

Renal function of workers with low-level cadmium exposure

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VERSCHOOR M, HERBER R, VAN HEMMEN J, WIBOWO A, ZIELHUIS R. Renal function of workers with low-level cadmium exposure. *Scand J Work Environ Health* 13 (1987) 232–238. The influence of occupational exposure to cadmium on renal function was examined in 27 male cadmium workers from plants with second-degree usage of cadmium. The levels of cadmium in the blood and urine and various protein concentrations in the urine and serum were determined. The urinary levels of β_2 -microglobulin, retinol-binding protein, and N-acetyl- β -D-glucosaminidase were statistically significantly increased in workers with urinary cadmium levels above 50 nmol/l. SDS-PAGE electrophoresis with silver staining is probably a sensitive indicator of the early effects of cadmium on protein excretion. The currently recommended biological exposure limits may have to be lowered.

Key terms: biological exposure limits, glomerular function parameters, occupational exposure, tubular function parameters.

While it is well known that cadmium (Cd) may affect renal function adversely, neither the no-effect level of exposure nor the critical location in the nephron has conclusively been established. In recent literature the reported no-effect level of cadmium in urine varies from 2 μ g Cd/g creatinine for the general population (10) to 15 μ g Cd/g creatinine for occupationally exposed workers (6). The aim of the present study was to assess early changes in renal function in relation to occupational exposure to cadmium. Related problems, such as the sensitivity of the renal parameters and the choice of the adjustment parameter for correction of the dilution of spot urine samples, are discussed.

Subjects and methods

Exposed and reference groups

In a cross-sectional study 27 men occupationally exposed to cadmium and eight men occupationally unexposed to cadmium were examined. The cadmium-exposed workers were employed in two plants. Plant A used cadmium compounds in pigments for the production of plastics and employed 19 of the studied workers (exposed group A). Plant B used cadmium in the welding of radiators until one year before the study and employed the other eight (exposed group B). The exposure levels were not measured in the air of either plant. The referents were male workers of similar age

and smoking habits from a grain elevator located in the same geographic area as plant A.

By means of a questionnaire, information on age, occupational history, present work, past and present illnesses, intake of medicines, smoking (cigarettes/day), drinking habits (alcoholic consumption/day), and possible exposure to nephrotoxic agents during leisure time was obtained for each participant.

The average age of exposed groups A and B and the reference group was 39 (range 21–58), 41 (range 22–59), and 45 (range 28–59) years, respectively. The group members smoked an average of 7 (range 0–20), 6 (range 0–20), and 6 (range 0–20) cigarettes/day, respectively. The mean time of employment was 8.7 (range 1–22) years for group A, 10.3 (range 1–20) years for group B, and 14.4 (range 1–43) years for the reference group. According to the questionnaire data the three groups of workers did not differ in social class and consumption of alcohol. Leisure-time activities did not lead to exposure to suspected nephrotoxic agents. No workers were excluded from further study due to intake of medicines.

One subject, from plant B, with known clinical renal dysfunction was excluded from the analysis. (This dysfunction had existed for more than 10 years and had not been caused by cadmium exposure.) Therefore, the analysis was carried out for 26 exposed workers and 8 referents.

Analytical methods

Spot urine samples and venous blood samples were collected by the same laboratory personnel using standard procedures against contamination. Cadmium-free disposable syringes and polythene tubes and boxes were used for the sample collection.

For the biological monitoring, cadmium in blood (CdB) and cadmium in urine (CdU) determinations were performed by electrothermal atomization atomic

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absorption spectrometry using the Perkin-Elmer 4000-HGA 500 combination (12) (United States and Federal Republic of Germany, respectively). The relative standard deviation of a duplicate determination was 13 % for CdB and 19 % for CdU. Accuracy was tested by participation in the EQAS survey (External Quality Assessment Scheme from the Health and Safety Executive in London, United Kingdom) for CdB and the International Union of Pure and Applied Chemistry's intercomparison study for CdB and CdU (14). The detection limit of CdB was 1 nmol/l. Values below the detection limit are specified as 0.5 nmol/l. Since lead exposure was a potential confounder, zinc protoporphyrin in blood was measured with a hematofluorometer (Environmental Sciences Associates, Bedford, United States). The relative standard deviation was 5 %.

