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DIRECTOR OF THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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The meeting was held at the International Agency for Research on Cancer, Lyon, France on 5th and 6th October, 1972. The Committee consisted of three panels - Epidemiology, Pathology, Physics and Chemistry.

Epidemiology Panel

Dr. M. Becklake	McGill University, Department of Epidemiology & Health, 3775 University Street, Montreal 110, Quebec, Canada.
Dr. H. Bohlig	Chefarzt der Strahlenabteilung des Stadtischen, Krenkenhauses Ludenscheid, 588 Ludenscheid, Germany
Dr. N. Day	Unit of Epidemiology and Biostatistics, International Agency for Research on Cancer, 150 Cours Albert Thomas, 69008, Lyon, France.
Prof. P. C. Elmes	Department of Therapeutics and Pharmacology, Queen's University of Belfast, Institute of Clinical Science, Grosvenor Road, Belfast, BT12 6BJ, N. Ireland, UK.
Dr. J. C. Gilson	Medical Research Council, Pneumoconiosis Unit, Llandough Hospital, Penarth, Glamorgan, Wales, UK. (Chairman)
Dr. J. Lepoutre	Medical Department, N.V. Eternit, Kapelle-op-den-Bos, Belgium.
Prof. J. C. McDonald	McGill University, Department of Epidemiology & Health, 3775 University Street, Montreal 110, Quebec, Canada.
Mr. C. E. Rossiter	Medical Research Council, Pneumoconiosis Unit, Llandough Hospital, Penarth, Glamorgan, Wales, UK.
Dr. H. Sakabe	Department of Industrial Physiology, Ministry of Labour, National Institute of Industrial Health, 2051 Kizukisumioyoshi-Cho, Kawasaki, Japan.
• Dr. I. J. Selikoff	Department of Medicine, Mount Sinai School of Medicine, Fifth Avenue and 100th Street, New York, N.Y. 10029, USA.
Dr. G.K. Sluis-Cremer	South African Medical Research Council, National Research Institute for Occupational Diseases, P.O. Box 4788, Johannesburg, S. Africa.
Dr. W. Smither	Cape Asbestos Co. Ltd., 114 Park Street, London W1Y 4AB England, UK.
Dr. G. Wright	Division of Medicine, St. Luke's Hospital, 11311 Shaker Boulevard, Cleveland, Ohio 44101, USA.

• Unable to attend.

PLAINTIFF'S EXHIBIT
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Pathology Panel

Dr. A. C. Allison	Clinical Research Centre, Watford Road, Harrow, Middlesex, HA1 3UJ, UK.
Mr. G. Berry	Medical Research Council, Pneumoconiosis Unit, Llandough Hospital, Penarth, Glamorgan, Wales, UK.
Dr. P. Bogovski	Unit of Environmental Carcinogens, International Agency for Research on Cancer, 150 Cours Albert Thomas, 69008, Lyon, France.
Dr. M. Kammerstein	Pathology Department, Barnert Memorial Hospital Centre. 680 Broadway, Paterson, N.J. 07514, USA
Prof. W.T.E.McCaughey	School of Pathology, Trinity College, University of Dublin, Dublin 2, Eire.
Prof. D. Magner	Canadian Tumour Reference Centre, Department of Pathology, University of Ottawa, Ottawa, Ontario, KIN 6N5, Canada.
Prof. H. Otto	Direcktor des Pathologischen Instituts der Stadt Krankenanstalten Beurhausstrase 40, 46 Dortmund, W. Germany.
Dr. H. T. Plantcydt	Stichting Streeklaboratorium"Zeeland", Noordpoortplein 2 Middelburg, Netherlands.
Dr. M. Stanton	Department of Health, Education and Welfare, National Institute of Health, Bethesda, MD 20014, USA.
Dr. J. C. Wagner	Medical Research Council, Pneumoconiosis Unit, Llandough Hospital, Penarth, Glamorgan, Wales, UK. (Chairman)
Prof. S. Watanabe	Department of Pathology, National Cancer Centre, Research Institute, Tsukiji, 5-1-1, Chuoku, Tokyo, Japan.
Prof. I. Webster	Medical Research Council South Africa, National Research Institute for Occupational Diseases, P.O. Box 4788, Johannesburg, South Africa.

