

Review Article

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Cadmium & its adverse effects on human health

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Cadmium (Cd), a by-product of zinc production, is one of the most toxic elements to which man can be exposed at work or in the environment. Once absorbed, Cd is efficiently retained in the human body, in which it accumulates throughout life. Cd is primarily toxic to the kidney, especially to the proximal tubular cells, the main site of accumulation. Cd can also cause bone demineralization, either through direct bone damage or indirectly as a result of renal dysfunction. In the industry, excessive exposures to airborne Cd may impair lung function and increase the risk of lung cancer. All these effects have been described in populations with relatively high exposures to Cd in the industrial or in heavily polluted environments. Recent studies, however, suggest that the chronic low environmental exposure to Cd now prevailing in industrialized countries can adversely affect the kidneys and bones of the general population. These studies show consistent associations between various renal and bone biomarkers and the urinary excretion of Cd used to assess Cd body burden. The public health impact of these findings are still unknown. Further research is needed to ascertain that these associations are truly causal and not secondary to parallel changes in Cd metabolism and in the bone or kidney function occurring because of ageing or diseases unrelated to Cd exposure.

Key words Biomarkers - cadmium - retinol-binding protein - tubular proteinuria

Introduction

Cadmium is typically a metal of the 20th century, even though large amounts of this by-product of zinc production have been emitted by non-ferrous smelters during the 19th century. Currently, Cd is mainly used in rechargeable batteries and for the production of special alloys. Although emissions in the environment have markedly declined in most industrialized countries, Cd remains a source of concern for industrial workers and for populations living in polluted areas, especially in less developed countries¹. In the industry, Cd is hazardous both by inhalation and ingestion and can cause acute and chronic intoxications. Cd dispersed in the environment

can persist in soils and sediments for decades. When taken up by plants, Cd concentrates along the food chain and ultimately accumulates in the body of people eating contaminated foods. Cd is also present in tobacco smoke, further contributing to human exposure. By far, the most salient toxicological property of Cd is its exceptionally long half-life in the human body. Once absorbed, Cd irreversibly accumulates in the human body, in particularly in kidneys and other vital organs such the lungs or the liver. In addition to its extraordinary cumulative properties, Cd is also a highly toxic metal that can disrupt a number of biological systems, usually at doses that are much lower than most toxic metals²⁻⁴.

While the acute toxicity of Cd was discovered as early as in 19th century⁵, the possibility that this metal could cause chronic effects in humans was recognized much later with the first reports of pulmonary, bone and renal lesions in industrial workers published in the late 1930s-1940s⁶⁻⁸. It was the outbreak of the Itai-Itai bone disease in Japan in the 1960s⁹ that really drew the attention of the public and regulatory bodies to this heavy metal that had been discharged in the environment at an uncontrolled rate for more than one century. After these early reports of severe intoxication, a number of epidemiological and experimental studies were carried out worldwide in order to characterize the toxicity of Cd and to assess the exposure levels from which this widespread pollutant could threaten human health. These studies have demonstrated that Cd absorbed by inhalation or ingestion can cause irreversible damage to several vital organs, among which the most sensitive are the kidney, the bone and the respiratory tract¹⁰. Adverse effects on these organs were described in subjects with relatively high industrial or environmental exposures as compared to the small amounts of Cd absorbed by the general population. However, from the 1990s, several epidemiological studies conducted mainly in Europe, have reported observations suggesting that Cd can adversely affect the kidneys and bones of the general population of industrialized countries from much lower exposure levels than was believed^{2,11,12}.

The aim of the present article is to summarize current knowledge regarding the risks this widespread pollutant may pose to human health. The review will be focused on the kidney, the critical organ for which dose-response relationships are the best documented. The kidney is also the target organ that can be monitored using well-validated exposure and effect biomarkers. The review will also address some of the issues that complicate the risk assessment of Cd and in particular the inconsistencies between the critical exposure levels derived in industrial workers and in the general population with much lower exposures to environmental Cd.

