Pulmonary disease from exposure to an artificial aluminium silicate: further observations

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ABSTRACT A cross sectional analysis of the relation between exposure to an artificial aluminium silicate (alunite residue) and pulmonary function changes has been made in 32 subjects, 17 of whom had been previously reported and in whom there was suggestive evidence of a dose response relation between gas transfer and total silicate exposure. Longitudinal data were also available for nine subjects. No dose effect relation was observed in either analysis and only one of the three subjects previously observed to have an abnormal chest radiograph (the index subject) had deteriorated appreciably. Respirable particles of alunite residue were injected intratracheally into Syrian hamsters. No evidence of pulmonary toxicity was seen as judged by bronchoalveolar lavage measurements of the concentrations lactic dehydrogenase, albumin, and the lambda fraction of gold, and the numbers of macrophages, polymorphonuclear cells, and red blood cells (α -quartz and ferrous oxide were used as positive and negative controls). These results do not support a significant toxic effect of this aluminium silicate on the lungs.

There is evidence that at least some non-fibrous silicates (talc and kaolin, for example) may cause pulmonary fibrosis.^{1,2} The evidence for lung disease resulting from exposure to other silicates uncontaminated by free silica, however, is less consistent. Fuller's earth appears to cause nodular lesions in human lungs which do not result in abnormal function,³ and sillimanite may cause diffuse and nodular pulmonary fibrosis in rabbits.⁴ More recently, silicate pneumoconiosis of farm workers in California has been described in which the histology of the lungs showed birefringent silicate particles in association with interstitial inflammation and fibrosis.⁵ The disease was progressive and unresponsive to treatment with corticosteroids. Additionally, an artificial aluminium silicate used for cat litter has been implicated in the production of diffuse fibrosis in a group of workers employed in reclaiming, drying, and packaging it for sale as cat litter in Western Australia.⁶ The index case, who showed diffuse interstitial fibrosis with loosely formed granulomas on biopsy, and two others in this study had abnormal chest radiographs and gas transfer. Within the group there was also a tendency towards a relation between total exposure to the aluminium silicate and gas transfer of the lungs. This study has

now been extended to include additional exposed individuals. Nine of the original subjects have also been reviewed for evidence of radiographic deterioration or further decline in lung function which may have been caused by their exposure. The artificial aluminium silicate has also been tested for its pulmonary toxicity in Syrian golden hamsters.

Subjects

The previous report described the findings in four women and 13 men from a total of 25 subjects known to have worked with the cat litter up to 1978.⁶ In 1981 and 1984 attempts were made to contact and invite all these subjects to attend for further studies. Additionally, all subjects who were known to have worked with the material since the previous study were also invited. Six men and three women agreed to return to the laboratory for further lung function tests in 1981 or 1984 (between 23 and 71 months after first being studied (table 1)). These included the index case and the other two cases with abnormal chest radiographs and gas transfer. An additional 12 currently exposed men who had been exposed to cat litter only since the initial study in 1978 were included in 1981 or 1984, and three previously exposed men who were not currently exposed also attended in 1984.

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Table 1 Subjects included in studies

	Present in initial study only		Present in initial and at least one follow up study		Present in follow up study only	
	Men	Women	Men	Women	Men	Women
Currently exposed	7	0	5*	0	12	0
Not currently exposed	0	1	1	3†	3	0

*Includes one subject with abnormal radiograph.

†Includes two subjects with abnormal radiographs.

Methods

STUDY DESIGN

This study was designed to re-examine the relation between exposure and evidence of disease in all 28 men and four women seen at least once between 1978 and 1984 in a cross sectional manner as previously reported (table 1).⁶ Longitudinal information was available for nine subjects who were seen on more than one occasion to examine the relation between degree of exposure and rate of deterioration in lung function and chest radiographic appearance. Additionally, experimental results of the response of hamster lungs to the intratracheal injection of the silicate material are reported.

QUESTIONNAIRE

A symptom questionnaire and smoking and occupational histories were obtained at each visit as previously reported.⁶ An index of total exposure (exposure/months) for each subject was calculated as the product of duration of exposure in months and estimated intensity of exposure (1 = light, 2 = moderate, 3 = heavy). Intensity of exposure was ranked from a knowledge of the job and location of each person in the plant. No measurements of dust exposure levels were available.

PULMONARY FUNCTION

Forced expiratory volume in one second (FEV₁) was obtained from a digital spirometer (Hewlett-Packard, Burlington, Massachusetts). Transfer factor for carbon monoxide (T_L) was measured by the single breath carbon monoxide method.⁷ Effective alveolar volume (V_A) was estimated from the dilution of helium during the measurement of T_L. Total lung capacity (TLC) and vital capacity (VC) were measured in a body plethysmograph (Emerson, Cambridge, Massachusetts).⁸ Predicted values for pulmonary function studies were obtained from Cotes.⁹

CHEST RADIOGRAPHS

Standard posteroanterior chest radiographs were taken with the tube-object distance of 6 ft (1.82 m). The usual procedure required 150 kv for 6–10 m/sec

using a falling load tube current with ionisation chamber automatic exposure (Siemen's Iontomat) and a chest Buckey.

