Effects in animals

Most animal studies have indicated that cadmium may have a direct effect on bone mineralization, possibly related to calcium deficiency, and an indirect effect on calcium absorption through vitamin D hydroxylation,

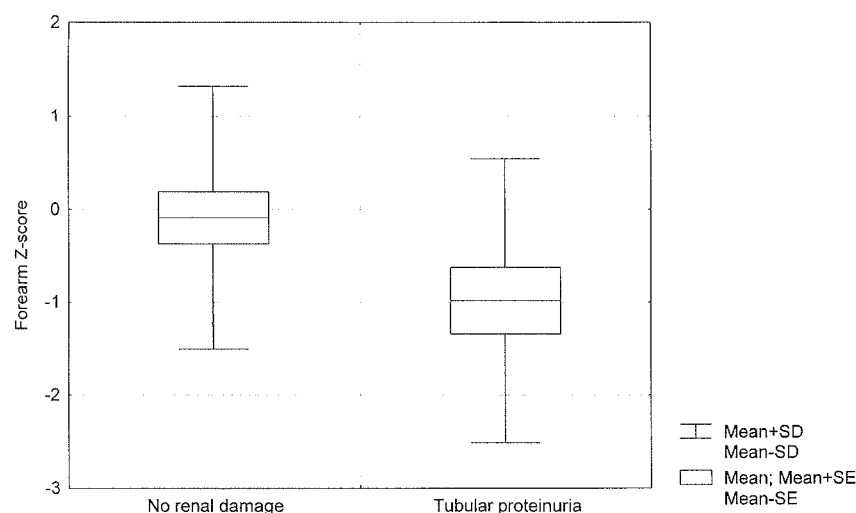


Figure 12. Forearm Z-score of cadmium-exposed workers with and without tubular proteinuria.

which may lead to osteomalacia. The direct effects develop after prolonged exposure to cadmium, whereas the indirect effects occur only after the appearance of renal damage in the animals. Although most animal studies indicate effects of cadmium exposure on bone, some investigators have shown contradictory results (5).

Decreased mechanical strength of bones in young rats has been reported by Ogoshi et al (186). The investigators showed a correlation between cadmium in bones and a decrease in bone strength, showing that cadmium directly affects the mechanical properties of the bone.

Experiments on rats have shown that exposure to cadmium via drinking water leads to an accumulation of cadmium in bone, in addition to the accumulation in liver and kidney. The bone cadmium level increased as a function of ingested dose and was 2.6 mg/kg dry weight after 5 weeks of ingesting drinking water with a cadmium concentration of 100 mg/l (187). The control rats had a cadmium concentration of 0.16 mg/kg of dry weight in their femurs. Cadmium accumulation in bone was a primary phenomenon, not secondary to renal failure.

Increased vulnerability to cadmium-induced bone injury among female animals

Animal experiments have also shown that dietary cadmium increased bone mineral loss to a significantly greater extent in ovariectomized mice than in controls (188) and that dietary cadmium exposure had a more pronounced effect on the skeleton of mice exposed to cadmium during pregnancy and lactation than on non-pregnant controls (189).

Another study showed that bone resorption was significantly increased in elderly female beagles within 96 h of exposure to a cadmium concentration of 15 mg/l in

drinking water (190). The effect was greater in ovariectomized animals than in controls and was not mediated by changes in the calciotropic hormone concentrations. The mean B-Cd concentrations were 3–8 µg/l (27–72 nmol/l) during the earliest bone resorption response. The bone mineral density was decreased the most in the ovariectomized animals exposed to cadmium. The authors concluded that the results indicated that cadmium may act directly on bone and that postmenopausal women may be at increased risk of cadmium-induced bone loss.

In a later study using beagles, whose skeleton is comparable to humans, the combined effects of estrogen depletion and cadmium exposure on bone resorption was assessed. The investigators also aimed at determining whether cadmium-induced bone resorption occurred independently of osteotropic hormone changes and renal tubular damage. The urinary cadmium concentrations ranged from 7 to 50 µg/l in the exposed dogs, but cadmium was not detectable in the controls. There was no difference in the urinary protein concentrations between the groups. Cadmium increased bone resorption in ovariectomized and sham-operated dogs without renal dysfunction or calciotropic hormone interaction. The investigators concluded that their results showed that cadmium may exacerbate bone mineral loss in postmenopausal osteoporosis (191).

Another study on mice supports the view that cadmium exposure in combination with calcium deficiency and pregnancy or lactation is a key etiologic factor in Itai-Itai disease. A calcium-deficient diet containing cadmium at both 5 and 25 ppm in conjunction with one round of gestation or lactation can induce the extreme demineralization characteristic of Itai-Itai like syndrome (192).

Cancer

by Lars Järup & Gunnar Nordberg

Lung cancer

Human evidence

In its latest evaluation of the carcinogenic risk of cadmium exposure, IARC concluded that there was sufficient evidence to classify cadmium as a human carcinogen, and the overall evaluation was that cadmium and cadmium compounds are carcinogenic to man (group I) (4). IARC noted, however, that there were several con-

straints influencing the evaluation. The number of persons (workers) that have been studied are rather limited, and historical data on cadmium exposure are sparse. Furthermore, possible confounding by smoking and other associated exposures (such as nickel or arsenic) has not always been possible to account for. In spite of these limitations IARC decided that there was sufficient evidence for the carcinogenicity of cadmium in humans.

