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INTEGRATED INDEXES OF OCCUPATIONAL EXPOSURE AS PREDICTORS OF KIDNEY DYSFUNCTION

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Abstract. The aim of the study was to evaluate the dose-effect and dose-response relationships between the integrated indexes Cd-A • t (mg/m^3 • years of exposure) and Cd-B • t (μg/l • years of exposure), and the increase in retinol binding protein excretion in urine (RBP-U) and β_2-microglobulin concentration in serum (β_2M-S).

The study was carried out in the nickel–cadmium battery factory in 1998–1999. Exposure to cadmium was formerly very high. The study group consisted of 116 persons for whom the results of determinations of Cd-B were available during two former observation periods (1983 and 1986–1988). The mean age of the group was 49 years and the mean period of exposure was 17 years.

The dose-effect relationship between Cd-B • t and RBP-U or β_2M-S was much better (r = 0.642 and 0.513) than between Cd-A • t and RBP-U or β_2M-S (r = 0.173 and 0.127). There was also correlation between Cd-U (μg/g creatinine), measured in 1998–1999, and RBP-U or β_2M-S (r = 0.343 and 0.198). Urinary cadmium should, however, be used with caution as a dose estimate because its excretion may increase as a result of renal damage.

According to the dose-response relationship, an increase in RBP excretion above 300 μg/g creatinine can be expected in 10% of subjects at the integrated exposure index (Cd-B • t) of about 450 μg/l • years, and an increase in β_2M-S above the accepted cut-off point of 2.4 mg/l can be expected in 10 % of subjects at Cd-B • t of about 190 μg/l • years.

The data obtained confirmed the validity of the recommended at present health-based limit for occupational exposure of 5 μg/l of blood, as well as the superiority of the biological monitoring of exposure to cadmium over the environmental monitoring.

Key words:
Cadmium, Tubular damage, Glomerular filtration rate, Dose-effect, Dose-response

INTRODUCTION

In chronic exposure, cadmium (Cd) is accumulated in the kidney, which in this case is the critical organ. Cadmium has a broad spectrum of effects on the kidney. Its accumulation in the kidney is likely to be caused by tubular damage with microproteinuria, enzymuria and decreased glomerular filtration rate [1–4].

Several indices were developed in the past to evaluate the cumulative Cd exposure in occupational settings. Cumulative Cd exposure in the air (Cd concentration in the air in μg/m^3 multiplied by years of exposure) was often used as a dose estimate [4–8]. A number of authors suggested that the cumulative Cd exposure index below 1100 μg/m^3 • years may prevent changes in the renal function. However, the internal Cd dose may considerably vary between individuals, depending on personal habits, absorption capacity (individual factors, speciation of Cd compounds) or metabolic functions.

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Cadmium concentration in urine (Cd-U) is proportional to its concentration in healthy kidney. On the basis of the dose-effect relationship against Cd excretion in urine, three main groups of thresholds of indicator of Cd effects on kidney associated with a significantly higher probability of urinary excretion, have been identified: (1) around 2 μg Cd/g creatinine associated mainly with biochemical alterations, (2) around 4 μg Cd/g creatinine from which the glomerular barrier function is progressively compromised and cytotoxic effects appear in the proximal tubule, and (3) around 10 μg Cd/g creatinine corresponding to the onset of the loss of tubular reabsorpion with increased excretion of low molecular proteins, such as $\beta_2$microglobuline (β_2M) or retinol binding protein (RBP) [1]. Urinary Cd values of workers with tubular dysfunction are, however, often higher than those predicted from the regression line and this may lead to an altered dose-response relationship [3].

Cadmium in blood (Cd-B) is not affected by tubular function. According to the common option, Cd-B reflects more recent (over month) than long-term exposure [9]. Järup et al. [3] suggested, however, that Cd-B measurements, made many years after the end of exposure, are likely to be good estimates of Cd body burden. The dose-response relationship has been found between the value of integrated index of exposure (Cd-B μg/l • years of exposure) and the frequency of increased urinary excretion of β_2M (β_2M-U) or RBP (RBP-U) above the cut-off concentration. Rogenfeld et al. [10] observed signs of cadmium-induced renal dysfunction in two men whose integrated exposure index exceeded 200 μg/l • years of exposure. In another study, Jakubowski et al. [11] observed an increase in β_2M-U and RBP-U in 10% of workers exposed to cadmium at the integrated exposure index of about 400 μg/l • years of exposure.

The aim of this study was to provide additional information on the dose-effect and dose-response relationships between different ways of evaluating exposure to cadmium and the occurrence of tubular and glomerular dysfunctions.

