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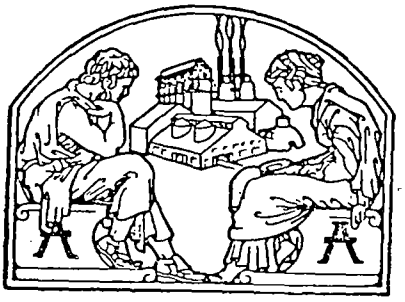

ASBESTOS BIOEFFECTS RESEARCH FOR INDUSTRY

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FOREWORD

During the past year, a number of industrial materials have come under attack in public news media as a result of heightened public interest in the environment. The potential of such materials to adversely affect the health of the general population through environmental contamination has been raised.

One such material is asbestos. There have been articles in the professional literature[1,2] and in the lay press[3] which present highly exaggerated views of the nature and extent of the potential problem. Prompt criticism has followed pointing to erroneous interpretation of existing facts and publication of misinformation.[4-9]

At the suggestion of several of its members, Industrial Hygiene Foundation held a meeting on July 19, 1966 to summarize what industry is doing to develop information to protect the health of its employees and the public from potential environmental hazard. Such information should be of considerable value to all those responsible for planning of environmental and occupational health research, whether in industry, universities or government.

It is appropriate that Industrial Hygiene Foundation, a nonprofit research association of industries for advancement of health conservation in matters related to industry's operations, products and wastes, should assist in development of national environmental and occupational health research to help insure that industry's needs are provided for at all stages of program development.

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1. Thomson, J.G. and Graves, W.M. "Asbestos as an Urban Air Contaminant." Arch. Path. 81:458, May 1966.
2. Thomson, J.G. and Graves, W.M. "Asbestosis in Urban Populations." JAMA 196:732-733, May 1966.
3. Anonymous. "Asbestos: Awaiting 'Trial'." Chem. Week, p. 32, Sept. 10, 1966.
4. Gross, P. Letter to Editor "Today's Pressing Question—How Safe is Urban Air." Arch. Path. 82:195, Aug. 1966.
5. deTreville, R.T.P. Letter to Editor. Arch. Path. (to be published)
6. Gross, P. Letter to Editor. JAMA. (to be published)
7. Hackney, R. Letter to Editor. Chem. Week, p. 7, Oct. 8, 1966.
8. Brown, M. C. Letter to Editor. Ibid.
9. Editorial Note (following refs. 7 and 8). Ibid.

Subject: Summary of Needs and Plans for Asbestos Research

The purpose of this session of the Industrial Hygiene Foundation Management Planning Meeting, held in the Hunt Room of the Webster Hall Hotel on July 19, was (1) to help develop a better concept of the asbestos industry's environmental and occupational health research needs and what is being done to meet them and (2) to provide the U. S. Public Health Service Surgeon General with a summary report and any recommendations which may be developed from the meeting to aid in setting, clarifying, and reaching sound and realistic health conservation goals in the national interest.

The meeting was sponsored by the Foundation's Policy and Planning Committee.

Those attending the meeting were:

Name	Company
Bowman, H.M.	Thiokol's Reaction Motors Division
Colwell, M.O.	Aluminum Company of America
Cralley, L.J.	U.S. Public Health Service
Davison, E.K.	Davison Sand & Gravel Company
deTreville, R.T.P.	Managing Director of IHF
Edwards, F.H.	Owens-Corning Fiberglas Corporation
Grant, L.B.	Pittsburgh Plate Glass Company
Gross, Paul	Director of IHF Research Laboratory
Hatch, T.F.	University of Pittsburgh
Hazard, W.G.	Owens-Illinois Glass Company
Minard, David	University of Pittsburgh
Schrenk, H.H.	Secretary, IHF Board of Trustees
Smith, F.W.	Mine Safety Appliances Company
Smith, K.W.	Johns-Manville Corporation
Smyth, H.F.	Mellon Institute
Wright, G.W.	St. Luke's Hospital

Mr. Bowman opened the meeting and asked Dr. deTreville to conduct the session on Asbestos. Dr. deTreville, who had asked several of those present to be prepared to discuss their areas of special interest and research needs, first called on Dr. George W. Wright to report briefly on his activities of the past year in behalf of the Quebec Asbestos Mining Association (QAMA).

