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Association of man-made mineral fibre exposure and sarcoidlike granulomas

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It is assumed that sarcoidosis is caused by inhalation of air borne agents in susceptible persons triggering the inflammatory reaction. The association of metallic dust exposure, such as beryllium and aluminium, and sarcoidlike pulmonary disorders is well known. The ability of man-made mineral fibres (MMMF) to cause granulomatous lung disease has not been appreciated until now. Recently, we observed the association of sarcoidlike granulomatous reaction and occupational history of glass fibre exposure. We hypothesized that there might be a relationship between MMMF exposure and the development of sarcoidlike granulomas. Therefore, the records of 50 sarcoidosis patients—who visited our outpatient clinic between 1996 and 1999—were reviewed. This revealed that 14 cases recalled a history of exposure to either glass fibres or rock wool, both MMMF fibres. The available obtained tissue specimens ($n = 12$) were reviewed. In six cases electron microscopy qualitative analysis of small fragments of the tissue revealed among others silica, aluminium and sometimes titanium. A distinct relation between fibre deposits fibre deposits and granulomas was found. These findings indicate that in susceptible people MMMF exposure might be related to a chronic granulomatous disease similar to chronic beryllium disease.

Key words: berylliosis; glass fibre; man-made mineral fibres; rock wool; sarcoidosis; sarcoidlike granulomatosis.

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Introduction

Although the cause(s) of sarcoidosis remain unknown, there are lines of evidence supporting the idea that sarcoidosis results from exposure of genetically susceptible hosts to specific environmental agents triggering the inflammatory reaction (1). Several infectious organisms such as viruses, *Proprionibacterium acnes* and mycobacteria have been implicated as potential causes of sarcoidosis. Also, non-infectious inorganic and organic environmental agents can elicit a granulomatous response with many features that are similar to sarcoidosis (1).

The association of metallic dust exposure, such as beryllium and sarcoidlike pulmonary disorders is well known (1,2). Similar manifestations are occasionally reported in relation to other metal dust exposures, such as aluminium, zirconium, titanium, earth metals (or lanthanides, such as cerium) and talc which contains—among other compounds—variable amounts of aluminium and silica (1,3–7). As many oxidative agents, infectious and (in)organic, may trigger the granulomatous response in susceptible individuals (1–7), it is highly likely that there is no single cause of sarcoidosis. Therefore, the search for any possible relevant exposure of a patient with suspected sarcoidosis seems mandatory.

Recently, we observed the presence of sarcoidlike granulomas within a patient with an occupational history of glass fibre exposure (8). This association prompted us to evaluate whether exposure to certain MMMF, such as rock wool or glass fibres, may elicit a granulomatous response similar to sarcoidosis.

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Materials and methods

STUDY POPULATION

The records of 50 sarcoidosis patients—who visited our outpatient clinic between 1996 and 1999—were reviewed. All cases were asked for their medical history, with particular reference to any occupational and/or environmental exposure. This screening revealed that 14 cases had a history of exposure to either rock wool or glass fibres

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(group I). To determine the possible association of MMMF exposure and the development of sarcoidlike granulomas, the clinical records and tissue specimens of these sarcoidosis patients were reviewed carefully. Of these 14 patients 12 biopsy specimen were available.

PULMONARY FUNCTION TESTS

Pulmonary function measurements included the forced expiration volume in 1 sec (FEV_1) (Compactbody, Jaeger, Würzburg, Germany). The best measure of three efforts was selected. All volumes are expressed as percentages of the reference values (9). The diffusing capacity for carbon monoxide (D_LCO) was measured using the single-breath method (Masterlab, Jaeger, Würzburg, Germany). Values were expressed as a percentage of those predicted (9).

EXERCISE CAPACITY

Patients performed a symptom limited incremental exercise test on an electronically braked cycle ergometer (Cornival 400, Lode, Groningen, The Netherlands). After a period of rest and 2 min of unloaded pedalling, a progressively increasing work rate test was started in order to determine peak work rate (W peak) and oxygen uptake ($\dot{V}O_2$ peak) of the subject. The work rate increase was set at 10 W min^{-1} for each patient and 15–30 W min^{-1} for the healthy volunteers, depending upon their training status. Pedal frequency was selected by the subjects between 60 and 70 rpm and held constant throughout the test. Breath-by-breath gas exchange was measured throughout the test by a ventilated hood system (Oxyconbeta, Jaeger, Bunnik, The Netherlands). An infrared electrode was placed on a finger to measure oxygen saturation (Fasttrac, Sensor Medics Co., Anaheim, California, U.S.A.). Heart rate was measured throughout the test using a sport tested (PE3000, Polar Electro cy, Kempele, Finland). In rest and during maximal exercise arterial blood samples were taken and arterial blood gas analyses were performed.

