



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE  
NATIONAL TOXICOLOGY PROGRAM  
P.O. BOX 12233  
RESEARCH TRIANGLE PARK, N.C. 27709

PLAINTIFF'S EXHIBIT

DOW-860

Biological Effects of Ingested Asbestos

Status Report January 22, 1981

Introduction

The NIEHS is conducting a series of studies on the effects of ingested asbestos. These studies are part of the NIEHS commitment that is directed by the recently established National Toxicology Program. The Environmental Protection Agency has contributed approximately 10% of the total funding. A summary of the evolution of the study is to be found in Appendix A. A paper, given at a Workshop on Asbestos, Gaithersburg, Maryland, July 1977, detailing the studies' design and implementation is attached (Appendix B).

Current Status

Test Materials - Two samples of chrysotile, and single samples of amosite and crocidolite asbestos plus a tremolite material are being tested. A repository of these materials was established and has also served as a source for other scientific studies on asbestos.

Each material has been extensively characterized as to physical and chemical properties. The fiber size characterization performed by the Illinois Institute of Technology Research Institute (IITRI), Chicago, Illinois, has been completed and a final report received. The chemical and physical property characterization performed by the U. S. Bureau of Mines is also completed.

Hamster Studies

Three asbestos materials are being studied at IIT Research Institute, Chicago, IL. The lifetime exposure phase of these experiments has been completed. There was no indication of major differences in the mortality rate between the hamsters receiving the asbestos diet or the control diet. Histopathologic examination of tissues from female hamsters has been completed. The contractor has reported that a preliminary analysis of the hamster data indicates that no carcinogenic or cocarcinogenic effect was observed. A standard independent quality review of the pathology results has been completed for the female hamster. A similar review of the male hamsters is in progress and is expected to be completed in March 1981. Analyses of the verified data and preparation of the draft report is in progress. The report is expected to be completed and submitted to the NTP Board of Scientific Counselors' Technical Report Subcommittee for independent public peer review in May 1981.

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#### Rat Studies

Five test materials are being studied in this species at the Hazleton Laboratories, Vienna, Virginia. In addition, a subset of two studies includes neonatal as well as lifetime oral exposure to asbestos. The lifetime exposure phase of the study has been completed. Although data has not yet been statistically analyzed, it appears that longevity was not affected by exposure to the various types of fibers, although the known carcinogen (DMH) did significantly shorten lifespan. The histopathologic phase of the study is in progress and is projected to be completed in October 1981--there are a total of 5,158 rats to be examined. The histopathologic evaluation is to be completed by group and then subjected to pathology quality review. Sequential issuance of final reports by asbestiform type is being considered with the first reports projected to be available for public peer review in December 1981.

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## BIOLOGICAL EFFECTS OF INGESTED ASBESTOS

Background Summary

While there has been growing concern for the past two decades about the pathogenic effects of inhaled asbestos, relatively little attention was given to the biological effects of ingested asbestos. Early in 1973, it was recognized that fairly extensive pollution of Lake Superior waters with mine residues containing asbestiform fibers was resulting in contamination of the municipal water. In addition, other sources of asbestiform fibers find their way into material which man consumes; examples are natural contamination from serpentine rock, transmission of water through asbestos cement pipes, and use of asbestos filters for such products as beer and wine.

A conference on the Biological Effects of Orally Ingested Asbestos was organized and held in 1973 co-sponsored by the National Institute of Environmental Health Sciences and the Environmental Protection Agency; the conference was held in Durham, North Carolina, November 8-20, 1973. The proceedings of this conference were published in Environmental Health Perspectives 9, December 1974.