Dr. Wright said that he had been aware of industry's interest in asbestos since about 1940, as a result of his work at Saranac Laboratory for QAMA. At that time no question was raised concerning possible malignancy. At a meeting in Antigua in 1965, QAMA expressed its intention to learn, "What is known, what we need to know, and what is unknown" concerning the bioeffects of asbestos.

Concerning what is known, Dr. Wright listed the following scientists who were present in Antigua:

Dr. John Beattie Cambridge, England	Dr. John C. Gilson Penarth, Glamorgan, Wales
Dr. H. Bohlig Ludenscheid, W. Germany	Dr. Roger Grainger Asbestos, Quebec
Dr. Paul Cartier Thetford Mines, Quebec	Dr. Fernand Gregoire Montreal, Quebec
Dr. A. Claass Luxembourg, Belgium	Dr. Paul Gross Pittsburgh, Pa.
Dr. L. J. Cralley Cincinnati, Ohio	Dr. Roland Guy Cartierville, Quebec
Dr. A. J. deVilliers Ottawa, Ontario	Prof. A. Houberechts Hasselt, Belgium

Dr. J. C. McDonald Montreal, Quebec	Dr. Arthur J. Vorwald Detroit, Michigan
Dr. Leo Noro Helsinki, Finland	Dr. J. C. Wagner Penarth, Glamorgan, Wales
Dr. Sherman S. Pinto Tacoma, Washington	Dr. George W. Wright Cleveland, Ohio
Prof. Paul Sadoul Nancy, France	Dr. Philip Enterline Montreal, Quebec
Dr. K. W. Smith New York, New York	Dr. Philippe-Duval Noranda, Quebec
Dr. J. A. Vidal Montreal, Quebec	Dr. Eugene Pendergrass Philadelphia, Pa.
Prof. E. C. Vigliani Milan, Italy	Mr. K. W. Nelson Salt Lake City, Utah

In the course of the QAMA Meeting, much of "what is known" was reviewed and discussed. Dr. Wright found the meeting very valuable from a personal standpoint, chiefly regarding discussions of the very pertinent questions, "What we need to know" and "what is unknown."

For example, he stated that the word "asbestos" is as general a term as "bacteria" and that it is not possible to translate data from one type to another. The types vary with origin and chemical composition and almost never exist in a "pure" form. It is very difficult to categorize an exposure environment because of the need to capture, identify, recognize, and quantitate the material we now call "asbestos". During processing, asbestos, which is not indestructible, may undergo dissolution or change in form. Is the material redisseminated identical to the original, or does it differ?

Dr. Wright indicated that it had been sobering to realize the extent to which asbestos is distributed in various forms in the general population,

and we must have better knowledge of where asbestos may come into contact with humans and better recognize any adverse bioeffects which may have resulted.

Dr. deTreville next asked if Dr. Kenneth W. Smith had any comments concerning the Asbestos Textile Institute program. Dr. Smith related that the Asbestos Textile Institute is cooperating in an extensive investigation with the asbestos textile industry by the U. S. Public Health Service under the direction of Dr. Lewis J. Cralley. The ATI has felt the impact of adverse criticism in the form of press releases, radio, and television appearances concerning asbestos. Aside from knowing the facts concerning the true effects of asbestos upon man, the industry must be increasingly concerned with preservation of its markets as a matter of survival. All the individual company can do to help solve this pressing problem is to provide funds, environments, and individuals for study.

The basic research needs will have to be "farmed out", but studies are already being conducted on insulation workers on the West Coast and in the Midwest. In Canada, Johns-Manville Company is studying all insulation workers who have permits, and this study has government approval. The ATI, as mentioned, is cooperating in an extensive survey by the U. S. Public Health Service, Division of Occupational Health. The National Insulation Manufacturers Association is vitally interested in developing information to pass on to insulator employer groups.

As he has pointed out repeatedly, Dr. Smith feels that the primary need is better definition of asbestos exposure, especially important in epidemiological studies. What is an asbestos worker? In this regard

he said, the loose thinking concerning asbestos exposure was demonstrated recently in Pennsylvania when the occurrence of mesothelioma in a three-year old child was attributed to the father's working in industry under the union category of an asbestos worker. Actually, this union category title covers many individuals who have no occupational exposure to asbestos.