CHEST RADIOGRAPHS

Chest radiographs were made in the posterior–anterior and lateral projections, and were classified by a single experienced reader, blinded to the patients' clinical history, in a standard manner according to the radiographic stage (0 to IV).

HIGH-RESOLUTION COMPUTED TOMOGRAPHY

Thin section scans with 1 mm collimation were obtained at 10-mm intervals through the chest. The scanning parameters included 137 kVp, 255 mA, and 1-sec scanning time. Both mediastinal (width, 400 HU; level, 40 HU) and lung (width, 1600 HU; level, −800 HU) window images were obtained. Scans were reconstructed with a high-frequency reconstruction algorithm. A single experienced reader, blinded to the patient's clinical history classified the scans. The typical patterns of parenchymal involvement were qualitatively registered as thickening or irregularity of the bronchovascular bundle (BVB), intraparenchymal nodules (ND), septal and non-septal lines (LS) and parenchymal consolidation (including ground glass opacifications) (PC) as well as the volume affected which was quantified by a visual score: 0 no lesions found; 1 = up to 33%; 2 = up to 66%; 3 = more than 66% of the volume affected. Similarly, the quantification of the focal pleural thickening (PL) respectively the enlargement of the lymph nodes (LN) was done: 0 = no pathological findings, 1 = minor, 2 = moderate, and 3 = pronounced changes (10). The total score was obtained by counting the individual scores (BVB, ND, LS, PC, LN and PL) together.

X-RAY ANALYSIS

The presence of MMMF in the biopsy specimen was evaluated by qualitative X-ray microanalysis in small fragments of tissue. X-ray energy dispersive microanalysis is based on the interaction of accelerated electrons with inner orbital electrons of an atom. Some of these inner electrons are ejected and the hole is filled by an electron from a shell of higher energy, resulting in X-ray radiation (peaks) characteristic for shells transversed. X-ray analysis provides a qualitative analysis of the chemical composition of the scanned area (either the present foreign body or the control area without any foreign body) generating multiple peaks (11). Lung tissue or lymph node biopsy specimens, embedded in paraffin, were rehydrated and fixed in glutaraldehyde, in some cases post-fixed in osmiumtetraoxide (OsO_4), dehydrated in graded series of ethanol and embedded in Epon 812 (Agar Scientific Ltd, Stansted, Essex, U.K.). Ultra thin sections (60 nm) were observed at 120 kV in a Philips CM 12 electron microscope (Philips Eindhoven, The Netherlands) and analysed with an EDAX pv9900 system (Philips Eindhoven, The Netherlands). The analysed area, a small spot (2·5 μm) exactly covering the foreign body, was scanned (rectangular pattern; $n = 7$) and a similar area adjacent to this foreign body used for background determination. The volume analysed of the area with or without a foreign body was similar, e.g. $\pm 0{\cdot}4\ \mu m^3$. The target area was an identified foreign body within a granuloma of the lung tissue obtained from an exposed or an area of lung tissue without the presence of any foreign body.

STATISTICAL ANALYSIS

The data of the exposed sarcoidosis patients (group I) and non-exposed patients (group II) were compared using one way analyses of variance (ANOVA) for ordinal values and χ^2-tests for nominal values. In all tests a probability value of less than 0·05 was considered to be statistically significant. All analyses were performed using the Statistical Package for Social Science (SSPS) for Windows.