MATERIALS AND METHODS

Study populations and exposure

The study population consisted of male and female workers from a cadmium-battery factory in Poland. The workers were employed at the three factory departments: chemistry, production of panels and assembly. Exposure (inhalation of Cd dust) was very high in the past and since 1984 it has been continuously decreasing (Table 1). Concentrations of Cd-B and Cd-U also confirmed very high exposure in the past (Table 1).

Investigations in this factory were performed three times: in 1983, during the years 1986–1988 [11] and in 1998–1999. Eligible for the study were the subjects for whom historical records of Cd-B were available. The measurements of Cd-B were always carried out by the same laboratory of the Nofer Institute of Occupational Medicine in Łódź. In all, 116 workers (53 men and 63

Table 1. Concentrations of cadmium in the air and in blood and urine of workers of cadmium battery factory

	1983			1986–1988			1998–1999		
	n	$\overline{X}_G \pm$ GSD	Range	n	$\overline{X}_G \pm$ GSD	Range	n	$\overline{X}_G \pm$ GSD	Range
Cd-B µg/l	43	31.8 ± 2.14	9.11–166	91	29.1 ± 2.01	4.1–120.3	116	9.2 ± 2.14	0.5–42.1
Cd-U µg/g creat.	43	23.3 ± 2.24	3.2–126.5	94	55.7 ± 2.77	4.6–379.9	116	12.9 ± 2.05	1.3–96.6
Cd-A* mg/m^3			0.08–0.51			0.03–0.38			0.03–0.032

* The range of mean concentrations of cadmium in air in different departments in alkaline battery factory.

women) were included in the study. The mean age of the group was 49.4 years for women and 49.7 years for men. The mean period of Cd exposure accounted for 16.7 years for women and 17.1 years for men. Of this group, 25 workers were still employed in 1999.

To set up the cut-off concentration of β_2M-S the determinations of this low-molecular protein were performed in the control group in Poland (22 women and 18 men).

Blood and urine sampling

Blood and urine samples were collected in the factory polyclinic located outside the factory or in some cases at home of disabled persons.

Blood samples were collected by venipuncture using Venoject vacutainers (Li-Heparine, Oxford). Samples were stored at -20^{0}C until determination.

Spot urine samples were collected in polyethylene tubes. Specific gravity and creatinine concentrations were measured. Urine used for cadmium determination (5 ml) was acidified with 50 μl 50% nitric acid (Merck) and stored at -20^0 C, while to further 4.5 ml urine, 0.5 ml of 0.4 mol phosphate buffer, pH 7.4, containing 1% sodium azide, was added. This sample was stored at -20^0 C until determination of RBP.

Cadmium and lead analyses

Cadmium and lead was determined by graphite furnace atomic absorption spectrometry (Perkin Elmer 4100 ZL). Cadmium in blood was determined by the method of Stoeppler and Brandt [12], lead in blood, using the method of Christensen et al. [13] and cadmium in urine by the method of Perkin Elmer [14].

For internal quality control, Seronorm^{TM}, trace Elements Urine 5.1 μg Cd/l; Seronorm^{TM}, trace Elements Whole Blood 0.9 μg Cd/l, and 12.1 μg Cd/l and 385 μg Pb/l, and CRM (BCR 194) 126 μg Pb/l, (BCR 195) 416 μg Pb/l, were used.

Since 1983, the laboratory has participated in the U.K. National External Quality Assessment Schemes for lead and cadmium in blood. It also participates in the External Quality Control according to the Guidelines of German Federal Medical Council and has been certified to determine cadmium in blood and urine in the occupational and environmental medical fields.

Low molecular proteins analysis

RBP in urine and β_2M-S were measured by means of latex immunoassay (LIA) after Bernard et al. [15]. The laboratory has used this method since 1983. The results of determinations were verified against determinations of urine and serum samples in other laboratories.

Urinary elimination of RBP has been chosen for evaluating tubular proteinuria as this protein is much more resistant than β_2M, and no significant degradation occurs under normal conditions of urine collection and storage [15]. The cut-off point of 300 μg/g creatinine was accepted [9,16].

Determinations of β_2M-S were performed to estimate indirectly the glomerular filtration rate (GFR) [2,7,17]. According to Viberti et al. [18], β_2M-S concentration was raised in all patients with diminished glomerular filtration rate (below 80 ml/min/ 1.73 m^2).

The cut-off concentration of β_2M-S (mean + 2SD) of 2.4 mg/l (mean 1.6 μg/l ± 0.40 mg/l) was accepted on the basis of determinations performed in the control group in Poland. Similar results (mean 1.60 ± 0.34 for females and 1.59 ± 0.36 for males) were obtained by Evrin and Wibel [19].

Concentrations of cadmium in the air (Cd-A)

The results of Cd determination in the air for the period from 1981 to 1996 were obtained from the industrial hygiene department of the factory.