At this point Dr. deTreville called on Dr. Lewis J. Cralley to provide a brief report on U.S. Public Health Service, Division of Occupational Health plans.

Dr. Cralley stated that he would like to cover briefly three areas of U.S. Public Health Service, Division of Occupational Health interest.

(1) A prospective longitudinal epidemiological study is now under way in four industry exposure categories:

(a) Asbestos textiles

(b) Asbestos friction products

(c) Asbestos cement products

(d) Asbestos insulating materials

The aim is to cover at least 2500 workers in each category with a wide range of exposure from office to production worker and with built-in controls. Exposures are being defined in detail including factors other than asbestos. In addition, the past history of plants regarding asbestos exposure is being recorded in an attempt to develop retrospective studies designed to compliment those of a prospective nature. Detailed information on each worker is being developed using a questionnaire approach, which includes occupations, hobbies, and smoking history. These studies will be carried out over the

lifetime of these individuals whether or not they stay in the industry. At intervals a follow-up will be made using Bureau of Old Age and Survivor's Insurance records and State Department of Health death records from which a trend of causes of death will be developed for each group. A designated number in each group will have periodic medical follow-ups to establish health profiles. While the prospective study itself will require 25-30 years of workers' experience, it may be possible to recognize trends as early as 5-10 years from the time of the base line study.

(2) Concurrently, a study will be made of the lungs of individuals in the cohorts who died of cancer. This will include complete mineral analysis of trace metals including nickel, cobalt, chromium, etc. In this regard, individuals will be categorized into two groups — those having significant exposure before mid 1940 and those entering exposure after this period. Technology has changed markedly since the 1930's, and contaminant fines of asbestos have been reduced 30% or more. Exposure of workers is generally no longer massive. Data collected should help provide insight in understanding past and present worker health experience.

(3) The U. S. Public Health Service is also very interested in identifying the various types of pulmonary ferruginous bodies that have been observed in a number of persons coming to autopsy in hospitals in urban areas. For example, talc has been found to contain about 10% fibers. In veiw of the widespread use of talc in cosmetics, etc., could some of the ferruginous bodies be from this source? Also, just what does the presence of these bodies mean?

A U.S. Public Health Service records study begun by Dr. Philip Enterline is designed to detect contrasting differences in trends in causes of death of workers in different asbestos product cohorts. The importance of Knox's and

Doll's study is that early data indicates that industrial hygiene control of dust exposures will reduce the incidence of lung cancer in asbestos workers.

Dr. deTreville then requested Dr. Gross to provide a detailed description of IHF's Fibrous Dust Research Proposal.

Dr. Gross said that Thomson[1] has found that about 30% of the people that had died in hospitals in Capetown (500 consecutive autopsies) had "asbestos bodies" in the lungs. The same author[2] had found a similar prevalence of "asbestos bodies" among the hospital deaths in Miami, Florida. Cauna, Totten and Gross[3] examined the lungs of 100 non-selected hospital deaths for which autopsy permission had been obtained and found that 40% of these had "asbestos bodies" in their lungs. Ian Webster[4] recently reported a 47% prevalence in Johannesburg.

There is, at present, a reasonable doubt that "asbestos bodies" are specific indicators of the inhalation of asbestos fibers. Such bodies have been found in coal miners and talc workers where they have been called

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(1) Thomson, J.G., et al. Asbestos as Modern Urban Hazard. S. Afr. Med. J. 37:77-81, 1963.

(2) Thomson, J.G., et al. Asbestos as an Urban Air Contaminant. Arch Pathol. 81:458-464, May 1966.

(3) Cauna, Dzidra; Totten, Robert S.; and Gross, Paul. Asbestos Bodies in Human Lungs at Autopsy. JAMA 192:371-373, May 3, 1965.

(4) Webster, Ian. Report of progress quoted in the Annual Report of the Pneumoconiosis Research Unit of the South African Council for Scientific and Industrial Research, 1965.

