Scand J Work Environ Health 1982;8(1):122-130
Issue date: 1982

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This article in PubMed: www.ncbi.nlm.nih.gov/pubmed/6980459

Print ISSN: 0355-3140 Electronic ISSN: 1795-990X

Scand j work environ health 8 (1982): suppl 1, 122—130

Cross-sectional study of pulmonary function in cadmium alloy workers

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SAKURAI H, OMAE K, TOYAMA T, HIGASHI T, NAKADATE T. Cross-sectional study of pulmonary function in cadmium alloy workers. *Scand j work environ health* 8 (1982): suppl 1, 122—130. Two groups of cadmium workers (7 and 9 men) and a group of reference workers (122 men) were studied for the purpose of determining the pulmonary effects of cadmium. Indices of pulmonary function, based on the forced expiratory flow volume curve and respiratory impedance, were measured for all the groups, and indicators of cadmium exposure and effects on renal tubular reabsorption functions were also measured in the two groups of cadmium workers. The mean blood and urinary levels of cadmium were 2.08 μg/100 ml (185.06 nmol/l) and 32.6 μg/l (290.04 nmol/l), respectively, and the level of inhalation exposure was estimated at about 1 mg/m^3 as the 8-h average concentration for about 5 a in the high exposure group. The percentage of the predicted function values of the highly exposed workers was significantly deteriorated for forced vital capacity (FVC), forced expiratory volume in 1 s ($FEV_{1.0}$), peak expiratory flow, maximum expiratory flow at 75, 50, and 25 % of the FVC, percentage of $FEV_{1.0}$ to FVC, and respiratory impedance, whereas those of the slightly exposed workers were reduced only for FVC and $FEV_{1.0}$. A paired comparison between the highly exposed workers and matched referents disclosed the same results. It was concluded that chronic obstructive pulmonary changes had been induced by cadmium in Japanese workers without a history of acute or subacute cadmium pneumonitis.

Key terms: chronic bronchitis, chronic obstructive pulmonary effect, emphysema, forced expiratory flow volume curve, matched referent study, percentage predicted value, questionnaire, renal tubular reabsorption function, respiratory impedance.

Cadmium is known to cause adverse effects on the lungs when excess exposure takes place, either in an accidental or protracted manner, by the inhalation route (8). Earlier reports (1, 2, 3, 7, 10) have described more or less manifest signs and symptoms of respiratory injury among workers with long-term cadmium exposure. The nature of the effects was considered to be emphysematous on the basis of clinical and physiological observation (2, 7). However, more recent reports (13, 15, 17, 18) could not find evidence to support the notion that cadmium gives rise to pulmonary emphysema. Lauwerys (12), after reviewing relevant literature, concluded that the type of functional and morphological disturbances induced by cadmium has not been made clear, and, in the absence of acute episodes of overexposure, lung changes may usually be mild. On the other hand, pulmonary effects caused by cadmium have not been found in Japan even though both clinical and epidemiologic observations have been made of groups of Japanese workers exposed to cadmium (19).

We planned the present study with the purposes of clarifying whether any cadmium-induced pulmonary effects could be found in Japanese cadmium workers and obtaining information on any found effects. In order to improve the quality of

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0355-3140/82/050122-09USD3.25

the epidemiologic inference, more than 100 reference workers were collected from other factories manufacturing petrochemical products.

Subjects and methods

The highly exposed group (group 1) consisted of seven workers who had been exposed to considerably high levels of cadmium fumes in a melting and casting shop in a factory manufacturing cadmium alloys. Most of the alloys were hard solders containing silver, zinc, and copper, in addition to cadmium. Nine such workers could be listed up until 1980, the time of the study, of whom six had been transferred to other cadmium-free jobs in 1975 because slight or more advanced renal tubular injury had been detected. Two of the nine men, one former and one current cadmium worker, did not participate in the study. The reasons of their dropping out were acute respiratory infection with moderate coughing (former cadmium worker) and absence from the factory due to private business (current cadmium worker).

