PLAINTIFF'S
EXHIBIT
tabbies
UC-1278

Health Hazards of Asbestos: A Review of Recent Trends

HILTON C. LEWINSOHN
Chief Medical Officer, TBA Industrial Products Limited, PO Box 40, Rochdale, Lancs.

Reprinted from *The Journal of the Society of*
OCCUPATIONAL MEDICINE (1974) **24**, 2–10

John Wright and Sons Limited, 1974

AU2228

CTC008854

The 1964 Working Group recommended that standard reference samples of respirable size of amosite, chrysotile, tremolite, anthophyllite and crocidolite be prepared from as pure parent material as possible. Timbrell (1972a) reported that samples of chrysotile and crocidolite had been prepared in Johannesburg from donations by various asbestos producers. The two distributing centres for the 'UICC samples', Johannesburg PRU (Pneumoconiosis Research Unit), and the Medical Research Council PU (Pneumoconiosis Unit), Penarth, have recorded 250 recipients and many more researchers have obtained supplies from colleagues.

The UICC samples have been analysed for their important physical and chemical properties in several countries (Timbrell, 1970). The samples have been checked for homogeneity, contamination and oil content. The chemical composition of the reference samples has been compared with that of commercial fibre of the same type and has been found to be unchanged. The samples have been prepared in such a manner that the fibre length distributions will extend up to 200 μm., being comparable with asbestos fibre lengths detected in lungs. Longer fibres are undesirable because they impede the use of the sample for injection experiments. A special dispenser has been developed to generate dust clouds for inhalation experiments (Timbrell et al., 1968).

Gilson (1966) has stressed the importance of fibre length and aerodynamic equivalent diameter in determining the respirability of airborne dust. Timbrell (1972a) has reviewed the importance of the physical properties of asbestos in the aetiology of asbestos diseases. He states that the ability of long fibres (up to 200 μm.) to reach the alveolar regions, if they are thin enough not to be deposited earlier by sedimentation and impaction, explains satisfactorily the numerous long fibres found in lung sections. He points out that 'the epidemiological, pathological and experimental evidence presents a series of paradoxes which are useful in testing ideas concerning the aetiology'. The marked difference in physical properties between the asbestos minerals from the north-western Cape Province and the Transvaal may be a clue to the difference in the incidence of mesotheliomas in these two mining regions.

Timbrell (1972b) suggests that long fibres are preferentially deposited in the respiratory bronchioles at bifurcations and that this may explain why fibrosis tends to be associated first with respiratory bronchioles and with long fibres. Rats exposed to dust clouds of chrysotile and amphibole UICC samples at equal concentration retain six times more amphibole than chrysotile after six months. Timbrell suggests that this may be partly due to the characteristic 'rectilinear' shape of amphibole fibres compared to the 'curly' morphology of chrysotile fibres, allowing the amphiboles to penetrate to deeper parts of the lung more efficiently than chrysotile fibres. He has demonstrated this by means of studies using lung casts. A reasonable theory has thus been proposed to explain the reason for the development of mesotheliomas. It is based upon the ability of certain types of fibre to penetrate deeper into the lungs than others and to reach the pleural cavity by direct penetration. Timbrell points out that in rats exposed to dust clouds of UICC samples at equal concentrations and killed immediately after a 'short exposure', small numbers of crocidolite fibres have been detected near the visceral pleura, fewer amosite fibres have been found in this region, still fewer anthophyllite fibres and chrysotile fibres have very seldom been found near the pleura. Work is currently in progress using radioactive tracer studies to attempt to confirm this observation. It is possible that short, straight, chrysotile fibres may behave aerodynamically like amphibole fibres.

The significance of Timbrell's theory regarding the role of interception and penetration in the ultimate deposition of asbestos fibres, either in respiratory bronchioles or near the pleural surface, is that it offers a reasonable explanation for the difference in incidence of pleural mesothelioma in crocidolite exposed populations as opposed to chrysotile exposed populations. The difference between the incidence of mesotheliomas in the north-west Cape and the Transvaal (where tumours are very rare), may be related to the fact that differences in particle size in the crocidolite from these regions affect their aerodynamic behaviour and deposition in the lung. It has been shown that Transvaal fibres, both crocidolite and amosite, are on average three times the diameter and three times the length of north-western Cape crocidolite fibres. Hence a sample of north-western Cape asbestos will produce twenty-seven times the number of fibres as the same mass of

AU2230

CTC008856

3. It is physically altered in biological residence enabling clearance by (1), (2), or phagocytosis to be more readily achieved.

