

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Date:

Reply to
Attn of: BD-413

Subject: Memorandum of Need - Body burden and distribution of asbestos in common laboratory animals.

To: Chief, Contracts and Grants Branch (CA-270)

Through: Director, Division of Financial Management (CA-100)

Associate Commissioner for Science (CS-1)

Director, Bureau of Drugs (BD-1)

Assistant Director for Planning & Analysis (BD-3)

Executive Officer, Bureau of Drugs (BD-15)

Deputy Director, Office of Scientific Coordination (BD-201)

A. Statement of Work

For some time it has been suspected that some forms of asbestos, mainly chrysotile, a known carcinogen, occur as contaminants in parenteral solutions, probably traceable to asbestos-containing filter units in production. Results of a survey of some parenteral drugs have appeared recently. Owing to wide use of talc(s) in production of other dosage forms, in association with food, and in cosmetics and dusting powders - all forms of talc potentially containing asbestos - a very large variety of consumer products may likewise be contaminated. There are also suggestions that the incidence of stomach cancer is higher in consumers of rice treated with talc for gustatory purposes than in the general population. Since asbestos fibers or fibrils of carcinogenic dimensions have been shown to migrate in the body from the initial deposition site to the tissues primarily sensitive (mesothelial, i.e., pleura, pericardium, peritoneum), all products, respirable, ingestible, parenteral, etc., must be regarded as hazardous if they contain known carcinogenic asbestos forms. While it appears established that contamination of some parenteral drug forms with asbestos exists, the amount of asbestos likely to be injected in such forms relative to existing body burden is unknown. Because of wide exposure to asbestos occupationally, and other exposure in urban areas such body burdens of environmental origin must be assumed to exist, including those in animals which must eventually be used to test and estimate the hazard of contaminated drugs and other products.

Data sought in the proposed contract work will form the basis and background required for systematic, controlled and valid tests of the toxicological significance of asbestos - contaminated drugs and other products.

- (1) The contractor will conduct tests designed to detect asbestos fibers, in tissues of laboratory mice, rats, rabbits and guinea pigs which have been reared and maintained in housing facilities normally provided for each species.

- (2) Conditions of housing will include air (asbestos-monitored supplied through standard filters, bedding of standard natural (wood shavings, corn cob, etc.) and synthetic materials such as vermiculite. Feeding will consist of standard, balanced laboratory chows of adequate nutritional value.
- (3) In groups of 100 each equally divided between sexes, the control animals will be maintained from weaning onward; at six months approximately $\frac{1}{2}$ of each species (and sex) will be sacrificed, and at 1 year the remainder will be sacrificed. Similarly, test animals of 20 each per subgroup will receive 10.0, 1.0, 0.1, 0.01, 0.001 mg of finely divided chrysotile asbestos in suspension intravenously, and sacrificed at similar intervals. (A pilot test in 5 rats each of 10.0 mg and 1.0 mg of berberine-tagged chrysotile intravenously will examine lungs, liver, spleen and kidney 24 hours after administration by fluorescent and electron microscopy).
- (4) Complete gross autopsies on each animal will be performed; heart, lungs, stomach, lymph nodes (thoracic and mesenteric), bladder, liver, parietal and visceral peritoneum and pleura, stomach, small and large intestine, and brain will be examined for the presence of asbestos fibers by high power, visible polarized light, and by electron microscopy.

B. Release of Information by the Contractor

The contractor will be encouraged to publish his data after the final report has been accepted.

C. Relation of Work to be Performed to the FDA Statutory Mission

The FDA is responsible for safety and efficacy of drugs and for safety of food, cosmetics and other consumer products. Within FDA, BD is responsible for drugs and drug products. Among the criteria for safety is freedom from contaminants, specifically particulate matter in parenteral drugs.

D. Prior and Present Related Work

- (1) Inhalation, intrapleural, intraperitoneal, and subcutaneous routes of administration of asbestos has produced lung, pleural, and peritoneal cancers, i.e. at sites often removed from the site of administration, presumably through lymphatics or other migratory mechanisms. The amounts required may, moreover, be large compared with the amounts contaminating pharmaceuticals, foods, and other products. This is additional reason for the uncertainty which requires data on the background of tissue asbestos burden against which tests of contaminated products must be made. There is no indication that such background data are being sought elsewhere (Stanton).

- (2) Current work at NCI indicates strongly, in the opinion of the workers there, that any substance (e.g., glass, wool(s), fiberg etc.) of the dimensions, metabolic durability, and non-excretab of known asbestos carcinogens will likewise prove carcinogenic. Should this eventuate, the area of concern of FDA will be widen considerably.
- (3) "Medical Hazards of Asbestos and Related Mineral Particles," copy attached, treats the literature fully up to that date.
- (4) References:
 - a. W.J. Nicholson, C.J. Maggiore, and I.J. Selikoff, Asbestos Contamination of Parenteral Drugs, Science, Vol. 177, p. 171 (July 1972).
 - b. R.R. Merliss, Talc-Treated Rice and Japanese Stomach Cancer, Sci., Vol, 173, p. 1141, (1971).
 - c. F.J.J. Roe, R.L. Carter, M.A. Walters and J.S. Harrington, The Pathological Effects of Subcutaneous Injections of Asbestos Fibres in Mice: Migration of Fibres to Submesothel Tissues and Induction of Mesotheliomata, Int. J. Cancer, 2, p. 628-638, (1967).
 - d. J.S. Harrington, Mesothelioma, in R.W. Raven and F.J. Roe (e The Prevention of Cancer, p. 207, Butterworth, London (1967)
 - e. Mearl F. Stanton, and Constance Wrench, Mechanisms of Mesoth Induction With Asbestos and Fibrous Glass, J. Nat Cancer Ins Vol. 48, p. 797-821, (March 1972), Bethesda, Maryland 20014.

E. Funding of the Project

Estimated cost - \$60,000

Appropriation symbol -

Allotment symbol -

F. Project Officer

Stephen Krop, Ph.D.

G. Project Advisory Group

J. K. Lamar, Ph.D.

M. A. Gross, Ph.D.

W. W. Wright, Ph.D.

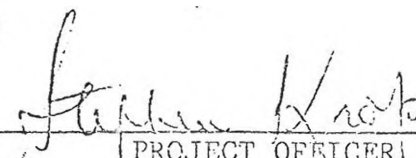
Mearl Stanton, M.D. (NCI)

H. Period of Contract

18 months from award date

I. Prospective Contractors

1. NCTR
2. Dr. I. J. Selikoff, Mt. Siani School of Medicine, New York, N. Y.
3. Dr. W. E. Smith, Health Research Institute, Fairleigh-Dickinson University, Madison, New Jersey



PROJECT OFFICER

DIRECTOR, OFFICE OF PHARMACEUTI
RESEARCH AND TESTING

Julian Kramer (BD-411)
Acting Director
Division of Drug Biology

Approved: _____
Deputy Director, Office of
Scientific Coordination

Date: _____

Approved: _____
Executive Officer, Bureau of Drugs

Date: _____

Approved: _____
Assistant Director for Planning & Analysis, BD

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Director, Bureau of Drugs

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Associate Commissioner for Science

Date: _____

Approved: _____
Director, Division of Financial Management

Date: _____

cc:

CS-1

CA-100

CA-270

CA-228

BD-1

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SKrop:jhw 10-18-72