The general clinical parameters and kidney function parameters creatinine in serum and creatinine in urine, urea in serum (blood urea nitrogen) and total protein in urine were determined by the usual clinical-chemical methods. The Beckman ICS analyzer (United States) was used for determining albumin in urine by nephelometry; the relative standard deviation of a duplicate determination was 3 %. Immunoglobulin G (IgG) in serum and urine was measured with the radial immunodiffusion method (NOR-partigen and LOW-partigen plates, respectively, Hoechst, Federal Republic of Germany); the relative standard deviation was 15 %. The determinations of retinol-binding protein in urine and β_2 -microglobulin in urine and serum were performed with the use of the latex immuno assay according to Bernard et al (5); the relative standard deviation was 10 %. Only samples with pH > 5.5 were used for the determination of β_2 -microglobulin in urine. N-acetyl- β -D-glucosaminidase was determined in urine according to Lockwood & Bosman (19); the relative standard deviation was 5 %. Urinary density was measured with an Atago refractometer. Urinary density was chosen for adjustment and the following formula was used (15):

$$\text{urinary parameter}_{\text{corr}} = \frac{0.020}{\text{urine dens} - 1.000} \times \text{urinary parameter}_{\text{uncorr}}$$

where corr = corrected, dens = density, and uncorr = uncorrected.

From the spot urine samples the relative clearance of β_2 -microglobulin was calculated as:

$$\frac{\text{Cl } \beta_2\text{M}}{\text{Cl creat}} \% = 100 \times \frac{\beta_2\text{MU} \times \text{creat-S}}{\beta_2\text{MS} \times \text{creat-U}}$$

where Cl = clearance, $\beta_2\text{M}$ = β_2 -microglobulin, creat = creatinine, U = urine, and S = serum.

For the unconcentrated urine samples, protein electrophoresis was performed with 7.5 % sodium dodecyl sulfate-polyacrylamide gel (SDS-PAGE) and silver

staining according to the method of Morrissey (20). The relative standard deviation for within a batch was 5 %, and the day-to-day variation was 10 %. The stained electrophoretic patterns were scanned with a Shimadzu CS-910 densitometer (Japan). The electrophoretic scans were divided into high-molecular mass proteins with molecular masses above 100 000 da, medium-molecular mass proteins with molecular masses of 57 000–100 000 da, and low-molecular mass proteins with molecular masses below 57 000 da (da = dalton = atomic mass unit).

Statistical methods

The differences between the cadmium-exposed workers and the referents were tested with the analysis of variance. The parameters with a skewed distribution were transformed logarithmically. A correlation analysis was carried out for the whole group. The relationships between the exposure and renal parameters were studied by linear regression analysis. Hotelling's T^2 test (21) was used to test for equality between groups with different CdU levels for several variables simultaneously.

Results

Adjustment of the urinary parameters

The choice of the parameter for adjustment depends upon possible differences between the levels of the parameter in the cadmium-exposed and reference groups. In this study one of the cadmium groups had significantly lower levels of urinary creatinine than the other groups [group A 10.3 (SD 5.5) mmol/l, group B 14.6 (SD 3.5) mmol/l, referents 14.9 (SD 7.5) mmol/l], whereas the levels of the urinary density did not show any difference. Therefore, the urinary density was chosen for adjustment.

Exposure parameters

The levels of the exposure parameters used for both cadmium and lead are presented in table 1. The zinc protoporphyrin level was higher in group B than in the referents, but the difference was not statistically significant. The low level indicates that the lead exposure was insignificant. The mean values for CdB and CdU clearly differed between the exposed and unexposed workers.

Between the logarithm of CdB and that of CdU and also between the logarithm of CdB and smoking habits, a significant relationship was found ($P < 0.001$) (table 2). No relationship between the logarithm of CdU and smoking habits was found.

No relation was observed between the exposure parameters and age, drinking habits, or duration of exposure.

A scattergram for the logarithm of CdU with that of CdB is presented in figure 1.