Exposure and metabolism

Primary exposure sources of Cd for the general population include food and tobacco smoking. The highest concentrations of Cd (10-100 ppm) are found in internal organs of mammals, mainly in the kidneys and liver (offals) as well as in some species of fish, mussels and oysters, especially when caught in polluted

seas. Consumption of staple foods such as wheat, rice also significantly contributes to human exposure. In the industry, Cd exposure is mainly by inhalation although significant amounts of Cd can be ingested via contaminated hands or cigarettes. The amounts of Cd ingested daily with food in most countries are in the range of 10 to 20 µg per day. Tobacco smoking is an important additional source of exposure for smokers. Since one cigarette contains approximately 1 to 2 µg Cd, smoking one pack per day results in a daily uptake of Cd that approximates that derived from food. Absorption by the oral route varies around 5 per cent but can be increased up to 15 per cent in subjects with low iron stores. When exposure is by inhalation, it is estimated that between 10 and 50 per cent of Cd is absorbed, depending on the particle size and the solubility of Cd compounds. In the case of Cd in tobacco smoke (mainly in the form of CdO), an average of 10 per cent of Cd is absorbed. Absorption of Cd through the skin is negligible^{2,10}.

Regardless the route of exposure, Cd is efficiently retained in the organism and remains accumulated throughout life. The Cd body burden, negligible at birth, increases continuously during life until approximately the age of about 60-70 yr from which Cd body burden levels off and can even decrease. Cd concentrates in the liver and even more in the kidneys, which can contain up to 50 per cent of the total body burden of Cd in subjects with low environmental exposure. Accumulation of Cd in liver and kidney is due to the ability of these tissues to synthesize metallothionein, a Cd-inducible protein that protects the cell by tightly binding the toxic Cd²⁺ ion. The stimulation of metallothionein by zinc probably explains the protective effect of this essential element towards Cd toxicity. Because of its small size, metallothionein is rapidly cleared from plasma by glomerular filtration before being taken up by the proximal tubular cells. This glomerular-filtration pathway is at the origin of the selective accumulation of Cd in proximal tubular cells and thus in the renal cortex where this segment of the nephron is located (Fig.). Cd does not cross easily the placental or the haemato-encephalic barriers, explaining its very low toxicity to the foetus and the central nervous system as compared with other heavy metals. Cd is mainly eliminated via the urine. The amount of Cd excreted daily in urine is however very low, representing somewhat 0.005 to 0.01 per cent of the total body burden. This low fractional excretion corresponds to

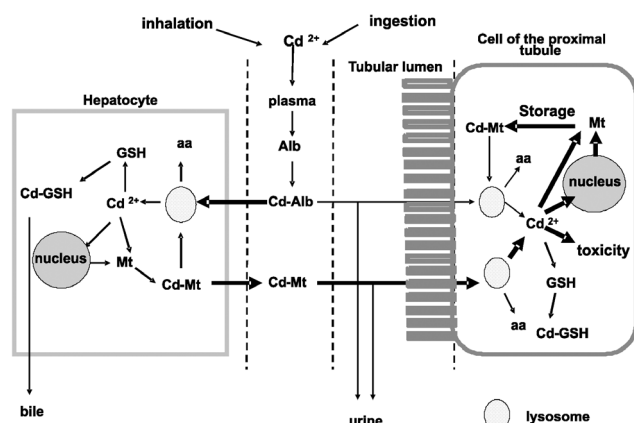


Fig. Scheme illustrating the mechanism responsible for the selective accumulation of cadmium in proximal tubular cells. Alb, albumin; Mt, metallothionein; GSH, glutathione; aa, amino acid.

a biological half-life of more than 20 yr. Of note, the elimination half-life of Cd is reduced to less than 10 years in subjects with tubular dysfunction^{2,10}.

Renal effects

There is now a consensus among scientists to say that in chronic Cd poisoning the kidney, which is the main storage organ of Cd, is also the critical target organ, *i.e.* the first organ to display signs of toxicity^{2,3,10,11}. Cd nephropathy has been described in industrial workers exposed mainly by inhalation and in the general population exposed via contaminated foods. The various studies conducted on human populations and experimental animals have demonstrated that Cd exerts its renal toxicity in a strictly dose-dependent manner, the adverse effects occurring only when the Cd concentration in kidney cortex reaches a critical threshold. The total concentration of Cd in renal cortex from which renal effects are likely to occur has been estimated at 150-200 ppm ($\mu\text{g/g}$ wet weight of renal cortex), both in human subjects and in experimental animals^{2,10,11}. As most renal Cd is bound to metallothionein, the form of Cd responsible for renal damage is the highly toxic Cd^{2+} ion that avidly reacts with cellular components. The critical concentration of free Cd in renal cortex corresponding to the critical concentration of 200 ppm for total Cd has been estimated at about 2 ppm¹³. The earliest manifestation of Cd-induced renal damage considered as critical consists in an increased urinary excretion of microproteins (molecular weight <40 kD). Among these proteins, β_2 -microglobulin, retinol-binding protein and α_1 -microglobulin have been the most validated for the routine screening of tubular proteinuria. The increased loss of these proteins in urine is a reflection

