Lung function in workers using cadmium containing solders

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ABSTRACT The lung function of 57 male workers previously exposed to cadmium in connection with the use of cadmium containing solders was examined by spirometry (FVC, FEV₁, FEV%, and MMF) and single breath nitrogen washout (CV, CV%, and phase III). A reference group (n = 31) from a nearby industry was examined at the same time. Despite the fact that the exposure in previous years had been relatively high, in the order of 0.05–0.5 mg Cd/m³, and that 24 (42%) of the workers had cadmium induced renal damage in the form of β_2 -microglobulinuria there was no evidence of pulmonary damage. There were no significant differences in lung function data from the exposed and reference group and there was no dose-response relation within the exposed group. It thus appears that signs of kidney toxicity in the form of low molecular weight proteinuria precede those that may be identified in the lung with commonly used lung function tests.

In 1950 Friberg reported that long term occupational exposure to cadmium could induce renal damage and obstructive lung changes.¹ During the 1950s and 1960s additional reports of cadmium induced respiratory effects were published by investigators in the United Kingdom^{2–5} and West Germany.⁶ In the 1970s Lauwerys and coworkers in a study of 25 cadmium fume and dust exposed workers and 25 matched controls found significantly reduced forced vital capacity (FVC), forced expired volume in one second (FEV₁), and peak expiratory flow rate (PEFR).^{7,8} The exposed group had been exposed to cadmium for more than 20 years. In a later and more thorough examination of 18 of the workers the pulmonary effects from exposure to cadmium previously seen were not confirmed⁹ and the very existence of chronic respiratory effects from exposure to cadmium has been questioned.^{9,10} Furthermore, it has been discussed whether renal effects precede the pulmonary effects or not.^{8,11}

We have examined the lung function of 57 workers exposed to cadmium in connection with the use of cadmium containing solders and 31 non-cadmium exposed referents. The objective of the work was to examine dose response relations with regard to exposure to cadmium and early signs of obstructive lung changes and to determine whether or not renal

effects in the form of low molecular weight proteinuria precede the respiratory effects.

Material and methods

FACTORY, PRODUCTION, AND EXPOSURE LEVELS The company started to use cadmium containing solders in 1955 but no air measurements were carried out until 1976.¹² Stationary measurements showed high cadmium exposure, from 0.060–0.497 mg Cd/m³, average 0.20 mg Cd/m³. Personal samplers carried by 11 workers using cadmium containing solders showed even higher values; 0.095–1.958 mg Cd/m³. Measurements one year later showed 0.091–0.191 mg Cd/m³. In July 1978 the production hall was renovated and painted and since that date no cadmium containing solders or other materials containing significant amounts of cadmium have been used. More details about exposure are given in another report based on the same group of workers.¹³

EXAMINED GROUPS AND INDIVIDUAL EXPOSURE Rather more than 500 blue collar workers had been employed by the company since 1954. Sixty eight had been employed for at least five years before 1978 and it was considered likely that this subgroup would include most of the workers who might possibly show chronic effects. All, including those who were retired or working elsewhere, were invited to take part in a health examination. Two had died and 57 of the

Table 1 Number of subjects, smoking habits, age, height, and exposure time for exposed and reference groups

	No	Smokers	Non-smokers	Age (years)		Height		Exposure time	
				Mean	SD	Mean	SD	Mean	SD
Exposed	57	24	33	48	13	176	6	14	7
Referents	31	16	15	45	14	176	7		

remaining 64 men (89%) took part in this study. All four retired men took part and 31 of the 32 who were working elsewhere. Consequently most of the drop outs (6 men) were among people still employed in the company and for various reasons not taking part in the examination.

The exposed group comprised 57 men whose mean age at the time of examination was 48; the period of exposure ranged from five to 24 years with a mean of 14 years (table 1). Each individual's exposure was classified into four categories; high, medium, low, and no cadmium exposure. Welding or soldering using cadmium containing solders was classified as a high exposure. Activities carried out in the production hall, when cadmium was in use, were classified as given rise to a medium exposure. Tasks that were only partly carried out in the production hall were considered to result in a low exposure. Before 1955 and after 1978 there was no exposure at all to cadmium.

The number of years that each worker had been occupied in activities that gave rise to high, medium, low, and no exposure were recorded. Based on the measurements carried out in 1976¹² it was estimated that high, medium, and low exposure was about 0.5, 0.15, and 0.05 mg Cd/m³, respectively. A cumulative dose estimate was calculated for each workers as mg Cd/m³ times year (mg Cd/m³ · y).¹³

From a nearby company a reference group of 31 men was selected. They had similar work tasks (soldering, welding) but no known exposure to cadmium

and were matched with regard to age and height (table 1).