"pseudo-asbestos bodies." Recently Davis[5] and Collet[6] have demonstrated the intracellular development of "asbestos bodies" secondary to amorphous material.

Asbestos occupies an anomalous position in its ability to produce lung damage, causing diffuse fibrosis and possibly also lung cancer. It is anomalous inasmuch as no other silicate has been shown to possess this ability. The fibrosis encountered in talcosis is limited to the tremolite variety, which is asbestos-like. On the other hand, the pneumoconiosis associated with the mining of mica (another silicate) has not been investigated experimentally, and the fibrogenic activity of the dusts coexisting with the mica has not been evaluated. Other silicates may evoke either minimal or relatively slight inflammatory changes, and are incapable of producing lung cancer.

Inasmuch as certain polycyclic hydrocarbons and trace metals known to be potent cancer-producing agents have been demonstrated in asbestos, particularly nickel, chromium and benzopyrene, the possibility exists that the trace metals and/or the polycyclic hydrocarbons may be solely responsible for the observed pathogenicity.

This possibility is supported by two findings:

1. The report of Braun and Truan[7] which indicated that the prevalence of lung cancer among Canadian asbestos miners was no greater than that of the general population. This was in contrast to the report of Doll[8]

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(5) Davis, J.M.G. Electron-Microscope Studies of Asbestosis in Man and Animals. Ann. N.Y. Acad. Scie. 132:98-111, 1965.

(6) Collet, A. Personal Communication, 1965.

(7) Braun, Daniel C. and Truan, T. David. An Epidemiological Study of Lung Cancer in Asbestos Miners. AMA Arch. Ind. Health 17:634-653, June 1958.

(8) Doll, R. Mortality from Lung Cancer in Asbestos Workers. Brit. J. Ind. Health 12:81, 1955.

which indicated a greatly increased risk of lung cancer among British workers exposed to asbestos dust while fabricating the asbestos.

2. In a recent investigation in the laboratory of the Industrial Hygiene Foundation, lung cancers were found in rats exposed for 18 months to high concentrations of chrysotile dust.[9] Because rats exposed to chrysotile dust by other investigators failed to develop lung cancer, there is a good probability that the chrysotile dust that produced lung cancer was significantly different from that which did not have this effect. It is possible that this difference is caused by a coating of nickel steel alloy applied to the asbestos dust particles during the continuous hammer milling process used for rendering the dust respirable. This method has not been used by previous investigators. Nickel has been found capable of producing lung cancer in trace amounts.

Although asbestos and glass are both silicates, the industrial health experience with workers of these two materials has been vastly different. No pulmonary disease has been reported in workers exposed to glass dust.

Nevertheless, the dust of filamentous glass has been labeled as highly dangerous in the lay press by association with asbestos. It is a fact that although the effect of flake glass dust on the lungs of animals has been reported, no similar study has been made of the dust of filamentous glass which does not have an associated resin or filler.

It is proposed to examine the response of animals' lungs to different inorganic fibrous materials of contrasting chemical composition, and to characterize the differences and similarities in the response.

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(9) Gross, P. and deTreville, R. T. P. Experimental Asbestosis: Studies on the Progressiveness of the Pulmonary Fibrosis Caused by Chrysotile Dust. To be published.

It is also proposed to investigate the influence of trace minerals and polycyclic hydrocarbons (i.e., benzopyrene) associated with chrysotile ore or the subsequent processing on the long-term response of the lung to the dust.

Another objective of this phase is to obtain definitive data on the long-term effect of dust derived from filamentous glass upon the lungs. Three varieties of such glass dust will be investigated:

1. with the phenol-formaldehyde-type of binder
2. with the binders used in textiles
3. without binder

In addition, a comparative study of the three main types of asbestos dust (chrysotile, amosite and crocidolite) is proposed to attempt to pinpoint the cause of biological activity — i.e., whether due to silicates per se or the associated trace metals or hydrocarbons. Positive findings would be a basis for identifying any possible health hazards and for suggesting specific engineering or other process controls to eliminate such hazards.

