

The pathogenic effects of fibrous ceramic aluminium silicate glass administered to rats by inhalation or peritoneal injection

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For many years it has been realized that the industrial use of asbestos can involve considerable health risks. Workers exposed to asbestos dust may develop pulmonary interstitial fibrosis (asbestosis), bronchial carcinomas or mesotheliomas (1).

Because of the hazards of asbestos use, industry has attempted to substitute other types of fibres, many of them man-made. However, knowledge accumulated over the past few years indicates that, for glasses at least, this cannot be done with impunity. As early as 1968 Gross et al. (2) reported that many types of mineral fibre could stimulate the production of pulmonary ferruginous bodies that were similar to asbestos bodies. Potentially more serious, however, was the report by Stanton and Wrench (3) that some preparations of glass fibres implanted into the pleural cavities of rats produced mesotheliomas in similar numbers to those produced by asbestos fibres. This work was later expanded by Stanton et al. (4), and it was suggested that the most carcinogenic size for mineral fibres was $> 8 \mu\text{m}$ in length and $< 1.5 \mu\text{m}$ in diameter, and that the chemical composition of fibres was not important. Davis (5), Pott et al. (6) and Wagner et al. (7) confirmed the carcinogenicity of glass fibres following intrapleural or intraperitoneal injection into rats, and Wright and Kushner (8) reported pulmonary fibrosis following the intratracheal injection of long glass fibres into guinea pigs. No fibrosis occurred following the injection of short glass fibres.

So far, inhalation studies with glass fibres have shown little pathological tissue reaction at all. In 1976 Gross (9) reported studies in which rats and hamsters had been exposed to high airborne concentrations of three types of glass fibre with an average diameter of about $1 \mu\text{m}$. Almost no fibrosis was found and no tumours developed. A similar study was reported by Lee and his co-workers (10). Here the dust concentration used was also high and some alveolar proteinosis occurred but no fibrosis and no tumours were found. In a follow-up paper (11) the same group reported studies in which rats, hamsters and guinea pigs were exposed for three months to a dense cloud of glass fibre dust. No

Fig. 1: the glass fibres were partly treated with hydrochloric acid or sodium hydroxide *in vitro*.

fibrosis occurred in any of these species but two benign pulmonary adenomas were found in both the rats and the guinea pigs. Hardy (12) exposed rats to glass fibre for eight weeks with a follow-up period of four weeks. No effects on pulmonary function were noted during this period and no pulmonary fibrosis developed.

At the same time that experimental studies have been in progress, human populations of workers exposed to glass fibre have also been examined. Here again, the results have so far been negative. In 1968 Wright (13) examined chest radiograms from 1400 men in the American glass fibre industry who had been exposed for at least 10 years. He found no evidence of radiological abnormality. In 1971 Gross et al. (14) examined the lungs obtained at autopsy of 20 workers exposed during the manufacture of glass fibre. Very little dust was present in these lungs and no dust-associated pathology. In 1973 Hill et al. (15) examined a group from the British glass fibre industry. Only 70 men were involved, but their mean exposure was 20 years and both chest radiograms and lung function data were available. Once again no evidence of lung damage could be detected. Enterline and Henderson in 1975 (16) and Bayliss et al. in 1976 (17) reported studies of the incidence of pulmonary tumours in two groups of American glass fibre workers consisting of 416 and 1448 men. They found that the incidence of pulmonary tumours was slightly less than in the general population.

So far, no information is available on the pathogenic effects of the ceramic aluminium silicate glass forms of man-made mineral fibre. The present paper reports the findings from a long-term inhalation and injection study in which this material was administered to rats.

Materials and Methods

A group of 48 SPF Wistar rats of the AF/HAN strain was exposed to fibrous ceramic aluminium silicate glass (ceramic fibre) dust for 7 hours a day, 5 days a week, for a total of 224 days during a period of 12 months. The animals were approximately three months old at the start of dusting. A batch of 40 undusted animals was maintained within the same unit as controls during the same time period. The planned dust concentration was 10 mg/m³ of respirable dust. Initially the bulk ceramic insulation material was passed through two steel rollers to break up the longest fibres which were often several millimetres long. Finally the dust clouds were generated with a Timbrell dust generator and inhalation chambers, as described by Timbrell et al. (18) but modified as described by Beckett (19). Size-selecting the airborne dust by a cyclone system prior to injecting it into the chamber airstream ensured a high proportion of respirable dust in the clouds. Gravimetric monitoring was carried out during all dust exposure time. Daily mass concentrations were measured with an open filter-holder to collect total dust, and an NCB MRE sampler (Casella Type 113A, Dunmore et al. (20)) to collect respirable dust. The

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On 100 separate days additional dust samples were obtained for the estimation of fibre numbers and dimensions by means of the standard sampling method described by the Asbestosis Research Council (21). Each membrane filter sample was taken with an open Gelman filter-holder facing downwards at a flow rate and sampling time calculated to give an optimum density for counting by phase-contrast microscope. All fibres longer than 5 μ m were counted provided that they had an aspect ratio of at least 3 : 1 and their diameters were less than 3 μ m. Some samples were obtained with Nuclepore filters for subsequent examination by a Cambridge Instruments S600 scanning electron microscope at a (10 000x) magnification higher than available by optical microscopy (500x). Some of the samples originally collected on Nuclepore filters were also examined by transmission electron microscopy with an AEI CORA microscope. For both light and electron microscope counts, fibres were considered to be all particles with an aspect ratio greater than 3 : 1.