Table 1. Exposure parameters of the exposed and unexposed workers. The geometric range is defined as the backtransformed standard deviation belonging to the geometric mean. The urinary cadmium values have been adjusted for urinary density. (Hb = hemoglobin)

Group	Cadmium in blood (nmol/l)		Cadmium in urine (nmol/l)		Zinc protoporphyrin ($\mu\text{mol/l Hb}$)	
	Geometric mean	Range	Geometric mean	Range	Geometric mean	Range
Exposed group						
Plant A (N = 19)	11.2	3.3—38.0	23.0	11.0—47.9	15.9	10.0—25.1
Plant B (N = 7)	51.4	18.8—154.9	111.4	30.3—410.2	25.3	15.9—39.8
Referents (N = 8)	1.8	0.6—5.7	6.8	4.6—9.9	12.6	7.9—20.0

Table 2. Correlation coefficients of the relationships between the logarithm (log) of the cadmium level in blood (CdB), the logarithm of the cadmium level in urine (CdU), and smoking habits.

	log CdB	log CdU
log CdB	—	—
log CdU	0.76***	—
smoking habits (number of cigarettes/d)	0.67***	0.15

*** $P < 0.001$.

Renal function parameters

As glomerular parameters, β_2 -microglobulin and creatinine in serum, blood urea nitrogen, and IgG and albumin in urine were used. Retinol-binding protein and β_2 -microglobulin in urine and the lysosomal enzyme N-acetyl- β -D-glucosaminidase in urine were used as indicators of tubular function changes. The total urinary protein was used as an overall renal parameter.

The values of some of the renal parameters are presented in table 3. The mean values of urinary retinol-binding protein, urinary β_2 -microglobulin, N-acetyl- β -D-glucosaminidase, and serum β_2 -microglobulin were significantly higher ($P < 0.05$) for the workers of plant B (with the highest CdB and CdU values) than for the reference group. No significant differences were observed for creatinine in serum, blood urea nitrogen, total urinary protein, and albumin in urine. The mean value of IgG in serum was lower for the workers from plant A. The urinary IgG levels of all the workers studied were below 8 mg/l, which is the detection limit of the method used.

The relationship between the logarithm of CdU and that of β_2 -microglobulin was significant ($P < 0.05$) (figure 2). Also between the logarithm (log) of CdU and that of N-acetyl- β -D-glucosaminidase (NAG) a significant relationship was found [$\log \text{NAG (MU/l)} = 1.38 + 0.20 \log \text{CdU (nmol/l)}$, $N = 34$, $P < 0.05$]. The tubular parameters the logarithm of retinol-binding protein and the logarithm of N-acetyl- β -D-glucosaminidase were highly correlated with the logarithm of β_2 -microglobulin in urine (both $P < 0.001$). A significant relationship was found between the glomerular parameter β_2 -microglobulin in serum ($\beta_2\text{MS}$) and the logarithm of CdU [$\beta_2\text{MS (mg/l)} = 0.75 + 0.82 \log \text{CdU (nmol/l)}$, $N = 34$, $P < 0.05$]. For CdB

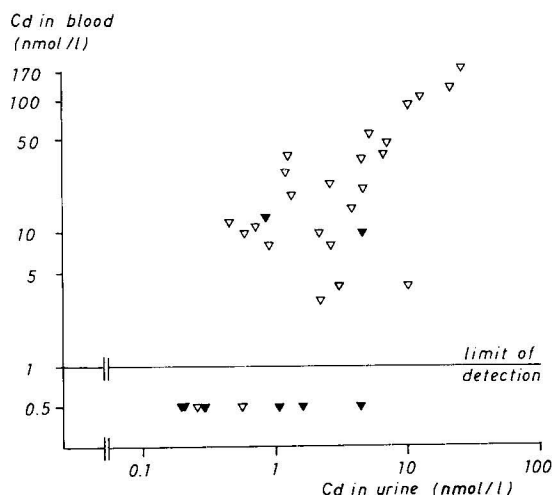


Figure 1. Relation between $\log \text{CdU}$ and $\log \text{CdB}$ ($\log \text{CdB (nmol/l)} = -0.27 + 0.98 \log \text{CdU (nmol/l)}$, $r = 0.76$, $N = 34$). (▼ = referents, ▽ = exposed workers, log = logarithm, Cd = cadmium, U = urine, B = blood)

no relation with the tubular or glomerular parameters was found.

