

March 23, 1972

MEMORANDUM OF CONFERENCE

Between: Drs. Herman Kraybill, Armand Casola, John Gowdy,
Alfred Weissler and J. K. Lamar (for FDA)

and

Dr. Irving J. Selikoff and his staff of the
Environmental Sciences Laboratory, Mount Sinai
School of Medicine, CUNY

Subject: Medical Hazards of Asbestos, Talc, and Other Mineral Particles

The conference took place at the Mount Sinai School of Medicine at 9 a.m. Dr. Selikoff introduced members of his staff, Carl Maggiore, Physicist; Dr. William Nicholson, Biophysicist; Dr. Art M. Langer, Physicist; Duncan Haladay, Industrial hygienist and chemical engineer; Harry Heimann, occupational medicine; Art Roe, Mineralogist; Ira Rubin, Expert on electron microscope and X-ray diffraction, Ann Mackler, Mineralogist; and Dr. Kingsley Kay, Toxicologist.

Dr. Selikoff then introduced the subject by citing the risks from asbestos, among industrial workers, members of their families, and persons living close to industrial applications. He stated that besides asbestosis, 20% of workers will die of lung cancer, 5 to 10% of mesothelioma, 10% of gastrointestinal cancer, and 5 to 10% of other cancers, including astrocytomas, oropharyngeal tumors, cancers of pancreas, ovary, and thyroid, a total of 50% deaths from cancer. He stated that Dr. E. C. Hammond will report tomorrow at Clearwater, Florida on the increased incidence (X10) and association of these other tumors with history of exposure to asbestos. As with most human carcinogens, the latent period is over 20 years.

As to the relationship of cancer with size of asbestos particle, this is unstudied, and difficult to study, for chrysotile asbestos continues to break down in cells, until only small fibrils are found. Size may be only one factor. Others may be crystalline structure, surface charge, etc.

Dr. Selikoff stated he knew of the glucose-talc coating of rice 6 years ago. He experimented on hamsters, using talc by mouth and got only one adenoma of the colon, so did not report it. Dr. Langer is now looking at mineral particles in bowel wall of humans and animals. He finds asbestos fibrils in the bowel wall of deceased asbestos workers. Diatomaceous particles and clay particles also get in. Submicroscopic particles go through with no difficulty. Volkheimer of Berlin has had several papers in the last few years on particles up to 100 μ going through the bowel wall, by "persorption," into the basal lymphatics. Fine iron particles and even starch granules go through.

Selikoff is planning a study, along with Dr. E. C. Hammond, to have Dr. Oscar Auerbach, a quantitative morphologist, to read bowel slides "blind," for mineral particles. Such particles may cause granulomas in other organs, e.g. liver, kidney, spleen, thyroid, and pancreas. In rats, talc particles get through the bowel wall.

Dr. Selikoff discussed mesotheliomas, the "marker" cancer of asbestos exposure. Lung cancer is so common in the general population that only a distinct rise in rate can prove an association with asbestos, but mesotheliomas are so rare that association is easy to demonstrate. Exposures in childhood, or as a member of the family of an asbestos worker, or living close to asbestos applications (plants, mines, navy yards) can be enough to cause the disease. There is not only the matter of a brief but heavy exposure but also small cumulative exposures. Either is enough, for there is little elimination of the particles from the body. R. Doll has a theory of cancer involving repeated insults. Molly Newhouse has a case control study where a fair percentage of those exposed succumb.

Next discussed was asbestos particles in talc. Claim was made that even the best talc (J&J) may have up to 0.01% w/w of chrysotile fibrils but no tremolite. Other talcs have chrysotile, tremolite and anthophyllite. The fine fibrils of chrysotile can only be discovered by electron microscopy, and there may be 10^5 fibrils in 0.1 gm of the best talc.

It is true that ultrasonic fragmentation breaks up chrysotile, but is also true that whole chrysotile fibers are rare in lungs of asbestos workers. Cells break up fibers. Adsorption of fibrils onto diatoms, etc. is possible, with aggregates being 6.1 to 2.0 μ . New York State ore is made of such aggregates.

