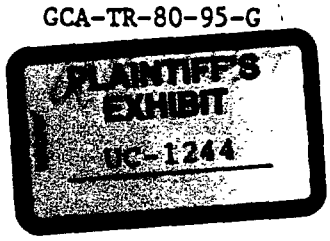
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PROCEEDINGS OF THE NATIONAL WORKSHOP ON SUBSTITUTES FOR ASBESTOS

Revised Draft Final Report

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A 16538

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ACL Doc 16408 · Page 1 of 16 asbestosclaims.law/library/16408/1

CHEMICAL DETOXIFICATION OF ASBESTOS FIBERS

by

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ABSTRACT

Exposure to asbestos materials is associated with a variety of biologic responses which include ferruginous body formation, chronic fibrosing processes, and development of cancers. Formation of a ferruginous body is an early response of tissues to asbestos, and a variety of such bodies involving deposition of iron containing materials on the fiber have been described. One type of ferruginous body is formed by the deposition of inorganic iron on the fiber surface. Acting on the premise that the addition of ferric oxides or other metal oxides to asbestos would detoxify silicates and other toxic sites on the fiber, several metal micelle forms of asbestos, including chrysotile, amosite, crocidolite, and anthophyllite have been prepared. Biologic testing of iron micelle forms of chrysotile and amosite show that the treatment with iron salts decreases the cytotoxity of these forms of asbestos when compared with untreated materials. The treatment of chrysotile with an iron salt also decreases hemolytic activity and adverse effects on membrane permeability of cells. Testing of the iron treated chrysotile in a variety of applications using Grades ranging from AAA to 7 RF 99 in quality indicates that the treated asbestos retains desirable physical properties and can substitute for asbestos in all its current applications. The chemical treatment has been extended to show that metal oxides of cobalt, chromium, manganese, aluminum, and copper also add to an asbestos fiber.

Exposure to asbestos in the environment is associated with increased risk of developing chronic fibrosis in the lungs and two forms of cancer, bronchiogenic carcinoma and mesothelioma. Asbestos has been characterized as an unavoidably unsafe material, but its desirable physical properties including heat resistance, reinforcing strength, chemical resistance, flow characterization and versatility in applications including cements, boards, papers, textiles, friction materials and numerous other products has supported the continued and essential use of asbestos minerals. Considerable efforts have been made to find substitutes for the use of asbestos in its varied applications, but these efforts have met with limited success. Invariably, proposed substitutes do not measure up to the use of asbestos itself, or there are considerable costs that make use of the substi-

A 16559

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ACL Doc 16408 · Page 2 of 16 asbestosclaims.law/library/16408/2

tute prohibitive. One approach to this issue is to develop a substitute by chemical detoxification of asbestos fibers. The objectives of this report are to discuss the basis for chemical detoxification of the asbestos surface, to present initial results of in vitro tests of treated materials, and to discuss the effects of chemical treatment on the desirable attributes of asbestos.

The most hazardous asbestos fibers are those characterized as being deposited in the alveoli. Once deposited at critical tissue sites, asbestos produces a variety of responses including irritation of cells and tissues, increased oxygen consumption, formation of ferruginous bodies, chronic fibrosis, an increased risk of bronchiogenic carcinoma, and an increased risk of developing mesothelioma. In 1974,[1] I developed a hypothesis that these various responses to asbestos were related. Silicate groups on the asbestos surface were characterized as active sites for formation of ferruginous deposits, and the leaching of magnesium ions from the surface was identified as being involved in some of the toxic effects.

Figure 1, adapted from my paper in 1974,[1] summarizes the hypothesis concerning the relationship between exposure to asbestos, ferruginous body formation, chronic fibrosing processes, and carcinomas. A sequence of dependent events is thought to occur leading to increasingly adverse toxic effects. The underlying mechanisms are depicted as involving two independent pathways. In one pathway, after phagocytosis and fiber encapsulation, a ferruginous body is formed consisting primarily of substances containing ferric oxides, such as ferritin, hemosiderin, or inorganic ferric hydroxides. The driving force for deposition of ferric containing species is the presence of electronegative sites produced by formation of hydrated silicates on the asbestos surface. The removal of ferric ions in the formation of a ferruginous body requires the oxidation of ferrous ions to replace the ferric ions in solutions and to reestablish redox equilibrium. This results in an increased glycolysis as indicated by increased oxygen consumption by tissues exposed to asbestos. Excessive glycolysis leads to release of a fibrogenic factor characterized by Heppleston[2] as possibly a galactan. This factor induces an increased synthesis of elastic fibers such as collagen at tissues which are remote from the site of deposition of the asbestos fiber.

