

The Biological Effects of Asbestos

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EXHIBIT

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A group of representatives from 20 countries met at the IARC, Lyons, from October 2-5, 1972. The meeting was organized by Dr. P. Bogovski (IARC) and Dr. J. C. Wagner (UK).

Dr. J. Higgenson, Director of the IARC, in welcoming the group whose meeting would inaugurate the new conference hall, said that the aim of the meeting was to assess current knowledge about asbestos cancers and progress towards meeting the Recommendations of the UICC Working Group on Asbestos and Cancer in 1964. Since 1970 the responsibilities for the *ad hoc* UICC Committee had by agreement been taken over by the Agency. Common membership of Committees concerned had ensured continuity of policy. The IARC had been supporting work on asbestos cancers as part of the wider programme of investigating environmental carcinogens (IARC, 1970, 1971).

Research into asbestos cancers provided opportunities of international co-operation and experimental studies to complement the epidemiological evidence in man. Asbestos is mined in many different countries and exposure to the four main types of fibre occurred most often during extraction of the fibre in pure form from the rock. Differences in risk for the different types of fibre, if they could be established, would be of use in prevention. Production could be concentrated on the safer types of mineral. Most of the asbestos-associated cancers seen in man could also be produced in animals. Animal experiments could, therefore, be used to test hypotheses arising out of epidemiological or other research.

Dr. J. C. Gilson (UK) in an introductory paper, referred to the success achieved in the adoption of the 1964 UICC recommendation on the standard reference samples of asbestos; the development of an international classification of the radiographic appearances of asbestosis and the establishing of the international and national panels of pathologists interested in the asbestos cancers.

The work of the group covered five main topics: 1) A critical assessment of the methods used to detect, measure, and study the effects

of asbestos in man and animals; 2) The epidemiological evidence of differences in risk of asbestosis and cancers of the lung, pleura, peritoneum and other sites related to occupation, type of asbestos fibre and other factors; 3) The severity and significance of the asbestos burden present in the lungs of occupationally-exposed individuals and members of the general public; 4) A consideration of possible mechanisms of induction of tumours by asbestos; 5) The uses of asbestos by the community and the value of a cost/benefit analysis relating safety, health, social, and economic indices. Fifty review papers had been prepared and precirculated.

It was clear that the earliest detection of effects of asbestos on the lungs required clinical, radiological, and lung function tests [Dr. Harries (UK) Dr. H. Bohlig (FDR), Dr. M. R. Becklake (Canada)] but it was still not certain whether there was a definable stage at which progression ceased if there was no further exposure to the dust.

Many methods for assessing asbestos bodies in the lungs had been compared, no one method was clearly the best, the easiest to use therefore seemed preferable. There were large differences in numbers of bodies reported on the same tissue by different observers but all methods detected differences between different lungs. The number of bodies was least in rural and highest in urban areas (Dr. P.D. Oldham, UK).

Dr. F. D. Pooley (UK) and Dr. Langer (USA) emphasized the large number of sub-microscopic fibres only detectable by electron microscopy. There was general agreement on this. The positive identification of the type of asbestos still requires more than one method. Quantification of the amounts of chrysotile, crocidolite, and amosite separately when present together in tissue is not yet practicable. A possible means of performing this, using differences in magnetic and other properties of the fibres, was suggested by Dr. V. Timbrell (UK).

Dr. K. F. W. Hinson (UK) and his colleagues proposed a revised scheme of classifying the severity of asbestosis pathologically to replace

1964 proposals which had been found unsatisfactory. Dr. W. T. E. McCaughey (Ireland) showed that even skilled observers differed considerably in their diagnosis of mesotheliomas, and that an experiment to determine why this occurred by recording detailed features of the sections did not provide clues as to how to improve the agreement. Dr. B. Butler (UK) showed how useful cytology of the pleural fluid could be in diagnosing mesotheliomas. Histochemical and chemical detection of hyaluronic acid was discussed by Dr. Kannerstein (USA) and Dr. Ilavetz (France). The electron microscopic appearance of hyperplasia and neoplasia of the mesothelium was demonstrated by Dr. Y. Suzuki (USA) and Dr. P. Stoeckner (Fr). The usefulness of long-term survival experiments in rats given asbestos by various routes and the opportunities provided in organ cultures of lung and pleura were described by Dr. J. C. Wagner (UK) and Dr. K. T. Rajan (UK).

