Health significance of cadmium induced renal dysfunction: a five year follow up

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ABSTRACT To assess the health significance of the early renal changes after chronic exposure to cadmium, 23 workers removed from exposure because of the discovery of an increased urinary excretion of β_2 -microglobulin or retinol binding protein, or both, have been examined once a year for five years. Eight of these workers had also an increased albuminuria. These workers had been exposed to cadmium for six to 41.7 years (mean 25 years) and their first follow up examination took place when they had been removed from exposure for six years on average. At that time, their mean age was 58.6 years (range: 45.5-68.1). It has been confirmed that the proteinuria induced by cadmium is irreversible. The most important finding, however, is a significant increase of creatinine and β_2 -microglobulin concentrations in serum with time, indicating a progressive reduction of the glomerular filtration rate despite removal from exposure. It is estimated that on average this rate has decreased by 31 ml/min/1.73 m² during the five year follow up study. This decrease is significantly greater (about five times) than that accounted for by aging and is not more pronounced in workers with impaired renal function at the start of the study than in those presenting only with subclinical signs of renal damage. Serum alkaline phosphatase activity also increases significantly with time. In conclusion, the present study indicates that the early renal changes induced by cadmium should be regarded as adverse effects; they are predictive of an exacerbation of the age related decline of the glomerular filtration rate.

The kidney is the critical organ after long term exposure to cadmium (Cd). An increased urinary excretion of plasma proteins usually represents the earliest biological sign of cadmium interference with kidney function. It is known that cadmium can decrease the tubular reabsorption of low molecular weight proteins—for example β_2 -microglobulin and retinol binding protein (RBP). An enhanced glomerular filtration of high molecular weight proteins such as albumin may also represent an early manifestation of excessive exposure to cadmium.¹² Since both nephron sites may be concomitantly affected by cadmium, it has frequently been assumed that the microalbuminuria of cadmium nephropathy also results from an impairment of tubular reabsorption. Nevertheless, recent investigations from our laboratory on the renal handling of plasma proteins³ and on the mechanism of cadmium action on the kidney⁴ have shown that a reduction of the polyanionic charges of the glomerular basement

membrane may be responsible for the early albuminuria.

The health significance of the enhanced excretion of plasma proteins after chronic exposure to cadmium remains a matter of controversy.⁵ Cadmium proteinuria is usually irreversible⁶⁻⁸ but no conclusive data are available to assess whether it is predictive of a progressive alteration of renal function. To get some insight into this problem, we have followed up workers who were no longer exposed to cadmium because of the discovery of an increased urinary excretion of β_2 -microglobulin or RBP, or both, alone or associated with albuminuria.

Subjects and methods

STUDY POPULATION

Twenty three male workers, previously exposed to cadmium oxide dust and fume in two non-ferrous smelters, volunteered to be examined once a year for five consecutive years. These workers had been exposed to cadmium for nearly 25 years on average

(range 6 to 41.7 years) and had been removed from exposure because of the finding of an enhanced excretion of β_2 -microglobulin ($> 300 \mu\text{g/l}$; $n = 18$) or RBP ($> 300 \mu\text{g/l}$; $n = 17$), or both. Eight had also an increased albuminuria ($> 20 \text{ mg/l}$). At the time of removal from exposure to cadmium, the concentrations of serum creatinine were normal ($< 13 \text{ mg/l}$) in 18 subjects, marginally increased in three (13.3, 13.7, 13.9 mg/l), and raised in two (20.3 and 22.3 mg/l). Their first follow up examination took place when they had been removed from cadmium exposure for six years on average. At that time 17 workers were retired and six were still occupationally active but in jobs with no exposure to cadmium. They were invited once a year for a medical check up in the medical department of the factory where they had been previously employed. About three years before the first survey, 21 of these workers also had their concentrations of cadmium in liver and in kidney measured by neutron activation analysis.^{9,10} The cadmium concentrations ($\mu\text{g/g}$ wet weight) in liver and in kidney cortex ranged from 24 to 158 (mean 61) and from 133 to 355 (mean 231), respectively. Examination of medical records and the medical questionnaires collected at the start of the study did not disclose previous or current diseases or drug consumption habits that might interfere with renal function. In particular, none of the cadmium workers had a history of hypertension, gout, urinary tract infection, renal stone, acute lead poisoning, or regular consumption of analgesics. The job history of each worker was also reconstructed; special attention was paid to possible past exposure to other heavy metals, particularly lead. Eleven workers had spent their whole professional life in the cadmium department of the plants where there was no risk of excessive exposure to lead. Four workers had initially been occupied (6–17 years) in other departments before being transferred to the cadmium department for the rest of their professional life (14–40 years). None had ever been engaged in jobs where a lead risk was considered to be present. Eight subjects had initially been assigned to the cadmium department (for 7–29 years) and were then moved to other jobs when a tubular proteinuria was discovered. For six of them the new job did not involve exposure to lead. The other two workers may have been slightly exposed to lead for six years but the biological monitoring data found in their medical records indicate that their exposure to lead has never been excessive since the concentration of δ -aminolaevulinic acid in urine has never exceeded 5 mg/l .