The second cadmium group (group 2) consisted of nine workers who had been engaged in other processes in the manufacture of cadmium-containing alloys at the same factory. Their level of cadmium exposure was thought to be negligible because, though they handled cadmium alloys, there was no process which may have generated cadmium dust or fumes, either by mechanical force or heat. However, they may have been exposed to some irritating airborne agents such as oil mists, acid mists, and/or mixed metal dusts.

The third group, the reference group, consisted of 122 subjects who had worked in several factories manufacturing petrochemical products. They had not been exposed to any chemicals to the extent that the exposure in question was known to cause health effects. There was a possibility that their pulmonary function was not completely normal when compared with that of the general population living in a pollution-free environment. However, on the contrary, there is no reason to suppose that their pulmonary function was better than that of an average worker population.

Cadmium concentrations in the air of the melting and casting shop were determined by us three times during the 10 a preceding the study. The first measurement in 1970 revealed that the mean and standard deviation of the cadmium concentration of 14 air samples taken in the breathing zones of workers during several cycles of melting and casting were 2.34 mg/m^3 and 3.03 mg/m^3, respectively. The range was 0.06—8.40 mg/m^3, and the median 0.76 mg/m^3. Characteristic yellow cadmium fumes were scattered from the melting furnaces to the surroundings. However, the workers were not wearing authorized protective masks, but were occasionally wearing gauze masks on a voluntary basis. This high exposure operation occupied about half of their normal workhours. After this measurement the workers were strongly urged to wear protective masks and the work environment was considerably improved. The second measurement, performed in 1974, disclosed that the mean cadmium exposure concentration, determined by 8-h personal sampling, was 53.8 μg/m^3 (number of samples 18, number of workers 5). In the third measurement, in 1977, the mean cadmium concentration in the breathing zones was 38.5 μg/m^3. The mean duration of cadmium exposure for group 1 was 10.6 a, as shown in table 1. In 1970 group 1 had spent about 5 a, on the average, exposed to an estimated 8-h average cadmium concentration of 1 mg/m^3. Their exposures in the following 5 a appear to have been far less. No history of acute respiratory distress suggestive of acute cadmium poisoning was found for group 1.

No data on the cadmium concentration in the air were available for group 2.

Blood and spot urine samples were collected from both groups of cadmium workers at the alloy factory in the morning of the day when the respiratory function tests were performed. The cadmium concentrations in the blood and urine are shown in table 2. The data for group 2 indicate that it had not received any significant exposure to cadmium.

Cadmium concentrations were determined for blood and urine by flameless atomic absorption spectrophotometry. Creatinine, uric acid, and inorganic phosphate in serum and urine were determined

Table 1. Physical characteristics, smoking habits and duration of exposure of the three groups [a] of workers.

	Group 1 (N = 7)	Group 2 (N = 9)	Group 3 (N = 122)
Age (a), mean ± SD	46.1 ± 7.5	31.1 ± 8.3	36.4 ± 8.7
Height (cm), mean ± SD	161.0 ± 5.1	165.2 ± 5.3	167.8 ± 6.1
Weight (kg), mean ± SD	56.3 ± 6.5	59.6 ± 8.1	63.6 ± 8.0
Number of smokers	5 (71 %)	6 (67 %)	87 (71 %)
Number of exsmokers	2	1	18
Number of nonsmokers	0	2	17
Number of cigarettes being consumed per day,[b] mean ± SD	16.4 ± 12.5	17.8 ± 14.6	16.8 ± 14.3
Duration of exposure (a), mean ± SD	10.6 ± 5.7	7.3 ± 4.5	—

[a] Group 1 = high cadmium exposure, group 2 = low cadmium exposure, group 3 = reference group.
[b] Total number of cigarettes consumed daily by smokers divided by the total number of workers.

Table 2. Biological indicators of exposure and several renal effects induced by cadmium in the two groups [a] of cadmium workers — Mean ± SD.