The cadmium-exposed workers were also divided into groups according to their CdU levels as follows:

- CdU $< 30 \text{ nmol/l}$ ($< 3 \mu\text{g/g creatinine}$): no increased exposure;
- CdU $30\text{--}50 \text{ nmol/l}$ ($3\text{--}5 \mu\text{g/g creatinine}$): low occupational exposure;
- CdU $> 50 \text{ nmol/l}$ ($> 5 \mu\text{g/g creatinine}$): considered the no-effect level according to Piscator (23).

Table 4 shows the β_2 -microglobulin levels in urine and serum, the β_2 -microglobulin clearance, the retinol-binding protein, and the N-acetyl- β -D-glucosaminidase levels of the three groups. It can be seen that all of the parameters were highest among the workers with CdU values above 50 nmol/l . Moreover, particularly the average concentration of β_2 -microglobulin in urine increased consistently with the increase in CdU, and the difference between the lowest and the highest group was much larger relatively than the corresponding differences of the other four parameters.

Hottelling's T^2 test was performed to test the influence of CdU on various combinations of the tubular

or glomerular parameters. When the group with CdU values of less than 30 nmol/l was compared with the group whose CdU levels were above 50 nmol/l, the difference between the two was significant for the combination β_2 -microglobulin in urine, retinol-binding protein, and N-acetyl- β -D-glucosaminidase ($P < 0.05$). The greatest contribution came from β_2 -microglobulin in urine ($t = -2.94$), followed by N-acetyl- β -D-glucosaminidase ($t = -2.47$). Retinol-binding protein ($t = -1.18$) contributed much less to the difference. For the combinations of glomerular parameters, Hotelling's T^2 test showed that only β_2 -microglobulin in serum was related to the CdU excretion.

The electrophoretic pattern of the urinary proteins showed that workers with CdU values above 50 nmol/l excreted relatively significantly more low-molecular mass proteins and less high-molecular mass proteins than workers with CdU values lower than 50 nmol/l. (table 5).

Discussion

In recent years there has been much discussion about the choice of the parameter to be used for adjusting urinary parameters. Sanford et al (25) has stated, "Creatinine is assumed to be excreted at a more or less constant rate, whereas the urinary density is a measure

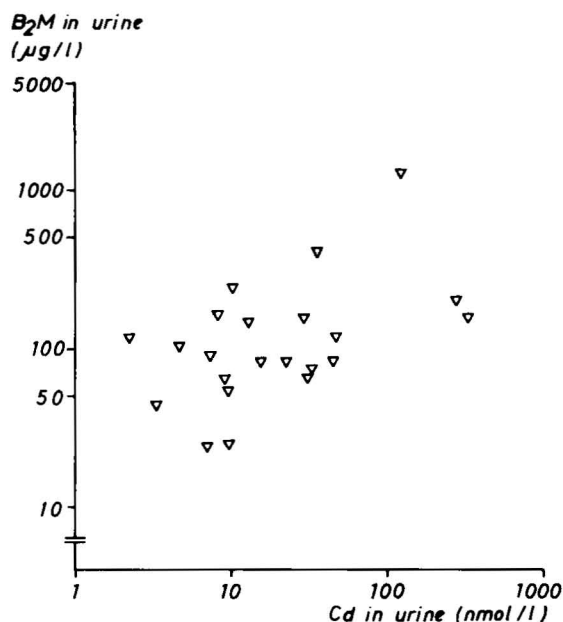


Figure 2. Relation between log CdU and log β_2 MU ($\log \beta_2$ MU ($\mu\text{g/l}$) = $1.14 + 0.73 \log \text{CdU (nmol/l)}$, $r = 0.42$, $N = 23$). ($\log$ = logarithm, Cd = cadmium, U = urine, β_2 M = β_2 -microglobulin)