Two groups of control male subjects (volunteers) were also examined, one at the time of the first survey and the other at the end of the study. They were matched for age with the cadmium workers but they had never been occupationally exposed to heavy

metals, such as cadmium and lead, and were in good clinical health (no history of diabetes or kidney or cardiovascular diseases). The first control group included 23 subjects, aged 46 to 69 (mean = 58.8) and the second 23 subjects, aged 50 to 74 (mean = 63.3).

METHODS

At each survey, the workers were questioned about their health status and drug consumption and a sample of venous blood (20 ml) and urine (100 ml) was collected. The examination took place between 0900 and 1200, the subjects having had a light breakfast. Since the study had to be performed on ambulatory subjects, only spot urine samples were obtained. The following biological analyses were made using standardised or previously published methods: cadmium in blood and in urine,¹¹ lead in blood,¹² total proteins¹ and amino acids¹³ in urine, β_2 -microglobulin in serum and in urine,¹⁴ RBP in urine,¹⁴ albumin in urine,¹⁴ δ -aminolaevulinic acid in urine,¹⁵ creatinine in urine¹⁶ and in serum,¹⁷ packed cell volume, zinc protoporphyrin in erythrocytes (ZPP) using a haemato-fluorimeter (Aviv Associates, Lakewood, NJ), alkaline phosphatase activity and uric acid in serum,¹⁶ and calcium in serum and in urine by flame atomic absorption spectrometry using a Varian Techtron, model 1100. Quality control programmes were run during the whole study period to exclude analytical bias.

STATISTICAL ANALYSIS

The data collected during the five surveys were analysed by variance analysis. A paired t test was used to compare the results of some parameters measured at the beginning and at the end of the follow up period. Differences between the prevalences of abnormal values found at the first and last survey were ascertained by a one tailed binomial test or a McNemar χ^2 test.¹⁸ Association between variables was evaluated by Pearson's correlation coefficients and Student's t test was used to assess the significance of the differences between the controls and the cadmium workers.¹⁹ For β_2 -microglobulin, RBP, albumin, and total protein in urine, the statistical treatment was applied after log transformation. Differences were considered statistically significant if $p < 0.05$.

Results

CADMIUM WORKERS

The table summarises the main characteristics of the cadmium workers and the results of several biological parameters measured at each survey. A variance analysis showed that cadmium concentration in blood and in urine significantly ($p < 0.001$) decreased with time, whereas β_2 -microglobulin, creatinine, and alk-

Characteristics and biological parameters of 23 male subjects with signs of cadmium induced renal changes and removed from exposure to mium.* summary of a five year follow up