Results

Job histories and exposure estimates differed. Upon further questioning six patients recalled that they worked — or had worked in the past — in the same rock wool factory at the same plant prior to the presentation of sarcoidosis, whereas two patients processed rock wool for many years. Additionally, six patients had a history of occupational or environmental glass wool exposure. None of these cases used dust masks or any other protection to reduce inhaling amounts of dust consisting of MMMF. So, 14 cases appeared to have a history of exposure to MMMF (group I). The remaining 36 (group II) cases did not remember any exposure to MMMF. The personal, clinical and laboratory characteristics are summarized in Table 1. The mean serum ACE levels, CRP levels, calcium as well as uric acid levels were more or less increased compared to the reference values (Table 1). Furthermore, a non-specific elevation of serum immunoglobulins was noted in seven cases in group I. Cellular bronchoalveolar lavage fluid (BALF) analysis revealed a profile similar to sarcoidosis with an increased total cell count, predominantly lymphocytes (12). The CD4/CD8 ratio appeared to be $3{\cdot}4 \pm 3{\cdot}8$ in group I and $4{\cdot}7 \pm 3{\cdot}6$ in group II, respectively. No statistical differences were found regarding the cellular and non-cellular BALF analysis results between both groups.

In group I, pulmonary function test results demonstrated mild decreased mean values (60–80%) according to the American Medical Association classes. Three cases appeared to have a moderate decrease (40–60%). Desaturation during exercise was found in eight cases (57·1%) of group I compared to 10(27·7%) of group II.

All patients suffered from fatigue, dry cough, dyspnoea on exertion, chest pain and, occasionally, arthralgias, weight loss, night sweats and fever. Based on the presumptive diagnosis and more or less severity of the disease at presentation—indicated by the pulmonary function test results, presence of desaturation during exercise, and imagining features (Table 1)—all patients group I and 11 (30·5%) of group II were treated with prednison orally. However, substantial disease relapses occurred after tapering-off the corticosteroids. Therefore, this treatment had to be continued in most cases (13 cases from group I (92·8%) and seven cases from group II (19·4). In four cases of group I and one case of group II the initial improvement in symptomatic and pulmonary function tests was not sustained despite corticosteroid treatment. The radiological findings as well as the pulmonary function parameters deteriorated. Therefore, in four of these cases (group I; $n=3$ and group II; $n=1$) cyclophosphamide (100 mg daily) was started, whereas in one case of group II methotrexate (15 mg orally once a week) was given. Follow-up of respiratory symptoms and related clinical features revealed that the non-treated patients of group II ($n=25$) recovered spontaneously ($n=18$) or did not deteriorate ($n=7$), in contrast to none of group I.

The available obtained tissue specimens of group I ($n=12$), either lung biopsy specimen ($n=11$) or mediastinal lympth nodes ($n=1$), were reviewed. In all lung biopsy slides the main component was a submucosal, interstitial and occassionally subpleural located non-confluent non-necrotizing granulomatous inflammation. In some granulomas multinucleated giant cells of Langerhans or foreign body type were present.

TABLE 1. Summary of personal and clinical characteristics of the 14 studied sarcoidosis cases exposed to man-made mineral fibres (group I) and the non-exposed sarcoidosis cases (group II; $n=26$)

	Group I	Group II	*P*-value
Age (years)	42·5(10·3)	41·1(12·8)	n.s.
Gender (male/female)	12/2	16/20	<0·01
Smoking (yes/never/past)	0/11/3	5/21/7	n.s.
Time elapsed since diagnosis sarcoidosis (years)	4(3·5)	2(2·5)	n.s.
Exposure to rock wool/glass fibres	8/6	not known	
Exposure time (years)	2·8(4·5)	—	
Radiographic stage 0/I/II/III/IV	0/0/2/10/2	5/7/16/6/1	<0·01
HRCT total score	7·2(2·9)	3·6(2·8)	<0·02
SACE Ul^{-1} (9–25)*	23·5(12·1)	24·4(8·1)	n.s.
C-reactive protein mgl^{-1} (2–9)*	19·1(17·5)	12·4(14·8)	n.s.
Calcium $mmol\,l^{-1}$ (2·10–2·60)*	2·76(0·08)	2·41(0·09)	0·02
Uric acid $mmol\,l^{-1}$ (0·20–0·42)*	0·53(0·09)	0·33(0·09)	<0·01
FEV_1 (% predicted)	74·2(16·2)	90·0(16·7)	<0·01
FVC (% predicted)	79·3(16·6)	98·3(21·2)	<0·02
*D*LCO (% predicted)	71·4(14·2)	85·6(19·9)	0·05
Desaturation during exercise (yes/no)	8/6	11/25	0·01

Data are expressed as mean with standard deviation in parentheses or numbers if appropriate; n.s: not significant; SACE: serum angiotensin converting enzyme; *D*LCO: diffusing capacity for carbon monoxide; FEV_1: forced expiration volume in 1 sec; FVC: forced vital capacity; *Reference ranges.