At the end of the 12-month dusting period four dusted animals were killed and six months later four more were killed. The experiment was terminated at 32 months for comparison with previous long-term inhalation studies from this unit, by which time seven dusted animals remained alive. Four control animals were killed 12 months after the start of the experiment but the remainder were allowed to live out their full life span or until the experiment was terminated. Lung tissue from all dusted animals from the fixed killing dates at 12 and 18 months, and six animals from the final killing date of 32 months, was used for estimations of pulmonary fibrosis and examined for the presence of pulmonary neoplasms. Lungs from the remaining animals were examined only for the presence of neoplasms. Tissue used for histological examination was fixed with 10% formal saline solution and embedded in paraffin wax. Lungs were fixed by inflation in situ until they filled the thoracic cavity. Sections were stained by either haematoxylin and eosin, Van Gieson's method for collagen, or Gordon and Sweet's stain for reticulin. Lungs and heart were embedded together and sections were cut in the coronal plane. Sections were cut at several different levels in each block, at least 1 mm apart, and the groups of serial sections were mounted from each of these levels for use with the different staining techniques. For quantitative estimations of pulmonary interstitial fibrosis four slides from each animal were examined with an electronic image analyser (Graphic Information Systems Ltd., GDS1). The areas of interstitial fibrosis were calculated and expressed as a percentage of total lung tissue. Finally the results from all animals in each group were averaged.

For the four dusted animals killed 18 months after the start of dusting, the left lung was used for dust extraction and only the right was available for histological study. Dust retained in the lungs was

recovered by a low-temperature plasma ashing process (22) with a Nanotech P100 apparatus. The residues were washed in 0.2 M HCl at room temperature before the amounts of ceramic fibre recovered were estimated by means of the infra-red spectrophotometric techniques described by Beckett et al. (23). Studies in this laboratory have shown that in rats the dust content ratio between left and right lungs after experimental inhalation of fibrous dust such as asbestos is 0.6 : 1; this correction factor was therefore used to calculate the total pulmonary dust burden of each animal.

In addition to the inhalation studies, the ability of the ceramic fibre to produce mesotheliomas was examined by means of the intraperitoneal injection assay. A dose of 25 mg of dust suspended in 2 ml of Dulbecco's phosphate buffered saline was injected under ether anaesthetic into the peritoneal cavities of a group of 32 rats of the AF/HAN strain. The dust was collected from the inhalation exposure system and was as similar as possible to the dust entering the inhalation chamber (24).

Results

The target mean mass concentration of 10.0 mg/m³ of respirable dust was achieved with some variation from day to day, as indicated by a standard deviation of 4.8 mg/m³. The total dust mass concentration was 8.4 mg/m³ (standard deviation 9.6 mg/m³). Phase-contrast microscope counts of fibres (longer than 5 µm, narrower than 3 µm, and aspect ratio greater than 3 : 1) gave a concentration of 95 fibres/cm³. This mean number concentration is less than those previously found for a series of UICC standard reference samples of asbestos (25), which exceeded 500 fibres/cm³. This difference in number for the same respirable mass concentration is due not only to differences in size distribution but also to the presence of considerable numbers of non-fibrous particles in the ceramic dust cloud (Fig. 1). By light microscope estimation, the ratio of particles (more than 1 µm diameter) to fibres (longer than 5 µm) was approximately 4 : 1.

Fibre length distributions for the fibres > 5 µm in length were obtained by both light microscopy and scanning electron microscopy; the numbers of fibres sized were 2000 and 900 fibres respectively. The results were almost identical (Fig. 2). This was because the diameters of almost all fibres longer than 5 µm were found to be > 0.3 µm; thus, theoretically, they should all have been visible on light microscope examination. While long and thin fibres were extremely rare, however, complete length and diameter distributions obtained by scanning electron microscope of all fibres longer than 0.04 µm showed the presence of large numbers of short thin fibres (Fig. 3 and 4). Approximately 90% of fibres were shorter than 3 µm and less than 0.3 µm in diameter. Most of these short thin fibres did not have the neat cylindrical shape of the larger ceramic fibres and in outline were often irregular (Fig. 5). Their method of formation has not yet been determined. While they made up the bulk of

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the dust cloud by numbers, they could have represented only an extremely small proportion by mass. They could have been present in the original bulk sample of ceramic fibre or been formed by the fragmentation of larger particles during dust generation. The same problem arises with the many non-fibrous particles present in the dust cloud.