The DHEW Committee to Coordinate Toxicology and Related Programs formed a subcommittee to review existing knowledge of the biological effects of ingested asbestos and recommend future research needs. This subcommittee had representation from the Food and Drug Administration, National Cancer Institute, National Institute of Environmental Health Sciences, as well as working observers from EPA and other agencies. It concluded that there was not sufficient data to determine biological effects of oral ingestion of asbestos, and it proposed that specific studies be undertaken. The subcommittee then prepared a working draft of a research protocol which was widely distributed for comments both within and without the government. An open meeting was held on February 18, 1976, in Bethesda, Maryland, to receive comments, suggestions, and criticisms on this draft protocol. Based on comments received at the open meeting as well as other comments provided, the Subcommittee revised its original working draft and prepared a final protocol which it again submitted to various agencies for comments. Subsequently, the National Institute of Environmental Health Sciences developed research contracts to study the effects of oral ingested asbestos in rats and hamsters. The EPA is also funding a portion of these studies.

The studies on rats are being conducted by Hazleton Research Laboratories, Vienna, Virginia; and the study on hamsters by the Illinois Institute of Technology Research Institute, Chicago, Illinois. Other research is being performed at the National Institute of Environmental Health Sciences and the U.S. Bureau of Mines. The NIEHS is being advised in the contract by an ad hoc committee composed of Dr. R. Shapiro, NIEHS (DHEW CCTRP); Dr. R. Tardiff, EPA (replaced by Dr. R. J. Bull, December 1977); and Dr. M. Stanton, NCI.

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### Asbestos

The current protocol is to study two forms of chrysotile, one which represents a range of fibers primarily less than 10 microns in length and a second which has a broader range of fiber lengths. In addition to the two chrysotile samples, one form of amosite, tremolite, and crocidolite will be evaluated. All are to be extensively characterized as to chemical and physical properties. The characterization is being accomplished by the U.S. Bureau of Mines and IITRI Fine Particles Laboratory.

### Animal Studies

All materials will be tested in rats, whereas the two chrysotile samples and amosite will also be tested in hamsters. The hamster represents the "second species;" as such, it is being fed a material that represents a serpentine and an amphibole type of asbestos. Each material is to be fed continuously in the diet at a 1% level.

All studies are to encompass the life span of the animal, which is defined as the age an animal begins eating solid food until its death. To determine newborn effects, a segment of the study incorporates exposure by gavage from birth to weaning, followed by consumption of asbestos in the diet till death.

A portion of the study seeks to determine if there is an interaction between asbestos and a chemical known to cause tumors of the gastrointestinal tract.

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## Previous Progress (through February 1977)

### Test Materials

1. Two chrysotile samples were purchased and physical and chemical characterization started.
2. A tremolite sample was received and characterized.
3. Contracts were awarded for preparation of two amosite samples and a crocidolite sample under the supervision of the U.S. Bureau of Mines.

Contractor was unable to provide two samples of amosite that had a distinct fiber size distribution. Therefore, decision was made to test only one sample of amosite.

4. A satisfactory method for incorporating asbestos in asbestos diets was developed.
5. A chemical carcinogen for interactive experiments was selected. Twelve month experiments were performed in rats and hamsters to determine appropriate dose of either dimethylhydrazine or methyl-azoxymethanol to be used in the interactive study. Dimethylhydrazine was selected for use in both species.

### Animal Studies

#### Rats

Lifetime studies on the biological effects of asbestos at 1% in the diet were started for the two chrysotile and amosite materials.

## Progress (February 1977 - February 1978)

### Test Materials

1. Amosite and crocidolite material received in spring and summer of 1977. Physical and chemical characterization work is underway.
2. All five materials to be tested are in possession of NIEHS: Short range chrysotile; intermediate range chrysotile; amosite; crocidolite; and tremolite.
3. Final reports on physical/chemical characteristics are expected in late spring of 1978.

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## Animal Studies

### Rats

1. Original test group on chrysotile and tremolite diets developed a respiratory infection. Since this type of infection would severely compromise the experiment in its later stages, NIEHS directed termination of ongoing experiments. Complete review of procedures undertaken and additional safeguards against reoccurrence of respiratory disease were performed. Experiments were then restarted.

2. Current Status:

Chrysotile Short Range - Rats receiving 1% chrysotile in diet are entering second month of experiment.

Chrysotile Intermediate Range - Rats receiving 1% chrysotile in diet are completing the first month of experiment.

