Usefulness of Biomarkers of Exposure to Inorganic Mercury, Lead, or Cadmium in Controlling Occupational and Environmental Risks of Nephrotoxicity

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ABSTRACT

A successful prevention of renal diseases induced by occupational or environmental exposure to toxic metals such as mercury (Hg), lead (Pb), or cadmium (Cd) largely relies on the capability to detect nephrotoxic effects at a stage when they are still reversible or at least not yet compromising renal function. The knowledge of dose-effect/response relations has been useful to control nephrotoxic effects of these metals through a “biological monitoring of exposure approach”.

Chronic occupational exposure to inorganic mercury (mainly mercury vapor) may result in renal alterations affecting both tubules and glomeruli. Most of the structural or functional renal changes become significant when urinary mercury (HgU) exceeds 50 µg Hg/g creatinine. However, a marked reduction of the urinary excretion of prostaglandin E2 was found at a HgU of 35 µg Hg/g creatinine. As renal changes evidenced in moderately exposed workers were not related to the duration of Hg exposure, it is believed that those changes are reversible and mainly the consequence of recently absorbed mercury. Thus, monitoring HgU is useful for controlling the nephrotoxic risk of overexposure to inorganic mercury; HgU should not exceed 50 µg Hg/g creatinine in order to prevent cytotoxic and functional renal effects.

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Several studies on Pb workers with blood lead concentrations (PbB) usually below 70 µg Pb/dl have disclosed either no renal effects or subclinical changes of marginal or unknown health significance. Changes in urinary excretion of eicosanoids was not associated with deleterious consequences on either the glomerular filtration rate (GFR) - estimated from the creatinine clearance ($C_{cr}$) - or renal hemodynamics if the workers’ PbB was kept below 70 µg Pb/dL. The health significance of a slight renal hyperfiltration state in Pb workers is yet unknown. In terms of Pb body burden, a mean tibia Pb concentration of about 60 µg Pb/g bone mineral (that is 5 to 10 times the average “normal” concentration corresponding to a cumulative PbB index of 900 µg Pb/dL x year) did not affect the GFR in male workers. This conclusion may not necessarily be extrapolated to the general population, as recent studies have disclosed inverse associations between PbB and GFR at low-level environmental Pb exposure. A 10-fold increase in PbB (e.g. from 4 to 40 µg Pb/dL) was associated with a reduction of 10–13 mL/min in the $C_{cr}$ and the odds ratio of having impaired renal function (viz. $C_{cr} < 5$th percentile: 52 and 43 mL/min in men and women, respectively) was 3.8 (CI 1.4–10.4; p = 0.01). However, the causal implication of Pb in this association remains to be clarified.

The Cd concentration in urine (CdU) has been proposed as an indirect biological indicator for Cd accumulation in the kidney. Several biomarkers for detecting nephrotoxic effects of Cd at different renal sites were studied in relation to CdU. In occupationally exposed males, the CdU thresholds for significant alterations of renal markers ranged, according to the marker, from 2.4 to 11.5 µg Cd/g creatinine. A threshold of 10 µg Cd/g creatinine (corresponding to 200 µg Cd/g renal cortex: the critical Cd concentration in the kidney) is confirmed for the occurrence of low-molecular-mass proteinuria (functional effect) and subsequent loss of renal filtration reserve capacity. In workers, microproteinuria was found reversible when reduction or cessation of exposure occurred timely when tubular damage was still mild ($\beta_{2}$-microglobulinuria < 1500 µg/g creatinine) and CdU had never exceeded 20 µg Cd/g creatinine. As the predictive significance of other renal changes (biochemical or cytotoxic) is still unknown, it seems prudent to recommend that occupational exposure to Cd should not allow that CdU exceeds 5 µg Cd/g creatinine. In groups of the general Belgian population with low-level Cd exposure due to historical pollution of the environment by zinc/cadmium smelters, much lower no-adverse effect CdU levels were found, viz. 3 µg Cd/24 hours for low-molecular-mass proteinuria and 2 µg Cd/24 hours for hypercalciuria (1985–1989 CadmiBel Study). As hypercalciuria may exacerbate the development of osteoporosis, especially in the elderly, a CdU of 2 µg Cd/g creatinine should be regarded as a measure of the maximum tolerable internal dose of Cd for individuals in the general population.

