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by [Roto P](#)

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Urinary β_2 microglobulin related to chronic low level exposure to metallic cadmium dust in Finnish cadmium processing workers

by PEKKA ROTO, M.D., M.I.H.¹

ROTO, P. Urinary β_2 microglobulin related to chronic low level exposure to metallic cadmium dust in Finnish cadmium processing workers. *Scand. j. work environ. & health* 4 (1978) 131—136. The determination of urinary β_2 microglobulin is a sensitive method for screening groups which run the risk of developing renal tubular damage due to cadmium exposure. In this study, the urinary β_2 microglobulin excretion of 78 male workers who had been exposed to cadmium dust levels of 6.3—11.0 $\mu\text{g}/\text{m}^3$ from 0.5 to 4 h daily for an average of four years was compared to 35 nonexposed male workers. Possible effects of smoking on renal β_2 microglobulin excretion were controlled. The results indicate that the levels of cadmium to which the workers were exposed have no measurable renal effects on the health of workers.

Key words: cadmium dust, cadmium exposure, cadmium processing, urinary β_2 microglobulin.

β_2 microglobulin ($\beta_2\text{m}$) is a polypeptide, which is closely related structurally to the heavy chain of immunoglobulin G (2). Since its isolation and characterization from human urine in 1968 (3), interest in the immunochemical role of $\beta_2\text{m}$ has increased greatly. $\beta_2\text{m}$ probably has an important role in the function of histocompatibility antigens like HL-A (2). The urinary level of $\beta_2\text{m}$ is increased in several disorders and diseases that lead to possible renal tubular damage. Examples of disorders with high urinary $\beta_2\text{m}$ are Fanconi syndrome, Balcan nephropathy, multiple myeloma, Wilson's disease, and chronic cadmium poisoning (14). High urinary or $\beta_2\text{m}$ concentrations have also been found in patients after renal transplantation (15).

In the normal Swedish population the urinary $\beta_2\text{m}$ level varies between 4 and 370 $\mu\text{g}/\text{l}$. Higher levels have been observed in older people, but the urinary excretion (expressed as $\beta_2\text{m}$ clearance/creatinine clearance) does not seem to change with age (4). There is no difference between the sexes. Apparently healthy people may have urinary $\beta_2\text{m}$ levels that are 5 to 10 times higher than expected. The cause of this phenomenon is not known (4).

A slow accumulation of cadmium in the renal tubular tissue may lead to irreversible damage with proteinuria (5, 9). There is no practical way to control kidney cadmium concentrations in exposed workers because direct biopsy is too risky.

Urinary and blood cadmium levels do not correlate with tissue concentrations (5, 16). Hair and nail sampling has appeared promising and attractive because of the easiness of the sampling procedure. Considerable analytical difficulties still remain due to contamination however (7, 16). Furthermore there seems to be no corre-

¹ Outokumpu Oy, Kokkola Works, Kokkola, Finland.

Reprint requests to: Dr. Pekka Roto, Outokumpu Oy, Kokkola Works, SF-67100 Kokkola 10, Finland.

lation between hair and renal cortex concentrations of cadmium (16).

Recently urinary $\beta_2\text{m}$ excretion has been considered a good early diagnostic test for detecting kidney damage due to occupational cadmium exposure. According to Kjellström and Piscator (8) a slight increase in urinary $\beta_2\text{m}$ excretion may already indicate irreversible tubular damage.

The aim of this study is to compare urinary $\beta_2\text{m}$ levels of apparently healthy exposed and nonexposed workers in a Finnish zinc plant, which has a separate cadmium separation process. This study hopefully also gives additional information about the validity of the Finnish threshold limit value (TLV) of cadmium dust, which is $20 \mu\text{g}/\text{m}^3$ of metallic dust in the work atmosphere. The TLV was adopted from the recommendation of the American Conference of Governmental Industrial Hygienists in 1971. It is so far the lowest TLV of cadmium in use in industrialized countries (1).

MATERIAL AND METHODS

Exposure

The present study was carried out in the Outokumpu Kokkola Zinc Plant, which has produced 200–300 metric tons of cadmium annually since it commenced operation in 1970. In the area where cadmium is separated, the workers are exposed to cad-

mium dust. Its main source is the processing and handling of briquets of cadmium sponge. In the final stage where the separated cadmium is cast, exposure consists of cadmium dust and fumes. In this stage there are also negligible amounts of mercury and lead dust (constantly less than $5 \mu\text{g}/\text{m}^3$). Cadmium fumes have been eliminated by the total enclosure of the casting furnace.