The extremely small amounts of asbestos in the general air, even in urban areas (of the order of 10 nanograms/m³ require EM analysis of the dust collected from samples of 1,000 m³ or more. Dr. S. Holmes (UK) and Dr. W. J. Nicholson (USA) reported results using this approach. Drs. A. Morgan (UK) and L. J. Cralley (USA) reported on the chromium, cobalt, iron, manganese, nickel, and scandium content of the UICC, and other, asbestos samples; also studies of the solubility of the principal types of asbestos. Chrysotile loses magnesium from the crystal lattice *in vivo*. The biological importance of this requires further study.

The group was not concerned with the setting of environmental standards as such, but with assessing the biological evidence used as part of the information for such standards. Mr. G. W. Gibbs (Canada) and Dr. R. S. J. Du Toit (South Africa) reviewed the information about past and present dustiness in the mines and mills where chrysotile and the amphiboles were obtained in Canada and South Africa. Mr. G. Berry (UK) discussed the theoretical basis of standards.

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Belmont) presented his analysis of the puzzling phenomenon of concomitant immunity and examined the role of the diverse components of the immune response involved in destroying tumors; the possibility of great variations existing on the function of these components in different anatomical sites was also raised. Other aspects discussed in this connection were the interplay between lymphocytes and macrophages, the existence of factors released by lymphocytes and, among the latter, the so-called macrophage-arming factor. The role of adjuvant immunotherapy of metastasis with BCG was most clearly explained by R. W. Baldwin (University of Nottingham). Employing tumors of different immunogenicity, he was able to demonstrate that, when BCG was in close contact with the tumor cells, it could suppress the growth of metastases, providing the cells possessed sufficient immunogenicity. An interesting report on his clinical experience with immunotherapeutic approaches was given by G. Hamilton Fairley (Chester Beatty Research Institute, Belmont).

In the second part of the program, dealing with the effects of drugs, the action of polyelectrolytes in reducing the spread of cancer was the subject of several papers. Although some of these compounds show a remarkable potency in certain systems and their structure-activity relationship is becoming somewhat clearer, no adequate explanation of their possible mechanism of action has yet been offered.

Among the polymers discussed, there is a group of compounds developed and tested by S. Garattini and his co-workers ("Mario Negri" Institute for Pharmacological Research, Milan), which appear to be of special interest, since they do not seem to affect the primary tumor but exhibit considerable potency in reducing cancer-cell dissemination and metastasis. While this work has, so far been only experimental, it does have potential clinical implications.

A. Goldin (National Cancer Institute, Bethesda), in raising the crucial question of whether cytotoxic agents are less active in advanced tumors than they are during the early

phase of the malignancy, concluded that the answer was unfortunately positive. He presented several possibilities to explain this reduced drug effectiveness and described certain procedures employed to counter-act this phenomenon.

Another group of compounds, bisdioxipiperazines, described by K. Hellman (Imperial Cancer Research Fund, London), served as a good example of the many agents used to interfere with cancer dissemination. It appears that the antitumoral effect of these drugs derives from their ability to normalize tumor vascularization which impedes the formation of metastases.

In conclusion, it may be said that, although a great deal of further research must be carried out in this complex area, where so many factors interact, the findings presented in this symposium offer a new approach to the treatment of cancer, namely a selective therapy of tumor dissemination and metastasis, a problem which has been largely neglected until now.