Key Words: Nephrotoxicity; Mercury; Lead; Cadmium; Biomarkers of exposure.
INTRODUCTION

Upon chronic exposures to inorganic forms of cadmium (Cd), lead (Pb), or mercury (Hg) nephropathy may occur which usually starts insidiously. A cascade of events may develop leading from initial dysfunction and focal damage to a clinically detectable disease (1). The kidney is characterized by its ability to compensate for renal damage and for this reason classical tests (e.g., serum creatinine or inulin clearance) are insensitive, since they only deviate late in the cascade of damage-events when already a large part of the nephron mass is lost (2). It is thus of paramount importance that tools for detecting heavy metal nephrotoxicity be sensitive enough to detect early events and ideally they should reflect subclinical reversible changes. During the last two decades much effort has been put in the development and validation of markers of early renal effects (3,4). Such biomarkers are not diagnostic tests, but hallmarks of early changes in the renal integrity that could later lead to clinical disease if exposure is not reduced. Knowledge about the predictive value of these markers is particularly useful for preventive purposes.

In order to control the nephrotoxic risk of chronic exposure to cumulative metals such as Cd, Pb, and Hg, which are often present in industrial settings and in the general environment, an epidemiological approach can be used to define acceptable exposure levels. This requires, however, the knowledge of the relationship between the dose of these metals and the probability of occurrence of adverse effects in populations at risk. Biomonitoring of the cumulative internal dose of these metals is possible through direct in vivo measurements using neutron activation analysis (NAA) or X-ray fluorescence (XRF) methods, such as for Cd in kidney and liver (5), Pb in bone (6), and Hg in kidney (7). However, these techniques are not easily available and not yet well suited for routine biomonitoring of exposure in the occupational or environmental settings. Therefore, indirect estimators are often used as surrogate biomarkers of the cumulative internal or target dose, viz. Cd in urine (CdU), cumulative blood lead index (CBLI), and Hg in urine (HgU). These surrogate biomarkers of cumulative exposure have shown satisfactory correlations with kidney cortex Cd in workers with no signs of Cd-induced proteinuria (5), tibial Pb (8), and renal Hg (7), respectively. On the other hand, currently available analytical methods allow to determine small amounts of endogenous substances in urine and blood which are useful as biomarkers of nephrotoxicity in order to assess function and integrity of specific nephron segments (2,4).

Several studies conducted by our laboratory in groups of workers exposed to Cd, Pb or Hg vapor allowed to establish dose-effect or dose-response relations which have highlighted the usefulness of biomonitoring of exposure to these metals for controlling nephrotoxic risks in the occupational setting. Our studies conducted in groups of the general population environmentally exposed to low levels of Cd or Pb demonstrated, however, that findings in industrial male workers are not necessarily applicable to the general population. The present paper gives an overview of the most significant findings obtained by these epidemiological investigations.

EPIDEMIOLOGICAL FINDINGS

Mercury

Excessive exposure to inorganic mercury compounds either through inhalation of elemental mercury vapor, ingestion of divalent mercury salts, or the use of skin-lightening cosmetics containing inorganic mercury may entail a nephrotic syndrome (severe albuminuria) or an acute
tubular necrosis (9). As environmental exposure to inorganic mercury is usually not a public health issue, most of the knowledge on renal effects of inorganic mercury exposure was obtained from studies in groups of subjects occupationally exposed to mercury vapor in chloralkali plants. Recently, there has been much debate on the health risk of dental amalgams, but the reports on symptoms and signs and the few epidemiological studies were inconclusive (9). It was previously believed that renal effects of exposure to mercury vapor occurred only at doses higher than those associated with the onset of signs and symptoms of central nervous system dysfunction. However, numerous investigations during the last two decades have shown renal effects in workers with relatively low exposure levels (9). In several of these studies significant associations between biomarkers of renal effects and HgU were found which allowed to assess an HgU threshold.