IARC's conclusion was, to a great extent, dependent on American studies, including rather few lung cancer cases. Stayner et al (193) performed a quantitative assessment of the risk of lung cancer from exposure to cadmium based on a retrospective cohort mortality study of cadmium-exposed workers, previously published by Thun et al (194). The findings were analyzed using various regression models to examine dose-response relationships. An excess mortality from lung cancer was observed for the entire cohort (SMR 149, 95% CI 95—222). Lung cancer mortality was significantly elevated among non-Hispanic workers, among those in the highest cadmium-exposure group, and among workers with 20 or more years since first exposure. A statistically significant dose-response relationship was evident in nearly all of the regression analyses. Based on their analyses, the lifetime excess lung cancer risk for cadmium fumes at 100 $\mu\text{g}/\text{m}^3$ was estimated to be approximately 50—111 lung cancer deaths per 1000 workers exposed to cadmium for 45 years (193).

The American findings have been criticized by others (195, 196), mainly because of the lack of control for confounding (by arsenic) in the studies in question.

Sorahan & Lancashire (197) have performed a reanalysis of the American cohort with the inclusion of data on arsenic exposure. They found an exposure-response relationship between cumulative cadmium exposure and lung cancer risk after adjustment for age, year of hire, and Hispanic ethnicity. The relative risks versus the lowest level ($<400 \text{ mg}/\text{m}^3 \times \text{days}$) were 2.30 (95% CI 0.72—7.36), 2.83 (95% CI 0.75—10.72), and 3.88 (95% CI 1.04—14.46) for the levels 400—999, 1000—1999 and $>2000 \text{ mg}/\text{m}^3 \times \text{days}$, respectively. In a separate analysis they then examined the independent effects of cadmium exposure received in the presence of arsenic trioxide and cadmium exposure without concomitant exposure to arsenic. A significant trend for lung cancer risk was found only for the combined exposure to arsenic and cadmium. The reevaluation of the American smelter data thus suggest that cadmium is carcinogenic only in the presence of concomitant exposure to arsenic.

In a recent study of cadmium-exposed workers in the United Kingdom, there was no excess of lung cancer and a nonsignificant negative trend between cumulative cadmium exposure and risks of mortality from lung cancer (198). Relative to a risk of unity for the lowest exposure category, the risks were 0.85 (95% CI 0.27—2.68) for the middle exposure category and 0.81 (95% CI 0.18—3.73) for the highest exposure category. The findings do not support the hypothesis that exposure to cadmium oxide fume increases risks of mortality for lung cancer.

The findings from the reanalyzed American and United Kingdom data are supported by a Swedish study that found 16 lung cancer cases among male battery workers. There was an increase in the SMR (SMR 177,

95 % CI 101—287) and a negative trend with increasing exposure, the SMR values being 317 for the lowest exposure category and 124 and 118 for the middle and highest category (Järup et al, unpublished results). A Poisson regression was also performed with control for smoking, which did not change the negative trend. It should be noted, however, that a negative trend based on SMR values may be artificial due to the problems of comparing SMR values between subgroups with heterogeneous age structures (199). Furthermore, a negative trend could be false due to the influence of the healthy worker effect, which is often more pronounced in subgroups with long durations of employment (200). Therefore, studies showing negative trends in relative risks should be interpreted with caution. They do not “prove” that the risk does not exist.

Animal evidence

Several studies have shown that cadmium may cause tumors in animals. A study of rats showed an exposure-response relationship between cadmium chloride aerosol exposure and the prevalence of lung sarcomas (201). (See reference 202 for a more complete review.)

IARC noted that there is limited evidence of cadmium as a carcinogen after oral administration to animals. The carcinogenic effects in animals have thus mainly been shown after the inhalation or injection of cadmium compounds. Nevertheless, IARC concluded that there was sufficient evidence for the carcinogenicity of cadmium compounds in experimental animals in its latest evaluation (4).

Prostate cancer

Human evidence

It was suspected early that cadmium may cause prostate cancer (203), but later studies have not been able to confirm this suspicion. Studies showing slightly elevated relative risks (204, 205), as well as no risk (206, 207), have been published. The data on dietary components that have been examined with regard to prostate cancer etiology (cadmium, zinc, vitamins C and D, beverages, and legumes) have been considered too incomplete at this time to draw any inferences as to their importance (208). The inconsistency of the findings associating cadmium exposure with prostate cancer risk was recognized by IARC (4).

Animal evidence

Cadmium has been established as a carcinogen in laboratory animals since 1960 (209). The literature covering

publications up to and including 1992 on studies of cancer in experimental animals has been reviewed by IARC (4). The findings concerning prostate cancer in experimental animals can be summarized from the IARC review as follows: In some limited studies on rats, the injection of cadmium chloride into the prostate produced malignant prostatic tumors (210).

Two adequate studies on cadmium chloride given orally to rats are available. In one study (211), with controlled dietary zinc levels, cadmium chloride produced dose-related increases in the incidences of leukemia, interstitial cell tumors of the testis and proliferative lesions of the prostate in male rats. In another study using the administration of cadmium chloride to rats, but no control for the zinc levels in the diet (212), no increase in tumor incidence was seen.

Waalkes & Rehm (213) summarized several aspects concerning available evidence, mainly from animal experiments, concerning the induction of prostate cancer by cadmium. In this review, the authors point out several aspects of prostate anatomy and physiology relevant to cancer, and, since the most often used model for human prostate cancer is the rat, they discuss similarities and differences between rat and human prostate.

Prostatic carcinogenesis in rodents is directly influenced by the remarkable acute testicular toxicity of injected cadmium salts in experimental animals. The testicular production of androgens is critical for the growth and maintenance of the prostate, and prostate tumors are often testosterone dependent. Thus the testicular toxicity of cadmium may well have been responsible for the lack of prostatic tumorigenesis at cadmium doses resulting in testicular atrophy.