Period of employment

All data on the period of employment of individual workers in different departments of the factory, as well as on the dates of retirement were provided by the personnel department of the factory.

Calculation of the integrated exposure indexes

Cd-B (μg/l • t) – mean values between Cd-B concentrations in 1983, 1986–1988 and 1998–1999 were calculated and multiplied by years. For persons employed before

1983 concentration of Cd-B in 1983 was multiplied by years of employment until 1983.

Cd-A (μg/m^3 • t) – concentrations of Cd-A in a given department of the factory in subsequent years, since 1981, were multiplied by years of employment. For persons employed before1981, Cd-A concentrations in 1981 were multiplied by years of employment. In the case of retired persons, the years between the retirement and the 1998–1999 investigations were multiplied by the default concentrations of Cd-A – 0.02 μg/m^3.

Statistical analysis

Statistical analysis of the results was performed by means of linear and multiparametric logistic regression.

RESULTS

Correlations between: Cd-B • t; Cd-A • t; Cd-U in 1998/99; Cd-B in1998/99 and RBP-U or β_2M-S are presented in Table 2. The results show that the best correlation was obtained when integrated index of exposure, Cd-B • t, was used as the estimate of Cd dose. Correlation coefficients amounted to 0.642 and 0.513 ($p < 0.001$) when RBP-U and β_2M-S were considered as markers of tubular dysfunction or glomerular filtration. For the second integrated index of exposure Cd-A • t, respective values of correlation coefficient amounted to 0.173 and 0.127 and were statistically insignificant. When Cd-U and Cd-B concentrations at the time of investigations in 1998/99 were used to evaluate Cd body burden, correlation coefficients amounted to 0.343 and 0.332 for RBP-U and to 0.198 and 0.358 for β_2M-S.

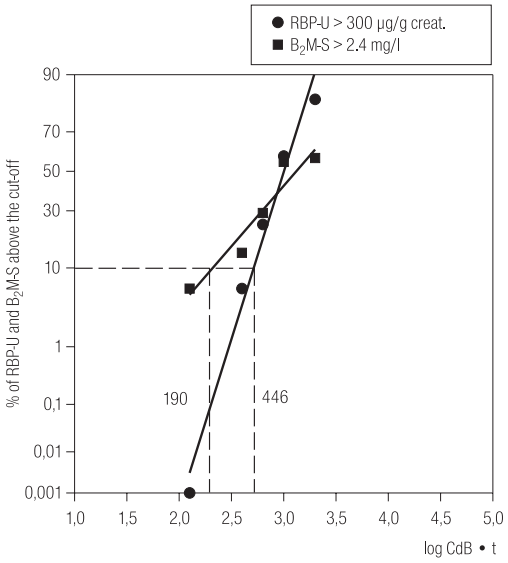

Fig. 1. Dose-response relationship between log CdB • t and prevalence of RBP-U and ß$_2$M-S values above the cut-off points.

The dose-response relationship between Cd-B • t and the prevalence of the RBP-U and β_2M-S values higher than the cut-off points of 300 μg/g creatinine and 2.4 mg/l, respectively are presented in Fig 1.

This relationship indicates a 10% risk of tubular dysfunction or decrease in GFR at an integrated index of exposure Cd-B • t of about 450 and 190 μg/l • years of exposure. The former value is similar to that of about 400 μg/l • t, obtained earlier in the same factory [11].

Table 2. Relationship between different indixes of exposure and RBP-U or β_2M-S

Parameter	RBP-U μg/g creatinine			β_2M-S mg/l		
	Equation (y = ax + c)	r	p	Equation (y = ax + c)	r	p
Cd-B • t (μg/l • years)	y = 0.001x + 1.6256	0.642	<0.001	y = 0.0005x + 1.7376	0.513	<0.001
Cd-A • t (mg/m^3 • years)	y = 0.0129x + 2.2385	0.173	<0.11	y = 0.0064x + 2.055	0.127	<0.11
Cd-B (98/99) (μg/l)	y = 0.0407x + 1.8397	0.332	<0.001	y = 0.0296x + 1.7466	0.358	<0.001
Cd-U (98/99) (μg/g creatinine)	y = 0.0256x + 1.8951	0.343	<0.001	y = 0.0099x + 1.9312	0.198	<0.1

Table 3. Influence of individual factors on the increased urinary RBP excretion (linear logistic regression)

RBP-U (98/99) > 300 μg/g creatinine				
Test parameter	Regression coefficient	Regression coefficient SE	Relative risk	P
Sex	-0.1660	0.4050	0.847	0.682
Age	0.0854	0.0259	1.089	0.001
Pb-B (98/99)	-0.0083	0.0058	0.992	0.155
Cd-B (98/99)	0.1370	0.0356	1.147	<0.001
Cd-U (98/99)	0.1010	0.0250	1.106	<0.001
Cd A• t	0.0421	0.0203	1.043	0.038
Cd B • t	0.0037	0.0007	1.004	<0.001
Time after cessation of exposure	0.1304	0.1820	1.139	0.474

SE – Standard error.