Throughout the study the animals tolerated the exposure regime well and none died during the dusting period. The numbers of animals surviving at varying time points throughout the remainder of the study are given in Table 1; these figures are better than any from groups previously exposed to asbestos (25). The figures for the control animals were very similar. Histological examination of lung sections from the groups of dusted animals killed at the end of the dusting period and six months later revealed a different pattern of pulmonary damage from that previously found in rats exposed to asbestos (25-27). There were very few areas of peribronchiolar fibrosis of the type found with some forms of asbestos, especially chrysotile; detailed quantitative estimations were not undertaken therefore. Often those areas of fibrosis that were present could be recognized with certainty only at magnifications higher than were usually used for these estimates. Instead of peribronchial fibrosis the lungs of animals treated with ceramic aluminium silicate fibre showed large areas of alveolar proteinosis (Fig. 6). Within the proteinaceous material many dust particles were visible with the light microscope. At the first killing date much of the dust was extracellular, but at the second the alveoli affected with proteinosis more frequently contained foamy macrophages as well as protein, and these cells usually contained many of the dust particles. Most of the visible dust appeared to be particulate rather than fibrous and those fibres that were visible were relatively thick, with diameters of 2-3 μ m. They ranged from 5 μ m to 50 μ m in length. However, the reaction of the rat lung tissue to these fibres appeared to have been different from that due to asbestos, in that many fibres had become coated with Perls positive material to become ferruginous bodies (Fig. 7). Asbestos fibres are rarely coated in rat lungs but other species produce ferruginous bodies readily.

Lungs of animals from the final killing date showed only small amounts of alveolar proteinosis, but where this did occur the proteinaceous material still contained some extracellular dust particles as well as dust-containing macrophages. However, in general much less dust was visible with the light microscope than at earlier dates. Most of this remaining visible dust was contained in pulmonary macrophages, aggregations of which occurred in the alveoli close to the respiratory bronchioles. By the end of the study many of the dust-containing cells also contained masses of Perls positive material, but with the light microscope it was not possible to determine whether this had originated from fragmented ferruginous bodies.

One animal from each of the first killing dates at 12 and 18 months had small amounts of interstitial fibrosis in its lungs although this

occupied less than 0.01% of total lung area in each case. However, this type of lesion occurred in most of the older animals and some were severely affected (Fig. 8). On average, 5.0% of the lung area of the six animals examined from the final killing data had interstitial fibrosis; this figure ranged from 0.2% to 14.5% for individual animals. Within these areas of interstitial fibrosis only small amounts of dust were visible and this was mainly particulate. Two of the control animals from the final killing date at 32 months had very small areas of interstitial fibrosis but in each case these did not exceed 0.01% of total lung tissue area.

In the present study eight animals in all were found with pulmonary neoplasms. One tumour was a benign adenoma and three were carcinomas. Two of the carcinomas showed only a squamous histological pattern but the other had areas of both squamous and adenocarcinomatous appearance. In addition to these tumours, however, which were of similar type to those found in rats after asbestos treatment, some animals in the present study had pulmonary deposits of tumours which appeared to be malignant histiocytomas. These consisted of irregularly shaped cells of epithelioid type interspersed with multinucleate giant cells (Fig. 9). In four animals the tumours were obviously malignant with very large masses occupying most of one or more lung lobes. In one of these cases multiple nodules were also present in the pleural cavity, and the mediastinal lymph nodes were involved, but in the others the tumour appeared restricted to the lung tissue. A further six animals showed small areas of histological pattern similar to the larger tumours, in the centres of areas of interstitial fibrosis. While in these cases there was no definite indication of malignancy it appeared likely that these were early stages of tumour development. No pulmonary tumours of any type were found in the control animals.

In addition to tumours primarily associated with the lung, eight benign and eight malignant tumours, including one peritoneal mesothelioma, were also found in other tissues in the group of animals exposed by inhalation to ceramic aluminium silicate. Similar numbers of non-pulmonary tumours were found in the control animals (Table 2). Three animals from the dust-exposed group and three from the controls had two neoplasms at autopsy. In two of the cases from the dust-exposed group one of the neoplasms was present in the pulmonary tissue.

The lung-dust burden of four rats killed six months after the end of dusting was extracted and its mass estimated with infra-red spectrophotometry. The mass of ceramic aluminium silicate in a complete lung ranged from 2800 ug to 6800 ug, with a mean of 4130 ug. This means that the mass of ceramic fibre recovered from the rat lungs at this point was approximately half of the figure found after inhalation of the same mass of UICC crocidolite or amosite, although it was more than six times higher than the figure found after inhalation of UICC chrysotile (25).

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After the intraperitoneal injection of 25 mg of elutriated ceramic aluminium silicate dust, three animals developed peritoneal tumours. This is in contrast to findings with most asbestos preparations, which show that at this dose level more than 90% of animals usually develop mesotheliomas (24). Only one of the three tumours was a typical multinodular mesothelioma, with blood-stained ascites. The other two consisted of large single masses with few, if any, minor nodules. The histological picture of the large masses was similar to that of a fibrosarcoma. In addition, the first tumour produced by aluminium silicate fibre did not occur until approximately 850 days after injection, in contrast to some types of chrysotile asbestos where the first tumours occurred in as little as 200 days.

Discussion

With the same types of generator as those previously used for different kinds of asbestos, it has proved possible to generate respirable clouds of ceramic aluminium silicate glass fibres. However, the number of fibres > 5 μ m in length and < 3 μ m in diameter, as seen with the light microscope, was only 95 fibres/cm³ in a cloud with a respirable mass of 10 mg/m³ of air. This compared with figures of approximately 500 fibres/cm³ and 2000 fibres/cm³ for previously examined clouds with the same respirable mass of UICC amosite and chrysotile (25). The reasons for the low fibre number in the case of ceramic fibre were that almost all the relatively long fibres were thick and that the dust cloud contained much particulate dust. There were also large numbers of short thin fibres, visible only by electron microscopy, but these could have constituted only an extremely small proportion of the total mass.