As mentioned, also in the monograph by IARC (4), there is evidence to indicate that also oral cadmium exposure can induce proliferative lesions in rat ventral prostate. In the studies by Waalkes & Rehm (211) with several levels of dietary cadmium (25, 50, 100 and 200 ppm) mixed with diets either adequate (60 ppm) or marginally deficient (7 ppm) in zinc over 18 months, a significant increase in the overall incidence of prostatic proliferative lesions (focal, atypical hyperplasia and adenoma) occurred in rats fed cadmium in zinc-adequate diets as compared with the incidence in rats fed cadmium in zinc-deficient diets or in controls. Waalkes & Rehm (213) made the following comment in relation to the evidence from chronic studies in rodents: "Chronic studies in rats have established that the rat ventral prostate is a target site for cadmium induction of neoplasia, whether exposure occurs via direct injection, orally, or parenterally. It is of note that cadmium treatment can induce the full spectrum of prostatic proliferative lesions, including invasive adenocarcinomas. These findings in rodents clearly support a possible role for cadmium in the aetiology of human prostate neoplasia".

Renal cancer

Some early evidence indicated an association between cadmium exposure and renal cancer (214). Later studies have not been able to confirm these early findings although a large multicenter study showed a significantly elevated relative risk (RR 2.0, 95% CI 1.0–3.9) (215). The authors stated, however, that they also found an inverse dose-response relationship that argued against a causal relation between cadmium exposure and renal cancer. A Finnish case-referent study found that the mean concentrations of cadmium were low in the renal cortex of renal cell cancer patients (216).

Breast cancer

Some recent studies indicate an association between cadmium exposure and human breast cancer, and it has been suggested that the effects of cadmium are mediated by the estrogen receptor independent of estradiol (217). A recent Finnish study found unexpectedly high concentrations of cadmium in breast adipose tissue samples, which may indicate that cadmium-binding proteins exist in human breast tissue. The correlation of cadmium with estrogen receptors in breast cancer was suggestive. The authors cautiously stated that their results neither proved nor disproved the role of cadmium initiation, promotion or progression in breast cancer (218).

Other cancers

There is some evidence, although weak, that cadmium may play a role in the development of other cancers, such as testicular cancer (219) and bladder cancer (220).

Concluding remarks

IARC has classified cadmium as a human carcinogen (group I) on the basis of sufficient evidence in both humans and experimental animals. As shown in the preceding discussion, recent studies on humans do not convincingly support this standpoint, whereas studies on experimental animals still indicate that cadmium may be carcinogenic. We conclude that the evidence for cadmium as a human carcinogen is rather weak, particularly after oral exposure. In our opinion a classification of cadmium as "probably carcinogenic to humans" (IARC group 2A) would be more appropriate. This conclusion also complies with the EC classification of some cadmium compounds (carcinogen category 2; annex 1 to directive 67/548/EEC).

Cardiovascular system

by Lars Järup

Data from animal experiments have indicated that cadmium may play a role in the causation of cardiovascular disease, but the associations in humans have been weak and inconclusive (2, 5).

The population-based Cadmibel study on environmental exposure to cadmium refuted the evidence that environmental exposure to cadmium would lead to an increase in blood pressure or to a higher prevalence of hypertension and other cardiovascular diseases (221).

On the other hand, a recent study in Japan showed an increased relative risk for cardiovascular mortality in cadmium-exposed persons. A long-term follow up study (from 1974 to 1991) was carried out on 2408 residents

living in the cadmium-polluted Kakehashi River basin region. Increased SMR values for cardiovascular diseases, especially heart failure, were found in a subgroup with evidence of tubular damage, whereas those without signs of proteinuria did not show any elevated risks (222).

In a follow-up of a cohort of Swedish workers in a factory manufacturing nickel-cadmium batteries, there was no elevated SMR values for ischemic heart disease. A Poisson regression analysis, within the cohort, of ischemic heart disease incidence showed a negative exposure-response relationship and thus refuted the hypothesis that cadmium may be a risk factor for cardiovascular disease (Järup et al, unpublished results).

Reproductive and developmental effects

by Gunnar Nordberg

Reproductive and developmental effects of cadmium have been reviewed and discussed by the Scientific Committee on the Toxicology of Metals (223), by Elinder (224), and in the criteria document of the International Programme on Chemical Safety (5). Discussions and conclusions from these reviews are summarized in the following text, but the references used in these documents will not be specifically given.

Male reproductive system

Effects on humans

As pointed out by Elinder (224), since humans are not exposed to cadmium by injection, acute effects similar to those seen in animals are not likely to occur in humans, although some acute poisoning cases in men have displayed histological damage to reproductive organs, including the testes. The relatively few human studies that have been published in recent years are described in this review.

Gennart et al (225) studied the effects of exposure to cadmium and some other toxic metals on male reproductive function in Belgian workers. There were 83 workers exposed to cadmium with a urinary cadmium level of

6.9 µg/g creatinine and a mean duration of exposure of 24 years. The fertility of these workers and of an unexposed population (N=138) was assessed from the birth experiences of the wives with a logistic regression model. The probability of a live birth did not differ between the unexposed workers and the cadmium-exposed workers before or after the onset of exposure.

Oldereid et al (226) found that the total quantity of zinc in the ejaculates of smokers was significantly lower than in nonsmokers. However, the cadmium concentrations in seminal fluid was unchanged, except when the person's consumption of cigarettes exceeded 20 per day.