	Surveys				
	1st	2nd	3rd	4th	5th
Age (y)	58.6 ± 1.38†	59.7 ± 1.37	61.1 ± 1.37	62.3 ± 1.37	63.3 ± 1.37
Years of removal from mium exposure	6.0 ± 0.86	7.1 ± 0.87	8.6 ± 0.83	9.6 ± 0.82	10.7 ± 0.83
Urine:					
Cadmium (µg/l)	22.2 ± 2.93	16.0 ± 2.28	15.5 ± 1.60	15.6 ± 2.08	18.0 ± 2.98
Creatinine (mg/l)	179 ± 28	159 ± 20	143 ± 16	141 ± 21	150 ± 18
Proteins (mg/l)†	226 (60-1395)	236 (70-1312)	235 (20-1126)	168 (9-1669)	293 (35-1624)
Amino acids (mg α-N/l)	184 ± 16	164 ± 15	209 ± 17	185 ± 19	200 ± 19
β ₂ -microglobulin (µg/l)†	1770 (31-48,900)	1550 (24-129,000)	2560 (48-165,000)	2570 (43-170,000)	2580 (66-123,000)
BP (µg/l)†	1570 (171-66,000)	985 (95-88,000)	1260 (28-96,000)	1870 (41-106,000)	2000 (59-100,000)
Albumin (mg/l)†	23 (3.1-51.7)	18 (2.5-22.0)	25 (1.9-20.7)	26 (2.5-33.0)	30 (5.0-42.5)
Creatinine (g/l)	1.37 ± 0.12	1.23 ± 0.10	1.52 ± 0.16	1.34 ± 0.13	1.48 ± 0.11
Blood:					
Packed cell volume (%)	43.6 ± 0.62	43.0 ± 0.60	43.1 ± 0.65	42.5 ± 0.78	42.5 ± 0.76
Cadmium (µg/l)	14.3 ± 2.0	11.8 ± 1.4	10.1 ± 0.9	9.3 ± 0.8	9.7 ± 0.9
Serum:					
Creatinine (mg/l)	12.0 ± 1.1	13.5 ± 1.3	13.9 ± 1.4	15.3 ± 1.6	15.1 ± 2.2
Calcium (mg/l)	89.5 ± 1.0	88.5 ± 0.7	86.9 ± 0.8	87.2 ± 0.8	90.7 ± 0.9
Alkaline pase (IU/l)	37 ± 2.3	41 ± 2.8	33 ± 1.7	43 ± 2.7	54 ± 3.7
Uric acid (mg/l)	40 ± 2.0	38 ± 2.2	38 ± 2.2	43 ± 2.9	42 ± 2.7
β ₂ -Microglobulin (mg/l)	1.89 ± 0.19	2.07 ± 0.18	2.35 ± 0.26	2.63 ± 0.32	3.00 ± 0.42

*Duration of exposure to cadmium: mean (SEM) range; 24.9 (1.97) 6.0-41.7 years.

†Mean ± SEM.
‡Geometric mean and (range).

alkaline phosphatase in serum significantly ($p < 0.001$) increased with time. On an individual basis, the other parameters did not exhibit a statistically significant time trend. For each worker, the results of biological parameters measured during the last four surveys have been expressed in percentages of the corresponding first survey results; the mean of these percentages and their 95% confidence interval are shown in figs 1 and 2.

Figure 3 illustrates for all the examined workers the decrease of cadmium concentration in blood ($p < 0.005$) and in urine ($0.1 > p > 0.05$) between the first and the last (about five years later) survey, whereas fig 4 shows the increase of the three most affected parameters, creatinine ($p < 0.025$), β_2 -microglobulin ($p < 0.001$), and alkaline phosphatase ($p < 0.001$) in serum between the first and the last survey. We have determined whether the prevalence of raised values of some urine or serum parameters increased with time using the following cut off levels: (urine) total proteins > 200 mg/l, amino acids > 200 mg α -N/l, β_2 -microglobulin > 300 µg/l, RBP > 300 µg/l, albumin > 20 mg/l; (serum) alkaline phosphatase activity > 60 IU/l, creatinine > 13 mg/l, β_2 -microglobulin > 2 mg/l. For urinary parameters, the prevalences of abnormal values did not vary sig-

nificantly as shown by the values obtained on the first and the last surveys: total proteins 48 v 61%, amino acids 35 v 43%, β_2 -microglobulin 78 v 83%, RBP 74 v 83%, albumin 35 v 39%. The prevalence of abnormal serum alkaline phosphatase activity did not increase significantly between the first and last survey (4 v 13%); on the contrary, the prevalences of raised values increased significantly between the first and the fifth survey for serum creatinine (30 v 52%) ($p < 0.05$) and serum β_2 -microglobulin (30 v 74%) ($p < 0.01$). The time dependent increase of the serum concentration of creatinine and β_2 -microglobulin during the follow up study is statistically significant whether one considers either the total population ($n = 23$) or the 21 subjects with serum creatinine below 15 mg/l at the start of the survey or only the 13 subjects with pure tubular proteinuria and normal concentrations of serum creatinine (< 13 mg/l) and serum β_2 -microglobulin (< 2 mg/l) at the start of the survey (fig 5). Creatinine and β_2 -microglobulin concentrations in serum were found to be highly correlated with each other. For example, at the last survey, the correlation coefficient between log creatinine in serum and log β_2 -microglobulin in serum amounted to 0.86 ($p < 0.001$). The correlation remained highly significant ($r = 0.80$; $p < 0.01$) when

Fig 1 Cadmium workers: time course of urinary parameters after removal from exposure to cadmium (mean $\pm$ 95% confidence interval; $n = 23$).

it was recalculated using only the values ($n = 20$) of serum creatinine and serum β_2 -microglobulin lower than 20 mg/l and 4 mg/l, respectively.