Regardless of the number of long fibres in the dust cloud, particles of ceramic fibre predominated at all times in histological sections and relatively few fibres could be found, although the mass of retained dust was relatively high. It is possible that most of the long but relatively thick fibres were deposited in the larger bronchial tubes and were rapidly cleared, and only particles and short thin fibres reached the alveoli in any numbers; or that the ceramic fibres are apt to break up in lung tissue fluids, with the result that few long fibres remain for any length of time. However, the ceramic fibre used in these studies is known to be particularly resistant to chemical attack by both acids and alkalis in laboratory conditions, and it is difficult to envisage chemical conditions within lung tissue that could cause it to break up.

Whether the process of ferruginous body formation could be associated with the subsequent break-up of ceramic fibre is uncertain, although Botham and Holt (28) have suggested that this process contributes to the break-up and removal of asbestos fibres in the lungs of some animal species. These workers believed the process was mechanical but Jaurand et al. (29) have reported that the chemical leaching of chrysotile fibres

in lung tissue was more marked in the case of fibres in the centre of ferruginous bodies than in the case of uncoated fibres.

Regardless of these considerations, the inhalation of ceramic aluminium silicate dust in rats produced considerable pathological change, including malignancy. However, the pattern of lesions was significantly different from that found with asbestos (25). Peribronchiolar fibrosis, which is particularly marked in rats treated with chrysotile and which reached its maximum by the end of the dusting period, was almost non-existent in animals treated with ceramic fibre. However, interstitial fibrosis, also common with chrysotile, did occur in animals treated with ceramic fibre, to a lower but not significantly different degree from that occurring in chrysotile treated animals.

From this it would appear that large numbers of long thin fibres are probably needed to produce peribronchial fibrosis but that such fibres may not be necessary for the development of interstitial fibrosis. Since in the studies mentioned, crocidolite and amosite clouds, which contained many short thin fibres, caused little interstitial fibrosis, the short fibres are unlikely in themselves to be the main cause of interstitial fibrosis in the experiments with ceramic fibre. Factors other than fibre length must therefore be considered. The occurrence of large areas of alveolar proteinosis in rat lungs at the end of the dusting period indicates that the ceramic dust (fibres and particles) may have a toxic effect on the lung tissue. Perhaps damage is done to the alveolar walls at this stage which, although not visible with the light microscope, nonetheless results in interstitial fibrosis as the animals age.

While relatively large numbers of neoplasms occurred in the lung tissue of animals treated with ceramic aluminium silicate, the pattern of tumour development was different from that previously seen with asbestos (25). Only one benign pulmonary adenoma was found, a finding comparable to that obtained previously with amphibole asbestos types and the same number of rats, but significantly less than the six or seven adenomas found in previous experiments with UICC chrysotile ($P < 0.05$). However, although the amphibole asbestos types at a dose of 10 mg/m^3 produced no malignant pulmonary tumours, three bronchial carcinomas occurred in animals treated with ceramic fibre; since eight bronchial carcinomas were found in animals treated with UICC chrysotile, the ceramic fibre takes an intermediate place, in that the number of tumours it produced was not significantly different from the numbers produced by either of the other two substances. However, the finding of malignant histiocytomas in the group of animals treated with ceramic aluminium silicate is completely different from any results so far published from experimental studies related to asbestos. In previous inhalation studies with asbestos in this laboratory an occasional animal was found with pulmonary deposits similar to the malignant histiocytomas. However, deposits were also present in other organs, and the lung did not appear to be the primary site. They were therefore classified under the general

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References

1. Selikoff, I. J. Press, 1968.
2. Gross, P. 1985: 539-548.
3. Stanton, J. C. Asbestos, 1968: 797-808.

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heading of lymphomas. In the present study all these tumours appeared to involve mainly lung tissue and there was evidence of systemic involvement in only one animal. This suggests that this type of tumour occurred in direct response to the inhalation of ceramic fibre, but at present there is no information as to why this specific response occurs with ceramic fibre but not with asbestos.

The occurrence of tumours caused by a non-asbestos dust in rats was also reported by Wagner and Wagner (30). In this case the tumours resulted from the intrapleural injection of quartz and grew mainly in the pleural cavity, being diagnosed as thymomas. However, some of the histological patterns reported were very similar to the malignant histiocytomas found in the present study.

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The ability of ceramic fibre to cause pulmonary neoplasms contrasts with the small numbers of mesotheliomas that developed following intraperitoneal injection. Only three tumours were produced by this dust when close to thirty would have been produced by similar doses of a number of asbestos types (24). Work by Stanton et al. (3,4) has suggested that the mineral fibres most likely to cause mesotheliomas after intrapleural implantation are those > 8 µm long and < 1.5 µm in diameter. Since the ceramic fibre dust used in the present study had relatively few fibres of this size per cm³, as well as much particulate material and many short thin fibres, the low production of mesotheliomas is in keeping with Stanton's suggestions. However, it had appeared likely that the fibres most able to produce mesotheliomas were also likely to be the most carcinogenic to lung tissue. The findings from the present study suggest that this may not be the case.