Keck et al (227) determined the cadmium concentration in the semen samples of 12 men with proved fertility (group I) and 44 normozoospermic patients (group II), as well as that of 118 unselected patients of an infertility clinic (group III) and 2 industrial workers with occupational exposure to cadmium. The mean cadmium concentration in seminal plasma did not differ significantly for groups I, II, and III (mean concentration 0.38–0.44 µg/l), but the 2 cadmium-exposed patients revealed higher levels, 3.5 and 3 µg/l. There was no significant correlation between the seminal cadmium concentrations and conventional semen parameters or between the cadmium concentrations and the fertility status of the patients. However, the mean cadmium concentrations in the semi-

nal plasma of the normozoospermic men were slightly higher for the smokers (0.54 µg/l) than the nonsmokers (0.42 µg/l).

Oldereid et al (228) determined the concentrations of cadmium, zinc, and lead in the reproductive organs of men who had died suddenly. The cadmium concentrations were highest in epididymides and seminal vesicles, and they increased with age in all the tissues studied. The zinc concentrations also increased in prostate with age, but decreased with age in testicles. The authors did not consider that the data gave any strong support for cadmium involvement in male infertility.

Effects on experimental animals

The acute effects of the injection of soluble cadmium salts to experimental animals include necrosis of the testicles, first reported by Parizek & Zahor (229) and Parizek (230) and later confirmed by many authors. The doses required are usually more than 1 mg/kg body weight given by injection. An inunction of cadmium on the scrotum and oral ingestion of cadmium in high concentrations may also give rise to this effect (224).

Indications of effects on testosterone production (231) and related effects on accessory genital organs were found (232) after the long-term treatment of mice with cadmium. There are also several more recent studies by Waalkes & Rehm (213), which have shown effects on androgen levels and accessory male genital organs, including the prostate of rats.

In a study of male Wistar rats by Saygi et al (233), cadmium was given in drinking water (10 mg/l) for 52 weeks. Reproductive capacity was lost in 40% of the animals, and pathological testicular changes, as well as liver and kidney damage, were found in the cadmium-exposed animals.

Female reproductive system

Effects on humans

Clarkson et al (223), in their overview of the reproductive effects of cadmium, discussed the possibility of placental vasculature as a critical tissue in long-term cadmium exposure and pointed out that there was insufficient evidence at that time to consider effects on that tissue as critical.

WHO (5), in a section dealing with fetal effects, among others, pointed out that maternal hypertension and a decrease in birthweight have been associated with elevated levels of cadmium in the neonate. In addition, it is well-established that babies of mothers who are cigarette smokers are smaller at birth than are babies of nonsmokers. However, neither the placenta nor the fetus was considered a critical organ in the further discussions

in the WHO document (5). In the following text more recent data are reviewed as a basis for further considerations concerning the possibility that reproductive and developmental effects could be critical effects in long-term cadmium exposure.

Eisenmann & Miller (234) compared the toxicity of cadmium and selenite on isolated human placenta using dual perfusion of human term placenta lobule. Cadmium (20 nmol/ml) produced adverse effects on the production and release of human chorionic gonadotropin in 4 hours. Selenite did not cause similar effects (234).

Effects of cadmium on the activity of myometrial strips from term pregnant women were examined by Sipowicz et al (235). Cadmium in a concentration of 10^{-9} M inhibited spontaneous contractile activity. Effects of Ca^{2+} and oxytocin were significantly increased by exposure to cadmium at low concentrations (10^{-9} M), whereas higher concentrations had an inhibitory action. The findings were discussed in relation to a possible role of cadmium in mechanisms of preterm labor.

A group of pregnant women residing in the vicinity of a copper smelter was studied by Tabacova et al (236). Pregnancy complications were recorded on the basis of an interview and clinical records. Patients were assigned to groups of normal or pathologic pregnancies (threatened spontaneous abortion, toxemia and anemia). Biochemical changes suggestive of increased lipid peroxidation and decreased antioxidant protection were found in the diagnostic group of pregnancy complications. Maternal exposure to metals (blood lead and cadmium) was associated with a decrease in reduced glutathione in blood. It was suggested by the authors that exposure to metals during gestation could enhance the development of pregnancy complications by increased lipid peroxidation [summarized from abstract — full article not yet obtained (236)].

In another publication by Tabacova et al (237), changes in glutathione protection were related to placental arsenic and cadmium and tobacco smoking in pregnancies in an area contaminated by metals near a copper smelter.

The influence of maternal iron stores and high fiber grain on the accumulation of cadmium in placenta was studied by Moberg-Wing et al (74). The mean value of the analyses of 4 samples from the placenta was used. The authors found lower cadmium concentrations in the placentas of women who consumed less grain fiber and had serum ferritin levels above 15 µg/l.

Goyer & Cherian (79) reported the concentrations of metals and MT in placental tissue from 55 mothers, from Ontario, Canada, all of whom stated that they were not smoking during pregnancy, but 16 (30%) acknowledged having smoked in the past. Placental tissue was sampled after perfusion for 5 minutes with normal saline immediately after delivery. The tissue was sampled from the

paracentral part, the mid-disc fetal half, the mid-disc maternal half, and peripheral zone. The mean cadmium concentration was reported to be 32 ng/g. There were strong positive correlations between the zinc and copper concentrations and the MT concentrations in placenta, but the correlation between the MT and cadmium concentration was negative.