Dr. Haladay stated that the idea that only particles $< 5 \mu$ can remain in lungs is false. There is a relation to size, shape and surface change. Studies with round latex particles of definite size show a retention curve which does not necessarily apply to asbestos particles. Nicholson thinks the standards set for counting asbestos particles of 5 μ were set because particles of this size are easily seen with light microscopy. When questioned about the new NIOSH standards for asbestos plants (5 particles/ml. now, 2 later) it was stated that this is not good enough. Furthermore, plants are rarely inspected. Standards should be focused on procedures to eliminate dusts. Many plants are below the NIOSH limits now. All could be. There are a few thousand workers involved. To extrapolate to millions of users of talc is ridiculous. One must consider the worst talcs and exposure of children now, who may succumb in 20-40 years. A plan is under way to do a study of persons exposed as children to asbestos near plants and shipyards. One difficulty is the mobility of the population.

Dr. Selikoff then cited his data from studies of Union members, those who smoked cigarettes, versus non-smokers or pipe and cigar smokers. There appears to be a great "multiplying effect" or potentiation, from smoking cigarettes. Of 283 smokers in 1963, 45 had lung cancer by July 1, 1971. (In non-smokers there was one lung cancer in 87). Animal experiments were started by Hanford (Cattell) two years ago using dogs and hamsters. Results are expected by approximately 800 days.

Dr. Kraybill asked about other silicates, such as those used as anti-caking agents. Dr. Selikoff has a list of 100 silicates known to have biological activity. Heat and chemical processing of silicates can change their structure and particle size. An example is diatomaceous earth heated with phosphates. This decreases particle size and has been associated with increased pneumoconiosis, cor pulmonale, and even pneumothorax. The lack of definition of silicate particles used as anti-caking agents was noted. Sources and specifications of identity and purity are not defined. All are apt to be fibrogenic.

A. C. Allison of London and Jerald Weisman of N.Y.U. Med. have recent unpublished work on silicates. The association of silicates with nephropathy in the Balkans was noted. There are amorphous silicates in food grains and this has been an economic problem with sheep in Australia (work of Baker).

Major concern is still asbestos, and particles have been found in lard, sugar, rice, salami, beverages, syringes, parenterals, etc. NCI is studying mineral particles in bowel walls of persons from Hawaii, and Puerto Rico. John Bird and Saffiotti are persons to contact there. A paper speaking counter to Merliss theories has been written by Hector Bleger, and Dr. Kraybill has a copy.

Dr. Selikoff mentioned a possible study of tissues from some 3000 persons dying in 1968-69 in 3 N.Y. hospitals, where case histories as to talc and asbestos exposure, and smoking habits were taken. Blocks from lung and bowel, and whole left lungs were taken at autopsy. Whole lungs were frozen. These await study. There are 2 techniques, the Langer search for particles by EM following digestion, and the Partin (Cardiff) technique.

Bulk tissue digestion with semiquantitation follows the monograph by D. Walton (published by Unwin of London). Langer's technique is in Arch. Environ. Health for 1971. The Langer technique as applied to parenterals is as follows:

1. Reconstitute drug with water filtered 2X thru a 0.22 μ millipore filter, and carry an aliquot of the water as a control (for background).
2. Filter the reconstituted drug thru 0.45 μ millipore. Clear an aliquot with diethylphthalate plus _____ (?)

3. Scan optically for asbestos from fibers (fibers 1μ long were found in one drug and there were 2 cases where larger fibers could be chrysotile).
4. Ash 1/2 of the remainder using ionized O_2 asher at 100-200° for 20-60 minutes (higher temperatures of muffle furnaces or heated crucibles causes loss by explosion of organic material).
5. Grind residue in watchglass in 1% nitrocellulose in amylacetate.
6. Disperse over 10cm^2 (2 slides) by smear technique. Transfer to EM grids.
7. Scan at 40,000X, and semiquantitate by appropriate multiplier.

This is the same technique presented at the Clean Air Conference, Washington, D. C. in 1970. It is laborious, and it can be automated, at a cost of \$100,000. There is a "background" of 2-3 fibrils/grid square, even with use of clean-air hoods. Even rural air has $2/\text{ng}/\text{M}^3$ of air, and up to $100\text{ng}/\text{M}^3$ in city air. Two drug samples had estimated levels of 1mcg./ampule (dose). Selikoff states that one may inhale 3-4 ng of asbestos particles/day and that a single dose of one of these drugs would supply approximately 250 X this amount. The increase to body burden is great. Mass is involved, as well as number of fibrils.