I. The following fibrous materials will be reduced to respirable particle size ($<3\mu$) and will be injected in amounts of 3.5 mg. to 30 mg. as aqueous suspensions:

1. chrysotile dust (prepared by milling in Wright mill and with demonstrated carcinogenic potential)
2. chrysotile dust (unmilled synthetic)*
3. aluminum nitride
4. tricalcium phosphate (filamentous)
5. fibrous glass
    a. with phenol-formaldehyde-type binder
    b. with binder used for textiles
    c. without binder
6. magnesium hydroxide (brucite)
7. mineral wool
8. zinc oxide (filamentous)

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* Synthetic chrysotile has been prepared at Mellon Institute by Dr. William Granquist. Electron photomicrographs show the characteristic tubular crystals.

These materials will be injected intratracheally into hamsters under ether anesthesia. Previous experience has demonstrated that asbestos bodies will form in response to chrysotile dust within five months. The animals will therefore be held for six months and then killed. Asbestos bodies will be sought in lung juice as well as in the lung tissues.

The lungs will be expanded with buffered formalin under a head of 10 cm. of water. Blocks removed from these lungs will be sectioned at 6 μ after paraffin impregnation. These sections will be stained by different methods and photographed sequentially to provide means for studying more completely the tissue reaction to these various materials. Search for the so-called asbestos bodies will be made using routinely stained sections, and sections stained for iron. In addition, unstained cleared sections will be examined under dark-field conditions for asbestos bodies. The latter glow when examined in this manner.

The difference in tissue reaction between the synthetic chrysotile dust and that which is known to be fibrogenic as well as carcinogenic will point to the contribution to pathogenicity made by one or more of the various trace substances which may be associated with chrysotile asbestos dust as a result of processing.

The development of "asbestos bodies," better termed Ferruginous bodies, to dusts other than asbestos would point to the non-specificty of these structures and to the desirability of collecting such "asbestos bodies" from human lungs in order to subject them to electron-probe analysis. Such

analysis could give information in regard to the chemical make-up of the dust responsible for the development of the Ferruginous ("asbestos") body.

II. In order to explore the etiologic role of the various components of chrysotile asbestos in the production of lung fibrosis and lung cancer, six series of rats will be injected intratracheally with the following:

1. chrysotile dust known to be carcinogenic[9]
2. synthetic chrysotile
3. synthetic chrysotile plus nickel
4. synthetic chrysotile plus chrome
5. synthetic chrysotile plus nickel, chrome and benzopyrene
6. nickel alone or with carbon as carrier
7. chrome alone or with carbon as carrier
8. benzopyrene with carbon as carrier.

These rats will be held for two years and then killed. The lungs will be prepared for examination and sections cut in the same manner as in Phase 1.

Three other series of rats will be injected intratracheally with the following dusts:

1. filamentous glass with phenol-formaldehyde-type binder
2. filamentous glass with the binders used for textiles
3. filamentous glass without binder.

These animals will also be held for two years and then killed. The lungs will be prepared and studied as in the preceding groups, with special attention to asbestos bodies in lung tissues or juice.

The number of animals per series will be such that there will be no doubt regarding the statistical significance of the results.

III. Because of the interest of a number of companies in biologic investigations similar to those planned for chrysotile asbestos, but using instead, amosite and crocidolite, an additional investigation is proposed to be undertaken concurrently.

As in the proposal dealing with chrysotile asbestos, the purpose of this supplemental, concurrent investigation is to attempt to pinpoint the cause of the biologic activity of all three main types of asbestos dusts: whether this lies in the silicates per se, in the associated trace metals, or in the associated hydrocarbons.

Because neither amosite nor crocidolite is available as a pure synthetic material, the investigation proposed for these two types of asbestos is necessarily different from that proposed for chrysotile. Nevertheless, in order to make the investigation complete, it is desirable to include also chrysotile in the new investigation since different methods are involved.

Inasmuch as the biologic activity of asbestos seems to have two components: (a) inflammatory — responsible for asbestosis, and (b) neoplastic — responsible for lung cancer and mesothelioma, it is advisable to investigate both of them. This can readily be accomplished within the four year span contemplated for this investigation.

In order to determine whether the biologic activity of asbestos resides in the silicate, in the associated trace metals, or in the associated hydrocarbons, attempts will be made to remove the trace metals and the hydrocarbons from their respective silicates and to compare the biologic activities of such "purified" asbestos samples from which these associated materials have been removed.