Berlin et al (73) studied cadmium accumulation in placentas and the birthweight of children of female nickel-cadmium battery workers. In a prospective part of the study 27 placentas were obtained from cadmium-exposed mothers. The placentas were subsampled according to a defined pattern. The placental cadmium concentrations correlated positively with maternal B-Cd. The mean placental cadmium was 21 ng/g. The birthweight of 226 children of 137 female workers was assessed. No effect of cadmium exposure on birthweight was detected, but a statistically significant effect was observed on the birthweight of smokers during pregnancy (73).

Loiacono et al (238) studied placental cadmium and birthweight in women living near a lead smelter. In non-smoking pregnant women who were exposed to low levels of smelter-derived cadmium (N=106) higher mean placental cadmium levels (0.73 nmol/g dry weight) were recorded when compared with the placental cadmium concentration in women (N=55) from a reference area. The placental concentrations of cadmium in exposed women were similar to what had been previously reported in placentas of smoking women. No association between placental cadmium and birthweight was found, and the authors therefore concluded that the effects of smoking on birthweight are not mediated through cadmium.

The usefulness of samples of human placenta in monitoring exposure to cadmium in human populations was discussed by Lagerkvist et al (60). The study consisted of 2 parts. The first detailed analyses of 6 different lobuli from each of 25 placentas. The decidua basalis and the chorion plate were removed before the samples were taken. In this part of the study a considerable variation was shown. In 36% of the placentas there were differences in cadmium concentration by a factor greater than 2 between different lobuli. On the basis of these results, it was decided to use the following procedure in further studies: homogenization was achieved by using 6 samples from different lobuli from each placenta; these were homogenized and the homogenized material was used for analyses. The second part used the same procedure as in part 1 and the concentration of cadmium in placentas from a smelter area (N=49) and from a reference area (N=53) in northern Sweden was determined. Appropriate precautions were taken to avoid contamination and an analytical quality control program gave satisfactory results. There were no statistically significant differences in the placental cadmium levels between the 2 areas

(geometric means of 5.0, 3.6 and 2.6 ng/g wet weight in smokers, ex-smokers and nonsmokers, respectively). It was noted that the placental cadmium concentrations were 4 and 6 times higher than maternal and umbilical cord B-Cd, respectively. It was concluded that placental samples, if taken according to the procedure used in this study, would constitute a useful material for monitoring human cadmium exposure (60).

Effects on animals

Since the first observations by Kar et al (239) that, in prepubertal rats, ovaries undergo morphological changes after the injection of cadmium chloride (6 mg/kg body weight), several subsequent studies have shown that ovarian hemorrhages occur in rats in persistent estrus after the injection of soluble cadmium salts. Similar effects have also been shown for mice. For prepubertal rats, endothelial damage in the blood vessels of the uterus and ovaries were reported, and normal ovulation was inhibited in hamsters. These effects occurred at injected doses higher than 2.3 mg/kg body weight. Long-term exposure to lower daily doses of 0.036 and 0.18 mg/kg body weight was reported to give rise to changes in the blood vessels of the myometrium of the uterus in female rats (224).

Piasek & Laskey (240) gave pregnant rats cadmium injections (up to 5 mg/kg). Normal steroidogenesis at a number of sites in the biosynthetic pathway with serum estradiol concentrations and ovarian estradiol production was affected. Acute cadmium effects on steroidogenesis are the most severe in rats evaluated in proestrus or in early pregnancy, while in late pregnancy steroidogenesis is relatively unaffected. This study supports previous findings showing similar changes.

In a study by Whelton et al (241) the transfer of ^{109}Cd from the diet to new-born pups was studied, and it was found that most of the cadmium in the pups originated from the diet of the dams and only 2% came from the tissue store of the dam (241).

Embryotoxic, teratogenic and developmental effects — animals

The uptake of cadmium into the fetus is dependent on several conditions, for example, the dose and stage of gestation. In most studies cadmium passage through the placenta into the fetus has been rather limited after closure of the vitelline duct.

Since the first studies on the teratogenic effects of injected cadmium on golden hamsters by Ferm & Carpenter (242), there have been several subsequent studies showing that the injection of cadmium during pregnancy at doses on the order of milligrams per kilogram of body

weight give rise to fetal death and severe malformations when given early in pregnancy. A factor that may be of decisive importance or a contributor to the development of the embryotoxicity and teratogenicity of cadmium is the interaction with zinc. Maternal zinc deficiency increases fetus susceptibility to maternal cadmium injections, and maternal cadmium injections inhibit the transport of zinc from the mother to the fetus and inhibits zinc-dependent enzymes in the fetus (224). Further confirmation of the interaction between cadmium and zinc when injected intravenously into hamsters has been contributed by Hartsfield et al (243).

It was first shown by Parizek (244) that subcutaneous injections of 2.4 mg/kg body weight to rats in the late stage of pregnancy (17–20 days) gave rise to vascular changes at sites of estrogen biosynthesis and the destruction of the placenta, which can subsequently cause fetal death. Toxicity to the dam also occurs — a condition similar to “toxemia of pregnancy” (245). Some data on long-term exposure indicate that also lower doses can increase the barrier between maternal and fetal circulation. High peroral exposure in pregnant animals may also result in reduced fetal weight and in some experiments also in malformations (224).

When pregnant mice were administered cadmium chloride in concentrations of up to 5 mg/kg of cadmium chloride on day 16 of pregnancy and spleen cells from the offspring (age 4 weeks) were tested, several changes in immune response were noted (246).

Brain development in rats can be affected by prenatal cadmium. One-way conditioned avoidance reactions were considerably more frequent in rats whose dams had been injected with a cadmium chloride concentration of 0.225 mg/kg compared with controls (247).