Table 3. Renal parameter values of the exposed groups from plants A and B and of the reference group. All of the values have been adjusted for urinary density (1.020). (BUN = blood urea nitrogen, β_2 M = β_2 -microglobulin, IgG = immunoglobulin G, TP = total protein, Alb = albumin, RBP = retinol-binding protein, NAG = N-acetyl- β -D-glucosaminidase)

Group	Serum								Urine									
	Creatinine ($\mu\text{mol/l}$)		BUN ($\mu\text{mol/l}$)		$\beta_2\text{M}$ (mg/l)		IgG (g/l)		TP (mg/l)		Alb (mg/l)		RBP ($\mu\text{g/l}$)		$\beta_2\text{M}$ ($\mu\text{g/l}$)		NAG (MU/l)	
	Mean ^a	SD	Mean ^a	SD	Mean ^a	SD	Mean ^a	SD	Mean ^b	Range ^b	Mean ^b	Range ^b	Mean ^b	Range ^b	Mean ^b	Range ^b	Mean ^b	Range ^b
Exposed																		
Plant A (N = 19)	89	10	5.8	1.5	1.6	0.5	6.2	0.9*	96	38—240	14	8—23	86	44—169	109 ^c	62—191	40	23—70
Plant B (N = 7)	94	8	5.2	0.9	2.4	0.5*	8.4	1.6	83	20—338	10	6—17	158	73—339*	297 ^d	129—684*	70	38—129*
Reference (N = 8)	91	8	6.1	1.3	1.8	0.5	9.2	4.4	95	34—268	12	7—21	70	27—179	108 ^d	76—155	42	33—55

^a Arithmetic.

^b Geometric.

^c N = 15.

^d N = 4.

* $P < 0.05$ (versus control group).

Table 4. Renal parameter values of the entire cohort (exposed workers and referents) according to urinary cadmium level. (NAG = N-acetyl- β -D-glucosaminidase)

Urinary cadmium level (nmol/l)	Renal parameters																	
	β_2 -microglobulin									Retinol-binding protein ($\mu\text{g/l}$)								
	Age (years)			Urine ($\mu\text{g/l}$)			Serum (mg/l)			Clearance ($10^{-2}\%$)			NAG (MU/l)					
	N ^a	Mean ^b	SD	N ^a	Mean ^c	Range ^c	N ^a	Mean ^b	SD	N ^a	Mean ^b	SD	N ^a	Mean ^c	Range ^c	N ^a	Mean ^c	Range ^c
<30	22	42	11	15	100	63—55	22	1.7	0.5	15	7.9	6.1	22	87	45—169	22	41	27—62
30—50	7	41	10	4	172	88—339	7	1.8	0.7	4	8.4	3.6	7	79	26—239	7	38	17—90
>50	5	39	5	4	258	97—689*	5	2.3	0.7*	4	11.4	9.6*	5	127	49—330	5	68	36—128*

^a N = number of workers.

^b Arithmetic.

^c Geometric.

* $P < 0.05$.

Table 5. Results of the SDS-PAGE electrophoretic analysis of the urine samples of the entire cohort (exposed workers and referents) according to their urinary cadmium level. (SDS-PAGE = sodium dodecyl sulfate-polyacrylamide gel)

Cadmium in urine (nmol/l)	Number of workers	High-molecular mass proteins (%)		Medium-molecular mass proteins (%)		Low-molecular mass proteins (%)	
		Mean	SD	Mean	SD	Mean	SD
<30	22	44	10	24	3	32	12
30–50	7	45	9	23	4	32	10
>50	5	33	9*	21	3	46	9*

* $P < 0.05$.

of the total concentration of all substances dissolved in urine at each point of time." Berlin et al (2) observed a similar correlation between the unadjusted CdU ($\mu\text{g/l}$) and both the CdU corrected for creatinine and that corrected for urinary density. They concluded that there was no special advantage in correcting CdU for either creatinine or urinary density. Sanford et al (25) observed however that, for nickel in spot urine samples, the urinary density provided a more appropriate adjustment than the creatinine excretion. Alessio et al (1) concluded that the two parameters used for adjusting spot urine samples only partly express the same phenomenon, and therefore the parameters cannot be used indifferently for adjustment. They also observed that urinary creatinine values showed marked intra- and interindividual variations. Kowal & Zirkes (15) stated that urinary density is the most straightforward and practical parameter to use in data adjustment for urine concentration. The creatinine concentration in urine may be influenced by many factors, eg, sex, age, diet, hormones, muscles, physical activity.