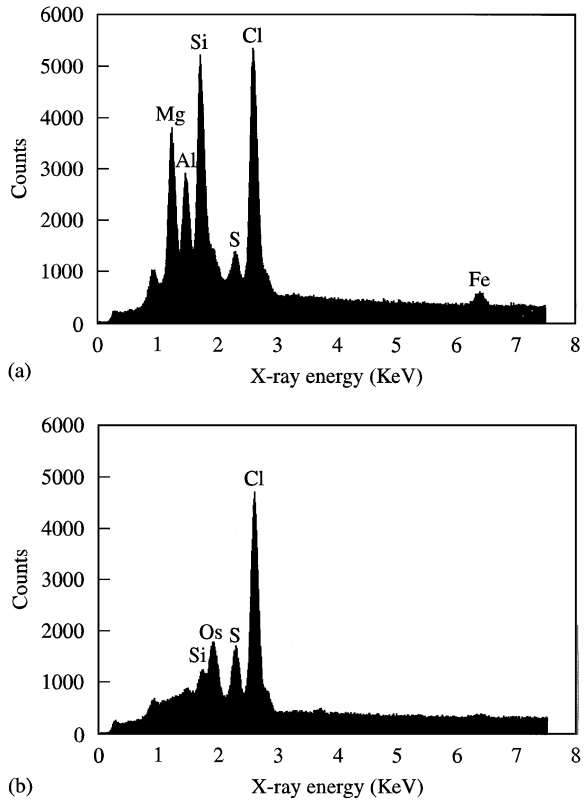

FIG. 1. (a) Energy-dispersive X-ray spectrum from a fibre determined in a lung biopsy specimen of a patient exposed to glass fibres showing peaks for Mg (1·253 keV), Al (1·486 keV) and Si (1,740 keV). The peaks for S and Cl originate from the supporting material. (b). Energy-dispersive X-ray spectrum from a similar area in the lung biopsy specimen adjacent to this fibre [see (a)] used for background determination.

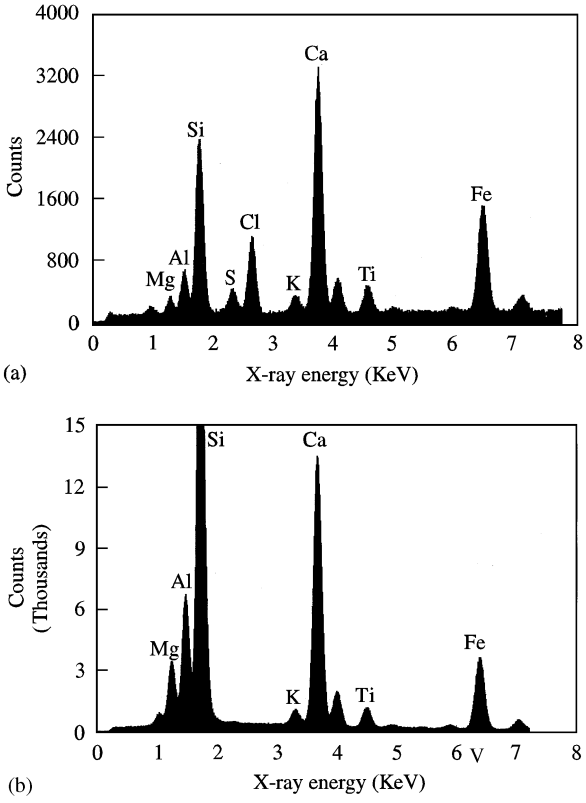

FIG. 2. (a) Energy-dispersive X-ray spectrum from a fibre determined in a granuloma present in a lung biopsy specimen of a patient exposed to rock wool showing peaks for Mg (1·253 keV), Al (1·486 keV), Si (1·740 keV), K(3·313 keV), Ca (3·691 keV), Ti (4·509 keV) and Fe (6·899) keV. The peaks for S and Cl originate from the supporting material. (b) Energy-dispersive X-ray spectrum from an original rock wool fibre.