In a study by Gupta et al (248), dams were given 20 ppm of cadmium in the drinking water from day 0 of pregnancy. In the pups, brain lipid peroxidation showed an increase in thiobarbituric acid reactive substance, amounting to 354% of the value in controls at day 21 after birth. There were some increases in total brain sulfhydryls and the activities of superoxide dismutase and glutathione peroxidase were increased by 45% and 104%, respectively, at day 1, but at days 7, 14 and 21 these enzymes were inhibited. There were elevated levels of brain catalase and glutathione reductase at all ages, with maximal alteration at 21 days of age.

When pregnant rats were given 50 ppm of cadmium chloride in water, with or without 10% ethanol, there were considerable concentrations of cadmium in the brains of their offspring (34 µg/g) when no concomitant ethanol was given, whereas the corresponding value for the ethanol-treated dams was only 1.8 µg/g. In contrast, the concentration in the liver was lower in the cadmium-treated animals (227 µg/g) and higher in the ethanol- and cadmium-treated animals (4089 µg/g) (249).

When cadmium (5 ppm) was given via drinking water to dams or pups or both during the postweaning period, no cadmium uptake could be detected in the brain of the young rats (examined at age 45–51 days) (exposed during lactation or after weaning or both). The brain cortical levels of serotonin and 5-hydroxyindoleacetic acid were significantly reduced (250).

Chan & Cherian (62) showed differences in MT isoforms in the livers of both prenatal and neonatal rats depending on cadmium or zinc injection. In another paper by Chan & Cherian (63), rats were repeatedly injected with cadmium chloride, and one subgroup was thereafter made pregnant. In the pregnant rats there was a faster decrease in the hepatic cadmium levels and a faster increase in the kidney cadmium levels than in nonpregnant rats. The pregnant rats also had higher plasma cadmium levels (and MT levels) than the nonpregnant rats (63). These observations were further supported by the studies of Chan et al (64), in which it was shown that basal levels of MT were increased already at day 8 of pregnancy in rats given no cadmium treatment. Plasma MT levels further increase in cadmium-treated animals.

Summary and concluding remarks

Male reproductive system

Since the evaluations by Clarkson et al, Elinder, and WHO, mentioned in the introduction to this section, only a few studies on humans have been published concerning the effects of cadmium, and no adverse effects have been documented at the exposure levels studied.

Cadmium can cause acute necrosis of the testicles of experimental animals if injected in a single dose of 1 mg/kg body weight or higher. In addition, when large doses are given by other routes, such effects can occur. Long-term exposure to cadmium offers protection from some acute effects but may cause other disturbances of the male reproductive system involving changes in male sex hormones and related changes in accessory reproductive organs.

Although the question must still be considered open (whether effects on male reproduction can be critical effects in human exposures to cadmium) and an effect on the development of prostate cancer cannot be excluded (see the section on cancer beginning on page 34), current evidence is not sufficient to state that such effects do occur at low exposures, and effects on male reproductive tissue in humans therefore cannot be considered as critical effects at present.

Female reproductive system, teratogenic and developmental effect

Pathologic changes can be induced in human placentas exposed to cadmium after delivery, and there is also

interference with the production and release of human chorionic gonadotropin.

In humans, elevated levels of cadmium in the neonate have been associated with decreases in birthweight. It is well known that babies of mothers who are cigarette smokers are smaller than those of nonsmokers. It is also known that smoking causes cadmium uptake, but it is difficult to decide whether cadmium plays any causal role in the lower birthweight. In female workers with considerably elevated cadmium levels in their placenta and in women exposed to environmental cadmium to the extent that they have placental cadmium levels similar to those in smokers, no effect on birthweight was noted. Although data are very limited and an effect on birthweight cannot entirely be ruled out, it must currently be considered unlikely that smoking-related increases in cadmium levels would cause effects on birthweight.

Hemorrhagic changes in ovaries, changes in ovarian hormonal production, and endothelial changes in the blood vessels of female rats have been documented after the injection of cadmium doses higher than 2.3 mg/kg.

A cadmium injection of 2.4 mg/kg in the late stage of pregnancy gives rise to placental necrosis, fetal death, and a condition in the dam similar to "toxemia of pregnancy". Similar doses given earlier in pregnancy can give rise to teratogenic effects in hamsters and changes in the immune system of the offspring in mice. Long-term exposure to lower doses and peroral exposures may give rise to reduced fetal weight and, in some experiments, also to malformations. Changes in brain development and related changes in brain enzymes have been reported in pups of rats treated orally with cadmium during pregnancy and lactation. A factor contributing to the embryotoxicity and teratogenicity of cadmium is that the transfer of zinc to the fetus is reduced by cadmium exposure.

These observations from animals indicate that there is a need for more studies on humans. However, since there are no convincing observations of similar effects in humans, reproductive, teratogenic, and developmental effects cannot be considered critical in humans at present.

Risk characterization

by Carl Gustaf Elinder, Marika Berglund, Lars Järup, Gunnar Nordberg, Marie Vahter

Renal tubular damage is probably the critical health effect of cadmium exposure, both in the general population and in occupationally exposed workers. As shown in this report, tubular damage may develop at much lower kidney cadmium concentration levels than previously estimated. On the basis of the evaluation of several recent studies, it can be concluded that, in the general population, an average U-Cd level of 2.5 µg/g creatinine is related to an excess prevalence of renal tubular damage of about 4%. In general, an average urinary excretion of 2.5 µg/g creatinine corresponds to an average concentration of cadmium in renal cortex of 50 µg/g wet weight, which would be the result of long-term (decades) intake of 50 µg per day. Compared with previous assessments, the present evaluation, which is based on data published in recent years, implies a more than 4-fold higher risk of tubular damage at this relatively low exposure level.