The role of particle length in the development of fibrosis and the other biological effects of asbestos has not been resolved. This factor must be considered in conjunction with the fibre type and the effects of asbestos on macrophages and other cells.

It is now generally accepted that certain types of asbestos can interact with cell membranes. MacNab and Harrington (1967), Secchi and Rezzonico (1968) and Schnitzer and Pundsack (1970) have demonstrated the marked haemolytic effects of chrysotile and have confirmed the absence of marked haemolytic properties in the amphiboles. Allison (1972) has studied the effects of asbestos particles on macrophages, mesothelial cells and fibroblasts. He has found that, irrespective of the asbestos type, short fibres (<5 μm) are readily and completely taken up by phagocytosis whereas long fibres (>25 μm) are never completely taken up. Part of the long fibre remains out of the phagocyte. Two or more cells can sometimes be seen attached to a single long fibre and there is a suggestion that cell fusion may eventually occur. Particles of intermediate size (5–25 μm) are sometimes completely ingested and sometimes not. Allison has shown that chrysotile can exert an early cytotoxic effect soon after entering the cell because of interaction with the plasma membrane or a late effect as a result of disruption of the lysosomal membrane. When asbestos particles are added to organ cultures of mesothelium, these cells prove to be highly phagocytic, showing delayed cytotoxicity to high doses of chrysotile. They tolerate small doses of crocidolite well.

The emphasis in experimental pathology has shifted from asbestosis to carcinogenesis. Stanton (1972) has shown that fibres about 20–200 μm in length or 0·5–5 μm in diameter are more carcinogenic than larger or smaller fibres. This applies to both asbestos fibres and to glass fibre particles (the latter having been specially prepared for experimental purposes only), and Stanton believes that carcinogenicity of such particles seems to be related to their shape and size rather than to their physico-chemical properties. Mesotheliomas can be produced experimentally by pleural implants of asbestos, glass fibre and aluminium-oxide fibres of similar size. Maroudas et al. (1973) in an elegant experiment *in vitro*, have shown that the lengths of glass fibres which will induce growth of fibroblasts in culture correlate with the lengths of asbestos and other mineral fibres which will induce mesothelioma in the rat.

Particles smaller than 20 μm. in length do not induce growth *in vitro* or mesothelioma *in vivo*. The experiments of Rajan et al. (1972) and Maroudas et al. (1973) demonstrate the value to be derived from the study of organ culture and cell culture systems in investigating the effect of various fibres, chemicals and carcinogens in a relatively short period.

The significance of labile cations attached to the silicon-oxygen lattice, metallic contaminants, and adsorbed organic compounds (of geological origin or from contamination during commercial handling) is being investigated. Harrington (1962) has demonstrated the presence of oils in asbestos samples, one of which is 3,4-benzpyrene. Harrington (1965) has also described the possible contamination of asbestos fibres by jute oils. Gibbs (1970) has shown that fibre stored in polyethylene bags may become contaminated with 'oils'. Wagner et al. (1970) have shown that the presence or absence of the oils found by Harrington does not appear to alter the incidence of mesotheliomas produced by intrapleural inoculation in rats. Reeves et al. (1971), reviewing progress in experimental asbestos carcinogenesis, point out that the major metallic components present in asbestos are aluminium, magnesium and iron. Trace levels of chromium, nickel and cobalt are regularly found. While iron itself is not regarded as carcinogenic, experimental tumours have been produced by iron-dextran complexes, where the bonding of iron to the polymer may have been similar to that in asbestos (Richmond, 1959 quoted by Reeves et al., 1971). The trace levels of chromium and nickel in asbestos may play a role as environmental carcinogens. Dixon et al. (1970) reported that Fe^{3+} and Cr^{6+} both of which can be found in chrysotile asbestos, inhibit the action of benzpyrene hydroxylase, a detoxifying enzyme that protects the organism from the effects of benzpyrene. The interesting possibilities which this observation opens up with regard to asbestos carcinogenesis and the role of tobacco smoke have not yet been investigated in any depth.