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Since the inhalation of dust from ceramic aluminium silicate insulation material has produced both pulmonary fibrosis and neoplasia in rats, the use of these man-made mineral fibres in industry should be undertaken with caution.

Acknowledgement

This work formed part of the research programme funded by the British Asbestosis Research Council.

References

1. Selikoff, I.J. & Lee, D.H.K. Asbestos and disease. New York, Academic Press, 1978 (Environmental sciences monograph series).
2. Gross, P. et al. Pulmonary ferruginous bodies. Archives of pathology, 85: 539-546 (1968).
3. Stanton, M.F. & Wrench, C. Mechanisms of mesothelioma induction with asbestos and fibrous glass. Journal of the National Cancer Institute, 48: 797-821 (1972).

4. Stanton, M.F. et al. Carcinogenicity of fibrous glass: pleural response in the rat in relation to fiber dimension. Journal of the National Cancer Institute, 58: 587-603 (1977).
5. Davis, J.M.G. Pathological aspects of the injection of glass fibre into the pleural and peritoneal cavities of rats and mice. In: Occupational Exposure to Fibrous Glass. Report of a Symposium held at the University of Maryland, 1974. US Department of Health, Education and Welfare, National Institute for Occupational Health, 1976, pp. 141-151 (HEW Publication No. (NIOSH) 76-151).
6. Pott, F. et al. Results of animal carcinogenesis studies after application of fibrous glass and their implications regarding human exposure. In: Occupational Exposure to Fibrous Glass. Report of a Symposium held at the University of Maryland, 1974. US Department of Health, Education and Welfare, National Institute for Occupational Health, 1976, pp. 183-193 (HEW Publication No. (NIOSH) 76-151).
7. Wagner, J.C. et al. Studies on the carcinogenic effects of fiber glass of different diameters following intrapleural inoculation in experimental animals. In: Occupational Exposure to Fibrous Glass. Report of a Symposium held at the University of Maryland, 1974. US Department of Health, Education and Welfare, National Institute for Occupational Health, 1976, pp. 193-198 (HEW Publication No. (NIOSH) 76-151).
8. Wright, G.W. & Kuschner, M. The influence of varying lengths of glass and asbestos fibres on tissue response in guinea pigs. In: Walton, W.H., ed. Inhaled particles IV. Oxford, Pergamon Press, 1977, pp. 455-472.
9. Gross, P. The effects of fibrous glass dust on the lungs of animals. In: Occupational Exposure to Fibrous Glass. Report of a Symposium held at the University of Maryland, 1974. US Department of Health, Education and Welfare, National Institute for Occupational Health, 1976, pp. 169-178 (HEW Publication No. (NIOSH) 76-151).
10. Lee, K.P. et al. Pulmonary response to glass fiber by inhalation exposure. Laboratory investigation, 40: 123-133 (1979).
11. Lee, K.P. et al. Comparative pulmonary responses to inhaled inorganic fibers with asbestos and fiberglass. Environmental research, 24: 167-191 (1981).
12. Hardy, C.J. Pulmonary effects of glass fibres in man and animals. Arhiv za higijenu rada i toksikologiju, 30(Suppl.): 861-870 (1980).
13. Wright, G.W. Airborne fibrous glass particles. Archives of environmental health, 16: 175-181 (1968).
14. Gross, P. et al. Lungs of workers exposed to fiber glass. A study of their pathological changes and their dust content. Archives of environmental health, 23: 67-76 (1971).
15. Hill, J.W. Glass fibres, absence of pulmonary hazard in production workers. British journal of industrial medicine, 30: 174-179 (1973).
16. Enterline, P.E. & Henderson, V. The health of retired fibrous glass workers. Archives of environmental health, 30: 113-116 (1975).
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lungs of animals.
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ational Health,
1981).
by inhalation
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and animals.
861-870 (1980).
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174-179 (1973).
red fibrous glass
116 (1975).