	Group 1 (N = 7)	Group 2 (N = 9)
Blood cadmium (μg/100 ml) [b]	2.08 ± 0.71 ***	0.71 ± 0.11
Urine cadmium (μg/l) [c]	32.6 ± 12.1 ***	2.4 ± 1.6
Serum		
Creatinine (mg/dl)	1.22 ± 0.16	1.10 ± 0.07
Uric acid (mg/dl)		
Inorganic phosphate (mg/dl)	3.30 ± 0.80 ***	5.66 ± 0.63
Urine	2.50 ± 0.44 **	3.22 ± 0.30
Total protein (mg/dl)	37.3 ± 33.7 *	10.7 ± 11.2
β_2-Microglobulin (μg/l)	2,225 ± 1,924 *	114 ± 62
Clearance ratio to creatinine clearance		
Uric acid (%)	18.7 ± 3.9 ***	9.0 ± 1.6
Inorganic phosphate (%)	21.6 ± 7.3 **	11.8 ± 4.4

[a] Group 1 = high cadmium exposure, group 2 = low cadmium exposure.
[b] 1 μg/100 ml = 88.97 nmol/l.
[c] 1 μg/l = 8.90 nmol/l.
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ for the difference between groups 1 and 2.

Table 3. Indices of pulmonary function for the three groups [a] of workers — Mean ± SD. (Forced vital capacity = FVC; forced expiratory volume in 1 s = $FEV_{1.0}$; peak expiratory flow = PEF; maximum expiratory flow at 75, 50 & 25 % of the FVC = MEF_{75}, MEF_{50} & MEF_{25}, respectively; percentage of $FEV_{1.0}$ to FVC = $FEV_{1.0}$ %; respiratory impedance = $|Z|_{3Hz}$)

	Group 1 (N = 7)	Group 2 (N = 9)	Group 3 (N = 122)
FVC (l)	3.40 ± 0.28	3.97 ± 0.35	4.46 ± 0.64
$FEV_{1.0}$ (l)	2.62 ± 0.31	3.55 ± 0.40	3.78 ± 0.58
PEF (l/s)	6.23 ± 2.00	9.39 ± 0.63	9.15 ± 1.36
MEF_{75} (l/s)	5.41 ± 2.08	9.04 ± 0.71	8.61 ± 1.48
MEF_{50} (l/s)	3.24 ± 1.25	5.38 ± 0.96	5.10 ± 1.44
MEF_{25} (l/s)	1.00 ± 0.43	2.19 ± 0.54	1.94 ± 0.67
$FEV_{1.0}$ %	77.5 ± 10.4	89.4 ± 3.2	84.8 ± 5.5
MEF_{50}/MEF_{25}	3.30 ± 0.77	2.51 ± 0.31	2.76 ± 0.63
$\|Z\|_{3Hz}$ (cmH_2O/l/s)	2.67 ± 0.44	2.28 ± 0.42	2.07 ± 0.44 [b]

[a] Group 1 = high cadmium exposure, group 2 = low cadmium exposure, group 3 = reference group.
[b] Number of subjects for $|Z|_{3Hz}$ of the referents was 134.

by routine methods of clinical chemistry, and the ratio of uric acid and inorganic phosphate clearances to creatinine clearance were calculated. Beta$_2$-microglobulin in serum and urine was determined by radioimmunoassay (5), and total urinary protein was determined by the membrane filter method (11).

The maximum expiratory flow volume curves were recorded with autospiroanalyzer ASC-1000 (Asahi Medical). Each subject performed at least four forced expiration maneuvers, and the following indices were read out: forced vital capacity (FVC), forced expiratory volume in 1 s ($FEV_{1.0}$), peak expiratory flow (PEF) rate, maximum expiratory flow (MEF) rate at 75 % (MEF_{75}), at 50 % (MEF_{50}), and at 25 % (MEF_{25}) of the FVC, percentage of $FEV_{1.0}$ to FVC ($FEV_{1.0}$ %), and MEF_{50} divided by MEF_{25} (MEF_{50}/MEF_{25}). The highest values among the satisfactory recordings were accepted for the analysis. Respiratory impedance ($|Z|_{3Hz}$) was measured by the oscillation method (9) with an apparatus assembled by us. Pulmonary function tests were administered to the two groups of cadmium workers in a day by trained physicians who had no information about the exposure status of the individuals. The tests for the referents were also performed in exactly the same manner. All the measurements were made within about two months in the autumn of 1980. Prediction equations to obtain expected pulmonary function for a given age and height were computed from the data of the referents by the multiple regression analysis.

The survey of respiratory symptoms was performed with the use of a slightly modified version of the British Medical Research Council's questionnaire form.