When the critical concentrations for the adverse effects of cadmium accumulation are evaluated, it is crucial to consider the great individual variation in kidney cadmium concentrations within the general population. Even if the population average is relatively low, a certain proportion will exceed the concentration at which renal tu-

bular damage may occur. This is illustrated in figure 1. Figures 13 and 14 show the predicted proportions of the general population that will attain a cadmium concentration in the kidney above 50 mg/kg and the proportions that will have cadmium-induced renal tubular damage at different daily cadmium intakes. In addition, there is variation in individual susceptibility.

It can be estimated that about 1% of high risk groups (women with low body iron stores, smokers, etc) will develop adverse renal effects in the form of tubular damage at the present average daily intake of cadmium in Sweden (about 15 µg/day). This estimation corresponds to several thousand people. As the effect is very rare, about 1% of susceptible groups, it is extremely difficult to discover in studies based on samples from the general population. Furthermore, it can be estimated that an average daily intake of cadmium of 30 µg/day would give rise to cadmium-induced renal tubular damage in about 1% (figure 14) of the general population. In risk groups, for example women with low iron stores, the percentage would be higher, up to 5%. This percentage would correspond to about 100 000 persons.

Although there are some studies indicating that glomerular damage may be a separate event, which may

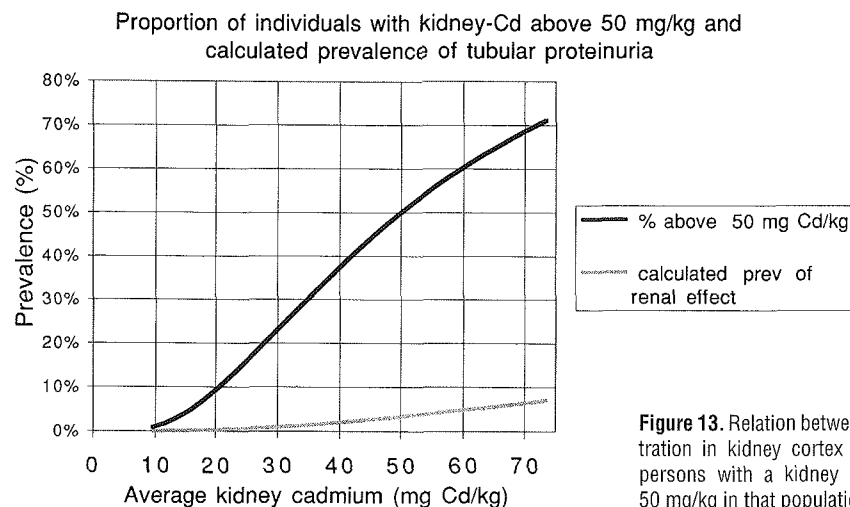


Figure 13. Relation between the population average cadmium concentration in kidney cortex (kidney-Cd) and the prevalence (prev) of persons with a kidney cortex cadmium concentration exceeding 50 mg/kg in that population.

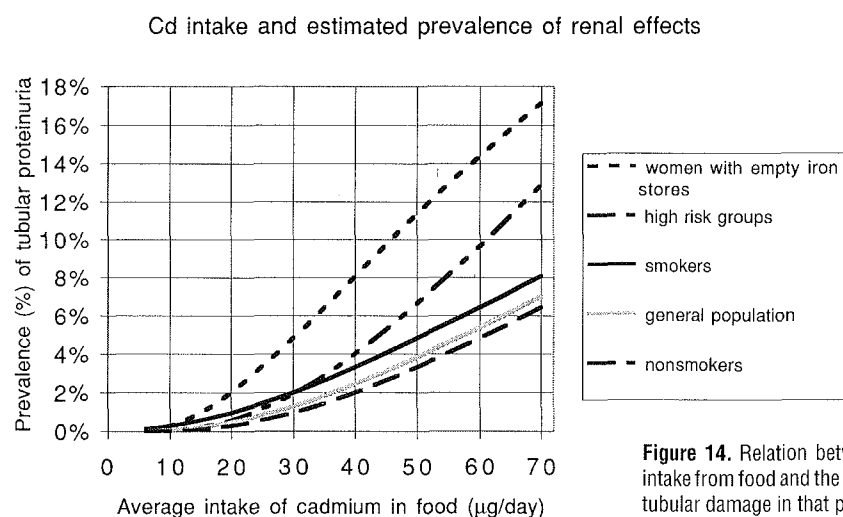


Figure 14. Relation between the population average cadmium (Cd) intake from food and the prevalence of persons with cadmium-induced tubular damage in that population.

occur independently of tubular injury, we conclude that the existing evidence implies that glomerular damage rarely occurs below the cadmium level at which tubular damage occurs.

Both human and animal studies indicate that skeletal damage (osteoporosis) may be a critical effect of cadmium exposure. We are of the opinion, however, that the present evidence is not sufficient to permit such a conclusion for humans. We would like to stress, however, that osteoporosis is a very important public health problem worldwide, and studies assessing the potential role of cadmium as a risk factor for osteoporosis are already in progress. The results from these studies will be available within the next few years and may lead to a reevaluation of the critical effects of cadmium exposure.

It should also be noted that women have a much higher risk than men of developing osteoporosis. Since women are also at higher risk of obtaining a high cad-

mium dose, they may be particularly susceptible to cadmium-induced osteoporosis.

