Lung retention of cerium in humans

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Abstract

A retrospective study was conducted to evaluate lung retention of particles containing cerium in subjects with and without previous occupational exposure to mineral dusts. Analytical transmission electron microscopy was performed on 459 samples of bronchoalveolar lavage (BAL) fluid and 75 samples of lung tissue. Study of the distribution of mineralogical species in human samples showed that particles containing cerium were encountered in less than 10% of subjects. The proportion of subjects with particles containing cerium in their biological samples was not different between controls and subjects with previous occupational exposure to fibrous or non-fibrous mineral dusts. This was considered as the background level of lung retention of cerium in the general population. By contrast, determination of the absolute concentration of particles containing cerium in BAL fluid and lung tissue samples showed that 1·2% (from BAL fluid) and 1·5% (from lung tissue) of subjects with previous exposure to mineral particles had high lung retention of particles containing cerium. This study is believed to be the first one in which lung retention of cerium was estimated in the general population.

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Cerium and other rare earth elements have several industrial applications, particularly because of their luminescent and magnetic quality as well as their abrasive, colouring, decolouring, and catalytic properties. Numerous occupational groups may therefore be exposed to rare earths, as in the manufacture and use of arc lamps, and in the glass, optical, electronic, watchmaking, nuclear, metallurgical, and chemical industries.[1 2] Cerium dust is generally considered to be relatively inert in experimental models.[3 4] So far, only case reports have been published dealing with lung diseases in humans potentially related to exposure to rare earth compounds.[5–14] Lung biopersistence of cerium has sometimes been described in individual cases, but no evaluation of lung retention and biopersistence of this mineral has been made in occupationally exposed groups or in the general population.

Lung dust load may be assessed either directly from chemical and mineralogical analysis of samples of lung tissue, or estimated from analysis of bronchoalveolar lavage (BAL) fluid. Previous studies in humans have shown that the concentration of asbestos bodies in BAL fluid was correlated with parenchymal concentration.[15] Less is known about non-fibrous mineral particles. Nevertheless, good agreement has been reported between the particle types in BAL fluid and lung samples of subjects free of known recent occupational exposure to non-fibrous mineral particles.[16] The interest in mineralogical analysis of non-fibrous mineral particles in BAL fluid of subjects with various occupational exposures has been previously noted.[17–20]

Our study was undertaken to determine the frequency of lung retention of particles containing cerium in the general population. For this purpose, we analysed BAL fluid and lung tissue samples retrospectively from patients with and without previous exposure to mineral dusts to estimate the background level of particles containing cerium in these samples. In subjects exhibiting significant lung retention of particles containing cerium, with previous occupational exposures to mineral dusts and especially to those associated with cerium, assessment was made of lung diseases found and of the biopersistence of particles containing cerium in the respiratory tract.

Methods

STUDY POPULATION

In the first part of the study, subjects included were those for which a mineralogical analysis of non-fibrous mineral particles in BAL fluid or in lung tissue samples had been requested in our laboratory between 1981 and 1993. These samples came from more than 30 hospitals. For each patient, information was collected on tobacco smoking, presumed diagnosis at the time of request for analysis of the samples, and job history, including dates of beginning and end of each occupation. This enabled us to classify subjects into two groups of exposure: subjects with previous known exposure to fibrous particles or non-fibrous mineral particles (occupationally exposed group: OE group) and subjects free of any previous exposure to mineral dusts (control group).

PARTICLE ANALYSIS

Preparation and mineralogical analysis of samples were performed as previously described.[16 20 21] We used an analytical transmission and scanning electron microscope (TEM SCAN JEOL EX II) fitted with an energy dispersive *x* ray spectrometer (TRACOR TN 5502). Briefly, two variables were