Results

The age, height, weight, and cigarette consumption for the three groups of workers are shown in table 1. The highly exposed group (group 1) was clearly the oldest, the shortest, and the lightest of the three comparison groups. However, the distributions of smokers and the mean number of cigarettes consumed per day were fortunately the same for all three groups without any selective sampling procedure.

The blood and urinary cadmium concentrations and some of the effects of cadmium mainly indicative of renal tubular reabsorption defects are listed for groups 1 and 2 in table 2. No abnormal value was found for group 2. On the other hand, the blood and urinary cadmium concentrations of group 1 were remarkably high in spite of the fact that five out of seven workers had been transferred to cadmium free jobs 5 a previously. Significantly lower values of uric acid and inorganic phosphate in the serum of the workers in group 1, along with the rise of clearance ratios of these substances, clearly indicated that the renal tubular reabsorption functions of these workers were considerably depressed. Significant increases in the total urinary protein and urinary β_2-microglobulin concentrations also supported this view.

The results of the pulmonary function tests are shown in table 3. Because the mean ages and heights were different for the three groups, a result shifting the pulmonary function of the highly exposed workers in an unfavorable direction, no meaningful comparison can be made directly from this table.

Table 4 lists the prediction equations for the individual lung function indices computed from the data of the 122 referents. Percentage pulmonary functions are shown in table 5 in reference to the predicted values computed by the prediction equations. The FVC, $FEV_{1.0}$, PEF, MEF_{75}, MEF_{50}, MEF_{25}, and $FEV_{1.0}$ % were significantly lower in group 1 than in group 3. The respiratory impedance was significantly higher in group 1 than in group 3. When groups 1 and 2 were compared, the $FEV_{1.0}$, PEF, MEF_{75}, MEF_{50}, MEF_{25}, and $FEV_{1.0}$ % were significantly lower in the former. Groups 2 and 3 were almost the same except for FVC and $FEV_{1.0}$, which were significantly lower in group 2 than in group 3.

In order to validate the findings further, a paired comparison was made between the seven highly exposed workers and the same number of age-, height-, and smoking-matched referents, who were selected from the 122 reference workers by the following method. First, smoking status was matched according to a tripartite classification into smoker, exsmoker, and non-

smoker. From the smoking-matched referents, those who were older and shorter than each exposed worker were grouped, and the closest individual among them in terms of age in months and height in centimeters was automatically accepted as an age-, height-, and smoking-matched referent.

The age, height, body weight, and smoking habits of the highly exposed workers (group 1) and matched referents (group 4) are listed in table 6. Group 1 was slightly younger than group 4, but the height of the two groups was almost the same. For the oldest subject among the seven highly exposed workers, no referent was found who was older and, at the same time, shorter. In this case, age was given priority over height, and an older but slightly taller referent was selected. Thus, the mean height became very slightly less in group 1 than in group 4, but the difference was by no means meaningful. The mean duration of smoking, expressed by the duration in years multiplied by the number of cigarettes consumed per day, turned out to be slightly less for group 1 than for group 4. It was found again that most of the lung function indices were significantly deteriorated in the cadmium-exposed workers, as shown in table 6.

Table 4. Prediction equations computed from data of the referents. (Forced vital capacity = FVC; forced expiratory volume in 1 s = FEV $_{1.0}$; peak expiratory flow = PEF; maximum expiratory flow at 75, 50 & 25 % of the FVC = MEF_{75}, MEF_{50} & MEF_{25}, respectively; percentage of $FEV_{1.0}$ to FVC = $FEV_{1.0}$%; respiratory impedance = $|Z|_{3Hz}$)

	Prediction equation [a]								
FVC	—4.969	—	0.01988	×	Age	+	0.06051	×	Height
$FEV_{1.0}$	—1.673	—	0.02936	×	Age	+	0.03888	×	Height
PEF	3.138	—	0.04415	×	Age	+	0.04544	×	Height
MEF_{75}	6.459	—	0.04145	×	Age	+	0.02183	×	Height
MEF_{50}	8.582	—	0.06470	×	Age	—	0.006726	×	Height
MEF_{25}	3.514	—	0.04562	×	Age	+	0.0005224	×	Height
$FEV_{1.0}$%	143.9	—	0.3012	×	Age	—	0.2867	×	Height
MEF_{50}/MEF_{25}	1.318	+	0.03805	×	Age	+	0.0003258	×	Height
$\|Z\|_{3Hz}$	5.771	—	0.002320	×	Age	+	0.02159	×	Height

[a] Age in years and height in centimeters.