The additional performed electron microscopy qualitative analysis of small fragments of the granulomas over a 'foreign body' revealed among others silica, aluminium and sometimes titanium [Fig. 1(a) and Fig. 2(a)]. This spectrum differed from the lung tissue without foreign body deposition [Fig. 1(B)]. Figure 2(B) shows the spectrum of an original rock wool fibre.

Discussion

Review of the occupational history of 50 cases with sarcoidosis revealed exposure to MMMF in 14 cases. Energy dispersive analysis of seven biopsy specimen revealed silica, aluminium and titanium, which are elements of MMMF [Fig. 2(B)]. A distinct relation between fibre deposits and granulomas was found. Therefore, we assumed that we identified a potential occupational environment, such as MMMF, that confers risk for sarcoidosis in persons with a certain (genetic) susceptibility. The development of a specific lymphocyte proliferation test—such as the beryllium specific lymphocyte proliferation test—would add weight to confirm this hypothesis. However, it is very difficult to develop such a test as MMMF contain various elements including aluminium, silica and titanium. Possibly, skin tests may provide specific reactive IgE antibodies. Furthermore, HLA typing may enable to identify a possible genetic suscepibility. Moreover, information regarding the number of workers at the plant who might have been exposed, as well as the total number of workers who finally develop a sarcoid-like disorder is important in justifying the hypothesis. Future research should be conducted in a cohort of MMMF-exposed workers and control cohort to identify the frequency of sarcoidosis in both populations.

A survey of workers in MMMF production plants conducted by Hughes *et al.* revealed no clinical relevant respiratory health effects (13). Occassionally, the association of MMMF exposure and the development of pulmonary fibrosis has been reported (14–16). However, the ability of MMMF to cause granulomatous lung disease was not appreciated until now (16). Assumably, the granulomas disappear when the disease progresses towards fibrosis. The association of exposure to foreign bodies with

the development of pulmonary sarcoidlike granulomatosis with helper T-cell alveolitis was considered by others (17). The morphological pattern of these granulomas is indistinguishable from the non-necrotizing granulomas occurring in sarcoidosis. Day *et al*. suggested that the inflammatory response induced by the presence of minerals within the tissue may trigger altered immunoregulation, accounting for the pathological changes (18). Metallic dust may act as antigen in a hypersensitivity reaction (2–7). Jacket *et al*. installed glasswool fibres within the lung of Wistar rats. Additionally, they observed a non-specific accumulation of macrophages in the alveoli and occasionally a granulomatous reaction (19). Studies performed to assess cytotoxicity, inflammatory and/or fibrogenic response, suggested that DNA damage could also be attributed to the production of hydroxyl radicals, which results from the interaction of metallic dust with the cell plasma membrane (2). The MMMF surface also may be involved in hydroxyl radical production, and therefore be a potential oxidative stress factor causing an uneven balance between free radical generation and scavenging reactions (20). Gilmour *et al*., showed the ability of MMMF to generate free radicals at the fibre surface (21). Moreover, Driscoll *et al*. described the activation of NF-κB by a range of pneumoconiotic particles (22). Recently, we demonstrated NF-κB activation in sarcoidosis (23). In line with these observations, refracting ceramic fibres have been reported to stimulate rat alveolar macrophages to release tumour necrosis factor. The detection of surface hydroxyl radical activity in a test fibre of unknown toxicity provides support for the contention that the fibre is toxic; however, failure to detect free radical activity cannot be taken as evidence for non-toxicity (24,25).

Insulation wools contribute more than 80% to the total MMMF production, they are used for thermal and acoustical insulation, for fire protection, in acoustic ceiling tiles and panels, in the manufacture of airconditioning and ventilation ducts and as growing media for horticulture (14). MMMF are manufactured from molten glass, rock, slag, kaolin clay or combinations of silicon and aluminium oxide.