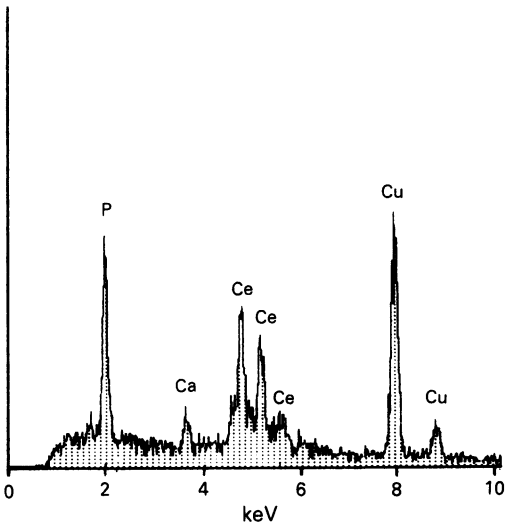

Figure 1 x Ray spectrum obtained when focusing the electron beam on a particle containing cerium (Ce). Energy location of definitely detected peaks: phosphorus (P) (K_α 1,2): 2013 eV; Calcium (Ca) (K_α 1,2): 3690 eV; Ce (L_α, $L_{\beta1}$, $L_{\beta2}$): 4839 eV; 5261 eV; 5612 eV. All peaks were attributed to the particles with the exception of copper (Cu) from the apparatus. Phosphorus was usually associated with particles containing cerium, suggesting metabolism of these particles in the respiratory tract.

registered for each sample: (1) the numerical concentration of all types of non-fibrous mineral particles greater than 0·1 μm, expressed per ml of BAL fluid or per g of dry lung tissue; (2) the relative percentage of different mineralogical species of 50 particles in randomly selected fields. Each particle was identified by morphological features, electron diffraction pattern, and microanalysis spectrum. Thus the x ray spectrum of cerium was: L_α: 4839 eV; $L_{\beta1}$: 5261 eV; $L_{\beta2}$: 5612 eV (fig 1). Particles containing cerium were counted regardless of the other associated mineralogical species. Only results of relative and absolute concentrations for particles containing elementary cerium are reported.

DESCRIPTION OF SUBJECTS SHOWING HIGH LUNG RETENTION OF PARTICLES CONTAINING CERIUM

As relative concentration of a given mineralogical species did not reflect lung retention of this mineral, the absolute concentration of particles containing cerium was calculated for each subject, whenever possible (when numerical particle concentration was available). This variable was obtained for both BAL fluid samples and lung tissue samples, as follows: absolute concentration of cerium = total numerical concentration of all particles (per ml of BAL fluid or per g of dry lung tissue) × percentage of particles containing cerium (in BAL fluid or lung tissue). This variable was considered as a good estimate of retention of cerium in the lung.

Those OE subjects for whom the absolute concentration of particles containing cerium was greater than five times the highest concentration found in BAL fluid or lung tissue of controls were studied in detail. Information was collected on presumed or known exposure to cerium, as well as clinical, functional, radiological, and pathological data when available.

STATISTICAL METHODS

The χ^2 test was used to compare sex ratio and smoking state in OE subjects and controls for BAL fluid samples and lung tissue samples. The t test was performed for comparison of age and cumulative smoking in OE and control subjects.

Because the distribution of particle concentrations was neither normal nor lognormal, analysis of this variable in BAL fluid or lung tissue between controls and OE subjects was performed with the non-parametric Wilcoxon rank sum test. Repartition of controls and OE subjects between the different classes of cerium lung retention was compared by χ^2 test.

All calculations were carried out with SAS statistical software.

Results

The first part of the study was performed on 459 BAL fluid samples and 75 lung tissue samples. Table 1 reports characteristics of study subjects. The sex ratio was different between controls and OE subjects for BAL fluid samples, as almost all OE subjects were men. The OE subjects were significantly younger than controls for lung tissue samples, but there was no statistical difference in age between OE subjects and controls for BAL fluid samples. No significant difference in cumulative smoking habit was found between the OE group and controls, but there were more smokers in OE subjects than in controls for BAL fluid samples.

As no significant difference was found in the total particle concentrations for male v female controls (data not shown), all controls were grouped in the analysis. Table 2 shows total particle concentration and relative percentage of particles containing cerium derived from qualitative distribution of mineralogical

Table 1 Characteristics of study subjects

	BAL fluid			*Lung tissue*		
	Controls	*OE subjects*	*p Value*	*Controls*	*OE subjects*	*p Value*
No	43	416		9	66	
Sex ratio	1·3	12·9		2	8·4	NS (p = 0·09)
Men : women	24 : 19	386 : 30	<0·001	6 : 3	59 : 7	
Age (mean (SD))	48·6 (16·8)	50·9 (13·4)	NS	57·3 (11·1)	47 (13·9)	<0·05
Smoking (%)						
Undetermined	7	15·4	<0·05	0	33·3	
Never smokers	41·9	25		11·1	15·1	NA
Ever smokers	51·1	59·6		88·9	51·5	
Pack-years for ever smokers (mean (SD))	30·8 (24·9)	26·1 (16·7)	NS	47·1 (21·4)	31 (35)	NS

NA = not applicable because of too few subjects.