17. Bayliss, D.L. et al. Mortality patterns among fibrous glass productive workers. Annals of the New York Academy of Sciences, 271: 324-335 (1976).
18. Timbrell, V. et al. Exposure chambers for inhalation experiments with standard reference samples of asbestos of the International Union Against Cancer. Journal of aerosol science, 1: 215-223 (1970).
19. Beckett, S.T. The generation and evaluation of UICC asbestos clouds in animal exposure chambers. Annals of occupational hygiene, 18: 187-198 (1975).
20. Dunmore, J.H. et al. An instrument for the sampling of respirable dust for subsequent gravimetric assessment. Journal of scientific instruments, 41: 669-672.
21. Asbestosis Research Council. The measurement of airborne asbestos dust by the membrane filter method. Rochdale, United Kingdom (ARC Technical Note No. 1).
22. Gleit, C.E. & Holland, W.D. Use of electrically excited oxygen for the low temperature decomposition of organic substances. Analytical chemistry, 34: 1454-1462 (1962).
23. Beckett, S.T. et al. The use of infra-red spectrophotometry for the estimation of small quantities of single varieties of UICC asbestos. Annals of occupational hygiene, 18: 313-320 (1975).
24. Bolton, R.E. et al. Variations in the carcinogenicity of mineral fibres. In: Walton, W.H., ed. Inhaled particles V. Oxford, Pergamon Press (in press).
25. Davis, J.M.G. et al. Mass and number of fibres in the pathogenesis of asbestos-related lung disease in rats. British journal of cancer, 37: 673-688 (1978).
26. Davis, J.M.G. et al. The effects of intermittent high asbestos exposure (peak dose levels) on the lungs of rats. British journal of experimental pathology, 61: 272-280 (1980).
27. Davis, J.M.G. et al. A comparison of the pathological effects in rats of the UICC reference samples of amosite and chrysotile with those of amosite and chrysotile collected from the factory environment. In: Wagner, J.C., ed. Biological effects of mineral fibres. Lyon, International Agency for Research on Cancer, 1980, pp. 285-292 (IARC Scientific Publication No. 30).
28. Botham, S.K. & Holt, P.F. Development of asbestos bodies on amosite, chrysotile and crocidolite fibres in guinea-pig lungs. Journal of pathology, 105: 159-167 (1971).
29. Jaurand, M.C. et al. Solubilité du chrysotile in vitro et dans le poumon humain. Revue française des maladies respiratoires, 4 (Suppl. 2): 111-120 (1976).
30. Wagner, M.M.F. and Wagner, J.C. Lymphomas in the Wistar rat after intrapleural inoculation. Journal of the National Cancer Institute, 49: 81-91 (1972).

Table 1. The survival pattern of rats treated with ceramic aluminium silicate glass fibre dust by inhalation^a

	Months after the start of dust exposure			
	12	18	24	33
Number of surviving dusted rats	48	44	33	7
Group size, 48				
Number of surviving controls	39	32	29	7
Group size, 40				

^a The survival pattern of a group of control animals is included for comparison. The experiment was terminated at 33 months after the start of dusting. Groups of four treated animals were killed at both 12 and 18 months. A group of four control animals was killed at 12 months.

Table 2. Sites of tumours, other than lung

Organ system	Ceramic fibre	Control	Malignant

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Table 2. Sites of tumours, other than lung

Organ system	Ceramic fibre		Control	
	Benign	Malignant	Benign	Malignant
Digestive/peritoneal	3	3 ^a	3	2
Urogenital	3	-	1	2
Endocrine	1	-	2	1
Musculo, skeletal and integumentary	1	2	3	2
RE/vascular	-	3	2	2
Total	8	8	11	9

^a Includes one peritoneal mesothelioma.

Fig. 1. Light microscope photograph of a sample of the ceramic aluminium silicate glass fibre used in the present study; magnification, 450x

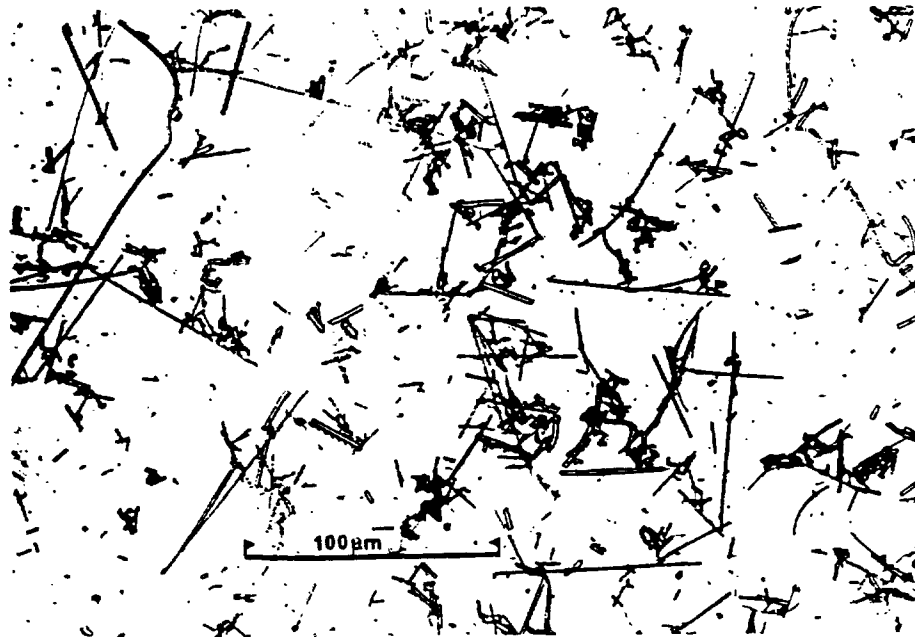


Fig. 2. Le
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Note: this dust was collected from the air in the inhalation chamber.