The concentrations of cadmium dust in the work areas are monitored by stationary dust samplers with Millipore® AAWP 037 filters at seven sites for 25 to 30 days each year. The average annual concentration of cadmium dust at the breathing level of the workers varies between a geometric mean of 6.3 and $11.0 \mu\text{g}/\text{m}^3$. A few exposure peaks between 50 and $500 \mu\text{g}/\text{m}^3$ were recorded in 1970–1975 (fig. 1). The results of the stationary samplers have been confirmed by personal sampling since 1974. Each worker's exposure time has been carefully recorded since the beginning of his employment in the zinc plant. The cadmium samples are analyzed in the Company's metallurgical laboratory with a Perkin Elmer 303 atomic absorption spectrophotometer. The workers do not usually use protective masks, except in maintenance operations, where the cadmium concentration in the ambient air has exceeded $20 \mu\text{g}/\text{m}^3$. (Siltox® dust respirators are used.) The total leakage of usual dust respirators varies between 1 and 10 %, depending on differences in using practices (10).

Fig. 1. Annual geometric means within ± 1 SD of cadmium dust concentrations measured at the breathing level with seven stationary Millipore samples in the cadmium processing area of the Outokumpu Kokkola Zinc Plant. (n = number of samples)

Subjects

A total of 110 male workers have been exposed to cadmium dust for a period of more than one year. Seventy-eight are still employed, while 32 have sought work elsewhere (12 in the company and 20 outside it). There was no evidence of ill health among these workers as the cause of quitting the job in the cadmium processing area. All the 78 workers currently exposed to cadmium were included in this study. Twelve of the former cadmium workers have had increased blood cadmium levels ($3\text{--}6 \mu\text{g}/\text{dl}$). Ten of these workers were available for examination. A reference group of 35 apparently healthy male workers was selected from other depart-

Table 1. Some characteristics of the groups included in the investigation.

Group ^a	N	Age	SD	Exposure (years)		Smokers %	Weight		Height	
				Mean	SD		Mean	SD	Mean	SD
Nonexposed	35	32.7	7.4	—	—	34	73.6	7.2	174.4	5.4
Exposed process workers	30	28.2	4.7	3.5	2.0	28	73.9	8.0	173.3	6.5
Exposed maintenance workers	48	32.1	7.1	4.3	2.0	37	73.2	9.5	172.8	3.9
Exposed for 0.5—2 h daily	53	31.6	8.7	4.0	2.2	32	73.0	9.8	173.3	4.8
Exposed for 2—4 h daily	25	28.8	4.8	3.8	2.1	44	76.7	12.1	174.0	5.9

^a No significant differences between the groups in the parameters ($p > 0.05$).

ments of the Outokumpu Kokkola Works. None of the referents are known to have been exposed to cadmium or to other trace metals. All the study subjects have participated in the occupational health program of the Company. Urinary and blood cadmium of each exposed worker has been checked two to three times yearly since 1970. The group mean of blood cadmium has been between 0.3 and 0.4 $\mu\text{g}/\text{dl}$ annually and the mean of urinary concentrations 0.1—0.4 $\mu\text{g}/\text{l}$. The exposed group was comparable to the referent group in respect to age, sex, height, weight, and smoking habits (table 1). None of the study subjects had ever suffered from renal disease. One referent and two exposed subjects had moderate hypertension, but except for these three persons, none of the subjects were on regular medication because of chronic disease.

The exposure time of the exposed group varied from 0.5 to 4 h per workday. This group was divided into two exposure categories according to daily exposure time. One group comprised 54 workers exposed for 0.5 to 2 h, and the other 24 workers exposed for 2—4 h. Forty-eight of the 78 exposed subjects belonged to the maintenance group. Maintenance workers are also exposed to minute amounts of metallic mercury and lead dust, the exposure levels of which range from 1 to 5 $\mu\text{g}/\text{m}^3$ for less than 1 h/workday.

Because tobacco contains about 1.2 μg of cadmium/cigarette (11), the effect of smoking has been taken into account in the analysis. Subjects who smoked or had smoked for more than five years were considered smokers. The others were allocated to the nonsmoker category.

β_2 may be degraded in the bladder at a low pH (3). Because of the lower acidity of morning urine, the samples were taken from noon or afternoon urine. The urinary cadmium samples were analyzed in the laboratory of the Outokumpu Company with atomic absorption spectrophotometry. The urinary β_2 samples, on the other hand, were analyzed with the Phadebas microtest® (12) method in the Yhtyneet Kliiniset Laboratoriot Oy in Helsinki.

NUMBER OF SUBJECTS

Fig. 2. Urinary β_2 distribution.

Fig. 3. Urinary β_2m level as a function of exposure years in workers whose daily exposure level has been $6.3\text{--}11.0\text{ }\mu\text{g}/\text{m}^3$ for $0.5\text{--}2\text{ h}$.