In the present study we chose urinary density for adjustment because of the differences in the urinary creatinine concentrations between the exposed groups. All the urinary parameters were adjusted for a urinary density of 1.020. In the literature the values for the adjustment factor vary from 1.020 (15) to 1.021 (24) to 1.024 (2). We chose 1.020 because it was the mean value of the urinary density of the group with CdU values below 50 nmol/l.

When the two exposed groups and the unexposed group were combined, a significant relation [correlation coefficient (r) = 0.76, N = 34] was observed between the CdB and CdU levels. In plant B, with the workers with the highest CdB and CdU values, cadmium had not been used in production for at least six months. Hassler et al (11) also found a significant correlation (r = 0.84, N = 18) between the CdB and CdU levels of workers currently exposed to low atmospheric concentrations of cadmium ($7.6 \mu\text{g Cd/m}^3$ air). They assumed that both the blood and urinary concentrations of cadmium reflect the body burden of cadmium to a certain extent and, therefore, also reflect exposure that took place months or years previously.

The urinary β_2 -microglobulin and retinol-binding protein values can probably be regarded as the most

consistent and sensitive indicators of early tubular proteinuria. However, it is questionable whether these effect parameters are sufficient to detect reversible renal damage (22). Elinder (7) and Elinder et al (9) concluded that a slight increase in the excretion of β_2 -microglobulin can already be regarded as a minor irreversible effect. In addition, after comparing the renal parameters before and after the cessation of exposure, Lauwerys et al (16) observed that cadmium-induced renal lesions were not reversible.

In the present study a significant correlation (r = 0.53, N = 23) was found between the β_2 -microglobulin and retinol-binding protein excretion in the urine. For practical reasons retinol-binding protein appears to be a more suitable index of early tubular damage; since β_2 -microglobulin degraded in the bladder already at a pH of < 5.5 (13). Also a significant correlation (r = 0.68, N = 23) between the β_2 -microglobulin level and the N-acetyl- β -D-glucosaminidase activity in the urine was found. Hotelling's T^2 test showed that the relation between the β_2 -microglobulin level and the CdU value was stronger than that between the N-acetyl- β -D-glucosaminidase activity or the retinol-binding protein in urine and the CdU concentration. Therefore, it may be better to determine both tubular parameters (β_2 -microglobulin and retinol-binding protein in urine) of suspected exposure to nephrotoxic agents. The measurement of N-acetyl- β -D-glucosaminidase activity in the urine may be added, but an increase in this activity seems to be less cause-specific (19) than an increase in the level of β_2 -microglobulin and retinol-binding protein in the urine.

A relationship between β_2 -microglobulin in urine and CdU has often been established. Braithwaite & Cowtan (6) observed an increase in β_2 -microglobulin with CdU values above $15 \mu\text{g Cd/g creatinine}$ in occupationally exposed workers (N = 57). Piscator (23) observed a dose-response curve of the hockey-stick type. In our study no effect was observed at CdU levels below $5 \mu\text{g Cd/g creatinine}$.

Bernard et al (3) has stated that the urinary excretion of N-acetyl- β -D-glucosaminidase was about two times less frequently increased than that of β_2 -microglobulin or retinol-binding protein in the urine. Most increased levels of N-acetyl- β -D-glucosaminidase occurred when the retinol-binding protein

concentration was increased 100-fold or more. However, their study referred to patients with suspected or established renal diseases. In the present study most of the urinary parameters were found to be within normal ranges. We did not find increased levels of 100-fold or more. The highest retinol-binding protein value was 712 $\mu\text{g/l}$ and the highest urinary β_2 -microglobulin value was 1 300 $\mu\text{g/l}$. However, urinary β_2 -microglobulin appeared to be more sensitive than the excretion of N-acetyl- β -D-glucosaminidase in the case of low cadmium exposure, although a significant relationship between the N-acetyl- β -D-glucosaminidase and CdU was found.