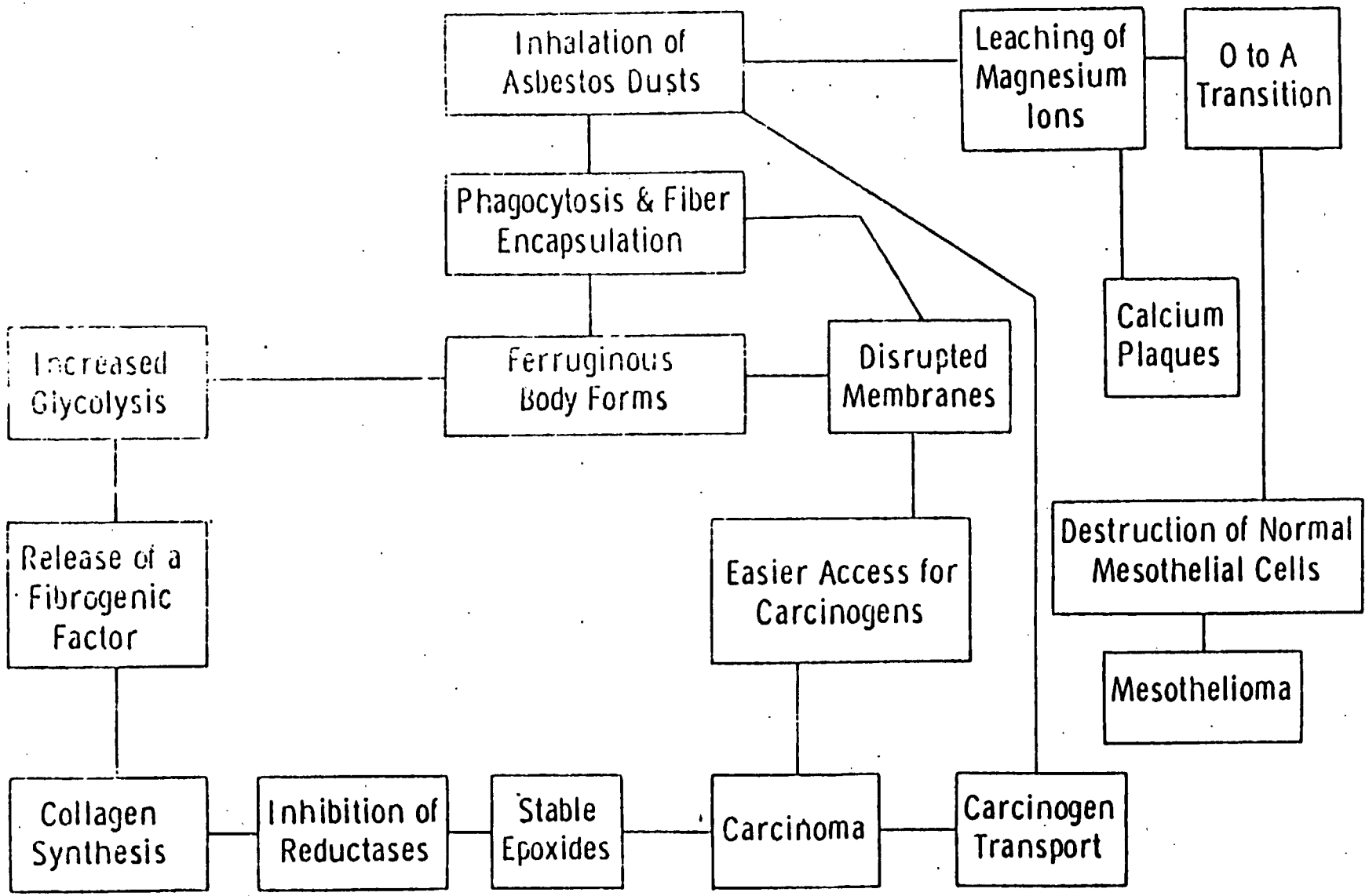
In Figure 2, the synthesis of collagen requires an oxidation of proline in protocollagen by molecular oxygen with reduction by a reducing cofactor to form hydroxyproline. This converts protocollagen to a more hydrophilic collagen and frees the RNA-template for continued production of protocollagen. Thus, continued release of a fibrogenic factor induced by increased glycolysis stimulates a chronic production of fibrous protein or chronic fibrosing processes.