Table 2 Relative concentration of particles containing cerium (Ce) in BAL fluid and lung tissue from OE subjects and controls

	*Median (range) concentration of all non-fibrous mineral particles**	*No of subjects according to relative concentrations of particles containing Ce*		
		Ce = 0%	*0% <Ce ≤ 4%*	*Ce > 4%*
BAL fluid:				
Controls (n = 43)	2 (0·14–71)	41	1	1
OE subjects (n = 416)	5·25† (0·01–1000)	382	27	7
p Value	<0·001			
Lung tissue:				
Controls (n = 9)	33 (22–280)	8	1	0
OE subjects (n = 66)	104 (8–10 000)	60	5	1
p Value	<0·05			

*Results are expressed as median $\times 10^5$ particles/ml for BAL fluid samples, and as median $\times 10^7$ particles/g of dry lung tissue for tissue samples; †Results were calculated from 392 subjects because relevant count was impossible in some BAL fluid samples. This was mainly explained by the presence of aggregated particles.

species of all samples. Two out of 43 controls and 34 out of 416 OE subjects had particles containing cerium in BAL fluid (NS). These particles were also identified in one out of nine controls and six out of 66 OE subjects in lung tissue samples (NS).

In the second part of the study, when absolute concentrations of particles containing cerium were calculated in BAL fluid or lung tissue for each subject, five subjects had a high retention of this mineral in BAL fluid and three in lung tissue (fig 2). Table 3 shows the main clinical, radiological, functional, and pathological data on these patients. All were affected with radiological interstitial lung disease. Time elapsed since the end of last exposure to cerium until time of mineralogical analysis was noted for each patient. It ranged from still exposed to 29 years after the end of exposure.

Discussion

Concentration of non-fibrous mineral particles in BAL fluid or lung tissue samples was found to be related to previous occupational exposure to mineral particles. The concentration of non-fibrous mineral particles was significantly higher in OE subjects than in controls and this was not explained by a difference in age distribution between these two groups, nor was it likely to be related to the role of smoking, as cumulative smoking was similar in the two groups. Such a difference

Table 3 Characterisation of patients with high lung retention of particles containing cerium (Ce) as estimated from BAL fluid or lung tissue samples

Patient (samples)	*Particles containing Ce in BAL fluid ($\times 10^5$/ml) or in lung tissue ($\times 10^7$/g)*	*Source of exposure to Ce particles (duration)*	*Exposure to other mineral particles*	*Time since end of exposure*	*Smoking (pack years)*	*Clinical data*	*Chest x ray film*	*Lung function*	*Lung pathological data*
1 (BAL fluid)	8	Photoengraving (30 years)	Asbestos	0	20	Cough, Weight loss Hippocratic finger	Reticulonodular opacities (confirmed by CT scan)	Obstructive impairment, distension, CO transfer: normal	Mild interstitial fibrosis
2 (BAL fluid)	4·96	Photoengraving (31 years)	None	29 y	0	Effort dyspnoea asthma	Reticulonodular opacities	Obstructive impairment, CO transfer: not reported	No data
3 (BAL fluid)	1·14	Not available	Coal dust	Not available	0	Normal	Nodular opacities	Normal	Anthracosis
4 (BAL fluid)	0·68	Stainless steel polishing (3 years)	Chrystalline silica, metals (Cr, Ni)	4 y	40	Dyspnoea	Reticulonodular opacities, emphysema on TDM	Obstructive impairment, distension, diminution of CO transfer	No data
5 (BAL fluid)	14	Glass polishing (4 years) projectionnist (13 years)	Asbestos	13 y	50	Crackles, mild cyanosis	Small parenchymal opacities (1/1, shape s), left diaphragmatic pleural plaque	Obstructive impairment, diminution of CO transfer hypoxaemia, increase of static elastic recoil	Diffuse interstitial fibrosis, Emphysema
(lung tissue)	49			21 y					
6 (lung tissue)	4·1	Foundry worker (16 years)	Metals (Cu, Zn)	7 y	0	Cough, effort dyspnoea	Reticulonodular opacities	Spirometry: normal diminution of CO transfer	Peribronchiolar fibrosis
7 (lung tissue)	4	Glass polishing (21 years)	Metals (AL)	0	28	Effort dyspnoea	Reticulonodular opacities	Obstructive impairment, hypoxaemia diminution of CO transfer	Mild interstitial fibrosis

in the non-fibrous mineral particle concentration in BAL fluid samples of OE subjects and controls has previously been reported.[20]