In 1980, we reported on a group of 63 Hg-exposed workers (mean age 36) compared with an age-matched control group of 88 male subjects (10). The mean duration of exposure was 7 years and HgU averaged 59 μg Hg/g creatinine (range 5–200). An increased urinary excretion of high-molecular-mass proteins (albumin, transferrin, IgG) was indicative of an early glomerular dysfunction; the proximal tubular cells were also affected as shown by an increased urinary excretion of lysosomal β-galactosidase activity. These biomarkers of tubular and glomerular effects correlated significantly with HgU. The likelihood of finding these nephrotoxic effects associated with exposure to mercury vapor increased significantly in workers with HgU > 50 μg Hg/g creatinine (10). Another study, carried out 5 years later in a group of 180 male and female workers evidenced only proximal tubular effects, viz. increases in β-galactosidase and urinary retinol-binding protein (RBP). Again, the prevalence of abnormal values of these tubular markers rose significantly when HgU exceeded 50 μg Hg/g creatinine (11). Recently, we assessed the usefulness of a battery of about 25 renal biomarkers in the frame of a European network study on a cohort of 44 moderately exposed chloralkali workers (12). The mean duration of exposure was 11 years and HgU averaged 22 μg Hg/g creatinine (range 5–90) which was less than half that in the two previous cohorts. Dose-response relations showed no changes in functional biomarkers since glomerular or tubular proteinuria was not detected. The main renal changes were indicative of tubular cytotoxicity, viz. increased leakage of tubular antigens (BB50, BBA, HF5) and enzymes such as the brush-border lysosomal N-acetyl-β-D-galactosaminidase (NAG) and the S3-segment-specific intestinal alkaline phosphatase (IAP). Significant changes in biochemical indicators were also found, viz. decreases in urinary eicosanoids (PGE₂, PGF₂α, TXB₂), glycosaminoglycans, and kallikrein. Most of these renal effects were found in workers excreting more than 50 μg Hg/g creatinine corroborating thus the previous proposal of an adequate HgU threshold (10,11). However, a significant reduction in the urinary excretion of eicosanoids, especially PGE₂, was noted at HgU values as low as 35 μg Hg/g creatinine. None of the changes in this less exposed group were related to duration of exposure, which supports the view that renal changes induced by moderate exposure to mercury vapor are reversible and mainly the consequence of recently absorbed elemental mercury.

It may be concluded from these three studies that except a few biochemical changes such as a decrease in urinary pH and a reduction in PGE₂ excretion of which the health significance is not yet well understood, the nephrotoxic response to moderate occupational exposure to mercury vapor does not involve cytotoxic and functional alterations when HgU remains below 50 μg Hg/g creatinine. There is, however, an increased probability of cytotoxic effects at the proximal tubuli (e.g. enzymuria and increase in urinary tubular antigens) and functional changes (e.g. glomerular and tubular proteinuria, increase in serum β₂-microglobulin) when mercury vapor exposure chronically entails HgU levels above 50 μg Hg/g creatinine. Disrupted renal handling of low and high-molecular-mass proteins did not lead to clinically significant altera-
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Sections of the kidney function, as tubular and/or glomerular proteinuria were shown to be reversible 9 to 12 months after cessation of exposure (11,13). The reversibility time course seems to parallel the elimination kinetics of renal mercury. In a chloralkali worker with an HgU of 200 μg Hg/g creatinine, for example, the concentration of mercury in urine will slowly decrease to reach "acceptable" values (10–20 μg Hg/g creatinine) in about one year after removal from mercury vapor exposure, because the elimination half-time of HgU is on average about 90 days (14).