In Figure 1, the significance of the chronic fibrosing processes is inhibition of reductases leading to asbestos acting as a cocarcinogen in producing bronchiogenic carcinoma. This decrease in the availability of reducing cofactors favors production of stable epoxides derived from toxic products of combustion, synthetic toxins or natural products. Another cocarcinogenic mechanism for producing an increased risk of carcinoma is the disruption of membranes by the mechanical irritation of cells and tissues. The resulting increase in membrane permeability would provide greater access for carcinogens and other toxic agents. Finally, another cocarcinogenic mechanism is by transport of a carcinogenic

A 10540

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ACL Doc 16408 · Page 3 of 16 asbestosclaims.law/library/16408/3

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ACL Doc 16408 · Page 4 of 16



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Figure 1.

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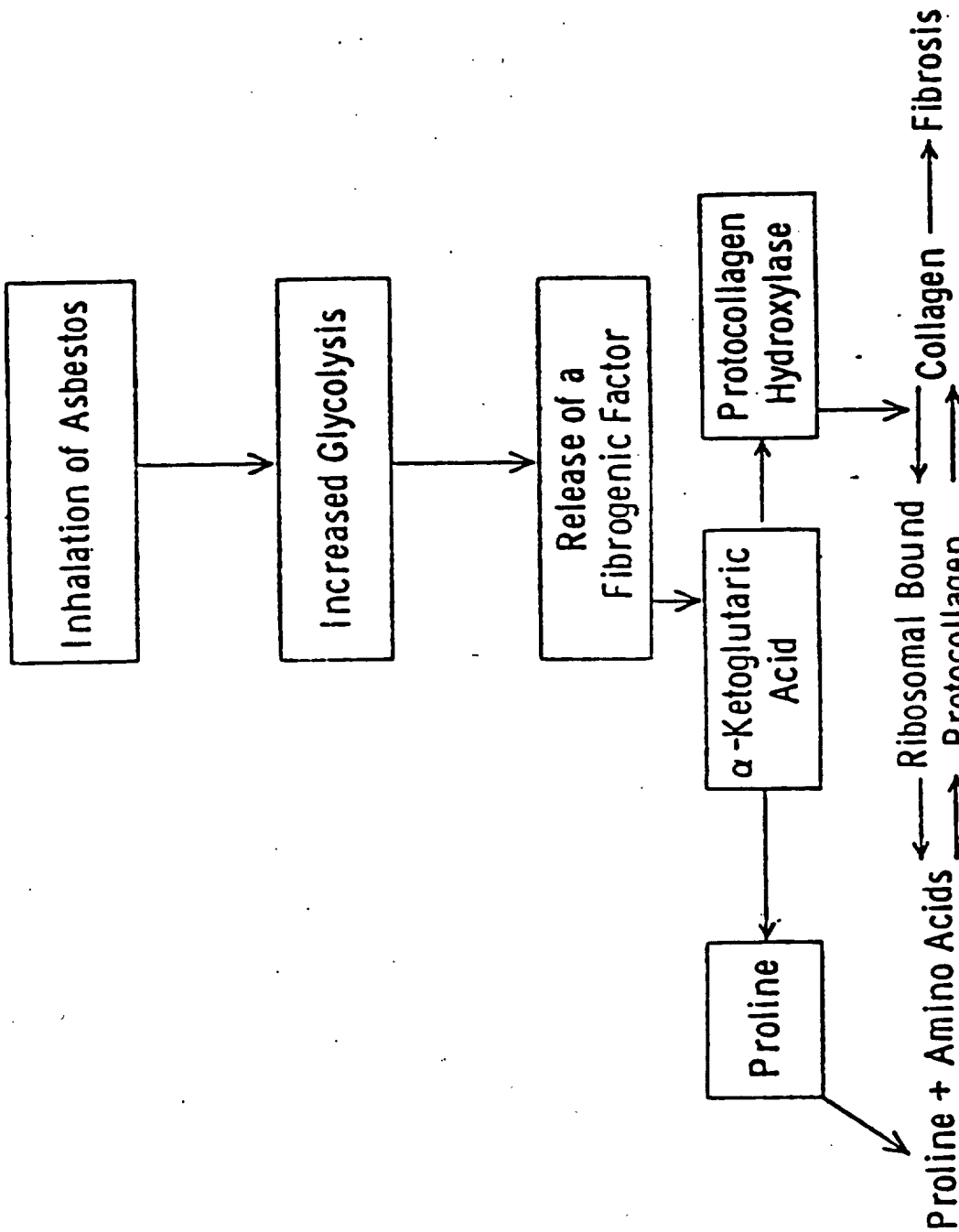