Since Gilson posed the questions regarding the role of asbestos bodies in the pathogenesis of

AU2232

CTC008858

and are being studied (Selikoff et al., 1972a). The British Occupational Hygiene Society published its Hygiene Standards for Chrysotile Asbestos Dust in June, 1968. The data used were scanty, and based on factory experience of continuous exposure during working hours at an asbestos textile factory situated in a conurbation with a high prevalence of chronic bronchitis. This, however, is the only population studied thus far where it has been possible, because of reasonable dust exposure records, to relate clinical findings and X-ray changes to dust counts. When the BOHS Committee on Hygiene Standards' Sub-Committee on chrysotile asbestos reviewed the Standard in 1973, it was recommended that no change be made at the present time but that the Standard be kept under review. The Standard is designed to reduce the risk of contracting asbestosis to 1 per cent of those who have a lifetime's exposure to dust. By asbestosis the Committee meant the earliest demonstrable effects on the lung due to asbestos. The probability that the risk of being affected to this extent will be less than 1 per cent depends upon a cumulative exposure of 100 fibre years per cm^3. If a man works in a dust concentration of 2 fibres per cm^3 for 50 years, he should have less than a 1 per cent risk of developing the earliest demonstrable effects on the lung due to asbestos. The size range of fibres to be counted, based upon pathological observation of fibres retained in the lungs, is expressed in terms of the number of fibres per cm^3 greater than 5 μm in length, as determined with the standard membrane filter method. In industrial practice it is customary to count fibres in the 5–100 μm range.

The standard is derived from the correlation between the development of basal râles and dust exposure, while X-rays were not considered by the Sub-Committee to reflect the earliest effects of asbestos exposure on the lungs. Since the standard was produced an internationally recommended classification of the radiographic appearances of pneumoconiosis, suitable for use in the surveillance of asbestos workers has been developed (International Labour Office, 1972). The early use of this classification indicates that the chest radiograph may well be the most important means for the detection and monitoring of the biological effects of asbestos in the lungs. Systematic studies have allowed wider recognition of the fact that bilateral pleural plaques, pleural thickening and pleural calcification are more often caused by asbestos inhalation than was previously recognized. The use of this classification has shown the importance of separating rounded and irregular opacities, pleural thickening and pleural calcification. Rounded small opacities are more prevalent where exposures have been to other mineral dusts as well as to asbestos, in particular silica. They relate more closely to estimates of past dust exposure intensity. Irregular opacities have not yet been related to the mass of asbestos or other dusts in the lung, and may well be an index of tissue response rather than the amount of dust present. In view of the development of this radiological classification and its apparent effectiveness in demonstrating early changes due to asbestos exposure, the next review of the Standard which is undertaken may have to be based on such changes rather than basal râles.

The evidence for a dose-response relationship for asbestosis appears to have been confirmed in the textile section of the asbestos industry by the decreasing incidence of the disease following the introduction of the Asbestos Industry Regulations (1931), which took effect in 1933 (Smither and Lewinsohn, 1972). In other industries, not covered by the Regulations, the incidence of asbestosis appeared to increase, and case-finding exercises in naval dockyards (Harries, 1968) and elsewhere added to the number. The Asbestos Regulations 1969 were made and took effect in May 1970. These Regulations were designed to apply to all manufacture or uses of asbestos where dangerous concentrations of dust are found. The standards to be applied in the interpretation of these Regulations are to be found in Technical Data Note 13, published by HM Factory Inspectorate in the Department of Employment (1969). Recognizing the apparent difference in biological effects between chrysotile and crocidolite, the Regulations specify certain stringent conditions relating to the use of the latter and impose a tighter standard in TDN 13. It is the hazard of malignant disease which stimulates the continued interest in the biological effects of asbestos. Merewether (1949) first demonstrated a clear-cut association between asbestosis and lung carcinoma. Over 50 per cent of asbestosis sufferers die as a result of lung cancer and in populations where asbestosis still occurs may be the main cause of excess deaths (Buchanan, 1965). It has been shown that where the level of exposure is reduced

AU2234

CTC008860

of chest radiography, including the use of 100 mm. films.

6. Development of statistical procedures for analysis and presentation of serial observations.

The diagnostic criteria for asbestosis have not been greatly altered since the days of Merewether (1930) except for the addition of lung function tests as confirmatory evidence of pulmonary fibrosis. Correlation between the dust content of the factory environment, the dust content in the lungs, radiographic appearances, physical signs and physiological changes is urgently required. The reason for the apparent differences between miners and millers of asbestos and asbestos textile workers might be forthcoming from such detailed studies.

The Department of Employment has commenced a prospective epidemiological survey of asbestos workers which should assist in clarifying the relationship between fibre type, dust concentration, radiological changes and physical signs. The data will be analysed after taking into account individual smoking habits, age, sex and dust exposure besides asbestos in order to determine their combined effects.