Physics and Chemistry Panel

Dr. L. Le Bouffant	Laboratoire du Centre D'Etudes et Recherches des Charbonnages de France, Verneuil-en-Hallatte, BP No.27. 60 - Creil, France.
Mr. G. W. Gibbs	McGill University, Department of Epidemiology & Health, 3775 University Street, Montreal 110, Quebec, Canada.
Dr. S. Holmes	Asbestosis Research Council, c/o Turner Bros. Asbestos Co. Ltd. P.O. Box 40, Rochdale, England, UK.
Mr. A. Morgan	Atomic Energy Research Establishment, Health Physics and Medical Division, Building 364, Harwell, Berks., England, UK.

Dr. P. D. Pooley	Department of Mineral Exploitation, University College of S. Wales and Monmouthshire, Newport Road, Cardiff, Wales, UK.
Dr. S. Speil	Johns Manville Research and Engineering Centre, P.O. Bo 159, Manville, New Jersey, USA.
Dr. V. Timbrell	Medical Research Council, Pneumoconiosis Unit, Llandough Hospital, Penarth, Glamorgan, Wales, UK.
Dr. R. du Toit	Government Mining Engineer's Division, Department of Mines, P.O. Box 1132, Johannesburg, South Africa.
Mr. W. H. Walton	Institute of Occupational Medicine, Roxburgh Place, Edinburgh EH 8 9SU, Scotland, UK. (Chairman)

The panels met in a separate session and at the final session (Chairman Dr. J. Gilson) prepared this report to the Director of the International Agency for Researc on Cancer.

TERMS OF REFERENCE

1. The Committee was to report on the present evidence relating exposure to asbestos dust to cancers, especially that obtained since the meeting of the UICC Working Group on Asbestos Cancers in 1964.

2. The Committee was to make recommendations for further research and indicate priorities for work of immediate and long-term value.

CO-ORDINATION OF INTERNATIONAL CO-OPERATION

Following the meeting of the UICC Working Group on Asbestos and Cancers in 1964, a Sub-Committee of the UICC Commission on Geographical Pathology and Environmental Carcinogens (Chairman Dr. J. Higginson) was formed to co-ordinate work required to achieve the recommendations.

In April 1970 agreements between the UICC and the IARC led to the winding up of the UICC Sub-Committee and the IARC taking on responsibility for the Sub-Committee's work and extending it by supporting certain projects on asbestos cancers in several countries. The Agency has done this as part of their wider programme of investigating environmental carcinogens. Common memberships between

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the UICC Sub-Committee and the Committee advising the IARC ensured continuity of policy.

In October 1972 the IARC held an international Conference with 137 participants from 20 countries to review all the evidence relating asbestos with cancers. Subsequently the Advisory Committee prepared its report. This is divided into two sections. First, a general review in the form of answers to a number of important general questions about the relation of asbestos to cancers of different sites and, secondly, recommendations for further research.

GENERAL REVIEW

1. Are all major commercial types of asbestos able to cause lung carcinoma?

Yes. Since 1964 the evidence of a causal relationship has been increased by epidemiological studies showing exposure-response relations for the incidence of lung carcinomas. The production of lung carcinomas in certain animals by all types of asbestos supports this conclusion. The epidemiological evidence in man, however, shows that there are clear differences in risk with type of fibre and nature of exposure.

2. Is there evidence of an increased risk of lung carcinoma at low levels of exposure to asbestos, such as have been encountered by the general population in urban areas?

The evidence of an exposure-response relationship based in part on past dust measurements and in part on the type of job within the industry suggests that an excess lung carcinoma risk is not detectable when the occupational exposure has been low. These low occupational exposures have almost certainly been much greater than that to the public from general air pollution.

3. Since 1964 has the evidence relating past exposure to asbestos and mesotheliomas changed?

The evidence has been greatly strengthened by further prospective and retrospective mortality studies in many countries of populations exposed to asbestos There is evidence that all commercial types of asbestos except anthophyllite may h

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responsible. Evidence for an important difference in risk in different occupations and with the type of asbestos has increased. The risk is greatest with crocidolite, less with amosite and apparently less with chrysotile. With amosite and chrysotile there appears to be a higher risk in manufacturing than in mining and milling. There is also evidence from population studies that a proportion of cases of mesothelioma have no known association with exposure to asbestos.