Lead

Chronic massive exposure to lead may cause progressive tubulointerstitial nephropathy that develops insidiously and often leads to kidney failure (15–18). The level of Pb exposure that may be associated with early adverse renal effects is however uncertain because incipient lead nephropathy is difficult to detect due to the lack of an appropriate bloodborne or urinary biomarker reflecting an early effect on the renal interstitial tissue. In chronically exposed Pb workers, a decline of glomerular filtration rate (GFR) has been reported in cases with long-standing exposure and lead in blood (PbB) exceeding 70 μg Pb/dL (16,17). A reduced GFR however, indicates that Pb nephropathy has already reached an irreversible stage. Hence, to better define the occupational exposure level without early adverse renal effects, a large number of cross-sectional studies were conducted during the last two decades in lead workers whose duration of exposure was less than 30 years and whose PbB usually remained below 60 μg Pb/dL (for a review, ref 19). The majority of these studies and also the European network study, involving the large renal biomarker battery, disclosed a lack of association between the urinary excretion of renal markers of tubular or glomerular toxicity and biomarkers of Pb exposure, viz. PbB, zinc-protoporphyrin in blood (ZPP), or tibia lead (6,10,19–22). Some studies have revealed significant changes in the urinary excretion of the distal tubular enzyme kallikrein (23,24), NAG (25–28), or eicosanoids, viz. two vasodilators 6-keto-PGF₁α and PGE₂ which decreased and a vasoconstrictor thromboxane B₂ which increased (22), but the clinical significance of these changes is not yet clear.

The crucial question is: What is the predictive value of these renal changes and should they be taken into account to assess the no-adverse-effect level of lead on the kidney?

First, the specificity of the reduced urinary activity of kallikrein (23,24) and the increased excretion of NAG in urine (25–28) found in these studies can be questioned, because concomitant albeit slight exposure to Cd, which frequently occurs in lead industries, has not been considered as a possible confounder. Indeed, contrast analysis in groups of Cd and Pb workers showed CdU but not PbB as determinant of urinary kallikrein activity (29), and as to urinary NAG activity, its association with biomarkers of lead exposure (viz. PbB, ZPP, or tibia lead) was abolished after adjustment for CdU in stepwise multiple regression analysis (6,30). The changes in urinary excretion of eicosanoids might, however, reflect a disturbance of their synthesis in the kidney (22). As the renal production of eicosanoids may play a role in the regulation of the GFR, we advanced the hypothesis of a possible effect of Pb on renal hemodynamics before the perturbation of other renal biomarkers. Therefore, in order to assess whether these eicosanoid changes had any impact on the renal hemodynamic response to an acute oral protein load, we compared 76 male workers (mean age 44, range 29–56) moderately exposed to lead with 68 male controls matched for age and socioeconomic state (6). The lead workers were exposed on average for 18 years (range 6–36), their historical PbBs rarely exceeded 70 μg Pb/dL, and they showed a threefold higher body burden of lead than the controls as estimated by in vivo XRF measurements of lead in tibia (66 vs. 21 μg Pb/g bone mineral). The baseline
and peak $C_{\text{Cr}}$ averaged 116 and 132 mL/min in the control group against 121 and 141 mL/min in the Pb-exposed group, respectively. All the subjects had a normal baseline $C_{\text{Cr}}$. In stepwise multiple regression analysis, both baseline and peak $C_{\text{Cr}}$ were inversely associated with age ($p < 0.01$), whereas a modest but positive association emerged only with tibial bone lead ($p < 0.05$). These findings suggest that the cumulative Pb exposure is associated with a slight state of renal hyperfiltration. In conclusion, it seems thus unlikely that the underlying changes in urinary eicosanoids have deleterious consequences on renal hemodynamics in this group of moderately exposed Pb workers. This study suggested that a mean tibia lead concentration of about 60 $\mu$g Pb/g bone mineral (that is about 5 to 10 times the average “normal” concentration) is not likely to affect the GFR and supports the view that adverse renal changes are unlikely to occur in adult male workers when the individual PbB is kept below 70 $\mu$g Pb/dL during the whole occupational career (31).