QUESTIONNAIRE AND RENAL FUNCTION

Each person was asked to answer a self administered questionnaire including questions about previous and present diseases, upper airways and lung symptoms, history of renal stones, use of drugs, and smoking habits.

The renal function of each cadmium exposed worker was examined by measuring urine and serum protein concentrations; the glomerular filtration rate (GFR) using CrEDTA clearance was carried out in 17 of the workers. Further details, and the results of the study of renal function, are given elsewhere.^{13 14}

LUNG FUNCTION TESTS

Respiratory effects were studied by spirometry and single breath nitrogen washout. Everyone, exposed and unexposed, was studied by the same nurse during a regular working day. A forced expired vital capacity manoeuvre was recorded with a low resistance bellows spirometer (OHIO). The subject was seated and was carefully instructed before the test was performed. Each individual performed three tests. The best result for each variable was chosen, even if this meant that results were selected from different recordings.¹⁵ The following variables were studied: forced expired vital capacity (FVC), forced expired volume in one second (FEV₁), FEV₁ divided by FVC times

Table 2 Frequency of symptoms and earlier diseases in upper and lower airways among the exposed and referents

	Exposed (%)	Referents (%)	χ^2 (1)
<i>Symptoms</i>			
Nasal obstruction	25	15.6	0.576
Nosebleed	12.3	21.9	0.791
Crusting	7.3	18.8	1.613
Non-productive cough	29.8	32.2	0
Non-productive cough > 3 m/y	10.5	3.3	0.574
Productive cough in mornings	22.8	19.3	0.011
Productive cough in morning > 3 m/y	17.5	3.3	2.422
Wheezing or chest tightness	17.5	12.5	0.105
Breathlessness	19.3	28.1	0.480
<i>Earlier diseases</i>			
Asthma	3.5	0	0.081
Pleuritis	0	6.3	1.355
Pneumonia	19.3	19.4	0.076
Bronchitis > 1 month	5.3	12.9	0.727
Other	5.2	6.3	0.082

Table 3 Spirometric and nitrogen washout data from the exposed group ($n = 57$) and the referent group ($n = 31$). Ratio (%) of measured and predicted value from published reports¹⁷⁻¹⁹

Lung function test	Exposed				Referents			
	Observed		Ratio obs/predicted (%)		Observed		Ratio obs/predicted (%)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
FVC (l)	4.82	0.98	92	13	5.02	0.80	95	11
FEV ₁ (l)	3.67	0.88	95	16	3.81	0.71	97	12
FEV% (%)	76.10	7.60	103	11	76.00	7.50	102	11
MMF (l/s)	3.55	1.40	97	35	3.53	1.44	94	33
CV (l)	0.83	0.22	95	28	0.83	0.22	98	25
CV% (%)	18.80	5.70	111	36	17.50	5.10	107	26
Phase III (% N ₂ /l)	1.77	1.31	146	95	1.41	0.94	118	72

100 (FEV%), and maximum mid-expiratory flow (MMF), calculated as the mean forced expiratory flow during the middle half of the FVC.

Two or three single breath nitrogen washouts were performed according to Anthonisen.¹⁶ Inspiratory and expiratory flow rates were kept at approximately 0.4 l/s, as directed by the examiner. The expired nitrogen concentration was measured at the mouth with an ionisation meter (OHIO 720) and was recorded against the expired volume on an X-Y-recorder (Bryans 26000). The slope of the alveolar plateau (phase III) and the closing volume (CV) were calculated as follows.

Phase III

Phase III is the slope of the alveolar plateau in per cent nitrogen per litre of expired gas as measured between 30% of expired vital capacity and onset of phase IV (see below) on the nitrogen volume recording.

Closing volume

Closing volume is the expired volume after the onset of phase IV, which was defined as the persisting

departure of the nitrogen level from the alveolar plateau. A translucent ruler was used as an aid in defining the point of departure. Recording for which the flow rate had not been kept approximately constant, or where inspired and expired volumes differed by more than 10%, were disregarded. Closing volume was expressed in per cent of the expired vital capacity (CV%).

Standard references values for spirometry were taken from Berglund *et al.*,¹⁷ whereas nitrogen washout data were compared with the normal values given by Buist and Ross.^{18,19} Since the standard reference values do not discriminate between smokers and non-smokers the predicted results for the exposed smokers and non-smokers were also calculated from the regression equations of the smoking and non-smoking referents. The dependent variables were age, height, and smoking.