Figure 2.

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ACL Doc 16408 · Page 5 of 16 **asbestosclaims.law/library/16408/5**

agent to critical tissues on the highly active surface of an asbestos fiber.

Also in Figure 1, the leaching of magnesium ions from the asbestos surface is thought to interfer with solubility and ionic distribution of calcium. One manifestation of a disturbance in calcium metabolism is the formation of pleural plaques. Another manifestation is the induction of an orthodox to aggregate transition (O to A Transition) of mitochondria causing destruction of normal mesothelial cells. Surviving abnormal mesothelial cells could grow in an uncontrolled environment according to the bioenergetics and tumor growth theory described by Racker.[3]

Thus, a successful chemical treatment to detoxify asbestos depends on three principles.

1. Silicate binding sites must be masked by an agent that remains in place under physiological conditions.

2. Leachable ions such as magnesium must be removed.

3. The desirable physical attributes of asbestos such as strength, bulk density, surface area, magnetic properties, flow characteristics, heat, and chemical resistance must be essentially unchanged.

As an initial approach and assuming that the formation of a ferruginous body is an attempt to detoxify the absorbed asbestos, a proprietary process has been developed which prepares a highly saturated synthetic ferruginous body. The process involving iron uses readily available, relatively inexpensive raw materials, and chemical compositions of treated asbestos have been prepared using chrysotile, amosite, crocidolite, and anthophyllite. The treatment process has also been extended to produce chemical compositions of asbestos containing cobalt, manganese, chromium, aluminum, and copper.

Treated samples of amosite and chrysotile were tested for cytotoxicity using human lung macrophage cells in tissue cultures according to the procedure recommended by Wade, et al.[4]

Figure 3 is an example of the results using a UICC chrysotile B. In the test, cell cultures are allowed to grow for a 24-hr pre-exposure period. The cultures are exposed to the material under test for 48 hours. The media and most of the asbestos are removed, and the cells are cultured using fresh media for an additional 24 hours. Viable cells are counted at 24-hr intervals during the test, and five fields are counted for each culture. The upper curve shows the average number of viable cells in the controls, the next curve shows the average number of viable cells in cultures exposed to a treated UICC chrysotile B, and the bottom curve shows the average number of viable cells in cultures exposed to untreated UICC chrysotile B. The amount of asbestos in this series of tests was 100 micrograms/ml. Similar, but less dramatic results were obtained in tests using a treated amosite. From these results, the chemical treatment of asbestos decreases the cytotoxicity of the asbestos fiber to human lung macrophage cells.

A 10543

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ACL Doc 16408 · Page 6 of 16 asbestosclaims.law/library/16408/6