Previous studies from the USA (15) and Australia (18) have shown that environmental Pb exposure may severely compromise renal function and entail important implications for public health. As to the possibility of renal impairment with low-level lead exposure in humans, there is growing evidence (32,33) suggesting that the no-adverse-effect PbB level of 70 $\mu$g Pb/dL for occupational lead exposures cannot be extrapolated to the general population which is usually exposed to lower lead levels. A random sample of about 2000 adults (20 $\mu$g Pb/g bone 88 years old) from the Belgian population was investigated (32) using the database generated in the frame of the CadmiBel Study (see also below “Cadmium”). After adjustment for covariates (age, body-mass index, and diuretic treatment) significant inverse relations were found in men and women between the measured $C_{\text{Cr}}$ and PbB or ZPP. A tenfold increase in PbB (e.g. from 4 to 40 $\mu$g Pb/dL) was found associated with a reduction in $C_{\text{Cr}}$ of 10 and 13 mL/min in men and women, respectively. In men and women without diabetes and analgesic or diuretic drug use, the 5th percentile of the $C_{\text{Cr}}$ was 52 and 43 mL/min, respectively. The subjects with lower $C_{\text{Cr}}$ were classified as having impaired renal function (men 48/965, women 62/1016). In multiple logistic-regression analysis with adjustments for covariates (viz. age, the presence of diabetes, and the use of analgesic or diuretic drugs), the probability of having an impaired renal function was positively associated with PbB and in the total study population the odds ratio for a tenfold increase in PbB was 3.8 (CI 1.4–10.4; $p = 0.01$). Since several studies suggested that renal insufficiency itself does not raise bone lead (34) or PbB (35,36), our results (32) and those of Payton et al. (33) lend support to the hypothesis that low-level environmental exposure to lead may reduce the GFR. However, the critical cumulative Pb dose in the general population, e.g. bone lead concentration or cumulative blood lead index, which is associated with the onset of a marginal impairment of the GFR remains to be assessed (37).

**Cadmium**

Cadmium is a very cumulative toxic metal that under conditions of chronic occupational or environmental exposure has the kidney as its critical target organ in the human organism. Epidemiological studies performed in the 1970s and early 1980s on groups of male Cd workers have shown that Cd may interfere with the renal handling of plasma-derived proteins. This was usually characterized by microproteinuria due to impairment of the tubular reabsorption of low-molecular-mass proteins, e.g. $\beta_2$-microglobulin ($\beta_2$-M) and RBP (38,39). An isolated glomerular effect with increased permeability of high-molecular-mass proteins, e.g. albumin and transferrin, was less commonly found (39,40). In male Cd workers, the risk of microproteinuria increased significantly when Cdu regularly exceeded 10 $\mu$g Cd/g creatinine which corresponds to a critical Cd concentration in renal cortex of about 200 $\mu$g Cd/g wet weight as estimated by in vivo neutron activation analysis (5,38,41).
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In the frame of the collaborative network-project, involving laboratories of 5 European countries, we applied recently the battery of 25 renal tests on a cohort of 37 male Cd workers (CdU: 2 to 16 μg Cd/g creatinine) and an age-matched control group (n = 43; CdU < 2 μg Cd/g creatinine). The aim was to assess the usefulness of various urinary and bloodborne analytes as potential biomarkers of Cd toxicity on distinct nephron segments (42). The battery comprised functional markers (e.g. creatinine and β2-M in serum; low and high-molecular-mass proteins in urine, and urinary calcium), cytotoxicity markers (e.g. tubular antigens or enzymes in urine), and biochemical markers (e.g. glycosaminoglycans, kallikrein. sialic acids, and eicosanoids in urine). Cd exposure was found to cause a broad spectrum of site-specific effects on the kidney with significant alterations in various markers of nephrotoxicity. Dose-response relations and logistic regressions between the renal markers and CdU showed that the probability of abnormal values significantly increased with CdU in a dose-dependent manner. Three main groups of CdU thresholds could be identified on the basis of various urinary biomarkers: one around 2 μg Cd/g creatinine associated with biochemical alterations (6-keto-PGF1α and sialic acids), a second around 4 μg Cd/g creatinine associated with cytotoxic effects (renal brush-border antigen BBA, IAP, and NAG) and glomerular barrier dysfunction (albumin and transferrin), and a third around 10 μg Cd/g creatinine associated with dysfunction of the tubular reabsorption (microproteinuria: (β2-M and RBP), hypercalciuria, and changes in other biomarkers (renal brush-border antigen HF5 and glycosaminoglycans).