of the decreased tubular reabsorption capacity. In health, these proteins are almost completely reabsorbed by the proximal tubular cells, meaning that a minute decrease of their fractional reabsorption drastically increases their urinary excretion. A modest increase in the urinary excretion of these proteins, as found at the early stage of Cd nephropathy (in the range of 300 to 1,000 $\mu\text{g/g}$ creatinine for retinol-binding protein (Table I), is unlikely to compromise the renal function⁴. Such a small increase might even be reversible after removal from Cd exposure. By contrast, when the urinary excretion of these proteins is increased by more than one order of magnitude, tubular dysfunction caused by Cd becomes irreversible and may be associated with a lower glomerular filtration rate (GFR) and an accelerated decline of the GFR with ageing⁴ (Table I). Other solutes excreted in greater amounts in the urine of subjects with Cd nephropathy include total protein, albumin, amino acids, enzymes (*e.g.* N-acetyl- β -D glucosaminidase), tubular antigens, glucose, calcium and phosphate. The disturbances of calcium and phosphate metabolism accompanying Cd nephropathy may lead to bone demineralization, the formation of kidney stones and bone fractures. Prospective studies among inhabitants living in Cd-polluted areas in Japan have shown that the development of Cd-induced proteinuria is predictive of an increased mortality by heart failure, cerebral infarction, nephritis and nephrosis¹⁴. There is some epidemiological evidence that diabetics are more susceptible to the nephrotoxic action of Cd, a finding consistent with animal studies^{1,15}.

Table I. Interpretation of elevated values of urinary β_2 -microglobulin (β_2 -M) and retinol-binding protein (RBP) induced by occupational or environmental exposure to Cd

| β_2 -M or RBP in urine ($\mu\text{g/g}$ creatinine) | Significance |
|--|---|
| < 300 | Normal value |
| 300 - 1,000 | Incipient Cd tubulopathy (possibility of some reversal after removal of exposure if urinary Cd is not too high <i>i.e.</i> below 20 $\mu\text{g/g}$ cr) |
| 1,000-10,000 | Irreversible tubular proteinuria that may accelerate the decline of glomerular filtration rate with age. At this stage glomerular filtration rate is normal or slightly impaired. |
| $>10,000$ | Overt Cd nephropathy usually associated with a decreased glomerular filtration rate |

Modified from Ref. 4

Although cases of over Cd nephropathy have been described in the context of high occupational or environmental exposures, recent studies suggest that Cd at the low environmental exposures currently found in industrialized countries can cause subtle renal effects, leading to modest increases in the urinary excretion of microproteins or in small variations of the GFR¹⁵⁻¹⁸. The health significance of these findings is however difficult to assess. Assuming that these renal effects found in population-based studies are causally related to Cd, these could be potentially adverse, rendering for instance the kidneys more sensitive to other stressors. These effects might also reflect an early renal response to Cd, which could be purely adaptative and/or reversible in nature. Another possibility that should be also considered is that these effects, especially those at very low exposure levels and observed on the same matrix (urine), might be linked through non causal associations. For instance, the associations emerging between proteins and Cd in urine might be the reflection of the dependence of each other on the filtration or reabsorption capacity of the kidneys, which indeed widely varies across the general population, especially among the elderly¹⁹.