Since 1964 new prospective mortality studies have shown that there are important differences in cancer risks in different parts of the industry. The differences seem to be related to the type of fibre, part dustiness, and other factors. Separation of occupational factors (which probably include the actual dose of longer but respirable fibre) from that due to the type of fibre itself has not yet been fully achieved. Populations exposed to only one type of fibre have been largely limited to those in the mines and mills where the mineral is extracted from the rock. With the notable exception of the chrysotile mines in Quebec and possibly those in Italy and Finland, the records elsewhere are not good enough to define populations for strict comparative prospective mortality studies. Information from the large chrysotile mines in the USSR was not available. Dr. J. C. McDonald (Canada) showed that for the chrysotile miners and millers in Quebec, the excess lung and gastro-intestinal tract cancer risk was small. The link with pleural mesotheliomas was weak, and there was no evidence of peritoneal tumours. However, the excess lung and gastro-intestinal tract tumours was dose-related and restricted to those with the longest and heaviest exposure. These findings contrast strikingly with the very marked excess of lung and mesothelial tumours in workers manufacturing and applying insulation materials reported by Dr. I. J. Selikoff (USA), Dr. M. L. Newhouse (UK) and others. The groups studied had all been exposed to more than one type of fibre. The small amounts of crocidolite used in insulation work in the USA until recently make it very unlikely that the much higher risk in the insulation workers as a group is caused only by crocidolite. A group of workers only exposed to amosite, and chrysotile. These results might be interpreted, when taken in conjunction with the findings in Quebec, as indicating that the risk due to chrysotile is small and that amosite was primarily responsible for the excess risk in the insulation

workers. However, records of the relative amounts of chrysotile and amosite used many years ago in the insulation workers in USA make this hypothesis unlikely. Evidence from the surveillance of amosite miners and millers in South Africa indicates that the excess cancer and mesothelioma risk is much less than in those mining crocidolite (Dr. I. Webster, South Africa). There are still opportunities to sharpen the comparisons between the experience of chrysotile textile, and mine and mill workers from existing records, including information about the relative dustiness and the type of dust to which these groups have been exposed. The follow-up of those exposed only to crocidolite in industry may add to the evidence linking exposure to crocidolite and mesotheliomas (Dr. J. S. P. Jones, UK). Dr. M. L. Newhouse (UK) showed that in manufacturing processes, where exposures have been to chrysotile, amosite, and crocidolite, the risk of lung cancer and mesothelioma was dose-related. This and other evidence show that there are occupational sub-groups where exposure has been very high compared to that of the general public but where no excess cancer risk has been detected after 20 years. Further follow-ups will be required to measure the full extent of the risk, if any, in these groups. Dr. P. E. Enterline (USA) reported that the mortality from lung cancer was greater in retired asbestos cement workers if they had been exposed to crocidolite and chrysotile, than to chrysotile alone. Dr. F. D. Pooley had examined lung tissue from over 100 cases of mesotheliomas, from four countries, by EM and other methods. When compared with tumour-free lung tissue, the mesothelioma-bearing tissue contained more asbestos and amphiboles. Not all mesotheliomas can be related to past exposure to asbestos. Dr. H. T. Planteydt (The Netherlands) reported urban/rural differences in incidence of mesotheliomas, the reasons for which are not yet clear. Dr. E. C. Hammond (USA) stressed the importance of recognizing that many factors were probably concerned in increasing the cancer risk. The enhancement of the lung-cancer risk by cigarette smoking was great. In

non-smokers the risk of death from asbestos exceeded that of lung cancer. Several surveys of asbestos workers had now shown an excess of gastro-intestinal cancers; though lower than the lung cancer excess, it was now well enough established to require detailed study. Dr. M. Greenburg (UK) described the comprehensive prospective survey of all asbestos workers now in operation in the UK.

Dr. J. C. Wagner (UK), Dr. M. Stanton (USA) and Dr. V. Timbrell (UK) reviewed animal experimental and other evidence on the mechanism of induction of mesotheliomas. The diameter and length of fibre may be critically important in these tumours in the pleura. Fibres of materials quite different from asbestos have been shown to produce pleural mesotheliomas, but only if they are in such a form that the fibre is comparable in size to that of asbestos. Dr. J. S. Harrington (SA) reviewed the evidence that chemical factors of asbestos itself, or metal contamination, or absorbed hydrocarbons might be important factors in tumour induction. Their importance cannot be excluded particularly in the light of the synergistic action between cigarette smoking and asbestos in the production of lung carcinomas, but neither the experimental nor the epidemiological evidence at present has produced strong clues indicating the importance of a definable chemical factor. Cell toxicity of asbestos was reviewed by Dr. A. C. Allison (UK). The information so far appears to be more relevant to an understanding of the fibrogenicity than of the carcinogenicity of asbestos. Dr. P. C. Elmes (UK) reviewed the natural history of mesotheliomas; treatment is entirely palliative at present. Immunological methods for the detection of fibrosis [Dr. M. Turner Warwick (UK)] and mesotheliomas [Dr. J. S. P. Jones (UK)] are being intensively studied. The uses and irreplacability of asbestos for some purposes were reviewed by Dr. K. N. Lindell (Canada). Mr. R. Akehurst (UK) outlined the type of information needed from industry and from medical services to carry out cost/benefit analyses.