A critical question is whether or not there enough information as to the predictive value of these renal biomarkers to propose a meaningful biological exposure limit value for CdU. Earlier retrospective findings showed that severe microproteinuria was irreversible in retired Cd workers and associated with raising serum creatinine (43) that in some workers turned into end-stage renal insufficiency (unpublished data). We have carried out three studies to better assess the health significance of Cd-induced microproteinuria in male Cd workers.

The first study was a 5-year prospective study conducted in 23 Cd workers removed from exposure because of the discovery of microproteinuria (44). They were exposed to Cd for 25 years on average and at the time of the first examination the mean age of the group was 59 (46–68 years), the mean (SEM) CdU amounted to 22.2 (2.9) μg Cd/L, the geometric mean of urinary β2-M and RBP amounted to 1770 and 1570 μg/L, respectively, and serum creatinine was normal (< 1.4 mg/dL) in all subjects, except two (2.0 and 2.2 mg/dL). At the end of the study, urinary β2-M and RBP were increased by about 50 and 30%, respectively. Moreover, serum creatinine significantly increased with time indicating a progressive reduction of the GFR, which was estimated to decrease five times more rapidly than what could be expected due to aging alone. Elevated microproteinuria predicts thus an exacerbation of the age-related decline of the GFR and, hence, it should be regarded as an early adverse health effect.

The previous finding raised the question whether a CdU threshold value of 10 μg Cd/g creatinine prevents not only the occurrence of microproteinuria, but also the loss of nephron mass. In other words, does an increased CdU not yet sufficient to modify the urinary excretion of plasma-derived proteins impair the renal filtration reserve capacity? In a second study we have estimated the GFR in Cd workers without (n = 31) or with (n = 12) increased microproteinuria, viz. urinary β2-M and RBP > 300 μg/g creatinine (45). The subjects in both groups aged 50 to 64 (mean 55 years), had normal serum creatinine (< 1.4 mg/dL), and the geometric mean (range) of CdU was 4.7 (2.1–8.8) and 11.1 (5.8–21.7) μg Cd/g creatinine, respectively. GFR was estimated as the CrCl under baseline conditions and after an acute oral protein load to assess the hyperfiltration capacity of the kidney. The baseline CrCl was normal in both groups (mean 116 ml/min). The CrCl after protein load, however, failed to rise in the group with
microproteinuria (mean 114 mL/min) and remained significantly lower than that in the group without microproteinuria (mean 124 mL/min). The mean peak Ccr of the latter group was similar to that of an age-matched control group (n = 35; CdU < 2 μg Cd/g creatinine). In conclusion, this study showed that the filtration reserve capacity of the kidney is lost when elevated microproteinuria is present, but there was no functional impairment at a renal Cd burden that had not yet caused microproteinuria. This study validated thus the CdU estimate of 10 μg Cd/g creatinine as biological exposure limit to prevent the occurrence of microproteinuria in male Cd workers.