As a prerequisite to any biologic testing (insofar as the lungs are concerned), it is necessary to reduce the asbestos to a respirable particle size. This will be done in the following manner: the amosite and crocidolite will be ball-milled and then fed into continuous hammer mills modified from a design by Holt and Young.[10] The dusts emerging from the hammer mills will be collected in electrostatic precipitators. This method has been used successfully by us to reduce chrysotile asbestos to a particle size, 70% of which was respirable. A sufficient quantity of finely divided chrysotile dust is available for the purposes of this investigation.

All three types of asbestos dust will be deprived of the greater portion or of all of their hydrocarbon content in one of two ways:

1. by continuous extraction with various solvents
2. by heating beyond the decomposition point of the hydrocarbons

The trace metals will be removed from the three types of asbestos dust by treatment with aqua regia followed by treatment with EDTA (ethylene diamine tetraacetic acid, a chelating agent).

One batch of each type of asbestos dust will be subjected to both procedures, i.e., removal of trace metals and removal of hydrocarbons.

Accordingly, each of the three types of asbestos dust will consist of five batches, each with a different composition:

1. the unaltered dust as collected in the precipitators
2. the dust minus the hydrocarbons (heat-treated). Here, it is anticipated that there may also have been some change in the chemical structure of the asbestos through loss of some molecules of water of hydration.

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(10) Holt, P.S. and Young, D.K. A Dust-Feed Mechanism Suitable for Fibrous Dust. Ann. Occ. Hyg. 2:245, 1960.

3. the dust minus the hydrocarbons (solvent extraction). Here, it is anticipated that the extraction may not be 100% complete.
4. the dust minus trace metals
5. the dust minus trace metals then subjected to solvent extraction to remove most of the hydrocarbons

In order to investigate the inflammatory component of the various (15) batches of asbestos dust, these will be injected intratracheally into rats and hamsters. The lungs of these animals are expected to show definitive changes within one year after the intrapulmonary introduction of the dusts.

In order to explore the lung cancer aspect of the neoplastic component of the biologic activity of asbestos dust, additional rats will be injected with the same batches of dust as above and allowed to live out their lives. Most of the animals, however, will have died before the end of the third year.

The other (mesotheliomatous) aspect of the above neoplastic component will be investigated by injecting the 15 different batches of asbestos dust within the pleural cavity of rats and hamsters and allowing them to live out their lives. Most of these animals will also have died before the end of the third year.

For the investigation of the inflammatory component of asbestos dust, a large enough number of animals will be put on test to allow sampling at intervals throughout the year and still have an adequate number remaining to represent the 12 month old lesion.

The final report covering the entire investigation will be issued toward the end of the fourth year. This report will probably be in the form of several manuscripts suitable for publication.

In the discussion which followed, Dr. Lee B. Grant asked if chrysotile asbestos was soluble in acid and Dr. Gross replied affirmatively, indicating about 5% in 8 hours.

Dr. deTreville inquired concerning the status of support which the U. S. Public Health Service has developed through congressional appropriation. Dr. Cralley indicated that the present budget was very minimal but there was hopeful indication that increased support in the future would permit research of a higher level of effort.

Dr. deTreville asked concerning the status of the extension of the IHF's five-year epidemiological study reported by Braun and Truan in 1958. Dr. Wright said this was one of the areas under consideration within QAMA. In answer to Dr. deTreville's question regarding possible areas of IHF-QAMA coordination, Dr. Wright indicated that he would certainly be interested in assistance in funding any projects recommended by the Scientific Council which could not be funded by the Administrative Council of QAMA. There being no further discussion, Dr. deTreville indicated that a report of the minutes of this session would be prepared. There was no objection or further discussion and the Chairman asked Dr. deTreville to perform such follow-up as seemed appropriate to carry out the intent of the meeting, as previously stated in the purpose.

Note: At a meeting of the Foundation's Board of Trustees on October 18, 1966, approval was given to publish these minutes for the benefit of the Foundation's membership and that an information copy be sent to the U. S. Public Health Service Surgeon General.