4. Is there evidence of an increased risk of mesothelial cancers at low levels of exposure to asbestos, such as have been encountered by the general population in urban areas?

There is evidence of an association of mesothelial tumours with air pollution in the neighbourhood of crocidolite mines and of factories using mixtures of asbestos fibre types. The evidence relates to conditions many years ago. There is evidence of no excess risk of mesotheliomas from asbestos air pollution which has existed in the neighbourhood of chrysotile and amosite mines. There are reported differences on incidence of mesothelioma between urban and rural areas, the causes of which have not been established. There is no evidence of a risk to the general public at present.

5. Since 1964 has the evidence changed on the importance of other factors such as cigarette smoking, waxes, oils and trace elements as contributory factors to the cancer risks?

The evidence has accumulated indicating:

(1) Cigarette smoking is an important factor enhancing the lung carcinoma risk in asbestos-exposed workers, in both men and women. Asbestos workers have specially strong grounds for giving up smoking to protect their health. No association has been demonstrated between cigarette smoking and mesotheliomas.

(2) Animal experiments designed thus far to test the importance of waxes and oils as contributory factors in the production of

mesothelioma have shown these contaminants are unlikely to be relevant.

(3) From animal experiments there are no good clues suggesting that trace elements are likely to be a major factor in the production of asbestos cancers.

6. What other types of cancer are related to exposure to asbestos?

Prospective surveys of occupational groups exposed to asbestos have in general shown a small excess risk of some other types of cancers (in addition to bronchial and mesothelial), especially those of the gastro-intestinal tract. The excess of these tumours is relatively small compared with that for bronchial cancer. Evidence for an association with ovarian tumours has not been supported by the first large mortality survey of women previously exposed to asbestos.

7. Is there evidence of an increased risk of cancer resulting from asbestos fibres present in water, beverages, food or in the fluids used for the administration of drugs?

Such evidence as there is does not indicate any risk.

8. Is there evidence of a risk of lung fibrosis from low levels of exposure to asbestos such as have been encountered by the general population in urban areas?

There is at present no evidence of lung damage by asbestos to the general public. The amount of asbestos in the lungs of members of the general public is very small, compared to those occupationally exposed. It is greatest where asbestos is mined or worked and lowest in rural areas.

9. Has the relationship between asbestos exposure and the development of pleural plaques been established?

Pleural plaques have been associated with past exposure to all commercial types of asbestos. But additional factors, other than asbestos itself, are involved. The plaques may remain fibrous or become calcified. Not all pleural plaques are associated with asbestos.

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RECOMMENDATIONS FOR FURTHER RESEARCH

Projects which the Panels rated high in priority are marked *; those which will require close co-operation between the Panels are marked ✓.

EPIDEMIOLOGY

The Panel agreed that asbestos related cancers occur in several sites in the body. The incidence of the different cancers varies with a number of definable factors and for other reasons, such as competing causes of death. Epidemiological studies will usually provide information on more than one type of cancer. Research directed at only a single type may, on occasions, be useful but in general the inevitable uncertainties, in some cases in the differential diagnosis of, for example, peripheral lung carcinomas and pleural mesotheliomas, and between peritoneal mesotheliomas and other intra-abdominal cancers will require that more than one type is studied at the same time.

The Panel recognised that some of the epidemiological projects could only be pursued if there was close co-operation between epidemiologists, pathologists, physicists and chemists, and others, because their success will depend upon the development of improved techniques, some of which are referred to in the recommendations of the other two Panels.

PROJECTS

(1) Further development of objective methods for early detection and surveillance of effects caused by asbestos. Topics for particular study include :

(a) Immunological techniques for screening for fibrosis and neoplasia.

(b) Functional tests of changes in the peripheral airways.

(c) Detection of pleural thickening.

(d) Assessment of the specificity of small irregular opacities in the chest radiograph as defined in the ILO U/C Classification (1971).

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(e) Tests of the usefulness of different techniques of chest radiography, including the use of 100 mm films.

(f) Development of statistical procedures for analysis and presentation of serial observations.