The third study aimed at a more precise evaluation of the time trend of Cd-induced microproteinuria by assessing its evolution in 32 Cd workers according to criteria of CdU (cutoff 10 μg Cd/g creatinine) and severity of the microproteinuria at the time that the exposure was substantially reduced or had ceased (46). The finding that 15 workers (63%) with CdU > 10 μg Cd/g creatinine showed a urine β2-M exceeding the upper reference limit of 300 μg/g creatinine corroborated our earlier finding that the risk of abnormal microproteinuria dramatically increased when CdU regularly exceeded 10 μg Cd/g creatinine. When reduction of Cd exposure took place and urine β2-M did not exceed 300 μg/g creatinine, the risk of developing tubular dysfunction at a later stage was low even in cases with historical CdU values occasionally > 10 but always < 20 μg Cd/g creatinine. There is indication that the tubulotoxic effect of Cd is reversible, provided that the historical CdU values had never exceeded 20 μg Cd/g creatinine and urinary β2-M was mild (< 1,500 μg/g creatinine) at the time the Cd exposure was reduced. When severe urinary β2-M (> 1,500 μg/g creatinine) was found in combination with historical CdU values exceeding 20 μg Cd/g creatinine, Cd-induced tubular dysfunction was progressive in spite of reduction or cessation of Cd exposure.

These three studies on the health significance of microproteinuria confirm thus the estimate of 10 μg Cd/g creatinine as the biological limit value of CdU above which the probability is high that Cd-induced microproteinuria develops. Hence, tubular proteinuria should be considered as an adverse effect of Cd exposure, because it can lead to irreversible renal damage associated with an exacerbation of the age-related decline in GFR and a decrease in the filtration reserve capacity. Since the health significance of renal changes other than microproteinuria is still unknown and no treatment is presently available to remove Cd from its storage sites, the adoption by the American Conference of Governmental Industrial Hygienists (ACGIH) of 5 μg Cd/g creatinine as biological exposure index (BEI) for Cd seems logical (47). However, studies on the predictive value of renal changes other than microproteinuria are urgently needed to assess the validity of this BEI.

As to environmental Cd exposure in the general population, a more stringent guideline is justified as first suggested by earlier pilot-studies in Belgium (48–50) and as conclusively shown by the 1985–1989 CadmBel Study on the possible health effects of low-level Cd exposure in the Belgian population at large (51–55). The vast cross-sectional epidemiological investigation on the renal function comprised a sample of about 1700 adults (males and females aged 20–80 years) who had never been occupationally exposed to Cd, Pb, or Hg, and who were randomly recruited in two less polluted areas (rural and urban) and two other areas (rural and urban) characterized by environmental pollution due to the activities of various zinc/cadmium smelters in the past (51,52). After allowing for major covariates, e.g. age and smoking habits, the 24 h urinary Cd excretion averaged 25% higher in women than in men and was found in both genders 20 to 60% higher in the more polluted rural and urban areas (53). In stepwise multiple regression analysis, only the 24 h excretions of urinary markers of renal tubulotoxicity (viz. calcium, NAG, RBP, β2-M, and amino acids) were significantly and positively associated with CdU (51). In the rural areas (about 1100 subjects), a doubling of the Cd excretion was
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Table 1

Biological exposure thresholds for controlling health-significant nephrotoxic effects in adults chronically exposed to either moderate occupational or low-level environmental levels of inorganic mercury, lead, or cadmium.

