DIRECTOR OF THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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

Epidemiology Panel

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Dr. J. C. Gilson	Medical Research Council, Pneumoconiosis Hospital, Penarth, Glamorgan, Wales, UK.
Dr. J. Lepoutre	Medical Department, N.V. Eternit, Kapelle Belgium.
Prof. J. C. McDonald	McGill University, Department of Epidemio 3775 University Street, Montreal 110, Que
Mr. C. E. Rossiter	Medical Research Council, Pneumoconiosis Hospital, Penarth, Glamorgan, Wales, UK.
Dr. H. Sakabe	Department of Industrial Physiology, Mini National Institute of Industrial Health, 2051 Kizukisumiyoshi-Cho, Kawasaki, Jap
Dr. I. J. Selikoff	Department of Medicine, Mount Sinai Scho Fifth Avenue and 100th Street, New York,
Dr. G.K. Sluis-Cremer	South African Medical Research Council, Institute for Occupational Diseases, P.O Johannesburg, S. Africa.
Dr. W. Smither	Cape Asbestos Co. Ltd., 11/4 Park Street, England, UK.
Dr. G. Wright	Division of Medicine, St. Luke's Hospita Boulevard, Cleveland, Ohio 44101, USA.

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Mr. G. Berry	Medical Research Council, Pneumoconiosis Un Hospital, Penarth, Glamorgan, Wales, UK.
Dr. P. Bogovski	Unit of Environmental Carcinogens, Internat for Research on Cancer, 150 Cours Albert Th Lyon, France.
Dr. M. Kannerstein	Pathology Department, Barnert Memorial Hosp 680 Broadway, Paterson, N.J. 07514, USA
Prof. W.T.E.McCaughey	School of Pathology, Trinity College, Univ Dublin, Dublin 2, Eire.
Prof. D. Magner	Canadian Tumour Reference Centre, Departmer Pathology, University of Ottawa, Ottawa, On K1N 6N5, Canada.
Prof. H. Otto	Direcktor des Pathologischen Instituts der Krankenanstalten Beurhausstrase 40, 46 Dort W. Germany.
Dr. H. T. Planteydt	Stichting Streeklaboratorium"Zeeland", Noor Middelburg, Netherlands.
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Dr. J. C. Wagner	Medical Research Council, Pneumoconiosis U Hospital, Penarth, Glamorgan, Wales, UK.
Prof. S. Watanabe	Department of Pathology, National Cancer C Institute, Tsukiji, 5-1-1, Chuoku, Tokyo,
Prof. I. Webster	Medical Research Council South Africa, Nat Institute for Occupational Diseases, P.O. Johannesburg, South Africa.

Physics and Chemistry Panel

Dr. L. Le Bouffant	Laboratoire du Centre D'Etudes et Recherch Charbonnages de France, Verneuil-en-Halla 60 - Creil, France.
Mr. G. W. Gibbs	McGill University, Department of Epidemiol 3775 University Street, Montreal 110, Que
Dr. S. Holmes	Asbestosis Research Council, c/o Turner Br Co. Ltd. P.O: Box 40, Rochdale, England, U
Mr. A. Morgan	Atomic Energy Research Establishment, Heal Medical Division, Building 364, Harwell, D England, UK

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

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

TERMS OF REFERENCE

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

2. The Committee was to make recommendations for further research and 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 Ca 1964, a Sub-Committee of the UICC Commission on Geographical Pathology a Environmental Carcinogens (Chairman, Dr. J. Higginson) was formed to co-o work required to achieve the recommendations.

In April 1970 agreements between the UICC and the IARC led to the wind up of the UICC Sub-Committee and the IARC taking on responsibility for t Committee's work and extending it by supporting certain projects on asbe cancers in several countries. The Agency has done this as part of their programme of investigating environmental carcinogens. Common membership

of policy.

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

GENERAL REVIEW

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

Yes. Since 1964 the evidence of a causal relationship has been inc by epidemiological studies showing exposure-response relations for the i of lung carcinomas. The production of lung carcinomas in certain animal types of asbestos supports this conclusion. The epidemiological evidenc however, shows that there are clear differences in risk with type of fi nature of exposure.