(2) Evaluation of the usefulness of early detection in the prevention of progressive fibrosis and asbestos cancers, also in the identification of hazardous conditions. Routine health surveillance of industrial populations should be designed to assist epidemiological studies and/include measurement and recording of environmental dust levels. Surveillance of new entrants could be particularly valuable. Arrangements should be made to register workers so that their morbidity and mortality experience can be studied even after cessation of exposure to asbestos.

(3) Assessment of excess cancer risks following exposure to only one type of fibre.

(a) Chrysotile: The much higher cancer risk reported for chrysotile textile workers compared with mine and mill workers requires explanation. How much is explicable by differences in size of airborne fibres and/past dustiness? There is need to make more use of past dust records for relating to indices of disease.

(b) Amosite: The excess lung carcinoma and mesothelioma risk is apparently much greater in the manufacturing and application sections of the industry than in the mining and milling of this type of fibre. What are the important factors in this reported difference?

(c) Crocidolite: Further studies are required in occupational groups exposed only to crocidolite or amosite or chrysotile in the manufacturing and application parts of the industry to establish more clearly differences in risks due to different fibres.

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PATHOLOGY AND EXPERIMENTAL PATHOLOGY

The Panel reviewed the progress made on the 1964 UICC recommendations. It was agreed that considerable progress had been made on the majority of the recommendations. Some require further study, or modification of previous methods of investigation; these are included in the list of recommendations that follows. The recommendations are divided into three categories, morbid anatomy and histology, clinical research, and experimental studies.

PROJECTS

Morbid Anatomy and Histology

1. Asbestosis

(1) Further consideration should be given to methods for determining the amounts, types and structural features of asbestos in tissue. A Sub-Committee should be established with members of the Physics and Chemistry Panel, and others to accelerate work on this problem.

(2) The methods for assessing the severity of asbestosis (see paper 9) should be tested for consistency by different observers.

2. Carcinoma

(1) An investigation of whether reduction of asbestos exposure to levels below those producing asbestosis also abolishes excess risk of carcinoma was considered important.

(2) A comparison of lung carcinomas in persons occupationally exposed to asbestos and those not so exposed, including both cigarette smokers and non-smokers, in respect of sites of origin and cytology of tumours and presence or absence of asbestosis, would be of value.

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). Mesotheliomas

(1) The International Panel of Pathologists[1] and National Panels established following the 1964 meeting[2] have served a useful purpose. It is recommended that panels be established in other countries and membership of the International Panel be extended. The main purposes of these Panels is to ensure uniformity of diagnostic criteria and recording of histological types of diffuse mesotheliomas. Collaborative study of histology slides in National Panels is recommended. The diagnosis of mesothelioma can be made by exfoliative cytology of the pleural fluid. If the cytological diagnosis is made by a competent cytologist, biopsy may be unnecessary.

(2) To improve consistency of diagnosis there is an urgent need for Comprehensive Atlas on mesotheliomas, or alternatively, for inclusion of an enlarged section on mesotheliomas in the new edition of the WHO Monograph on Tumours of the Lung. Criteria for diagnosis by exfoliative cytology and a description of the fine structure of mesotheliomas should be included.

Clinical Research

(1) Monitoring by immunological methods of populations exposed to asbestos should be investigated to ascertain whether it is possible to recognize those who are developing, or will develop, tumours.

(2) The use of chromatographic methods for the study of mucopolysaccharide and other tumour-associated substances in pleural fluids should be explored. Sensitive methods might be developed and applied to identify secretory products of mesotheliomas in blood and urine.

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[1] The International Panel consists of: Dr. H. Kannerstein (USA), Prof. D. Magner (Canada), Dr. L. Neuman (Finland), Prof. W.T.E. McCaughey (Eire), Prof. H. Otto (FRG), Dr. H. T. Plantenydt (Netherlands), Dr. E. Roitzsch, (GDR), Prof. L. Santi (Italy), Prof. I. Webster (South Africa), and Dr. J.C.Wagner (UK) as Secretary.

[2] Great Britain, South Africa, United States, Canada, Netherlands.

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Further Experimental Studies

(1) Information is required about the role of fine particles, especially influence of fibre size, in the induction of tumours. These studies should be extended to include fibres other than asbestos. A Sub-Committee should be established to review the need for, and arrange the distribution of standard samples of asbestos and other fibres in addition to the UICC Reference Samples.