In 1993 IARC concluded that there was sufficient evidence to classify cadmium as a human carcinogen (category I). As WHO earlier pointed out, however, the human evidence was based on relatively few studies including a limited number of lung cancer cases and that the control of confounding was insufficient. Recent reevaluation of these studies, as well as new data from a Swedish cohort, indicate that the classification of cadmium as a "probable human carcinogen, group 2A" is more appropriate. This conclusion is also in agreement with the existing classification of some cadmium compounds in the EC countries (carcinogen category 2; annex 1 to directive 67/548/EEC).

In conclusion, recent data indicate that adverse health effects of cadmium exposure, in the form of renal tubular damage, may develop in 1% of the adult general popula-

tion at daily intakes of 30 µg of cadmium over a life-span. In high-risk groups, the percentage will be even higher (up to 5%). This intake is already exceeded by many persons in Europe, and the margin is very narrow for large groups. Therefore, measures should be taken to reduce cadmium exposure in the general population in order to minimize the risk for adverse health effects.

We have shown in this report that also a minor increase in the cadmium body burden will increase the number of people that may be affected. With a life-long average exposure to cadmium of 70 µg/day via food (corresponding to the present PTWI), 7% of the adult general population would be expected to develop cadmium-induced tubular damage. For high-risk groups, the percentage would be even higher (up to 17%). Thus, in our opinion, the current PTWI is unacceptable and needs to be lowered. As pointed out in the introduction to this chapter, the present evaluation implies a more than 4-fold higher risk of renal tubular damage (at an intake level of 50 µg per day) compared with previous evaluations. In order to achieve the same risk level as before, the PTWI would need to be lowered to less than 30 µg per day.

Discussion of the risk characterization

The following questions are often put forward when the possible health hazards from cadmium are discussed:

- Does a small increase in the urinary excretion of proteins really matter?
- If cadmium is that dangerous, why have we not noted an epidemic of cadmium poisonings already today?
- What is the situation in other countries, where average cadmium intake has been reported to be considerably higher than in Sweden?
- Is it really correct to make a generalization and to extrapolate from a series of epidemiologic studies that have been carried out on different populations, such as those presented in figures 8 and 9?
- Which is the "worst case", how many will develop clinically significant disease if cadmium exposure continues to increase at the same rate as previously in this century, that is to say, a doubling within 50 years?

An increased urinary excretion of low molecular-weight plasma proteins, such as β_2 -microglobulin, indicates that normal tubular function has been slightly damaged. This effect is irreversible. A person with a slight tubular defect will, in most cases, not experience any symptoms; thus in one sense the tubular proteinuria is, in principle, benign. He, or she, will, however, have an increased risk for kidney stones and renal colic. Studies of groups of persons with cadmium-induced tubular dam-

age in Japan have shown an increased overall mortality. A parallel may perhaps be made with so-called micro-albuminuria in persons with diabetes, which has been shown to be a very important risk factor for cardiovascular disease and death. Furthermore, the normal metabolism of vitamin D and calcium may be affected. If the exposure to cadmium is continued, the tubular damage may proceed to more generalized renal impairment. Chronic renal failure is the final and severe end point. Tubular proteinuria is the starting point for a slowly progressing general deterioration of renal function which at later stages will elicit several important subjective and clinical effects. However, if cadmium exposure is stopped, or is kept very low, the progression is so slow that the affected person is in most cases unlikely to ever suffer from severe renal damage.

In Japan, where cadmium exposure has been much higher than in Europe, tens of thousands of persons with cadmium-induced tubular lesion have been identified. One obvious reason why "epidemics" have not been seen in Europe is that they have not been thoroughly looked for. In order to identify effects in a small proportion (a few percent) of a population, one must, for statistical reasons (so-called statistical power), examine very large groups, on the order of thousands, provided that the exposure has not been high and the effects examined are relatively prevalent. This has not been the case in Europe, where exposure to cadmium has generally been considerably lower than in Japan. One major study has, however, been carried out, the Cadmibel study in Belgium, which showed clear evidence of renal effects from cadmium in the general population.

It has been claimed that daily intake of cadmium is very high in certain European countries or regions and that no health effects have been recorded. However, a high daily intake of cadmium has not been confirmed in studies with good analytical accuracy and neither have possible health effects been looked for in the populations considered exposed. Thus no "hard data" are available, and it is impossible to comment more specifically.

Figures 8 and 9 should, as pointed out in the text, be considered with caution. Different types of populations and methodology have been examined and used. That different populations have been examined is not necessarily a drawback. On the contrary, it may well be looked upon as an advantage as the merged analysis more appropriately reflects the great variation in susceptibility within the general population. The studies present the information we have available at present regarding exposure to cadmium, expressed as cadmium in urine, and the prevalence of tubular effects. We have depicted all studies presenting data detailed enough for inclusion in the figures. There is a considerable scatter between the different data points. This is to be expected. It is the overall pattern that is important and that has served as a basis for

table 5 and the calculations presented in figures 13 and 14. If the percentages of effects given in table 5 are changed somewhat, there will be a certain, but not very pronounced, influence on figures 13 and 14. The prediction curves are reasonably robust.

The “worst case scenario” obviously would be that populations outside some severely cadmium-polluted areas of Japan in the future will also experience epidemics of severe renal and bone disease. As in Japan,

women are at particular risk for environmental cadmium pollution. We have, in figure 14, shown the possible consequences of increasing cadmium exposure. We predict that a doubling of the daily intake of cadmium will result in significant health effects in the form of tubular damage, increased occurrence of kidney stones, a possible increased prevalence of osteoporosis, and increased renal morbidity and mortality in 1% to 5% of the adult population.

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