

DIRECTOR OF THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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

Epidemiology Panel

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Physics and Chemistry Panel

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Mr. A. Morgan	Atomic Energy Research Establishment, Heal Medical Division, Building 364, Harwell, I England. UK.

Dr. F. D. Pooley	Department of Mineral Exploitation, University of S. Wales and Monmouthshire, Newport Road, Wales, UK.
Dr. S. Speil	Johns Manville Research and Engineering Cent 159, Manville, New Jersey, USA.
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Dr. R. du Toit	Government Mining Engineer's Division, Dept of Mines, P.O. Box 1132, Johannesburg, South Africa
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 (Chairman 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 exposure to asbestos dust to cancers, especially that obtained since the meeting of the 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 Cancer in 1964, a Sub-Committee of the UICC Commission on Geographical Pathology and Environmental Carcinogens (Chairman, Dr. J. Higginson) was formed to co-ordinate the 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 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 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 answer a number of important general questions about the relation of asbestos to 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 evidence however, shows that there are clear differences in risk with type of sit 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 expc 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 greater with crocidolite, less with amosite and apparently less with chrysotile. amosite and chrysotile there appears to be a higher risk in manufacturing in mining and milling. There is also evidence from population studies that 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 air pollution which has existed in the neighbourhood of chrysotile and amosite mines. There are reported differences in 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 to the cancer risks?

The evidence has accumulated indicating:

(1) Cigarette smoking is an important factor enhancing the lung cancer 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

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 population is very small, compared to those occupationally exposed. It is greatest in areas 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 common 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.

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 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 depends upon the development of improved techniques, some of which are recommended in the recommendations of the other two Panels.

PROJECTS

(1) Further development of objective methods for early detection and study 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 population should be designed to assist epidemiological studies and include measurement of environmental dust levels. Surveillance of new entrants is particularly valuable. Arrangements should be made to register workers and 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 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 exposure to airborne fibres and 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 sections of the industry. What are the important factors in this difference?

(c) Crocidolite: Further studies are required in occupational groups exposed only to crocidolite or amosite or chrysotile in manufacturing and application parts of the industry to determine 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 with 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 estimate 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 to asbestos.

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

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

(12) Investigate talc-exposed groups in mining and manufacturing to examine any differences in morbidity or mortality which might be related to the size 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 recommendations 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 determining the amounts, types and structural features of asbestos in tissue. A Subcommittee 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) 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 Pathologists¹ and National Panels established following the 1964 meeting² have served a useful purpose. It 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 of 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 a 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 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 mucopolysaccharides 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.

¹ The International Panel consists of: Dr. M. Kannerstein (USA), Prof. D. B. Macgregor (Canada), Dr. L. Meurman (Finland), Prof. W.T.E. McCaughey (Ireland), Prof. H. T. Planteydt (Netherlands), Dr. E. Roitzsch (GDR), Prof. G. Scatena (Italy), Prof. I. Webster (South Africa), and Dr. J.C. Wagner (UK) as Secretary.

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

* (1) Information is required about the role of fine particles, the 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 :

✓ (2) The fate of inhaled particles of various sizes, shapes and compositions, should be studied to determine more precisely the quantitative 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 fibrogenic and carcinogenicity of fibres already retained in the lungs.

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

(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 and 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.

The Panel reviewed the progress made on the 1964 UICC recommendations for the preparation and characterization of the UICC reference of asbestos had been satisfactorily implemented, and the Panel recommended 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, 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, and 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 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 and characterization of particles and fibres in the lungs and other organs.

Available methods should be circulated, international comparison

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) 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 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 asbestos dust require standardization. This should be done by inter-laboratory 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, retention and migration of particles of compact shape. Recently developed methods, such as 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.

2. Conclusions

The use of both fibre counts and gravimetric methods for assessing dust concentrations should be encouraged. Data collected over an extended period will be particularly valuable in identifying the parameters of the dust which will 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.