(2) The fate of inhaled particles of various sizes, shapes and chemical compositions, should be studied to determine more precisely the quantities and sites of initial deposition, change within the body and later retention. The feasibility of increasing fibre elimination by various methods should be explored. Studies should be made of means of reducing the fibrogenicity and carcinogenicity of fibres already retained in the lungs.

(3) The use of cell and organ culture, including mesothelial tissue from man and other species, should be further investigated with a view to developing methods of screening dusts for fibrogenic and carcinogenic properties.

(4) Further studies should be carried out to determine the nature of the combined effect on tumour induction when animals are exposed to asbestos dust and cigarette smoke, metals or other chemical carcinogens, including those which act systemically such as nitrosamines.

(5) Inhalation experiments should be extended to test various types of fibre; of special interest are forms of chrysotile and crocidolite including the finer grade materials.

(6) It was felt that studies of the pathological effects of asbestos on species other than rodents would be of value.

(7) The effect of long-term ingestion of fibres of various sizes, shapes and chemical compositions should be studied.

(8) The effects of fibres and associated metals on the metabolism of target organs should be investigated.

PHYSICS AND CHEMISTRY

The Panel reviewed the progress made on the 1964 UICC Recommendations. The proposals for the preparation and characterization of the UICC reference samples of asbestos had been satisfactorily implemented, and the Panel recommended that a list of references to papers featuring the samples should be distributed to investigators in this field. Considerable progress had been made on methods of identifying the type of fibre in tissues but a quantitative method when several types of fibres were present had yet to be developed.

The Panel discussed the further contribution that physical and chemical studies can make to research on the biological effects of asbestos and other fibrous materials. Of especial interest are the effects of fibre size and shape on the retention of material in the lungs, the site of deposition, the migration of fibres within the body, and their carcinogenic or other biological activity. The following recommendations were made:

PROJECTS

1. Materials for experimental work

a) Supplies of asbestos from relevant sources should be obtained where there is evidence of variation in geological form, trace element content or significant biological findings.

b) Small samples of various fibrous materials should be prepared for studies on the influence of fibre size and shape on carcinogenicity. For this purpose the samples should be milled to different degrees of fineness.

c) For investigations on the influence of particle shape and size, on the inhalation and subsequent fate of asbestos fibres a chrysotile and an amphibole of fibre length greater than the UICC samples should be prepared.

2. Methods

a) There is an urgent need for the quantitative assessment, size analysis and characterization of particles and fibres in the lungs and other organs. Details of available methods should be circulated, international comparisons

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b) No methods are at present available for the preparation of fibres in narrow ranges of diameter and length in sufficient quantities for inoculation experiments. Techniques for these purposes are urgently required, especially in view of the advantages such graded samples could provide for investigating the influence of these physical factors on the carcinogenicity of fibres of different materials.

c) Since the degree of dispersion of fibres (especially chrysotile) used in inoculation studies may have a marked influence on their carcinogenicity, methods are required for quantifying dispersion.

d) Inhalation studies require precise control of the characteristics of the dust clouds. Improved methods of dispensing fibrous dusts in such investigations need to be developed.

e) Methods are available for collecting the important size fractions of dust clouds in inhalation studies when the particles are of compact shape. Similar methods must be developed for fibrous particles.

f) The present membrane filter methods of measuring the levels of airborne asbestos dust require standardization. This should be done by inter-laboratory trials on a continuing basis. Particle counting by electron microscopy should also be developed. Gravimetric assessment methods and the automation of particle counting should be explored.

3. Inhalation studies

Considerable information is now available on the deposition, retention and migration of particles of compact shape. Recently developed methods, especially radio-active tracer techniques, should be used to obtain similar knowledge for fibrous particles. This information is needed to identify the biologically important size fraction and to help interpretation of epidemiological and pathological studies.

4. Occupational and environmental studies

The use of both fibre counts and gravimetric methods for assessing asbestos dust concentrations should be encouraged. Data collected over an extended period will be particularly valuable in identifying the parameters of the dust which can be correlated with epidemiological evidence on the health hazard.

5. Physics and Chemistry Panel

It is recommended that an international Panel be established to assist in implementing these recommendations. The Panel would periodically review requirements for materials for experimental work; provide guidance on physical and chemical problems; and arrange national and international standardization trials.