STATISTICAL EVALUATION

Differences in symptoms between the groups were analysed by chi square test with Yates's correction. The differences in the lung function tests between the groups and deviations from predicted values were

Table 4 Lung function data (spirometric and nitrogen washout data), age, and length for exposed and referent workers, smokers, and non-smokers

Lung function test	Exposed				Referents			
	Smokers ($n = 24$)		Non-smokers ($n = 33$)		Smokers ($n = 16$)		Non-smokers ($n = 15$)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
FVC (l)	4.88	0.83	4.77	1.09	5.31	0.66	4.71	0.83
FEV ₁ (l)	3.63	0.84	3.70	0.92	3.93	0.57	3.69	0.83
FEV% (%)	74.04	7.89	77.80	7.21	74.06	6.82	78.13	7.95
MMF (l/s)	3.30	1.39	3.74	1.41	3.52	1.01	3.54	1.84
CV (l)	0.86	0.24	0.80	0.20	0.86	0.25	0.79	0.17
CV% (%)	19.33	6.49	18.50	5.19	17.38	5.38	17.54	4.86
Phase III (% N ₂ /l)	1.94	1.17	1.65	1.42	1.45	0.88	1.35	1.04
Age (years)	46	10	48	13	42	12	48	14
Length (cm)	176	6	176	6	178	5	175	9

Fig 1 Ratio (%) of measured and predicted spirometric and nitrogen washout data for referents ($n = 31$) and exposed workers ($n = 57$). Predicted values from published reports.¹⁷⁻¹⁹

tested using Student's paired two tailed t test and correlations were calculated with Pearson's product moment correlation. Five per cent significance levels were used.

Results

The calculated cumulative dose estimate ranged from $0.34-9.9 \text{ mg Cd/m}^3 \times \text{year}$ with a median of $1.7 \text{ mg/m}^3 \times \text{year}$. The prevalence of raised β_2 -microglobulinuria (levels exceeding $0.034 \text{ mg/mmol creatinine}$) was 42% and increased with the duration of cadmium exposure.¹³

Table 2 shows the frequency of symptoms in the exposed and referent groups. There were no significant differences between the two groups for any of the questions.

Spirometric and single breath nitrogen washout variables for the exposed and the referents were all within predicted limits, when compared with standard references, and there were no significant differences between the exposed group and the reference group neither in total (tables 3 and 4, fig 1) nor when the exposed group was dichotomised (figs 2 and 3) into "high exposed" ($\geq 1.70 \text{ mg Cd/m}^3 \times \text{year}$) and "low exposed" ($< 1.70 \text{ mg Cd/m}^3 \times \text{year}$) or with regard to β_2 -microglobulinuria ($U\text{-}\beta_2 > 0.034 \text{ mg/mmol creatinine}$). No significant correlations were found between lung function and accumulated exposure time or the cumulative dose estimate.

There were 24 (42%) smokers among the exposed and 16 (52%) in the non-exposed group (table 1), this difference was not significant. To evaluate the possible influence of smoking, data from smokers and non-smokers were treated separately and the statistical

Fig 2 Non-smokers. Ratio (%) of measured spirometric and nitrogen washout data in referents and exposed workers. Predicted values calculated from referents (age and height adjusted). Referents ($n = 15$), low exposed ($< 1.7 \text{ mg Cd/m}^3 \times \text{year}$) ($n = 12$) and high exposed ($\geq 1.7 \text{ mg Cd/m}^3 \times \text{year}$) ($n = 21$).

analysis showed no significant impairment in lung function between smoking exposed and non-smoking exposed and smoking unexposed and non-smoking unexposed, or when exposed smokers were compared with unexposed smokers and exposed non-smokers, with unexposed non-smokers, respectively (table 4, figs 2 and 3). There was a slight tendency towards an increase in phase III (table 4, figs 2 and 3) by the exposed workers, although this did not attain statistical significance.

Fig 3 Smokers. Ratio (%) of measured spirometric and nitrogen washout data in exposed workers. Predicted values calculated from referents (age and height adjusted). Referents ($n = 16$), low exposed ($< 1.7 \text{ mg Cd/m}^3 \times \text{year}$) ($n = 14$), and high exposed ($\geq 1.7 \text{ mg Cd/m}^3 \times \text{year}$) ($n = 10$).

Discussion

The results of the renal function tests indicate that the workers had been heavily exposed to cadmium, and to such a degree that tubular damage was evident in more than 40% of the exposed. Despite this there were no significant differences between exposed and non-exposed when symptoms (table 2) and lung function tests were compared (tables 3 and 4). This indicates that the kidneys rather than the lungs are the critical organ for long term occupational exposure to cadmium.