Rats receiving asbestos gavage from birth through weaning are now being placed on 1% chrysotile diet.

Rats on dimethylhydrazine/asbestos diet interaction study are completing the first month of experiment.

Tremolite - Rats are being born of mothers receiving tremolite diet.

Crocidolite - Rats are being born of mothers receiving crocidolite diet.

Amosite - Parental generation is currently in breeding.

Controls - Phased in to age match experimental groups.

All groups should be on dietary phase of study by end of February.

### Hamsters

Current Status:

Chrysotile Short Range - Hamsters are currently in 43rd week of study

Chrysotile Intermediate Range - Hamsters are currently in 37th week of study.

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Chrysotile Intermediate Range plus Dimethylhydrazine -  
Hamsters are currently in 33rd week of study.

Amosite - Hamsters are currently in 22nd week of study.

Controls - Hamsters are phased in to age match experimental groups.

It is anticipated that significant numbers of age related deaths will commence in the latter 6-8 months of 1978. There is no indication of increased deaths or other biological effects in any test group to date.

Prepared by Dr. John A. Moore  
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February 7, 1978

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ORAL ASBESTOS ANIMAL TEST GROUPS

HAMSTER

|                                                        | <u>CHRYSOTILE<br/>INTERMEDIATE</u> | <u>CHRYSOTILE<br/>SHORT RANGE</u> | <u>AMOSITE</u> | <u>CROCIDOLITE</u> | <u>TREMOLITE</u> |
|--------------------------------------------------------|------------------------------------|-----------------------------------|----------------|--------------------|------------------|
| Asbestos diet                                          | 500                                | 500                               | 500            | ND                 | ND               |
| Asbestos diet plus<br>chemical carcinogen <sup>a</sup> | 350                                | ND                                | ND             | ND                 | ND               |
| Prewearing asbestos<br>gavage plus asbestos diet       | ND                                 | ND                                | ND             | ND                 | ND               |
| Control diet <sup>b</sup>                              | 500                                | 250                               | 250            | ND                 | ND               |
| Control diet plus<br>chemical carcinogen <sup>a</sup>  | 250                                | ND                                | ND             | ND                 | ND               |
| TOTAL HAMSTERS: 3,100                                  |                                    |                                   |                |                    |                  |

<sup>a</sup>Numbers may be adjusted pending results of dose ranging studies to determine  $15 \pm 5\%$  tumor incidence in controls.

<sup>b</sup>Control allocations are descriptive only; it is expected that experimental response will be evaluated against total controls (1000). Subsets of controls will reflect temporal differences in commencing phases of study which is expected to aggregates of 250-350.

ND - NOT DONE

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ORAL ASBESTOS ANIMAL TEST GROUPS

|                                                        | RAT                               |                                  |                |                  |
|--------------------------------------------------------|-----------------------------------|----------------------------------|----------------|------------------|
|                                                        | <u>CHRYSTILE<br/>INTERMEDIATE</u> | <u>CHRYSTILE<br/>SHORT RANGE</u> | <u>AMOSITE</u> | <u>TREMOLITE</u> |
| Asbestos diet                                          | 500                               | 500                              | 500            | 500              |
| Asbestos diet plus <sup>a</sup><br>chemical carcinogen | 350                               | ND                               | 350            | ND               |
| Premeaning asbestos<br>gavage plus asbestos diet       | 200                               | ND                               | 200            | ND               |
| Control diet <sup>b</sup>                              | 200                               | 200                              | 200            | 200              |
| Control diet plus <sup>a</sup><br>chemical carcinogen  | 250                               | ND                               | 250            | ND               |

TOTAL RATS: 5,100

<sup>a</sup>Numbers may be adjusted pending results of dose ranging studies to determine  $15 \pm 5\%$  tumor incidence in controls.

<sup>b</sup>Control allocations are descriptive only; it is expected that experimental response will be evaluated against total controls (1000). Subsets of controls will reflect temporal differences in commencing phases of study which is expected to be aggregates of 250-350.

ND - NOT DONE

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