The increased excretion of urinary β_2 -microglobulin agrees with the enhanced excretion of low-molecular mass proteins in workers with slightly higher CdU values. This phenomenon suggests that the silver staining procedure for SDS-PAGE electrophoresis provides a sensitive method for detecting differences in the excretion patterns of proteins in unconcentrated urine. With this procedure both albumin and β_2 -microglobulin are easily detectable. However, retinol-binding protein was, in most cases, not detectable with the scanning pattern. For cadmium exposure the excretion of β_2 -microglobulin seemed to be more pronounced than for lead exposure. We observed that in the case of lead exposure the levels of retinol-binding protein were more elevated than those of β_2 -microglobulin (26). This phenomenon may explain why the electrophoretic patterns of lead workers did not differ from those of their referents, while the pattern of cadmium workers did. Bernard et al (4) applied SDS-PAGE electrophoresis using concentrated urine and staining with Coomassie Blue. These authors did not observe any changes in the pattern of urinary proteins in a group of lead workers (blood lead level up to 3 $\mu\text{mol/l}$) either. In highly exposed cadmium workers (urinary cadmium up to 60 $\mu\text{mol/mol}$ creatinine), an increase in low-molecular mass and high-molecular mass proteins was found. In the present study we observed CdU levels that were 10 times lower and found only an increase in the amount of low-molecular mass proteins.

As did Elinder et al (9), we found a wide scatter and no relationship ($r = -0.01$) between the urinary and serum levels of β_2 -microglobulin. This result indicates that the increased urinary excretion of β_2 -microglobulin was not caused by an increased endogenous production of β_2 -microglobulin but instead was associated with tubular impairment. For serum levels of β_2 -microglobulin Wibell (28) suggested a threshold level of 4.5 mg/l (normal levels of 1.7 mg/l), above which the urinary excretion of β_2 -microglobulin would be increased due to increased levels of β_2 -microglobulin in the serum. In the present study, however, most of the β_2 -microglobulin levels were much lower than 4.5 mg/l in the serum of the exposed workers.

The relative clearance of β_2 -microglobulin was reported to be a rather sensitive parameter (8). In this study we also observed a significantly higher clearance of β_2 -microglobulin at CdU levels above 50 nmol/l . Roels & Lauwerys (24) stated that the β_2 -microglobulin level in serum was a very sensitive parameter, being as good as or even better than the level of creatinine in serum, with which to diagnose impaired glomerular filtration. The concentration of β_2 -microglobulin increased significantly in serum when the glomerular filtration rate was reduced by 40 to 50 %. Increased levels of creatinine in serum could only be found in the case of a more substantial reduction in the filtration rate. However, in the present study the glomerular function was hardly affected (table 3). Lauwerys et al (17) regarded an increase in the relative clearance of β_2 -microglobulin as not being necessarily related to an increase in the relative clearances of the high-molecular mass proteins. The mechanism of glomerular proteinuria might be based upon an autoimmune response.

In a review of the health effects of cadmium, Lee & White (18) concluded that detailed information about the critical concentration of cadmium in the renal cortex should be studied further. Since 1980 many studies have been carried out, but further work still appears to be necessary, especially in regard of the immunological effects of cadmium and the no-effect levels in blood and urine. Our results agree with those of Piscator (23); we also observed a no-effect level of about 50 nmol/l (5 $\mu\text{g Cd/g}$ creatinine).

In conclusion, this study of workers moderately exposed to cadmium provides evidence that irreversible effects on renal tubular function may already occur at levels somewhat exceeding 5 $\mu\text{g Cd/g}$ creatinine. Although the study included only a small number of persons, the results are indicative of an effect of low-level cadmium exposure on the kidney. The literature cited in the Discussion section also confirms this statement. The most sensitive indicators of renal tubular alteration were urinary β_2 -microglobulin and N-acetyl- β -D-glucosaminidase and changes in the electrophoretic pattern of proteins in the urine. The maximal individual biological limit of 5 $\mu\text{g Cd/g}$ creatinine recommended by the World Health Organization (27) may have to be lowered because the safety margin, if it exists, may be too small. Further studies are needed to elucidate the true no-effect level of cadmium exposure.

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