The difficulties of this method are great. Only 4-8 grid squares can be counted and it takes hours. Even so, 30% of fibrils are missed, as proved by EM photographs. When asbestos fibrils are found in parenterals they are there in at least 7X background.

Selikoff's group does Xray diffraction also, but he claims this is a crude technique.

Discussion next centered on possible mechanism of carcinogenesis. Surface area/wt or/vol is very great for the small fibrils, and this large area could be the physical basis of carcinogenesis. Selikoff states that Cralley's theory of the mineral content is discredited by work of Meryl Stanton of NIH, who showed that Ni is not needed for carcinogenic effect. Selikoff's theory is that small fibrils, billions in number, are in many cells, even in nuclei, and they kill some cells, but may cause a few to grow wildly, and it is impossible to predict who will sustain a "hit."

As to a no-effect level for asbestos as a carcinogen, there is probably a level at which exposure will not produce a statistical increase in cancer above background. This may depend on definition; but for practical purposes it is no-effect.

What happens when ultrafine particles are injected i.v. or i.m.? They are probably ingested by macrophages and carried to regional nodes. We do not know of any increase in lymphomas, but there is certainly increased incidence of other tumors from inhaled/ingested asbestos and injected asbestos increases the body burden greatly.

Dr. Langer and Dr. Nicholson supplied Dr. Casola a list of parenteral drugs among 17 studied, in which asbestos form particles had been found at one time or another. Dr. Selikoff advised that FDA contact Dr. Newmark at Hoffmann-LaRoche who probably knows more than anyone about use of asbestos filters in production of parenterals. Roche has eliminated such use except for one Vet. drug.

Dr. Selikoff stated he could send Dr. Casola a JAMA manuscript on asbestos in parenterals in 2-3 weeks. JAMA does not send proofs ordinarily.

Dr. Selikoff volunteered that he has financial support for all the work he can do at present. He is engaged in an epidemiological study (cohort study) of persons exposed to PCBs. He has thoughts on an epidemiological study of the possible carcinogenicity of oral contraceptives.

Question was asked as to the possibility of final filter removing asbestos particles. Consensus was that this is feasible, by membrane (millipore) or stone filters, as is done for draft beer. Referred to FAO magazine for 1971.

Holmes and Morgan have a manuscript on the rapid transfer of radioactive chrysotile particles in vivo, soon to appear in Environ. Research. Roe, Harrington et al have published on transfer of particles in animals. Fibrils may have lymphatic or hematogenous spread.

Dr. Selikoff noted work indicating that inorganic particles have activity on kinin metabolism. Kinins and especially the Hageman factor, have effects on blood clotting. Certain silica particles cause hemolysis.

Having answered all questions phrased or implied, the staff began to go back to work. We thanked Dr. Selikoff and his staff for all the information and for his cordial and generous hospitality, and departed at about 1:15 p.m.

J. K. Lamar, Ph.D.

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Dr. Alfred Weissler
Acting Director
Division of Colors and Cosmetics Technology (BF-430)

DATE: March 20, 1972

FROM : Chief Chemist
Bureau of Drugs

SUBJECT: Specimens Containing Talc, for Dr. Lewin's examination

1. Enclosed are 5 drugs and a sample of USP Talc (Merck Chemical Co.) of which you may use any or all to transmit to Dr. Lewin in New York on Wednesday. These drugs and talc will have been examined by Dr. Lamar on phase-contrast microscope and Mr. Arnold Schulze on the polarizing microscope, by Tuesday. Reports will be available to you.

2. The drug samples are as follows:

Cleocin HCl, Upjohn 75mg Lot 450 APLI 3 caps plus a button of washed residue

Cleocin HCl, Upjohn 150mg 3498 E 884AG 3 caps plus a button of washed residue

Dopar (Eaton) Lot 1-2-70 250mg caps 5 caps

Dopar (Eaton) Lot E-7298 500mg CT 3 CT

Larodopa (Roche) Lot 101-06020 500mg caps 5 caps

I trust that the above information is sufficient for you and Dr. Lewin.

Armand R. Casola

Armand R. Casola, Ph.D.