In our series particles containing cerium were encountered in less than 10% of subjects in BAL fluid of lung tissue samples. Study of the distribution of mineralogical species in BAL fluid or lung tissue samples did not discriminate for cerium as no difference was found when comparing OE subjects with controls for the presence or absence of particles containing cerium. We consider that the frequency found in our population probably reflected the background level of the general population, as the chest physicians never specifically requested examination for the presence of particles containing cerium (except in one case) in the biological samples sent to the laboratory. Thus it was not expected that subjects exposed to cerium would have been over-represented in any of our groups.

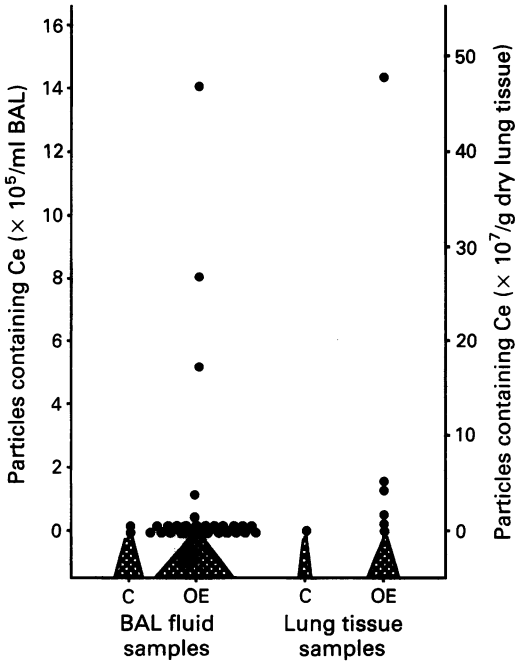

Figure 2 Lung retention of particles containing cerium (Ce) estimated from absolute concentrations of particles containing Ce in BAL fluid and lung tissue samples.

By contrast, determination of absolute concentration of particles containing cerium in BAL fluid and lung tissue samples made it possible to identify subjects with high levels of retention. We adopted, as the threshold value of significant lung retention of cerium, a concentration in a subject equal to five times the highest concentration found in controls. With this threshold value, only 1·2% of OE subjects had significant lung retention of particles containing cerium in BAL fluid, and only 1·5% in lung tissue.

As far as we know, this report represents the first systematic assessment of lung