Although direct measurements of the glomerular filtration rate (GFR) could not be performed in this follow up study, we thought that it would be useful to estimate indirectly the magnitude of GFR decrease on the basis of the increased serum concentrations of β_2 -microglobulin.²⁰ In the absence of malignancy the latter parameter is a better indicator of GFR²⁰⁻²⁵ than serum creatinine since the rate of β_2 -microglobulin production is not body mass dependent as is creatinine. Figure 6 illustrates the pronounced reduction in estimated GFR over the five year follow up study on an individual and on a group basis. All the subjects showed a decrease of the estimated GFR; the

decreases between the first and fifth survey ranged from 9 to 78 ml/min/1.73 m² (paired t test, $p < 0.001$). Furthermore, on a group basis, the decrease is linear with time as shown by the regression correlation between the estimated GFR at each survey (group mean) and the corresponding number of years after removal from exposure to cadmium ($r = -0.99$; $p < 0.001$). According to the regression line for the total population, the average decrease in GFR between the start and the end of the follow up period—that is, after 4.7 years—amounts to 31 ml/min/1.73 m². Similar results are obtained when considering separately the 21 subjects with serum creatinine below 15 mg/l at the start of the survey (decrease in estimated GFR = 31 ml/min/1.73 m²) or the 13 subjects with pure tubular proteinuria and normal serum creatinine.

Fig 2 Cadmium workers: time course of blood and serum parameters after removal from exposure to cadmium (mean $\pm$ 95% confidence interval; $n = 23$).

(<13 mg/l) and serum β_2 -microglobulin (<2 mg/l) concentrations at the start of the survey (decrease in estimated GFR = 30 ml/min/1.73 m²) (fig 6).

No significant correlations were found between the relative increase in serum creatinine or serum β_2 -microglobulin (or the relative decrease in estimated GFR) and the concentrations of cadmium in liver measured three years before the first survey or the concentrations of cadmium in blood measured during the follow up study. The relative increase in serum creatinine or serum β_2 -microglobulin (or the relative

decrease in estimated GFR) also did not correlate with the first survey values of urinary β_2 -microglobulin, RBP, or albumin.

The mean values of blood lead at the first and the last survey were 284 (SEM = 21) and 203 (SEM = 16) μ g/l, respectively. The concentration of δ -amino-laevulinic acid in urine and the ZPP level at the first survey averaged 3.9 (SEM = 0.18) mg/l and 1.6 (SEM = 0.29) μ g/g Hb, respectively. None of these indices of lead exposure was found to be correlated with the renal parameters.

Fig 3 Cadmium workers: cadmium concentrations in blood and in urine at first (six years after removal from exposure) and at fifth survey (nearly 11 years after removal from exposure). Paired *t* test ($n = 23$): cadmium in blood, $p < 0.005$; cadmium in urine, $0.1 > p > 0.05$.

CONTROL SUBJECTS

All the results of the various biological parameters measured in the two control groups were in the normal range (data not shown) except for eight subjects who had serum creatinine concentrations above 13 mg/l (range 13.7–16.2) and for 10 subjects who had serum β_2 -microglobulin concentrations above 2 mg/l (range 2.1–3.3). Figure 5 shows the mean values of the serum creatinine and serum β_2 -microglobulin concentrations in both groups. All the control subjects had normal concentrations of cadmium in urine ($< 2 \mu\text{g/l}$) and lead in blood ($< 350 \mu\text{g/l}$). The ZPP concentrations were also normal. In the first control group the GFR values (estimated from the serum β_2 -microglobulin concentration) ranged from 58 to 121 (mean $\pm$ SEM: 90 ± 3.2), whereas in the second group they ranged from 46 to 132 ml/min/1.73 m² (mean $\pm$ SEM: 91 ± 4.1).

Discussion

The results of this prospective study on workers removed from exposure to cadmium because of the finding of an enhanced urinary excretion of some

Fig 4 Cadmium workers: creatinine, β_2 -microglobulin, and alkaline phosphatase activity in serum at first (six years after removal from exposure) and at fifth survey (nearly 11 years after removal from exposure). Paired *t* test ($n = 23$): creatinine, $p < 0.025$; β_2 -microglobulin, $p < 0.001$; alkaline phosphatase, $p < 0.001$.