Table 5. Percentage pulmonary functions in reference to predicted values for the three groups of workers (group 1 = workers with high cadmium exposure, group 2 = workers with low cadmium exposure, group 3 = reference group) — Mean ± SD. (Forced vital capacity = FVC; forced expiratory volume in 1 s = $FEV_{1.0}$; peak expiratory flow = PEF; maximum expiratory flow at 75, 50 & 25 % of the FVC = MEF_{75}, MEF_{50} & MEF_{25}, respectively; percentage of $FEV_{1.0}$ to FVC = $FEV_{1.0}$%; respiratory impedance = $|Z|_{3Hz}$)

	Group 1 (N = 7)	Group 2 (N = 9)	Group 3 (N = 122)
FVC (%)	88.4 ± 5.7 [aa]	90.1 ± 5.2 [cc]	100.0 ± 10.1
$FEV_{1.0}$ (%)	81.6 ± 11.1 [aaa, b]	92.6 ± 5.6 [c]	100.0 ± 11.0
PEF (%)	74.4 ± 24.4 [aaa, b]	101.5 ± 8.8	100.0 ± 13.9
MEF_{75} (%)	67.4 ± 26.5 [aaa, bb]	103.2 ± 9.3	100.0 ± 16.7
MEF_{50} (%)	71.7 ± 25.2 [aa, b]	98.3 ± 13.5	100.0 ± 26.1
MEF_{25} (%)	66.5 ± 18.6 [aa, bb]	100.1 ± 17.6	100.0 ± 29.7
$FEV_{1.0}$% (%)	92.5 ± 11.4 [aa, b]	102.6 ± 4.0	100.0 ± 5.8
MEF_{50}/MEF_{25} (%)	104.9 ± 19.8	99.0 ± 13.7	100.0 ± 18.6
$\|Z\|_{3Hz}$ (%)	122.6 ± 21.4 [aa]	107.7 ± 21.7	100.0 ± 20.5

a, aa, aaa $p < 0.05$, 0.01 and 0.001, respectively, for the difference between groups 1 and 3.
b, bb $p < 0.05$ and 0.01, respectively, for the difference between groups 1 and 2.
c, cc $p < 0.05$ and 0.01, respectively, for the difference between groups 2 and 3.

No significant difference in the prevalence rates of the individual respiratory symptoms was found between the seven exposed and seven matched referents in the questionnaire survey. However, slightly but consistently larger prevalences were observed for the seven cadmium workers for such symptoms as cough, phlegm, breathlessness, wheezing, effect of weather, and rhinitis. Two of the highly exposed workers apparently showed a clustering of several respiratory symptoms, whereas the other cadmium-exposed group and the referents merely complained of one or two symptoms sporadically. Furthermore, these two symptomatic subjects showed the lowest percentage of the predicted values for most of the indices obtained from the MEF volume curve and the largest percentage of the predicted values for respiratory impedance among all the three groups of workers.

Discussion

The epidemiologic comparability of worker groups was limited in this study in two important aspects, age and height. Two different methods were applied to overcome this fault. Percentage predicted pulmonary functions calculated on the basis of data for 122 referents showed that most of the observed pulmonary function indices of the highly exposed workers had significantly deteriorated (table 5). It is also worthwhile noting that the workers with slight cadmium exposure showed almost the same mean predicted values as the reference group, except for FVC and $FEV_{1.0}$, while there were significant differences between the slightly exposed and highly exposed groups for six of the nine indices listed in table 5. Because these two groups were examined on the same day by the same persons without any knowledge of exposure status, the difference appears to be meaningful. However, there remains a possibility that the standardization of age and height by the multiple regression equations in table 4 could not sufficiently compensate for the extent of the differences observed in the age and height distributions in this study. The second approach was a matched-pair comparison between highly exposed workers and referents selected from the reference workers. The selection was made in such a way that a nearest individual was adopted without choice for each exposed