<table>
<thead>
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<th>Occupational exposure (healthy males; age 20-60)</th>
<th>Environmental exposure (general population)</th>
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<tr>
<td>Mercury (Hg)</td>
<td>Hg in urine</td>
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<tr>
<td></td>
<td>50 μg Hg/g creatinine</td>
<td>Not relevant</td>
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<td></td>
<td>reversible effect:</td>
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<td></td>
<td>glomerular and/or tubular proteinuria</td>
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<tr>
<td>Lead (Pb)</td>
<td>Pb in blood</td>
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<td></td>
<td>70 μg Pb/dL (31)</td>
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<td></td>
<td>decrease in GFR ?</td>
<td>decrease in GFR ?</td>
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<tr>
<td></td>
<td>no validated early biomarker</td>
<td>no validated early biomarker</td>
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<tr>
<td>Cadmium (Cd)</td>
<td>Cd in urine</td>
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<td>10 μg Cd/g creatinine</td>
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<td>microproteinuria</td>
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<td>5 μg Cd/g creatinine</td>
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<td></td>
<td>BEI adopted by ACGIH (47)</td>
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GFR: glomerular filtration rate; BEI: biological exposure index; ACGIH: American Conference of Governmental Industrial Hygienists.

associated with a 4, 7, and 9% increase in the excretion of RBP, urine β2-M, and NAG respectively, and living 1 km closer to the nearest smelter with a 1 to 2% increase in their excretion against 3% for the Cd excretion (54). After adjustment for covariates, logistic regression models between CdU and each of these five urinary biomarkers of tubular effects have shown that the likelihood of abnormal biomarker values (subclinical increases in excretion) were to occur with a probability of 10% at a urinary Cd excretion of 1.9, 2.7, 2.9, 3.1, and 4.3 μg Cd/24 h for calcium, NAG; RBP, urine β2-M, and amino acids, respectively (52). These results suggested that the no-adverse-effect level of urinary Cd in the general population approximates 3 μg Cd/g creatinine for microproteinuria (RBP and urine β2-M), which is at variance with 10 μg Cd/g creatinine for adult male Cd workers. This striking difference might illustrate the impact of selection biases operating in industrial worker cohorts, such as gender (usually males), restricted age group (no elderly), self-selection bias, healthy worker effect, and pre-employment medical examination preventing potentially more susceptible subjects to be hired for jobs involving exposure to cadmium, lead, or other nephrotoxic agents. A 5-year follow-up of the most heavily exposed subgroup in the CadmiBel Study (rural area) indicated however that the mild changes in microproteinuria were not predictive of an increased risk of renal dysfunction (manuscript in preparation).
The CadmiBel Study revealed also a dose (CdU)-dependent calciuria and suggested an increased prevalence of hypercalciuria when CdU exceeded 2 μg Cd/g creatinine, especially in post-menopausal women (52,55). This hypercalciuria should be considered as an early adverse tubulotoxic effect, because it may exacerbate the development of osteoporosis, especially in the elderly (56). We have therefore proposed that a CdU value of 2 μg Cd/g creatinine should be regarded as a measure of the maximum tolerable internal dose of Cd for individuals from the general population. It may be concluded that in the early 1990s, the Cd excretion in Belgium exceeded this threshold value in about 10% of the general population and reached 20% in the rural area historically polluted by Cd from nonferrous smelters. In this area, a clear-cut impact of a preventive action to decrease the Cd transfer from the environment to the inhabitants was observed in a follow-up study about 5 years later, because the Cd concentration had decreased by about 30% in blood and 15% in urine: the decrease was less in subjects living closer to the smelters and in pre-menopausal women (57).

CONCLUSION

The results of the various epidemiological investigations performed since the 1970s by our laboratory indicate that in Belgium the efforts made by industries and the health authorities to reduce occupational and environmental exposure to inorganic mercury, lead, and cadmium are fully justified. Table 1 summarizes the guidelines for a practical and sound biological monitoring of exposure to these heavy metals in order to control adverse nephrotoxic effects at an early stage and ensure an adequate health prevention in the occupational setting and the general population.

REFERENCES

Control of Nephrotoxicity from Hg, Pb, or Cd Exposure


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