ANIMAL STUDIES

A respirable fraction of the artificial aluminium silicate was prepared by gravity sedimentation in water, decanting, and filtering of the supernatant through an 8 µm Nucleopore filter. The filtrate was lyophilised for the bioassay. Syrian golden hamsters were exposed to saline suspensions of the particles in high (3.75 mg/100 g body weight) and moderate (0.75 mg/100 g body weight) doses by intratracheal instillation and sacrificed at one day. Their lungs were lavaged and the lavage fluid characterised using cellular and biochemical indicators of pulmonary damage. These indicators were: (a) changes in the *in situ* phagocytic ability of pulmonary macrophages; (b) damage to the air blood barrier as shown by increases in albumin and red blood cell numbers; (c) inflammation as shown by increases in polymorphonuclear neutrophils and macrophage numbers, and (d) damage to cells, measured by the concentrations in lung lavage supernatant of lactic dehydrogenase (LDH), a cytoplasmic enzyme and peroxidase, a lysosomal enzyme, in the extracellular supernatant of the lung lavage fluid. This system has been calibrated by using the response to highly toxic α -quartz and to non-toxic Fe₂O₃.¹⁰

Results

CROSS SECTIONAL EFFECTS OF EXPOSURE ON CURRENT AND PREVIOUS WORKERS

The mean values of the measured parameters of pulmonary function of all subjects at the time of their most recent study were normal (table 2), although six subjects showed T_L < 80% of the predicted value and four subjects had T_L/V_A < 80% of the predicted value. Only one subject (the index case) showed FEV₁ < 80% of the predicted value but this was accompanied by a similar reduction in VC and a reduction in TLC. Despite there being 18 current smokers and one ex-smoker in the group, there was no evidence of airflow obstruction, the mean levels of FEV₁ and FEV₁/VC

Table 2 Subject characteristics and lung function: most recent result

No	Age	Smoking status	Total exposure§	TLC	VC	FEV ₁	T _L	T _L /V _A
<i>Men</i>								
1*	29	Ex	8	112	109	113	125	117
2†	19	N	24	109	120	114	126	117
3†	19	N	90	93	94	109	106	117
4†	16	C	9	123	116	139	130	113
5†	41	C	24	118	122	123	109	100
6†	16	N	6	97	93	103	142	160
7†	36	C	42	89	92	100	113	112
8†	34	C	96	88	77	80	80	86
9†	16	N	18	97	96	92	105	110
10†	18	N	54	97	86	109	100	102
11†	18	C	98	95	94	93	90	98
12†	17	N	72	103	98	107	104	105
13*	18	C	3	96	92	91	86	89
14**	34	N	36	111	112	117	97	96
15**	20	N	18	105	111	98	113	106
16**	22	C	156	104	100	109	96	92
17*	16	C	2	86	89	80	79	89
18*	19	C	48	104	93	111	70	67
19**	37	C	264	115	116	130	125	113
20*	15	N	6	86	91	92	87	100
21*	18	C	24	93	85	100	75	74
22*	23	N	24	93	92	96	106	118
23**	20	C	10	100	106	109	91	89
24**	47	C	216	117	103	117	90	83
25†	29	C	6	99	98	102	93	94
26†	34	C	54	105	110	112	97	102
27†	20	C	11	94	103	113	97	106
28†	23	C	9	103	108	100	100	106
<i>Women</i>								
29*	36	N	6	96	100	96	86	89
30**	55	N	144	104	83	123	91	90
31**	57	C	252	133	109	111	60	62
32**††	49	N	54	74	54	52	30	72
Mean	27.2		58.9	101.2	98.5	104.3	96.8	99.2
SD	12.2		72.7	12.0	13.8	16.2	21.8	18.6

*Present 1978/9 survey.

†Present 1981 survey.

‡Present 1984 survey.

§ Sum of (grade of severity × months exposed) (grade-months).

C = Current smoker, Ex = ex-smoker, N = never smoked.

TLC = Total lung capacity (% predicted).

VC = Vital capacity (% predicted).

FEV₁ = Forced expiratory volume in one second (% predicted).T_L = Transfer factor (% predicted).V_A = Alveolar volume (% predicted).

being normal. The average total exposure of the group was 60.7 ± 72.1 grade-months. There was no relation between T_L/V_A and total exposure as previously suggested⁶ or log total exposure. The regression coefficient for T_L/V_A (% predicted) and total exposure (grade-months) was -0.08 ($r = 0.30$, $p = 0.10$) and for T_L/V_A (% predicted) and log (total exposure) was -3.7 ($r = 0.27$, $p = 0.14$). Multiple regression analysis using T_L/V_A (% predicted) as the dependent variable showed a significant effect of current smoking status only ($p = 0.007$). Chest radiographs of all subjects were reviewed and appeared normal apart from the three subjects (subjects 24, 31, and 32) previously considered abnormal⁶ and in whom there had been no significant change.