Table 6. Paired comparison between highly exposed cadmium workers (group 1) and their matched referents (group 4), the two groups being matched for age, height and smoking habits. (Forced vital capacity = FVC; forced expiratory volume in 1 s = $FEV_{1.0}$; peak expiratory flow = PEF; maximum expiratory flow at 75, 50, & 25 % of the FVC = MEF_{75}, MEF_{50} & MEF_{25}, respectively; percentage of $FEV_{1.0}$ to FVC = $FEV_{1.0}$ %; respiratory impedance = $|Z|_{3Hz}$)

	Group 1 (N = 7)	Group 4 (N = 7)
Age (a), mean ± SD	46.14 ± 7.47	47.57 ± 6.73
Height (cm), mean ± SD	161.0 ± 5.1	161.3 ± 5.4
Weight (kg), mean ± SD	56.3 ± 6.5	59.6 ± 8.1
Smoking		
Smoker, number	5	5
Exsmoker, number	2	2
Duration (a) of smoking, mean ± SD	23.8 ± 5.8	28.2 ± 6.4
Duration × cigarettes consumed per day by smokers and exsmokers, mean ± SD	497.1 ± 256.0	677.1 ± 364.1
FVC (l), mean ± SD	3.40 ± 0.28 ***	4.04 ± 0.41
$FEV_{1.0}$ (l), mean ± SD	2.62 ± 0.31 **	3.31 ± 0.35
PEF (l/s), mean ± SD	6.23 ± 2.00 *	8.19 ± 1.32
MEF_{75} (l/s), mean ± SD	5.41 ± 2.08 *	7.86 ± 1.47
MEF_{50} (l/s), mean ± SD	3.24 ± 1.25 **	4.20 ± 1.14
MEF_{25} (l/s), mean ± SD	1.00 ± 0.43 **	1.49 ± 0.47
$FEV_{1.0}$ %, mean ± SD	77.5 ± 10.4	82.2 ± 5.8
MEF_{50}/MEF_{25}, mean ± SD	3.30 ± 0.77	2.91 ± 0.68
$\|Z\|_{3Hz}$ (cmH_2O/l/s), mean ± SD	2.67 ± 0.44 *	2.05 ± 1.89

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ for the difference between groups 1 and 4 by the paired t-test.

worker with regard to smoking, age, and height in a direction that would make his respiratory function less favorable than that of the exposed worker. Although the age and amount of smoking turned out to be slightly less for the exposed workers, most of their functions were significantly lower for the indices derived from forced expiration maneuvers, and respiratory impedance was higher. Thus the same results were obtained by two different methods of analysis.

Indices obtained from forced expiratory flow volume curves such as FVC, $FEV_{1.0}$, and MEF rates (MEF_{75}, MEF_{50}, MEF_{25}) have become widely used as sensitive indicators of pulmonary effects induced by environmental pollutants (4, 16). However, the forced expiration maneuver requires effort and skill on the part of examined subjects to yield reproducible results. Although MEF rates at low lung volumes are considered to be relatively independent of effort, they are not completely free from the effect of such factors (4). Then, epidemiologic findings solely based on the forced expiratory flow volume curve must be interpreted with reasonable caution. On the other hand, the respiratory impedance, namely, the total respiratory resistance, including airways, tissue, and chest cage resistances, is easily measured by the oscillation method, and it requires little effort from the subjects. The fact that this index of pulmonary function also showed significant deterioration confirms the findings obtained from the forced expiratory flow volume curves. From these consistent results, it can be concluded that the respiratory functions of a group of Japanese cadmium workers were clearly affected by cadmium exposure. The failure of previous Japanese observations (19) to reveal an effect of cadmium on the lungs may have been due to a relatively mild degree of exposure or an insufficient duration of follow-up.