Fig. 4. Urinary β_2m level as a function of exposure years in workers whose daily exposure level has been $6.3\text{--}11.0\text{ }\mu\text{g}/\text{m}^3$ for $2\text{--}4\text{ h}$.

During the transportation of the urinary samples careful consideration was given to the conservation of the pH of the sample. The blood cadmium levels were analyzed in the laboratory of the Institute of Occupational Health in Helsinki.

In the statistical analysis, the Kolmogorov—Smirnov test was used for the comparison of the urinary β_2m values and the t test in the other comparisons of the exposed and reference groups.

RESULTS

In fig. 2 the urinary β_2m values are expressed per gram of creatinine. The distribution of the values is skewed and similar for the maintenance, process, and nonexposed groups. The $D_{\max}$ in the Kolmogorov—Smirnov test was 2. There did not seem to be a clear effect of exposure time on urinary β_2m excretion in the exposed group (figs. 3 and 4). In fig. 3 the linear regression coefficient is 0.187. It is not significant on a 95 % probability level. The smokers and nonsmokers did not significantly differ as to β_2m excretion. The duration of smoking had no clear effect on β_2m excretion (fig. 5).

The former cadmium process workers, who had been exposed in 1970—1972, showed no higher excretion than the current workers. Their β_2m mean was $102\text{ }\mu\text{g}/\text{g}$ of creatinine. No case of chronic cadmium poisoning has been reported among the workers of the Outokumpu Kokkola Zinc Plant.

Fig. 5. Urinary β_2m as a function of smoking years.

DISCUSSION

Evaluating exposure under actual work conditions is usually very difficult without prospective personal sampling programs. In comparison to those in most earlier studies, the overall exposure time and level in the present investigation have been carefully documented. The general background exposure of the exposed and nonexposed subjects is very similar. Large amounts of nephrotoxic compounds other than cadmium are not known in the plant complex. The results indicate that an exposure to $6.3\text{--}11.0\text{ }\mu\text{g}/\text{m}^3$ of metallic cadmium dust does not cause functional tubular changes within seven years if the exposure time does not exceed 4 h a day. In 1970—1973, 12 cadmium process workers had a blood cadmium concentration

between 3 and 6 $\mu\text{g}/\text{dl}$. According to Friberg et al. (5) the blood cadmium level increases after considerable exposure. In 1970–1975 the cadmium content of the work atmosphere temporarily exceeded 100 $\mu\text{g}/\text{m}^3$. The present exposed population has also been exposed to higher levels from time to time. However, these exposure peaks do not seem to have caused demonstrable tubular effects.

In the two exposed cases with a urinary $\beta_2\text{m}$ value exceeding 500, the importance of past exposure is not clear. Neither of the workers had earlier had increased blood or urinary cadmium concentrations. One of them was a process worker who has been exposed for 6.5 years 4 h daily, and the other a maintenance worker whose exposure time had been 7 years and 0.5–1 h a day. Both were smokers. Smoking of cigarettes contaminated by cadmium may explain these findings.

The maintenance group has a multiple trace-metal exposure, which is common in zinc plants where trace metals are separated from the main process. In the present study the principal exposure was, however, cadmium. There seem to be no synergistic effects between low cadmium and mercury exposure on the tubular function of maintenance workers (fig. 2 c).

It has been estimated that when the concentration of cadmium in renal cortex exceeds 200 μg of cadmium per gram of wet tissue, a functional tubular change may emerge (6). This study does not give additional information about the renal concentration of cadmium in the exposed group. Piscator (13) constructed a theoretical model for the calculation of critical renal tissue concentration. This model suggests that, depending on pulmonary absorption, a cadmium level of 5.3–12.0 $\mu\text{g}/\text{m}^3$ during a normal 8-h day may lead to 200 μg of cadmium in renal cortex in 25 years. Nutrition and smoking may add an additional burden, which may halve the time required for critical tissue concentration. According to the model of Piscator some smokers in the exposed group may reach the critical exposure time within 5–10 years.

Information from the literature, together with the results of this study, indicate that 20 $\mu\text{g}/\text{m}^3$ of metallic cadmium dust is rather safe for use.

Because the tubular damage caused by cadmium accumulation is irreversible, the measurement of urinary $\beta_2\text{m}$ is not a biological monitoring method suitable for the periodic examination of workers exposed to cadmium. Urinary and blood cadmium measurements seem so far to be the best method for this purpose (8). Urinary $\beta_2\text{m}$ screening is seemingly a good procedure for the early diagnosis of possible tubular damages caused by occupational cadmium exposure. Because of its potent error sources, e.g., low urinary pH and sample transportation, urinary $\beta_2\text{m}$ analysis requires still more standardization before it can become totally suitable for epidemiologic investigations.

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