It was clear from the meeting, which was attended by representatives of industry, that there is extensive international research into all aspects of asbestos health problems. Much progress has been achieved in the last 10 years. Possible clues as to how fibres may induce malignancy provide a challenge to design critical experiments to discover the mechanisms concerned. The action being taken to apply the results of new knowledge was not part of the programme but the need to do so was emphasized by many speakers. The Proceedings of the Conference and the Recommendations of the Advisory Committee to the IARC, which met subsequently, will be published shortly, and will provide a most valuable, authoritative international review of the asbestos cancer problem, and show where further research is most needed.

Resumé

Une réunion internationale sur les effets biologiques et l'action carcinogène de l'asbeste a eu lieu en octobre dernier au CIRC, à Lyon. Les participants, qui venaient de 20 pays, ont également étudié la mise en pratique des recommandations formulées en 1964 par le Groupe de travail de l'UICC sur l'asbeste et le cancer. La réunion a porté sur les cinq thèmes suivants : 1) Évaluation critique des méthodes utilisées pour détecter, mesurer et étudier les effets de l'asbeste sur l'homme et les animaux. 2) Différences épidémiologiques du risque d'asbestose et de cancers du poumon, de la plèvre, du péritoine, etc., selon la profession, le type de fibres d'asbeste et d'autres facteurs. 3) Gravité et importance des dépôts d'asbeste dans les poumons chez les travailleurs exposés et dans la population en général. 4) Modes possibles d'induction tumorale par l'asbeste. 5) Emploi de l'asbeste dans la collectivité et utilité de l'analyse coûts-bénéfices des indices sanitaires, sociaux, économiques et de sécurité. Cinquante communications portant sur ces thèmes généraux ont été présentées. La réunion a mis en évidence les progrès réalisés dans ce domaine au cours des dix dernières années et l'importance des activités actuelles de recherche internationale sur les problèmes sanitaires posés par l'asbeste.

Resumen

El pasado mes de octubre se ha celebrado en el CIRC (Lyon) una reunión internacional sobre los efectos biológicos y la acción carcinógena del amianto. Los participantes, procedentes de veinte países, se ocuparon asimismo de la puesta en práctica de las recomendaciones formuladas en 1964 por el Grupo de Trabajo de la UICC sobre Cánceres Asbestóticos. La reunión versó sobre los cinco temas siguientes : 1) Evaluación crítica de los métodos usados para detectar, medir y estudiar los efectos del amianto en el hombre y en los animales. 2) Diferencias epidemiológicas del riesgo de asbestosis y de cánceres de pulmón, pleura, peritoneo, etc. en relación con la profesión, el tipo de fibras de amianto y otros factores. 3) Gravedad e importancia de los depósitos pulmonares de amianto en los trabajadores expuestos y en la población general. 4) Posibles mecanismos carcinogénicos del amianto. 5) Empleo del amianto en la colectividad y utilidad del análisis costos-beneficios de los índices sanitarios, sociales, económicos y de seguridad. Sobre estos temas generales se presentaron cincuenta trabajos. La reunión puso de relieve los progresos realizados en la materia durante los últimos diez años y la importancia de las actuales actividades de investigación internacional sobre los problemas sanitarios planteados por el amianto.

Attention: TNM System

Fascicle enclosed contains the revised Classifications of malignant tumours for Breast, Larynx, Stomach, Cervix and Corpus Uteri. Please insert in your TNM Pocket-book*.

* The 2nd, revised Edition of the Pocket-book - to be available shortly from this Office - will incorporate the above-mentioned Classifications.