Table 4. Influence of individual factors on serum β_2M concentrations above the cut-off points (linear logistic regression)

β_2M-S > 2.4 mg/l				
Test parameter	Regression coefficient	Regression coefficient SE	Relative risk	P
Sex	-0.3226	0.4400	0.724	0.464
Age	0.1228	0.0312	1.131	<0.001
Pb-B (98/99)	0.0003	0.0040	1.000	0.936
Cd-B (98/99)	0.0919	0.0306	1.096	0.003
Cd-U (98/99)	0.0295	0.0168	1.030	0.080
RBP-U (98/99)	0.0002	0.0001	1.000	0.002
Cd A • t	0.0238	0.0156	1.024	0.127
Cd B • t	0.0026	0.0006	1.003	<0.001
Time after cessation of exposure	0.4017	0.1990	1.494	0.044

SE – Standard error.

Table 5. Influence of individual factors on increased urinary RBP excretion (multiple logistic regression)

RBP-U (98/99) > 300 μg/g creatinine				
Test parameter	Regression coefficient	Regression coefficient SE	Relative risk	P
Age	0.0099	0.0417	1.010	0.812
Cd-B (98/99)	0.0368	0.0461	1.037	0.425
Cd-U (98/99)	0.0678	0.0331	1.070	0.041
CdA • t	0.0271	0.0217	1.028	0.207
CdB • t	0.0029	0.0009	1.003	<0.001

SE – Standard error.

Table 6. Influence of individual factors on serum β_2M concentrations above the cut-off points (multiple logistic regression)

β_2M-S > 2.4 mg/l				
Test parameter	Regression coefficient	Regression coefficient SE	Relative risk	P
Age	0.0628	0.0393	1.065	0.110
Cd-U (98/99)	-0.0129	0.0258	0.987	0.616
RBP-U (98/99)	0.0001	0.0000	1.000	0.069
Cd B · t	0.0018	0.0007	1.002	0.012
Time after cessation of exposure	0.0024	0.0589	1.002	0.968

SE – Standard error.

The data on the potential influence of different parameters on the urinary RBP excretion and on the concentrations of β_2M-S above the cut-off levels, obtained by means of linear logistic regression are summarized in Tables 3 and 4. Significant parameters ($p < 0.05$) from Tables 3 and 4 were reevaluated by means of multiple regression analysis. The results presented in Table 5 suggest that the excretion of RBP-U above the cut-off level was influenced mainly by the cumulative exposure to cadmium expressed as Cd-B • t and by Cd-U concentrations in 1998/99. Cumulative exposure expressed as Cd-B • t constituted the only significant parameter responsible for the increase in β_2M-S concentrations above the cut-off level (Table 6).

DISCUSSION

The results of the investigations carried out in a population with past exposure to high concentrations of Cd dust provided information on the dose-response relationship between the cumulative exposure and early effects of exposure to cadmium, as well as on the value of different markers of exposure as predictors of the kidney dysfunction.

The results indicate an advantage of using Cd-B as predictor of kidney dysfunction in workers chronically exposed to cadmium over more common Cd determination in the air. The correlation between Cd-B • t and RBP-U or β_2M-S was much better than that of the remaining indexes of exposure. When integrated concentration of cadmium in the air was applied as an independent variable, the correlation with Cd-B and β_2M-S was insignificant. Also in the case of the actual Cd-U (1998/99) and Cd-B (1998/99), recommended by Lauwerys et al. [5] or Järup et al. [4] as the indexes of cumulative exposure, correlation coefficients were much lower than in the case of Cd-B • t. In view of the long half-life of Cd elimination from the body, the determination of Cd-B levels once a year during periodical examinations would seem sufficient. These results, kept in medical files, can serve as a basis for evaluating integrated exposure by an industrial physician.

The results on the dose-response relationships confirmed our previous findings [11]. The dose-response curves (Fig. 1) indicate a 10 % risk of tubular dysfunction in the form of the increased prevalence of RBP excretion and β_2M-S concentration above the cut-off points at an integrated exposure of about 450 and 190 µg Cd-B • years. The integrated index of exposure about 200 µg/l Cd-B • years of exposure can be proposed as the upper limit. This value confirm the validity of 5 µg/l Cd-B as a health-based biological action level [9,20].

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