Although the study is of a non-experimental design, the exposed group and the reference group were comparable with regard to sex, age, and height, factors known to influence the lung function tests. The results could be explained by a selection bias if people employed more than five years had changed their occupation because of lung disease and only "healthy workers" were left. In this study, however, retired workers and those who had moved elsewhere were examined and the drop outs were mainly among people still working at the plant who had no known lung disorders when checked with the occupational health care unit. Neither were the causes of death for the two who had died related to cadmium exposure.

It has been suggested that cadmium induced pulmonary effects are of the chronic obstructive type, mainly affecting the small airways.¹¹ Therefore we used lung function tests (closing volume and phase III) which are considered to be particularly sensitive in identifying small airway disease.²⁰ As indicated by the standard deviations in tables 3 and 4 and in the figures, however, the variability of these lung function tests may be relatively large. This experience is shared by other investigators^{21, 22} but cannot be supposed to invalidate the results when discriminating between groups.

The prevalence of various self reported symptoms and earlier diseases varied somewhat between the exposed men and the referent group (table 2). The men exposed to cadmium more often reported symptoms of non-productive and productive cough, indicative of airways irritation (table 2). On the other hand, the referents had a higher frequency of bronchitis and complaints of breathlessness. None of these differences was statistically significant ($p > 0.05$), however. The overall pattern of complaints (table 2) suggested that there were no major differences between the two groups. It should be pointed out, however, that the referent group comprised industrial workers occupied on similar work (soldering) as the exposed men, although they had not previously been exposed to cadmium. The frequency of symptoms and previous diseases may well have differed if, for example, white collar workers had been examined.

The purpose of this study was to examine the possible effect from cadmium and not that of soldering or welding.

Additional analyses were undertaken to assess the dose-response relation within the exposed group by using the cumulative years of cadmium exposure or the estimated cumulative dose. Such analyses showed no evidence of chronic respiratory effects associated with long term or high cadmium exposure.

The proportion of smokers differed slightly between the two groups, more smokers being present among the unexposed. Since smoking commonly results in decreased lung function, a higher proportion of smokers in the reference group would tend to impair the spirometric and single breath nitrogen washout variables and thereby possibly conceal any difference between the groups. Therefore the analyses were also made comparing exposed and non-exposed smokers and exposed and non-exposed non-smokers (table 4, figs 2 and 3), but no significant differences between these groups were seen. We found, however, that smokers had somewhat deteriorated in CV and phase III when compared with non-smokers, regardless of exposure status (table 4). This is in accordance with the previous experience that smoking affects the smaller airways and that CV and phase III become abnormal before FEV₁ and that the response to occupational dust exposure may differ from that to tobacco smoking.²³

The lowest concentration of cadmium in work-room air that has been associated with obstructive pulmonary function tests has been about 70 µg Cd/m³ as total dust and 20 µg Cd/m³ as respirable dust and more than 20 years of exposure.⁷ This would correspond to a cumulative dose estimate of about 0.5 mg Cd/m³ × year (25 years × 20 µg Cd/m³). Respiratory effects at that low level of cadmium exposure could not be confirmed in the present study where the median cumulative exposure was 1.7 mg Cd/m³ × year. In view of the findings in previous cross sectional studies of cadmium exposed workers^{1-5, 11} and the increased mortality from obstructive lung diseases that has been observed in several epidemiological studies of cadmium workers²⁴⁻²⁶ and the results from animal studies^{1, 27, 28} it seems clear that heavy cadmium exposure may induce severe obstructive lung diseases. Furthermore, the immediate hazards from inhalation of high concentrations of cadmium fumes (> 5 mg Cd/m³) should be remembered. This may cause severe and fatal pulmonary oedema.^{10, 29}

According to our data, renal effects in the form of low molecular weight proteinuria precede respiratory symptoms and signs. This is in accordance with the result of a cross sectional study of cadmium workers in Belgium,⁸ whereas Sakurai *et al* reported that pulmonary effects were as prevalent as renal ones.¹¹ The

average exposure of the seven cadmium exposed Japanese workers examined by Sukurai *et al* was, however, considerably higher ($5 \text{ mg Cd/m}^3 \times \text{year}$) compared with our group ($1.7 \text{ mg Cd/m}^3 \times \text{year}$).

The differences between this study and the others may therefore be primarily due to the differences in the concentrations to which the subjects were exposed. Taking into account also the effects on the kidneys,^{13 14} our results indicate that a time weighted average for respirable cadmium dust in air should be kept below 0.025 mg Cd/m^3 to prevent the pulmonary or renal effects of long term occupational exposure to cadmium.

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