Bone effects

Although first reported in French workers by Nicaud *et al*⁷, toxic effects of Cd on the bones really became evident with the outbreak of the Itai-Itai disease in the Cd-polluted area of Toyama, Japan, after World War II. Itai-Itai disease patients presented, indeed, a severe osteomalacia accompanied with multiple bone fractures and renal dysfunction⁹. They complained of pain in the back and in the extremities, difficulties in walking and pain on bone pressure (hence the name Itai-Itai meaning Ouch-Ouch in Japanese). Recent studies in China have confirmed the bone toxicity of Cd. Nordberg *et al*²⁰ have found decreased bone mineral density in Chinese farmers exposed to Cd from contaminated rice for more than 20 yr. The bone mass density was decreased in postmenopausal women with elevated Cd in urine or blood as well as among men with elevated Cd in blood. Bone lesions have been regarded for long as late manifestations of intoxication, occurring only after relatively high exposures in the industry or environment. Effects on the bone, especially at high exposure, are largely the consequence of Cd nephropathy, resulting in an altered vitamin D metabolism and a urinary waste of calcium and phosphate. According to studies on environmentally-exposed populations in Japan or China, the thresholds

of urinary or blood Cd associated with bone effects are higher than those associated with renal dysfunction²¹. This view, however, has been challenged by some recent studies reporting associations between urinary Cd and indices of bone mass density in the general population with very low environmental exposure²²⁻²⁴. An increased risk of bone fractures with increasing Cd levels in urine has been reported²². Other authors, however, have failed to evidence an association between urinary Cd and bone mass density or biomarkers of bone toxicity²⁵. Before translating these findings in terms of public health impact, an important issue to clarify is the direction of causality of these associations. The possibility cannot be excluded, indeed, that the metabolism of Cd and hence the levels of the metal in biological fluids can be altered by disturbances in calcium homeostasis due to menopause, ageing or renal diseases unrelated to Cd¹⁹.

Cancer

Various regulatory bodies have concluded that there is sufficient evidence to classify Cd as a human carcinogen. The most convincing evidence comes from the finding of increased risks of lung cancer in workers exposed to Cd by inhalation as well as from animal data showing that Cd administered by various routes can produce cancer at multiple sites, including in the lung²⁶. Although the evidence from animal studies is undisputable, data from occupationally exposed populations require a more careful analysis because of the possible confounding by concomitant exposure to arsenic. Recent studies having adjusted for the concomitant exposure to arsenic and nickel have reported lower relative risks of lung cancer than in the past². Cd exposure in the industry has also been linked to prostate and renal cancer but this linkage is much weaker than that for lung cancer. Until recently, studies on populations environmentally exposed to Cd had revealed no increase in cancer mortality, even in populations with Cd-induced renal effects. The possibility that Cd can be involved in environmental carcinogenesis cannot be excluded. In a Cd-polluted region in China, an association between urinary Cd and raised serum concentration of prostate-specific antigen has been found suggesting a possible implication of Cd in prostate carcinogenesis²⁷. Recently, in a prospective population-based study in Belgium, Nawrot *et al*²⁸ have found an association between increased Cd body burden as assessed based on urinary Cd and the development of lung cancer. However, the possibility of a confounding effect by arsenic cannot be excluded in this study². The mechanism of Cd carcinogenesis

remains largely unknown. Since the metal is not strongly genotoxic and does not cause direct genetic damage, epigenetic mechanisms and/or indirect genotoxic mechanisms such as a blockage of apoptosis, alterations in cell signaling or inhibition of DNA repair might be involved²⁶.

Other effects

Impairment of the pulmonary function suggestive of mild obstructive syndrome has been reported in workers exposed to relatively high concentrations of Cd by inhalation. Changes in lung function were however slight as compared to that caused by tobacco smoking¹⁰. With improvement of working conditions in most Cd plants, pulmonary changes are much less likely to occur than biological signs of renal damage. Although Cd can cause liver injury in animals receiving high doses, no study has reported signs of hepatic damage either in Cd workers or among inhabitants of polluted areas. Similarly, there is no report of adverse effects on the nervous system or the reproductive system caused by occupational or environmental exposure to Cd². Although epidemiologic studies assessing the effects of Cd exposure on blood pressure have provided largely inconsistent results, a recent study in US adults who participated in the 1999-2004 National Health and Nutrition Examination Survey (NHANES) found that Cd levels in blood, but not in urine, were associated with a modest elevation in blood pressure levels²⁹.