The concentration of fibres in air, chemical composition and size of fibres must be considered in evaluation of potential health risks. To reach the alveolar space, fibres must have certain dimensions ($<10\,\mu$m, aerodynamics) (14). The research concerning the pathogenesis of fibrosis due to MMMF such as glass fibres and rock wool, has focused on fibre dimensions, surface qualities and biopersistence. In a few studies the pathogenic properties of MMMF were related to their accumulation and to their persistence as fibres in target organs (13,15). This is actually a major field of concern in the evaluation of MMMF toxicity, since it is likely that these fibres are not rapidly cleared or dissolved in the lung. Raffinsson *et al*., indicated a relationship between sarcoidosis and exposure to the crystalline silica, cristobalite (26). Barbazza *et al*. suggested that the development of granulomas after inhalation of silica particles was not dependent on the amount of silica, but is an individual cellular response (27). There is good circumstantial evidence, particularly from beryllium workers, that an exuberant granulomatous response to organic and inorganic stimuli requires some form of host predisposition. Moreover, chronic beryllium disease occurred at both high and low levels of exposure, without a clear association between magnitude of exposure and disease incidence (2). Presumably, not only the quantity of the exposure (amount of exposure), but also the quality of the fibres (fibre components) provoked the granulomatous reactions in genetically susceptible persons. Richeldi *et al*. found that in a beryllium-exposed population carrying the HLA-DPB1 Glu marker was associated with an eightfold increase in the rate of disease in the group of workers with a history of higher exposure. Therefore, genetic as well as exposure factors may have an additive or multiplicative effect. Morever, the berylliosis model indicates genetic studies are useful in determining exposure-related risk levels for the genetically susceptible segment of the population (28). These observations may have serious implications as presently sufficient protection during exposure to MMMF are lacking, and many people—aware or unaware—are exposed to these fibres.

In conclusion, MMMF are of risk to elicit a sarcoidlike granulomatous response. Obviously, the progression from MMMF exposure to disease hinges partly on an individual's genetic susceptibility. It is tempting to speculate that to provoke a granulomatous reaction — like in hypersensitivity pneumonitis and berylliosis — not the amount of exposure but the components of the fibres are important. The presented findings, together with previous observations, highlight that studies assessing the potential risk of MMMF focused on the chemical composition as well as the fibre size or shape and free radical production to cause a granulomatous response are thoroughly needed, in addition to genetic screening.

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References

1. Hunnighake GW, Costabel U, Ando M, *et al*. ATS/ERS/WASOG statement on sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis*. 1999; **16:** 149–173.
2. Newman LS, Maier LA, Nemery B. Disorders due to beryllium and cobalt. In. Schwarz ML, King TE (eds). *Interstitial Lung Disease*. London: BC Decker Inc. Hamilton 1998: 367–392.
3. De Vuyst P, Dumortier P, Schandené L, Estenne M, Verhest A, Yernault JC. Sarcoidlike granulomatosis