The nature of cadmium-induced pulmonary effects has been a subject of considerable debate. Friberg (7) found that shortness of breath was among the main complaints of 43 workers exposed for more than 9 a to cadmium oxide dust in an alkaline storage-battery factory and that the residual volume : total lung capacity ratio was increased for about one-third of them. On the basis of this finding, he concluded that these workers had pulmonary emphysema. Succeeding reports from Germany (1) and Great Britain (2, 3, 10) also presented some pulmonary effects determined by clinical, radiographic, or physiological observation and considered them as emphysematous changes. However, Stanescu et al (17) could not find any evidence to support the concept of cadmium-induced emphysema in 18 workers exposed to cadmium dust and fumes above permissible limits for an average of 32 a in a cadmium-producing factory. The loss of elastic recoil of the lungs and single-breath lung diffusing capacity, which are recognized as the main result of alveolar destruction and the loss of the capillary bed in pulmonary emphysema (16), were not observed in their subjects. The authors stated that the diagnoses of cadmium-induced emphysema in earlier reports were not based on sound evidence compatible with the current concept of emphysema. Other reports (13, 14, 15, 18) also failed to detect positive evidence of emphysematous change.

Our findings in this study indicate that maximum expiratory flow rates for low volumes (MEF_{25}, MEF_{50}, MEF_{75}) were the most severely reduced, while FVC, $FEV_{1.0}$ and respiratory impedance were less clearly affected, and $FEV_{1.0}$ % was the least affected, by cadmium. This set of results suggests that cadmium-induced pulmonary effects are of the chronic obstructive type, mainly affecting small airways. Such predominance of small airway obstruction has not been described in the aforementioned reports in spite of the fact that fairly thorough examinations of respiratory function were performed. Lauwerys et al (13) found a significant reduction in FVC and $FEV_{1.0}$, but not significant changes in MEF_{50} and MEF_{25}, for 22 workers exposed to cadmium dust for more than 20 a. However, it can be seen from a table in the original paper that the mean values of MEF_{50} and MEF_{25} were about 10 % smaller for the cadmium workers than for the referents. These changes were of the same magnitude as in FVC and $FEV_{1.0}$, but the differences were not statistically significant simply because the coefficients of variation were larger for these indices than for FVC and $FEV_{1.0}$. Such a trend of larger coefficients of variation in MEF_{25} and

MEF_{50} compared to FVC and $FEV_{1.0}$ is a common finding in the analysis of forced expiratory flow volume curves. Stanescu et al (17) found that the percentage mean predicted values of MEF_{50} and MEF_{25} were 44.4 and 63.9 for cadmium workers, while those for referents were 62.3 and 76.6. Again, the coefficients of variation were large for these indices, especially in the lower ranges of the percentage of predicted values, but consistently lower values, a reduction in MEF_{25} of as large as 30 %, for the cadmium workers were neglected by the authors, and the reduction in both groups was estimated to have been secondary to smoking. The examination of these reported data suggests that our findings are not contradictory to previous observations. The considerably clear-cut results of the present study may be due to the high level of cadmium fume exposure, estimated to be an 8-h concentration of 1 mg/m³ for 5 a. A further differential diagnosis of cadmium-induced pulmonary effects in our subjects is not possible without additional studies. It is known that chronic bronchitis and emphysema frequently coexist in chronic obstructive lung diseases (16). In consideration of the fact that cadmium is an established irritant to the respiratory tract (7), it may be reasonable to assume that chronic cadmium exposure of sufficient severity will induce more or less pathological chronic changes throughout the respiratory tract, including the alveoli. Although none of the seven highly exposed workers could be classified as having chronic bronchitis by the questionnaire used (6), either emphysematous or bronchitic changes may by no means be excluded.

Lauwerys (13), after reviewing recent investigations, concluded that the critical organ following long-term exposure to cadmium is usually not the lung, but the kidney, on the basis of the fact that only mild pulmonary effects were found in workers who had received sufficiently prolonged exposure. The present study makes it clear that pulmonary effects can be almost as evident as renal effects in workers who have received chronic cadmium exposure but have not experienced any episode of respiratory distress suggestive of acute or subacute cadmium poisoning. The slight but significant reduction in FVC and $FEV_{1.0}$ found in the workers with low cadmium exposure (table 5) cannot be attributed to cadmium because their levels of exposure had been minimal, as indicated by the normal blood and urine cadmium concentrations. It might have been caused by other pollutants possibly released from the metallurgical processes in the alloy factory.

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