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Fig. 2. Length distribution of ceramic aluminium silicate fibres longer than 5 μ m



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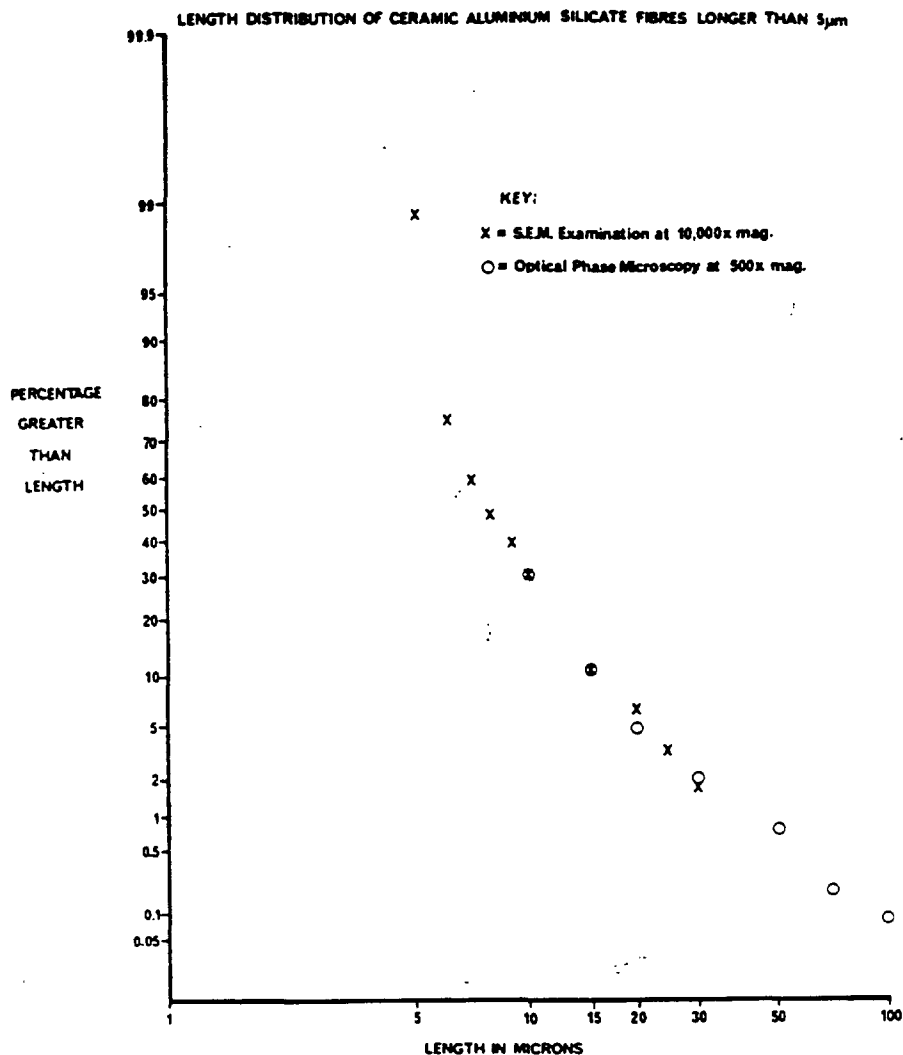
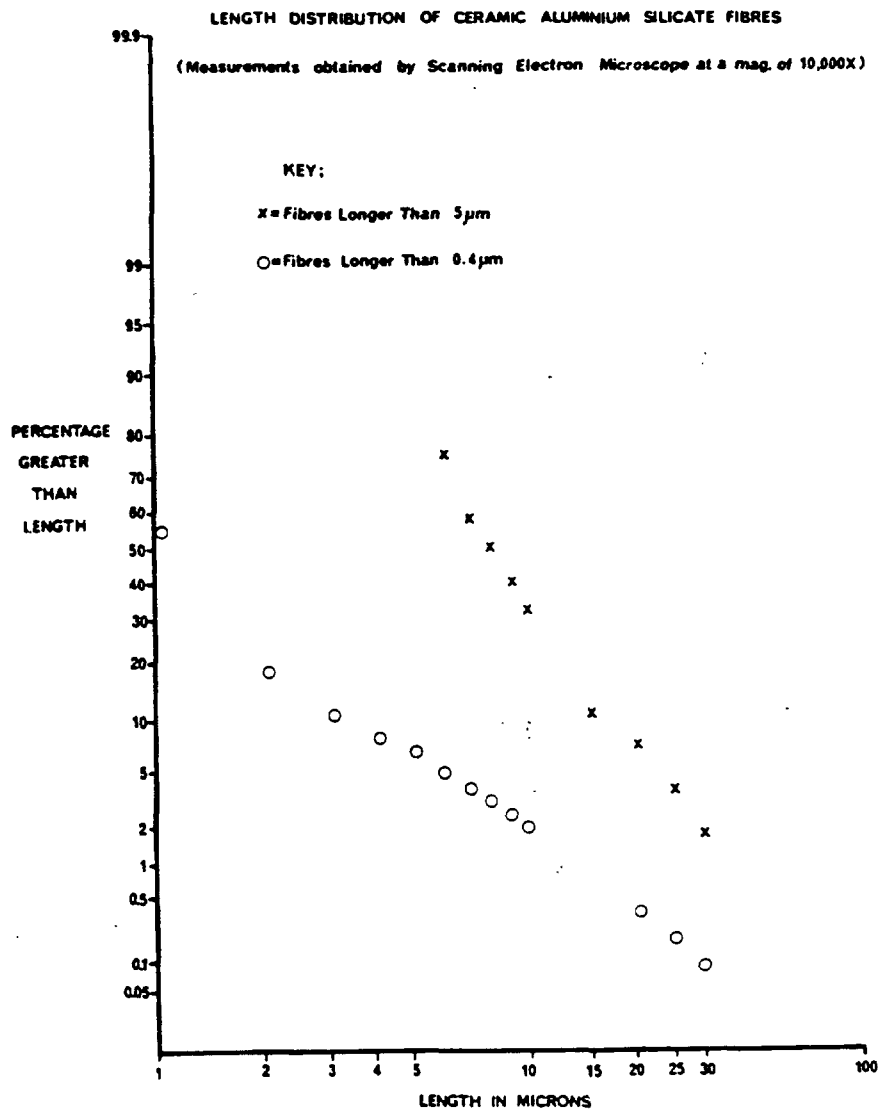
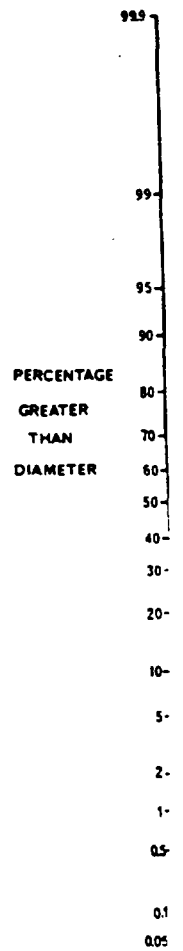