Table 4 Summary of reported cases of cerium (Ce) pneumoconiosis

Reference	*Occupational exposure*	*Duration of exposure (y)*	*Latency (y)*	*Clinical data/ chest x ray film*	*Smoking*	*Spirometry (other variables)*	*Pathological findings (LM or EM)*	*Ce mineralogical analysis**
Heuck and Hoscheck[5]	Photoengraving	35	—	Diffuse interstitial opacities, emphysema	—	N	—	—
(n = 3)	Photoengraving	—	—	Diffuse interstitial opacities	—	N	—	—
	Photoengraving	26	9	Diffuse interstitial opacities	—	R	—	—
Napée *et al*[6]	Fabrication of cerium oxide	15	—	Reticulonodular opacities	S	R	No lung fibrosis, some metaplasia	—
(n = 2)	Fabrication of cerium oxide	11	—	Reticulonodular opacities	—	R	Collagen sclerosis	—
								—
Le Magrex *et al*[7] Sinico *et al*[8] (n = 1)	Glass polishing	3	0	Dyspnoea, asthenia, Diffuse interstitial opacities	S	N	Open lung biopsy, no fibrosis, inflammatory granuloma	—
Husain *et al*[9] (n = 1)	Fabrication of rare earths	10	—	Diffuse interstitial opacities (profusion 2/2)	—	N CO transfer: N	—	—
Hecht and Wesch[10] (n = 1)	Photoengraving	40	9	Bronchitis, diffuse nodular opacities (profusion 1/0)	—	—	Necropsy, LM, fibroanthracosis, emphysema, diffuse bronchial ectasia	10·4 μg/g dry lung tissue
Vocaturo *et al*[11] (n = 1)	Photoengraving	46	—	Dyspnoea, cough, Reticulonodular opacities	S	Ob Hypoxaemia, diminution of CO transfer, increase of compliance	Open lung biopsy, LM, chronic inflammatory peribronchiolar infiltrates, sclerotic thickening of septal tissues	Increase of La, Ce in lymph nodes (Ce: 4·9 μg/g wet tissue) and lung tissue (Ce: 166·5 μg/g wet tissue)
Sulotto *et al*[12] (n = 1)	Photoengraving	13	17	Diffuse nodular opacities	S	R Diminution of CO transfer	—	Ce: 757 ppb in the BAL fluid of the worker (0·5 ppb in a control)
Ruettner *et al*[13] (n = 9)	Photoengraving	Average: 31	—	Diffuse interstitial opacities	—	—	Necropsy, LM emphysema, pronounced interstitial fibrosis, no granuloma	Dense deposits in AM and in extracellular interstitial spaces
Waring and Watling[14] (n = 1)	Movie projection	25	—	Radioopaque right paratracheal lymph node, no interstitial opacities	S	—	Necropsy, LM, no significant alteration	Ca,RE in lymph node, Ce: 52 μg/g wet lung tissue

*Quantification of Ce was performed with neutron activation analysis except for Waring and Watling[14] who used inductively coupled plasma spectroscopy. LM = light microscopy; EM = electron microscopy; AM = alveolar macrophages; RE = rare earths; — = not reported; N = normal; Ob = obstructive impairment; R = restrictive impairment; S = smoker.

retention of particles containing cerium. As no data are available on the proportion of subjects having occupational exposure to cerium compounds among the workforce,[1 2] it is difficult to estimate the biopersistence of cerium in the human respiratory tract. Moreover, experimental data are inadequate to assess biopersistence in animals.[4 22] Nevertheless, in our series four subjects had a significant lung retention of particles containing cerium 4, 7, 21, and 29 years after the end of exposure. Some data also suggesting biopersistence of cerium in the lung of humans have been published in previous case reports (table 4)

Cerium pneumoconiosis was clearly suggested by some authors in these case reports (table 4). Despite the fact that data were heterogeneous and that exposure was generally mixed (including cerium and other mineral particles), most authors mentioned radiological interstitial lung disease. It should be noted that reticulonodular opacities were shown in all of our subjects in whom a significant lung retention of particles containing cerium was found. Nevertheless, the specific role of cerium in the outcome of disease reported could not be ascertained. Available experimental studies have not shown any fibrogenic effect of inhaled cerium particles.[4 22] Published studies, however, had not been conducted according to recommended protocols for long term inhalation experiments.[23 24]

Conclusion

This retrospective study was, as far as we are aware, the first that systematically assessed lung retention of particles containing cerium in the general population. Besides a low background level in less than 10% of all subjects, a high retention of particles containing cerium was found in some subjects where the origin of exposure had been identified from an occupational questionnaire. All these patients had radiological changes suggesting interstitial lung disease, but the causal relation with exposure to cerium could not be established from this retrospective study. Prospective studies of respiratory impairment in subjects occupationally exposed to cerium dusts will be necessary to evaluate satisfactorily the biopersistence of this mineral in the respiratory tract of humans.