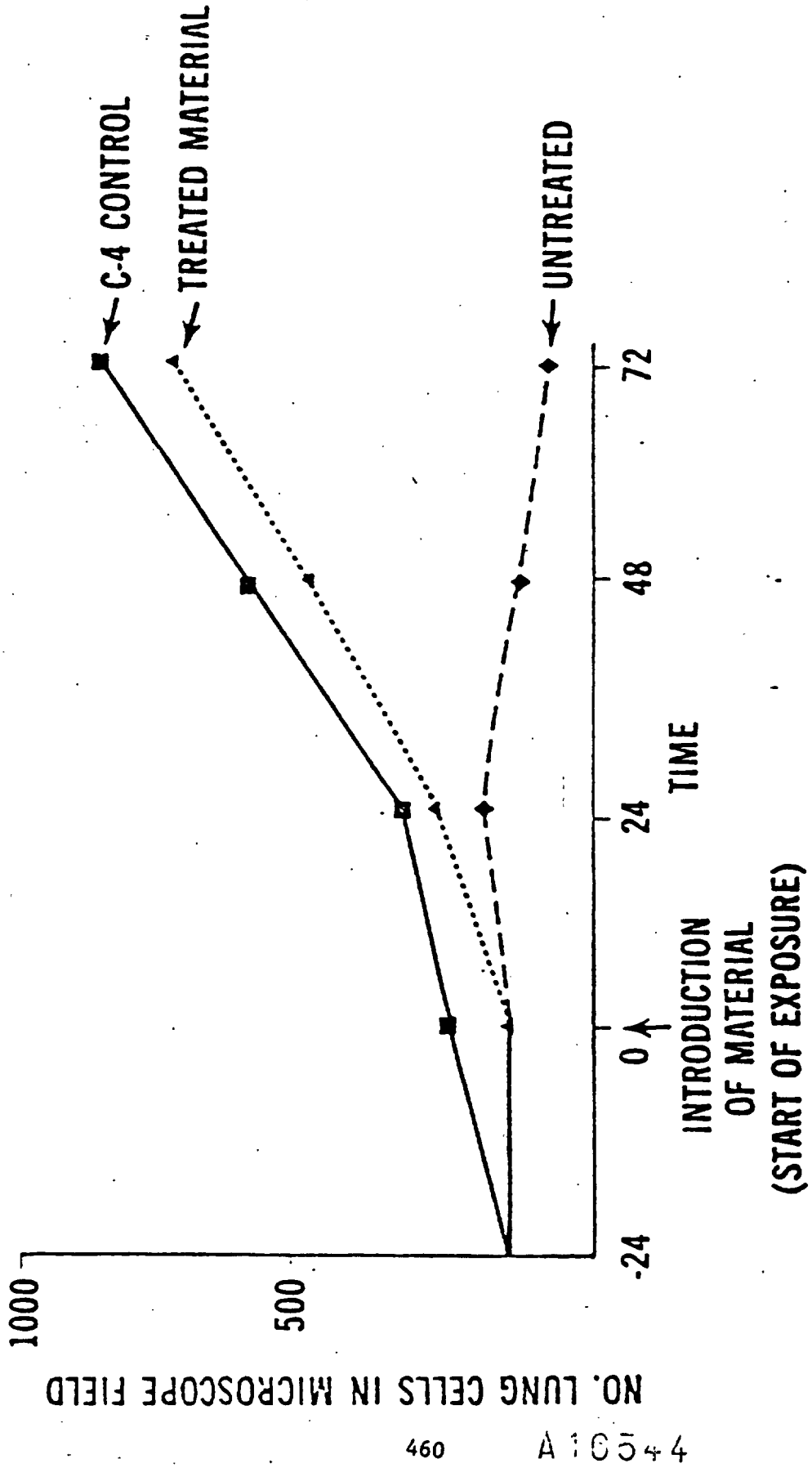


Figure 3. Biology: Initial data on cell viability -- UICC chyrosotile B.

A 10544

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Table I is a summary of physical attributes and differences caused by the treatment process. The magnetic rating decreases. This could be an improvement in the asbestos for certain electrical applications, but in other tests involving phenolic molding compositions, there is an increase in the preheating time. The magnesium oxide content decreases, and this is a desirable effect of the treatment. Color is dramatically changed. The disadvantage is that the color change may be unacceptable in certain products. An advantage is that the treated materials are readily identified. In cement formulations and phenolic resins, the color change is not a problem. The viscosity of a spinning solution containing AAA grade chrysotile decreases as a result of the treatment. A large scale test on a production line is needed to evaluate the impact of decreased viscosity on the quality of the textile produced. There is a decrease in cement strength at a high level of treatment, but no changes in cement strength were found at intermediate or low levels of treatment.