Dose-effect/response relationships

Cd is one of the environmental pollutants for which dose-response relationships are best documented. The reason for this is that the amount of Cd stored in the critical target organ *i.e.* the kidney, can be evaluated

non invasively using as surrogate indicator the concentration of the metal in urine. Most studies have assessed dose-response relationships for Cd nephrotoxicity by using as exposure indicator, urinary Cd and as critical effect, an increased urinary excretion of microproteins. Studies carried out among industrial workers in the 1980s have derived a threshold of urinary Cd of 10 µg/g creatinine for the development of tubular proteinuria with an increased urinary excretion of β₂-microglobulin or retinol-binding protein^{2,4,10,11}. The validity of this threshold is again confirmed by the data shown in Table II, showing the relationship between retinol-binding protein and Cd in the urine of workers manufacturing cadmium-nickel batteries (unpublished data, Bernard *et al*). This threshold of 10 µg/g creatinine for urinary Cd serves now the basis for the occupational exposure limit of 5 µg/g creatinine currently in application in most industrialized countries. While the threshold of urinary Cd for the development of kidney damage has been estimated with some accuracy in industrial workers, thresholds of urinary Cd derived from population-based studies vary by almost one order of magnitude despite the use of the same indicators as in industrial workers (Table III). For instance, studies conducted in Belgium and Sweden have concluded that tubular dysfunction is likely to occur in the general population from thresholds of urinary Cd in the range of 1 to 2 µg/g creatinine. By contrast, some studies on the general population of China and Japan have derived much higher thresholds in the range of 8 to 10 µg/g creatinine, which actually agree well with that observed in industrial workers (Table III). Such inconsistencies might be linked to differences in sensitivity between adult workers and the general population. Methodological differences related to the use of

Table II. Risks of increased urinary excretion of retinol-binding protein (RBP-U) according to the urinary concentration of Cd (Cd-U) in workers manufacturing nickel-cadmium batteries

| Cadmium in urine (µg/g cr, range) | Number of workers | Cd-U (µg/g cr) median (IQR) | Retinol-binding protein in urine (µg/g cr) | | | |
|--------------------------------------|----------------------|--------------------------------|--|-------------|---------------------------------------|----------|
| | | | median (IQR) | N > 300 (%) | Odds ratio for RBP-U >300 (95% CI) | P-value |
| 0 - 1 | 112 | 0.55 (0.35-0.71) | 95.1 (73.4-128) | 4 (3.57) | 1.00 (1.00-1.00) | - |
| > 1 - 2 | 92 | 1.40 (1.13-1.58) | 96.8 (67.4-134) | 3 (3.26) | 0.91 (0.2-4.18) | 0.90 |
| > 2 - 5 | 130 | 3.35 (2.59-4.03) | 98.0 (78.0-156) | 3 (2.31) | 0.65 (0.14-2.96) | 0.58 |
| > 5 - 10 | 67 | 6.97 (5.79-8.43) | 120 (98.4-158) | 2 (2.99) | 0.83 (0.15-4.60) | 0.83 |
| > 10 | 50 | 14.0 (11.1-17.8) | 178 (107-329)* | 15 (30.0)* | 11.6 (3.60-37.2) | < 0.0001 |

Statistical tests were performed using as reference the group of workers with a Cd-U value lower than 1 µg/g cr. $P < 0.05$ by the Dunnett's multiple comparison test; * $P < 0.05$ by the Chi² test. The *P* values given in the Table indicate the level of statistical significance of the odds for having a RBP-U higher than 300 µg/g cr.

Cd-U, cadmium concentration in urine; RBP-U, retinol-binding protein concentration in urine; IQR, interquartile range; cr, creatinine

Table III. Estimates of the critical concentrations of Cd in urine associated with tubular proteinuria in environmentally exposed populations