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1 Roscina TA. Rare earths. In: Parmeggiani L, ed. *Encyclopedia of occupational health and safety.* Geneva: International Labour Office. 1983;2:1903–4.
2 Peltier A. Exposition aux poussières de terres rares. *INRS Cahiers de Notes Documentaires* 1986;**122**:21–23
3 Das T, Sharma A, Talukder G. Effects of lanthanum in cellular systems. A review. *Biol Trace Elem Res* 1988;**18**:201–28.
4 Haley PJ. Pulmonary toxicity of stable and radioactive lanthanides. *Health Phys* 1991;**61**:809–20.
5 Heuck F, Hoschek R. Cer-Pneumoconiosis. *American Journal of Roentgenology* 1968;**104**:777–83.
6 Napee J, Bobrie J, Lambard D. Pneumoconiose au cerium. *Archives des Maladies Professionelles* 1972;**33**: 13–8.
7 Le Magrex L, Jacquemin-Gaillot M-J, Raguenaud A. Pneumoconiose et cerium. *Archives des Maladies Professionnelles* 1979;**40**:113–4.
8 Sinico M, Le Bouffant L, Paillas J, Fabre M, Trincard MD. Pneumoconiose due au cerium. *Archives des Maladies Professionnelles* 1982;**43**:249–52.
9 Husain MH, Dick JA, Kaplan YS. Rare earth pneumoconiosis. *J Soc Occup Med* 1980;**30**:15–9.
10 Hecht FM, Wesch H. Beitrag zum röntgenologischen Bild der Cer-Pneumokoniose. *Praxis der Pneumologie* 1980; **34**:169–73.
11 Vocaturo G, Colombo F, Zanoni M, Rodi F, Sabbioni E, Pietra R. Human exposure to heavy metals. *Chest* 1983;**5**:780–3.
12 Sulotto F, Romano C, Berra A, Botta GC, Rubino GF, Sabbioni E, Pietra R. Rare earth pneumoconiosis: a new case. *Am J Ind Med* 1986;**9**:567–75.
13 Ruettner JR, Spycher MA, Vogt P. Lung fibrosis associated with rare earth exposure. *Proceedings of the VIIth international pneumoconioses conference, August 23–26, 1988. Pittsburgh, Pennsylvania.* NIOSH-International Labour Office, 1988:1087–8.
14 Waring PM, Watling RJ. Rare earth deposits in a deceased movie-projectionist. A new case of rare earth pneumoconiosis? *Med J Aust* 1990;**153**:726–30.
15 Sebastien P, Armstrong B, Monchaux G, Bignon J. Asbestos bodies in bronchoalveolar lavage fluid and in lung parenchyma. *Am Rev Respir Dis* 1988;**137**:75–8.
16 Chariot P, Couste B, Guillon F, Gaudichet A, Bignon J, Brochard P. Nonfibrous mineral particles in bronchoalveolar lavage fluid and lung parenchyma from the general population. *Am Rev Respir Dis* 1992;**146**:61–5.
17 Gaudichet A, Pairon J-C, Malandain O, Couste B, Brochard P, Bignon J. Etude mineralogique des particules non fibreuses du lavage bronchoalveolaire. *Rev Mal Respir* 1987;**4**:237–43.
18 Christman JW, Emerson RJ, Hemenway DR, Graham WGB, Davis GS. Effects of work exposure, retirement, and smoking on bronchoalveolar lavage measurements of lung dust in Vermont granite workers. *Am Rev Respir Dis* 1991;**144**:1307–13.
19 Dumortier P, De Vuyst P, Yernault JC. Non fibrous inorganic particles in human bronchoalveolar lavage fluids. *Scanning Microsc* 1989;**3**:1207–18.
20 Pairon JC, Billon-Galland MA, Iwatsubo Y, Bernstein M, Gaudichet A, Bignon J, Brochard P. Biopersistence of nonfibrous mineral particles in the respiratory tract of subjects following occupational · exposure. *Environ Health Perspect* 1993 (in press).
21 Sebastien P, Billon MA, Janson X, Bonnaud G, Bignon J. Utilisation du microscope electronique a transmission (MET) pour la mesure des contaminations par l'amiante. *Archives des Maladies Professionelles* 1978;**39**: 229–48.
22 Schepers GWH. The biological action of rare earths. II. The experimental pulmonary histopathology produced by a blend having a relatively high fluoride content. *American Medical Association Archives of Industrial Health* 1955;**12**:306–16.
23 McClellan RO, Miller FJ, Hesterberg TW, Warheit DB, Bunn WB, Kane AB, *et al.* Approaches to evaluating the toxicity and carcinogenicity of man-made fibers; summary of a workshop held November 11–13, 1991, Durham, North Carolina. *Regul Toxicol Pharmacol* 1992; **16**:321–64.
24 World Health Organisation. *Validity of methods for assessing the carcinogenicity of man-made fibres. Executive summary of a WHO consultation. 19–20 May 1992.* Copenhagen: WHO, 1992:10.