Fig 5 Relations between group means ($n = 5$) of creatinine or β_2 -microglobulin concentrations in serum and time after removal from exposure to cadmium in three different subgroups of workers exposed to cadmium. $\circ$ Total population ($n = 23$): serum creatinine, $r = 0.94$, $p < 0.02$; serum β_2 -microglobulin, $r = 0.99$, $p < 0.01$. $\square$ Cadmium workers with serum creatinine below 15 mg/l at start of study ($n = 21$): serum creatinine, $r = 0.83$, $p \approx 0.05$; serum β_2 -microglobulin, $r = 0.99$, $p < 0.01$. $\triangle$ Cadmium workers with pure tubular proteinuria and normal concentrations of serum creatinine (< 13 mg/l) and serum β_2 -microglobulin (< 2 mg/l) at start of study ($n = 13$): serum creatinine, $r = 0.83$, $p \approx 0.05$; serum β_2 -microglobulin, $r = 0.95$, $p < 0.02$. $\bullet$ --- $\bullet$ Mean values of serum creatinine and serum β_2 -microglobulin in two age matched control groups (each 23 subjects).

plasma proteins (β_2 -microglobulin or RBP, or both, alone or associated with albumin) confirm those obtained previously but which were based on a retrospective examination of the data collected by our laboratory.⁶ The conclusions drawn previously were only tentative since the design of the study did not permit the exclusion of possible bias due to loss of follow up. The proteinuria induced by cadmium is not reversible. None of the values of urinary RBP, β_2 -microglobulin, and albumin, which were significantly enhanced at the time of the first survey, had returned to the normal concentration five years later. Serum alkaline phosphatase activity significantly increased during the five year follow up period; this may reflect an interference of cadmium with bone metabolism, possibly secondary to a reduction in the conversion of 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol by the kidney.²⁶

The increase of serum creatinine and serum β_2 -microglobulin (fig 5) with time observed in the present prospective study on workers removed from exposure to cadmium clearly indicates a progressive reduction

of the GFR despite removal from exposure to cadmium. On the basis of the concentrations of β_2 -microglobulin in serum,²⁰ it may be estimated that during the five year follow up study, the GFR of the examined cadmium workers has decreased on average by 31 ml/min/1.73 m² (fig 6). The normal age related decline of the GFR has been studied by several authors (for a review²⁷) and it may be estimated that in the age range 45 to 75 the expected decline (dashed line in fig 6) over five years should normally not exceed 6.5 ml/min/1.73 m². All the cadmium workers had during the follow up period of five years a reduction of their estimated GFR which is greater (on average about five times) than that value.

By contrast, both control groups had similar mean values for creatinine and β_2 -microglobulin in serum, 11.2 and 1.9 mg/l respectively (fig 5), and the mean estimated GFR values in those two control groups (90 and 91 ml/min/1.73 m², respectively) are in the normal range^{27,28} for these age groups (mean age 58.8 and 63.3 years, respectively). The mean estimated GFR in the first control group does not significantly differ from

Fig 6 Estimated glomerular filtration rate (based on concentration of serum β_2 -microglobulin). I Cadmium workers: individual values at first and fifth survey (paired *t* test: $p < 0.001$). II Relations between group means ($n = 5$) of estimated GFR and time after removal from exposure to cadmium in three different subgroups of workers exposed to cadmium (same subgroups as in fig 5). $\circ$ $r = -0.99$ ($p < 0.01$), slope -6.6 ml/min/1.73 m²/year; $\square$ $r = -0.98$ ($p < 0.01$), slope -6.6 ml/min/1.73 m²/year; $\triangle$ $r = -0.93$ ($p < 0.02$), slope -6.3 ml/min/1.73 m²/year. Expected age related decline in GFR ($\blacktriangle$ --- $\blacktriangle$) is about 1.3 ml/min/1.73 m²/year as estimated from published data.²⁷

that found in the cadmium workers at the first survey, whereas that in the second control group is significantly higher ($p < 0.001$) than that found in the cadmium workers at the last survey (mean $\pm$ SEM: 65 ± 5.9 ml/min/1.73 m²). This confirms that during the follow up period, the age related decline of the GFR in the cadmium workers is significantly greater than that accounted for by aging.