| Authors | Country | Population | Protein | Cd-U threshold ($\mu\text{g/g cr}$) | Remarks |
|---|---------|---|---------------------|---|--|
| Ishizaki <i>et al</i> 1989 ³⁰ | Japan | 3,178 persons, >50 yr in Cd-polluted area 294 persons, >50 yr in a Cd non polluted area | β_2 -M | Men, 3.8-4.0 Women, 3.8-4.1 | |
| Buchet <i>et al</i> 1990 ¹⁵ | Belgium | 1,699 persons, 20-80 yr in two Cd polluted areas and in two control areas | β_2 -M RBP | β_2 -M, 2.03 RBP, 1.83 | Response rate of 10%. Cut-off: β_2 -M, 189 $\mu\text{g/cr}$, RBP, 225 $\mu\text{g/g cr}$ |
| Jarup <i>et al</i> 2000 ¹⁶ | Sweden | 1,021 subjects environmentally or occupationally exposed | Protein HC | 1 | Inflexion point |
| Ikeda <i>et al</i> 2003 ³¹ | Japan | Literature survey: 12 publications, 32 groups of men and 58 groups of women | β_2 -M | 10 - 12 | Inflexion point |
| Ezaki <i>et al</i> 2003 ³² | Japan | >10,000 middle aged women | β_2 -M | Association with Cd-U without threshold | Similar associations with urinary Zn, Ca and Mg |
| Ikeda <i>et al</i> 2005 ³³ | Japan | Meta-analysis, 51 publications | β_2 -M | 8 - 9 | Cut-off, β_2 -M >1,000 $\mu\text{g/cr}$ |
| Akesson <i>et al</i> 2005 ¹⁸ | Sweden | 820 women, age 53-64 yr, in a non polluted area | Protein HC | 0.8 | LOAEL |
| Uno <i>et al</i> 2005 ³⁴ | Japan | 410 men and 418 women, aged 40-59 yr in Cd non polluted area | β_2 -M | Men, 0.6-1.2 Women, 1.2-3.6 | BMDL |
| Kobayashi <i>et al</i> 2006 ³⁵ | Japan | 1,114 men, 1,664 women, >50 yr, in non polluted areas | β_2 -M | Men, 2.4 Women, 3.3 | BMDL |
| Gamo <i>et al</i> 2006 ³⁶ | Japan | Populations environmentally exposed to Cd | β_2 -M | 2-3 | Cut-off, β_2 -M, 1,000 $\mu\text{g/cr}$ |
| Shimizu <i>et al</i> 2006 ³⁷ | Japan | 3,178 in a Cd polluted area; 294 in a non polluted area | β_2 -M | Men, 2.9-4 Women, 1.5-3.6 | Cut-off, β_2 -M, 1,000 $\mu\text{g/cr}$, BMDL |
| Kobayashi <i>et al</i> 2006 ³⁸ | Japan | 2,034 subjects, age>50 yr, in a non polluted area | β_2 -M | Men, 2.0 Women, 1.6 | BMDL, non smokers |

Cd-U, cadmium concentration in urine; β_2 -M, β_2 -microglobulin; RBP, retinol-binding protein; LOAEL, lowest observed adverse effect level; BMDL, benchmark dose lowest level; cr, creatinine

benchmark dose rather than the lowest observed adverse effect level (LOAEL), the study of small-sized populations or analytical aspects such as an insufficient adjustment for variations in diuresis, might account for part of the variation in these estimates. Another possibility that has received little attention is the confounding or distortion of dose-response relationships by parallel changes in the metabolism of Cd and in the renal function (related to ageing or diseases unrelated to Cd), generating secondary associations between protein and Cd in urine³⁹. Another possibility, also frequently overlooked, is a shift of the dose-response curve towards lower levels of Cd that necessarily occurs after removal from exposure, especially in subjects with renal damage^{4,40}.

Diagnosis, treatment and prevention

Diagnosis of chronic Cd poisoning basically relies on the screening of proximal tubular dysfunction and the assessment of the cumulative exposure to Cd using environmental or biological indicators. The earliest manifestation of Cd nephropathy consists in an increased urinary excretion of microproteins (tubular proteinuria). The most commonly microproteins are β_2 -microglobulin, retinol-binding protein and α_1 -microglobulin. These proteins are usually measured in untimed urine samples and the results are expressed per gram creatinine to adjust for variations in diuresis. The β_2 -microglobulin test presents the drawback that β_2 -microglobulin is unstable in urine samples with a pH above 5.6, which necessitates to collect a new urine sample in about 20-30 per cent of the cases. α_1 -microglobulin is very stable in urine but because of its larger size it is less specific of tubular damage and slightly less sensitive than the two other microproteins. Retinol-binding protein presents the advantage of being stable, specific and as sensitive as the β_2 -microglobulin. When tubular dysfunction is at an early stage, there is a possibility of some reversal at least when the Cd body burden is not too high (e.g. Cd in urine below 20 $\mu\text{g/g}$ creatinine). Otherwise, Cd-induced microproteinuria is irreversible and predictive of a faster decline of the GFR with ageing. There are no efficient treatments for chronic Cd poisoning. Even after cessation of exposure, renal dysfunction and pulmonary impairment may progress. The only possible intervention is removal from exposure. This means that in health surveillance programmes, the emphasis must be placed on primary prevention in order to maintain the levels of Cd in the environment or in the food chain as low as possible⁴.

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