The value of all this research to the industrial medical officer is that it enables medical surveillance programmes designed to monitor specific information to be developed, and thereby gives purpose and direction to his efforts on behalf of the exposed worker. There is, as yet, no cure for asbestosis other than that effected by the engineer controlling the emission of dust from industrial processes and reducing it to acceptable safe levels as indicated by epidemiological data obtained from studying those at risk. Asbestos is a useful mineral with unique properties applicable to modern technological developments more than ever before. There are substitutes for some of its conventional uses, but there are many uses of asbestos where no substitute will do the task as effectively or as cheaply. Providing asbestos can be used under controlled conditions there would seem to be no reason for discontinuing its production.

REFERENCES

Allison, A. C. (1972) *Effects of Asbestos Particles on Macrophages, Mesothelial Cells and Fibroblasts, WHO/IARC Meeting of a Working Group to Review the Biological Effects of Asbestos, 2–5 October 1972, Paper 15.* Lyon.

Ashcroft, T. and Heppleston, A. G. (1973) The optical and electron microscopic determination of pulmonary asbestos fibre concentration and its relation to human pathological reaction. *Journal of Clinical Pathology* **26**, 224–234.

British Occupational Hygiene Society Committee on Hygiene Standards (1968) *Annals of Occupational Hygiene* **11**, 47.

Buchanan, W. D. (1965) *Annals of the New York Academy of Sciences* **132**, Art. 1, 507–518.

Cunningham, H. M. and Pontefract, R. (1971) Asbestos fibres in beverages and drinking water. *Nature* **232**, 332.

Department of Employment (1969) *Factories: The Asbestos Regulations 1969.* Statutory Instruments 1969, No. 690. London, HMSO.

Department of Employment (1969) *Standards for Asbestos Dust Concentration for Use with the Asbestos Regulations 1969.* HM Factory Inspectorate—Technical Data Note 13.

Deutsches Zentralinstitut für Arbeitsmedizin—Berlin Gesellschaft für Arbeitshygiene und Arbeitsschutz in der DDR (1968) *Internationale Konferenz über die Biologischen Wirkungen des Asbestes*, 22–25 April 1968, Dresden.

Dixon, J. R. et al. (1970) The role of trace metals in chemical carcinogenesis: asbestos cancers. *Cancer Research* **30**, 1068–1074.

Doll, R. (1971) Cancer and ageing: the epidemiological evidence. In: *Year Book of Oncology*, Volume V. New York, Year Book Medical Publishers, pp. 1–27.

Gibbs, G. W. (1970) Asbestos fibre contamination by storage in polythene bags. In: Shapiro, H. A. (ed.), *Pneumoconiosis: Proceedings of the International Conference, Johannesburg, 1969.* Cape Town, Oxford University Press, pp. 165–167.

Gilson, J. C. (1966) Wyers Memorial Lecture 1965—Health hazards of asbestos: recent studies on its biological effects. *Transactions of the Society of Occupational Medicine* **16**, 62–74.

Gilson, J. C. (1973) Asbestos cancer: past and future hazards. *Proceedings of the Royal Society of Medicine* **66**, 395–403.

Hammond, E. C. and Selikoff, I. J. (1972) *Relation of Cigarette Smoking to Risk of Death of Asbestos-associated Disease among Insulation Workers in the United States, WHO/IARC Meeting of a Working Group to Review the Biological Effects of Asbestos, 2–5 October 1972, Paper 46. Lyon.* To be published.

Harries, P. G. (1968) Asbestos hazards in naval dockyards. *Annals of Occupational Hygiene* **11**, 134.

Harrington, J. S. (1962) Occurrence of oils containing 3,4 benzpyrene and related substances in asbestos. *Nature* **193**, 43–45.

Harrington, J. S. (1965) Chemical studies of asbestos. *Annals of the New York Academy of Sciences* **132**, Art. 1, 31–47.

International Labour Office (1972) *International Classification of Radiographs of Pneumoconiosis, ILO U/C Classification 1971.*

International Union Against Cancer, UICC (1965) Report and recommendations of the working group on asbestos and cancer. *British Journal of Industrial Medicine* **22**, 165–171.

Knox, J. F., Holmes, S., Doll, R. and Hill, I. D. (1968) Mortality from lung cancer and other causes among workers in an asbestos textile factory. *British Journal of Industrial Medicine* **25**, 293–303.

AU2236

CTC008862