induced by aluminium dust. *Am Rev Respir Dis* 1987; **135:** 493–497.
4. Voisin C, Fisekci F, Buclez B, *et al*. Mineralogical analysis of the respiratory tract in aluminium oxide-exposed workers. *Eur Respir J* 1996; **9:** 1874–79.
5. Orriols R, Ferrer J, Tura JM, Xaus C, Coloma R. Sicca syndrome and silicoproteinosis in a dental technician. *Eur Respir J* 1997; **10:** 731–734.
6. Schauble TL, Rich EA. Lymphocytic alveolitis in a crematorium worker. *Chest* 1994; **105:** 617–619.
7. Gysbrechts C, Michiels E, Verbeken E, *et al*. Interstitial lung disease more than 40 years after a 5 year occupational exposure to talc. *Eur Respir J* **11:** 1412–1415.
8. Drent M, Kessels BLJ, Bomans PHH, Wagenaar SjSc, Henderson RF. Sarcoidlike lung granulomatosis induced by glass fibre exposure. *Sarcoidosis Vasc Diffuse Lung Dis* 2000; **17:** 86–87.
9. Quanjer PH, Tammeling GJ, Cotes JE, Pederson OF, Peslin R, Yernault J-C. Lung volumes and forced ventilatory flows. Report working party. Standardization of lung function tests. European Commission for Steel and Coal. Official statement of the European Respiratory Society. *Eur Respir J* 1993; **6:** (Suppl. 16): 5–40.
10. Oberstein A, von Aitzewitz H, Schweden F, Müller-Quernheim J. Non invasive evaluation of the inflammatory activity in sarcoidosis with high-resolution computed tomography. *Sarcoidosis Vasc Diffuse Lung Dis* 1997; **14:** 65–72
11. Armbruster C, Dekan G, Hovarka A. Granulomatous pneumonitis and mediastinal lymphadenopathy due to photocopier toner dust. *Lancet* 1996; **348:** 690.
12. Drent M, Nierop van MAMF, Gerritsen FA, Wouters EFM, Mulder PGH. Computer program using BALF analysis results as diagnostic tool in interstitial lung diseases. *Am J Respir Crit Care Med* 1996; **153:** 736–741.
13. Hughes JM, Jones RN, Glindmeyer HW, Hammad YY, Weill H. Follow up study of workers exposed to man made mineral fibres. *Br J Ind Med* 1993; **50:** 658–667.
14. Ameille J, Pairon JC, De Vuyst P. Man-made vitreous fibers and respiratory health effects. In: Banks DE, Parker JE (eds). *Occupational Lung Disease*. London: Chapman and Hall Medical, 1998: 263–277.
15. Takahashi T, Munakata M, Takekawa H, Homma Y, Kawakami Y. Pulmonary fibrosis in a carpenter with long-lasting exposure to fiberglass. *Am J Industrial Med* 1996; **30:** 596–600.
16. De Vuyst P, Dumortier P, Swaen GMH, Pairon JC, Brochard P. Respiratory health effects of man-made vitreous (mineral) fibres. *Eur Respir J* 1995; **8:** 2149–2173.
17. Eklund A, Grunewald J. The riddle of sarcoidosis: have novel techniques brought any new insight as to the causative agent? *J Intern Med* 1996; **240:** 59–62.
18. Day MJ, Pearson GR, Lucke VM, Lane SJ, Sparks RSJ. Lesions associated with mineral deposition in the lymph node and lung of the dog. *Vet Pathol* 1996; **33:** 29–42.
19. Jackel M, Kerényi T, Pott F, *et al*. Lung damaging effects of glasswool-fibers. An experimental study. *Eur Respir J* 1999; **14:** 212s.
20. Brown DM, Fischer C, Donaldson K. Free radical activity of synthetic vitreous fibers: iron chelation inhibits hydroxyl radical generation by ceramic fiber. *J Toxicol Environ Health* 1998; **53:** 545–561.
21. Gilmour P, Beswick PH, Donaldson K. Detection of surface free radical activity of respirable industrial fibres using supercoiled $\Phi\times$ 174 plasmid DNA. *Carcinogenesis* 1995; **16:** 2973–2979.
22. Driscoll KE, Howard BW, Carter LM, Hassenbein DG, Janssen YMW, Mossman BT. Oxidative stress and silica induced increases in nuclear, NF-kB binding activity in alveolar epithelial cells. *Am J Respir Crit Care Med* 1995; **151:** A712.
23. Drent M, Berg van den R, Haenen GRMM, Berg van den H, Wouters EFM, Bast A. Systemic activation of the nuclear regulatory factor-kappa B in sarcoidlike granulomatosis disorders. *Sarcoidosis Vasc Lung Dis* 1999; **16 (Suppl 1):** 11.
24. Brown DM, Fisher C, Donaldson K. Free radical activity of synthetic vitreous fibers: iron chelation inhibits hydroxyl radical generation by refractory ceramic fiber. *J Toxicol Environ Health* 1998; **53:** 545–561.
25. Tinkle SS, Newman LS. Beryllium-stimulated release of tumor necrosis factor-α, interleukin-6, and their soluble receptors in chronic beryllium disease. *Am J Respir Crit Care Med* 1997; **156:** 1884–1891.
26. Raffnsson V, Ingimarsson O, Hjalmarsson I, Gunnarsdottir H. Association between exposure to crystalline silica and risk of sarcoidosis. *Occup Environ Med* 1998; **55:** 657–660.
27. Barbazza R, Calabro S, Tessarin C, *et al*. Granulomatous involvement of the liver in anthracosilicosis. *Appl Pathol* 1986; **4:** 276–281.
28. Richeldi L, Kreiss K, Mroz MM, Zhen B, Tartoni P, Saltini C. Interaction of genetic and exposure factors in the prevalence of berylliossis. *Am J Ind Med* 1997; **32:** 337–340.