LONGITUDINAL EFFECTS OF EXPOSURE

Nine subjects (nos 14, 15, 16, 19, 23, 24, 30, 31, and 32) had been studied on more than one occasion with an interval of between 23 and 71 months. The mean annual rate of change of VC was $+0.8 \pm 0.36$ l, of FEV₁ $+0.01 \pm 0.7$ l, and of T_L $+0.27 \pm 0.7$ ml/min/KPa. These subjects included the index subject and the other more highly exposed subjects in the study (average total exposure 137 grade-months). There was no relation between exposure and rate of change of pulmonary function. Gas transfer in the index subject had fallen from 4.1 ml/min/KPa to 2.6 ml/min/KPa over 71 months but three of the subjects (15, 16, and 23) recorded an increase in transfer factor and as a result there was an increase in the mean gas transfer of

Table 3 Response of hamster lungs to intratracheal instillation of artificial aluminium silicate, α -quartz and ferrous oxide*

	Saline	Dose of contaminant (mg/100 g)	α -quartz	Fe ₂ O ₃	Aluminium silicate
Lactic dehydrogenase (u/ml)	19.3 $\pm$ 1.0 19.3 $\pm$ 1.0	0.75 3.75	86.0 $\pm$ 10.6 135.7 $\pm$ 7.3	51.4 $\pm$ 4.7 69.1 $\pm$ 8.1	25.6 $\pm$ 3.9 17.9 $\pm$ 1.5
Albumin (u/ml)	— 64 $\pm$ 6	0.75 3.75	— 270.2 $\pm$ 416	— 432 $\pm$ 74	— 44.7 $\pm$ 8.7
Macrophages ($\times 10^6$)	6.3 $\pm$ 0.5 6.3 $\pm$ 0.5	0.75 3.75	4.7 $\pm$ 0.6 3.1 $\pm$ 0.3	6.3 $\pm$ 0.8 6.3 $\pm$ 0.3	7.5 $\pm$ 0.8 6.8 $\pm$ 0.7
Polymorphs ($\times 10^6$)	1.3 $\pm$ 0.8 1.3 $\pm$ 0.8	0.75 3.75	38.6 $\pm$ 10.4 21.1 $\pm$ 2.5	12.0 $\pm$ 1.4 10.3 $\pm$ 0.7	1.7 $\pm$ 0.4 3.1 $\pm$ 1.1
Red blood cells ($\times 10^6$)	— 9.5 $\pm$ 1.5	0.75 3.75	— 334.5 $\pm$ 92.5	— 15.0 $\pm$ 3.0	— 6.5 $\pm$ 0.7
λ Fraction gold	0.630 $\pm$ 0.034	0.75 3.75	— 0.249 $\pm$ 0.044	— 0.565 $\pm$ 0.052	— 0.828 $\pm$ 0.040

*Mean values $\pm$ SEM.

the group. Change in lung function was not related to subjects continuing to be exposed to alumite residue. The number of subjects, however, was small.

ANIMAL STUDIES

Exposure of hamsters to a moderately high dose (3.75 mg/100 g body weight) of the alumite residue did not alter the biological parameters tested in comparison with the animals exposed only to saline (table 3), whereas α -quartz and iron oxide produced pronounced effects on all parameters tested that were dose related for LDH.

Discussion

Initial concern over the possibility of pulmonary toxicity of this artificial aluminium silicate arose when the index case complained of respiratory and systemic symptoms in relation to exposure and was found to have abnormal lung function with a fall in gas transfer on inhalation challenge, and diffuse fibrosis with granulomas on lung biopsy.⁶ The findings in the other exposed subjects were consistent with an effect of the material on the lungs, and other reports indicated similar findings in subjects exposed to other silicates of aluminium.³⁻⁵ The present study extends the numbers of exposed subjects in the cross sectional analysis and provides limited longitudinal data on lung function. Additionally, the animal studies that have been performed do not increase the likelihood of a cause effect relation between this aluminium silicate and pulmonary fibrosis. Further follow up of the more heavily exposed subjects may provide additional useful information, especially if histology were to become avail-

able at some stage. This study has shown a statistically significant effect of current smoking status on T_L/V_A , consistent with many others.⁹

Some alternative explanation for the radiographic and lung function changes in subjects 18, 21, 24, and 31 is required. Although the pattern of functional changes in these subjects was not suggestive of emphysema in that airflow obstruction and overinflation were not present, all these subjects were current cigarette smokers. Gas transfer is known to be a sensitive test for destruction of alveolar walls and routine measurements may also be reduced by the presence of circulating carboxyhaemoglobin.⁹ Smoking may also give rise to diffuse shadowing on the chest radiograph.¹¹

Exposure categories in this and the previous report⁶ have been based on histories provided by the employees and may not accurately reflect relative severity. Dust concentrations were not measured in this plant because the dust was considered to be inert. Therefore calculations based on exposure categories may be incorrect, although there seems little doubt that subjects working on the bagging machine in the early days of the industry were most heavily exposed. Only one of these subjects (the index case) appears to have developed progressive lung disease. An alternative explanation for disease in the other subjects (smoking, for example) may exist.

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