Fig. 3. Length distribution of ceramic aluminium silicate fibres



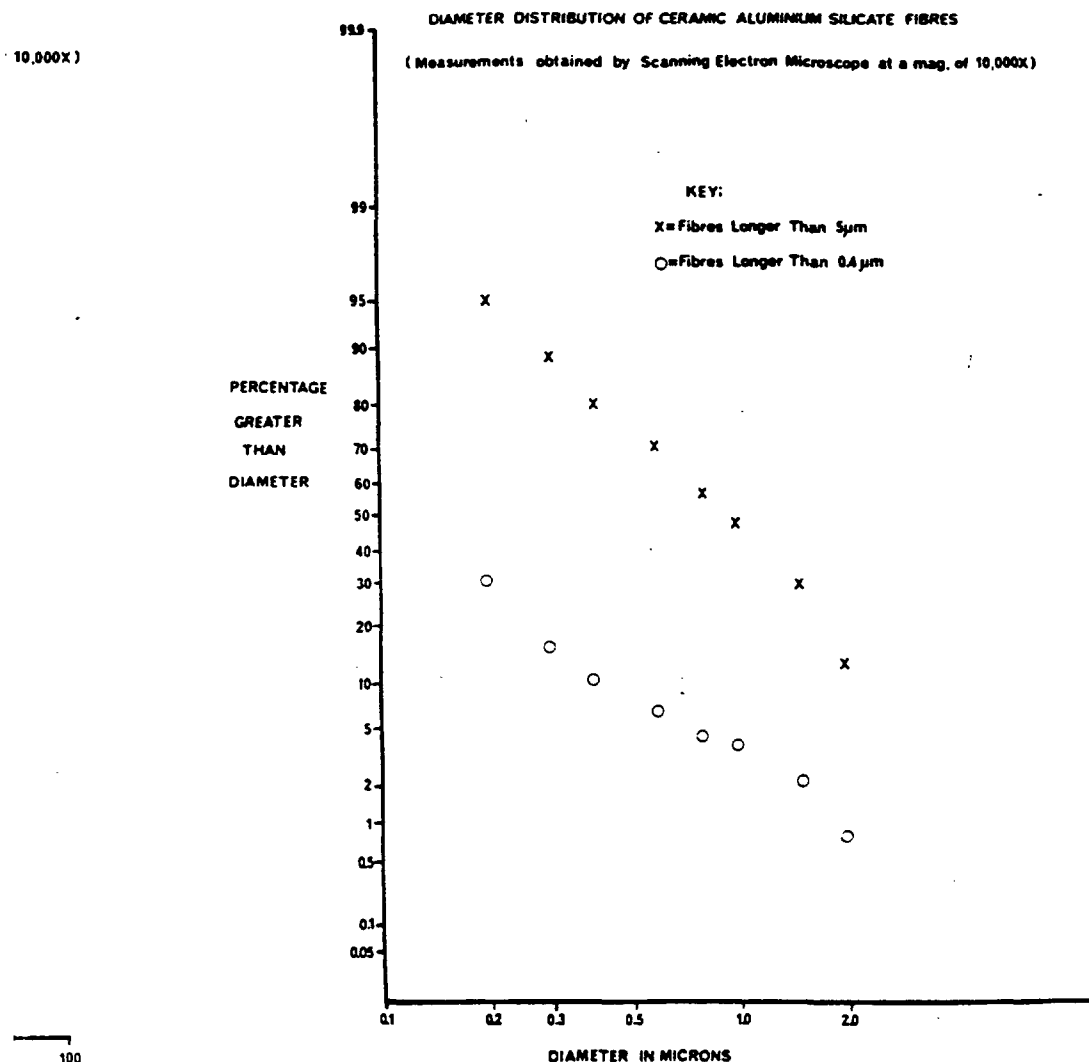
Note: measurements obtained by scanning electron microscope at a magnification of 10 000x.

Fig. 4. Diame



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Fig. 4. Diameter distribution of ceramic aluminium silicate fibres



Note: measurements obtained by scanning electron microscope at a magnification of 10 000x.