The job history of the cadmium workers allows us to conclude that excessive occupational exposure to lead is not a confounding factor. The measured concentration of lead in blood, δ -aminolaevulinic acid in urine, and ZPP in blood indicate that the lead body burden of these workers was not sufficient to cause or aggravate the observed renal effect.^{29,30} Furthermore, according to Alessio *et al*, in workers removed from exposure to lead a mean ZPP level of 1.6 μ g/g Hb would correspond to a urinary excretion of lead after intravenous administration of 1 g calcium edetate of about 500 μ g/24 h,³¹ a value lower than that which may be associated

with some degree of renal insufficiency in non-gouty patients.³²

Two hypotheses may be suggested to explain the glomerular impairment induced by cadmium. This could result (a) from the development of a certain degree of interstitial nephritis secondary to the tubular lesion or (b) independently from its tubular effects cadmium may also exert toxic effects in the glomerulus. The first hypothesis is commonly invoked to explain the decrease of GFR in workers exposed to cadmium.^{33,34} In a follow up of cadmium workers who had first been examined 13 years previously Piscator found that a slight tubular dysfunction was not accompanied by a reduction of GFR whereas the GFR was decreased in a few subjects with more severe tubular dysfunction, which according to the authors means that the reduction in GFR follows the tubular and interstitial changes.³⁵

The present study offers arguments against the first hypothesis. Firstly, the increase in serum creatinine

and serum β_2 -microglobulin (or the decline in estimated GFR) found in cadmium workers occurs in the absence of significant aggravation of the tubular impairment (figs 1 and 2). Furthermore, by contrast with the observations by Piscator^{8,35} and Elinder *et al.*,³⁶ no relation was found between the degree of tubular impairment observed at the beginning of the follow up study and the subsequent drop in estimated GFR. The correlation coefficients between the relative increase in serum creatinine or serum β_2 -microglobulin (or the relative decrease of the estimated GFR) and the urinary excretion of β_2 -microglobulin and RBP were statistically not significant.

Our observations are better explained by the second hypothesis, that of a progressive and independent impairment of glomerular function induced by cadmium. Several human and experimental data demonstrating an interference of cadmium with glomerular function at an early stage of the intoxication support this conclusion: (a) Kjellström and Piscator have reported data showing that increased serum concentrations of β_2 -microglobulin, which, as stated by these authors probably result from a decreased GFR, may occur in workers exposed to cadmium with normal urinary β_2 -microglobulin excretion³⁷; a similar observation has been reported recently by other Swedish investigators⁷; (b) in Japan, Nogawa *et al.* have suggested that a reduction in creatinine clearance may be detected at the early stage of chronic cadmium poisoning in man³⁸; (c) in cadmium workers a microalbuminuria may precede the onset of tubular proteinuria³⁹ (and unpublished observations); (d) chronic administration of cadmium to rats (100 ppm in drinking water) gives rise to an isolated albuminuria which precedes the rise of β_2 -microglobulinuria by several months⁴⁰; (e) our recent studies on workers and on rats chronically exposed to cadmium show that this metal can induce a microalbuminuria by reducing the negative charges on the glomerular capillary wall.⁴

It should, however, be recognised that in cadmium workers the presence of a microalbuminuria is not a prerequisite for predicting a loss of glomerular function because (a) a significant increase in serum creatinine and serum β_2 -microglobulin and a significant reduction in the estimated GFR (≥ 30 ml/min/1.73 m²) during the five year observation period were also found in workers who had only an increased urinary excretion of low molecular weight proteins at the first survey (figs 5 and 6), and (b) the relative increase in serum creatinine and serum β_2 -microglobulin (or the relative decrease in the estimated GFR) did not differ significantly between workers with or without increased albuminuria at the first survey.

The present study allows us to conclude that the early renal changes induced by cadmium—that is, the

increased urinary excretion of low (and high) molecular weight proteins—should be regarded as adverse effects; they predict an exacerbation of the age related decline of the GFR. This study suggests that in addition to the measurement of the urinary excretion of specific plasma proteins such as RBP and albumin, the health surveillance programme of workers exposed to cadmium would benefit from the inclusion of serum β_2 -microglobulin determination in order to detect a reduction of the GFR as early as possible. It would also be useful to assess whether an increased cadmium burden which has not yet caused an enhanced urinary excretion of plasma proteins may also affect the age related decline of renal function. Such knowledge is particularly relevant for assessing the validity of the proposed biological limit values for cadmium in urine (10 μ g/g creatinine) and in blood (10 μ g/l) which mainly aim to prevent the occurrence of increased specific proteinuria.⁴¹

Appendix

CONVERSION OF UNITS

Cadmium	1 μ g = 8.90 nmol
Lead	1 μ g = 4.83 nmol
Calcium	1 mg = 25.0 μ mol
Creatinine	1 mg = 8.84 μ mol
Aminolaevulinic acid	1 mg = 7.63 μ mol
Uric acid	1 mg = 6.33 μ mol

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