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

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

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

The evidence has been greatly strengthened by further prospective retrospective mortality studies in many countries of populations expos There is evidence that all commercial types of asbestos except anthopl

occupations and with the type of asbestos has increased. The risk is gr
with crocidolite, less with amosite and apparently less with chrysotile.
amosite and chrysotile there appears to be a higher risk in manufacturin
in mining and milling. There is also evidence from population studies t
proportion of cases of mesothelioma have no known association with expos
asbestos.

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

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

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

The evidence has accumulated indicating:

(1) Cigarette smoking is an important factor enhancing the lung ca
risk in asbestos-exposed workers, in both men and women. Asbe
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

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 ad to bronchial and mesothelial), especially those of the gastro-intestinal t The excess of these tumours is relatively small compared with that for bro cancer. Evidence for an association with ovarian tumours has not been sup by the first large mortality survey of women previously exposed to asbesto

7. Is there evidence of an increased risk of cancer resulting from asbes 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 expos asbestos such as have been encountered by the general population in urban

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

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

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

which will require close co-operation between the Panels are marked ✓.

EPIDEMIOLOGY

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

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

PROJECTS

(1) Further development of objective methods for early detection and su 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).

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 progressive fibrosis and asbestos cancers, also in the identification hazardous conditions. Routine health surveillance of industrial popula should be designed to assist epidemiological studies and/include measu recording of environmental dust levels. Surveillance of new entrants c particularly valuable. Arrangements should be made to register workers their morbidity and mortality experience can be studied even after cessa exposure to asbestos.

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

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

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

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

mesotheliomas (if possible by cell type) in (a) national survey of mesotheliomas, (b) representative samples of cases arising in groups wi a definable past exposure.

(5) Studies of secular changes in incidence of pleural and peritoneal mesotheliomas nationally and internationally.

(6) Epidemiological studies to investigate the association between past exposure to asbestos and cancer of sites other than lung, pleura, and peritoneum.

(7) Studies of secular trends in the asbestos content of the lungs in general population.

(8) Studies to relate amount and type of asbestos in the lung and esti of past dust exposure and interval since last exposure.

(9) Experimental and epidemiological studies to investigate possible differences of effect of continuous low and intermittent high exposure asbestos.

(10) Opportunities afforded by intercurrent deaths should be used to interrelate radiographic appearances, lung pathology, respiratory func dust content, and type in asbestos workers. Standardised techniques a classification recommended by the Panels should be used.

(11) Investigate the prognostic significance and actiological factors the development of calcified and uncalcified pleural plaques in differ environments.

(12) Investigate talc-exposed groups in mining and manufacturing to e any differences in morbidity or mortality which might be related to th and shape of the fine respirable particles.

(13) Development of cost/benefit analyses to study the health, safety social and economic interrelations of the use of asbestos.

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

PROJECTS

Morbid Anatomy and Histology

1. Asbestosis

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

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

2. Carcinoma

* (1) An investigation of whether reduction of asbestos exposure 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.

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

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

Clinical Research

* (1) Monitoring by immunological methods of populations exposed 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 mucopo and other tumour-associated substances in pleural fluids should be explo Sensitive methods might be developed and applied to identify secretory p of mesotheliomas in blood and urine.

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

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

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

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

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

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

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

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

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

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

The Panel reviewed the progress made on the 1967 UICC [illegible] proposals for the preparation and characterization of the UICC reference of asbestos had been satisfactorily implemented, and the Panel recommende a list of references to papers featuring the samples should be distribute investigators in this field. Considerable progress had been made on meth identifying the type of fibre in tissues but a quantitative method when types of fibres were present had yet to be developed.

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

PROJECTS

1. Materials for experimental work

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

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

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

2. Methods

a) There is an urgent need for the quantitative assessment, size and characterization of particles and fibres in the lungs and other o

[illegible] methods should be circulated, international comp

narrow ranges of diameter and length in sufficient quantities for inocula experiments. Techniques for these purposes are urgently required, especi in view of the advantages such graded samples could provide for investiga the influence of these physical factors on the carcinogenicity of fibres different materials.

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

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

e) Methods are available for collecting the important size fractions 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 a asbestos dust require standardization. This should be done by inter-lab trials on a continuing basis. Particle counting by electron microscopy also be developed. Gravimetric assessment methods and the automation of counting should be explored.

3. Inhalation studies

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

4. [illegible]

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

5. Physics and Chemistry Panel

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