No changes in resin absorption, alkali resistance, acid resistance, and thermal insulation properties were produced as a result of treatment. The fiber milling and processing is changed to a wet process. Cytotoxicity shows a substantial decrease. The drainage rates of cement formulations decrease with increasing levels of treatment. A decrease in drainage rate may require changes in the drying, curing, and forming of asbestos cement products. In working with several grades of asbestos from AAA to 7RF99, a wet process tends to increase the surface area and to decrease the bulk density of longer fiber materials, but these changes may be attenuated by controlling contact time in the wet process and by more efficient dewatering. The treated asbestos materials compare favorably with the desirable attributes of raw or untreated asbestos.

In summary, initial biological data show that chemical treatment of asbestos to form a saturated synthetic ferruginous body decreases the cytotoxicity of asbestos to human lung macrophage cells. Physical test data indicate that desirable attributes of the fibers are retained. If additional in vitro and in vivo biological tests are successful in demonstrating a decrease in toxicity as a result of the chemical treatment and the performance of treated material is acceptable in products, this would allow treated fibers to serve as substitutes for asbestos in appropriate applications.

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A 10545

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ACL Doc 16408 · Page 8 of 16 asbestosclaims.law/library/16408/8

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ACL Doc 16408 · Page 9 of 16

TABLE 1. DIFFERENCES CAUSED BY TREATMENT

Magnetic rating	Decrease
Magnesium oxide content	Decrease
Color	Yellow, brown, blue, green
Viscosity of spinning solution	Decrease
Resin absorption	No change
Cement strength	No change except at high level of treatment
Alkali resistance	No change
Acid resistance	No change
Thermal insulation	No change
Fiber processing	Wet process
Drainage rate of cement formulation	Decreases with increasing level of treatment
Biological effect (cytotoxicity)	Substantial decrease

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DISCUSSION ON CHEMICAL DETOXIFICATION OF ASBESTOS FIBERS

QUESTION (Mr. Taitenann): I am from Raybestos-Manhattan. I would like to raise the question about the use of the wet process. Could you describe the wet process to us, please?

ANSWER (Dr. Flowers): This may sound like blasphemy or a sacrilegious treatment of the asbestos fiber, but essentially, I make a slurry containing about 5 percent by weight of asbestos fiber, which would be about 95 percent by weight of water. There are two steps in addition to the treatment chemicals. The material is filtered initially and then put in a press. I have been using my wine press to dewater the asbestos. Then it can either be shipped as a wet cake containing about 30 percent moisture, or it can be dried and then fiberized.

I neglected to mention that in the laboratory scale operation, there are real problems with the wet process in terms of maintaining the desirable surface or bulk density of the material. I found, however, that in producing, say, a few grams of material I can control the contact time and the wet process. I can also filter the material fairly quickly and attenuate the possible adverse effects on enhancing or opening up the surface, which would make it unuseable in certain processes.

I can produce asbestos that is fairly equivalent in surface area by nitrogen permeability and such, but when I try to go to several pounds, tens of pounds, or hundreds of pounds, I have found that I just cannot scale up my laboratory to a reaction tank for this system.

So the wet process may be a problem and requires a lot more work.

QUESTION (Mr. Taitenann): One other question. You referred to viscosity in the spinning operation. What type of operation are you referring to there?

ANSWER (Dr. Flowers): Well, I am not very knowledgeable about textiles in the production of fibers, but Dr. Kunsey of the Ontario Research Foundation did the evaluation of the spinning property, and he said the viscosity changes, and to really know what this means you have to produce enough sample to put it in a production line and see what effect it has on that particular characteristic.

REMARK (Mr. Wright): I am from the Steel Workers Union.

Let me just make one historical comment. Let me first say that I think your research is very interesting, but I want to, perhaps, inject a note of caution about how readily it ought to be accepted.

First, I think that even if everything you say pans out, there are questions about the stability of the coatings in the environment,

A1657

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ACL Doc 16408 · Page 10 of 16 asbestosclaims.law/library/16408/10

and there are also, I think, some questions about the toxicity of various coating materials, especially things like manganese and possibly aluminum and chromium.

But let me make the historical comment, which is that back in the thirties, there was a lot of excitement about the idea that aluminum oxide therapy would be effective in protecting miners from silicosis. The idea was that if one went into the mines and then came out at the end of the day and breathed aluminum oxide fumes or dust for some period of time, the aluminum oxide would naturally coat silica particles in the lungs and thereby protect the miner. The therapy was based on two things: the first was some preliminary biochemical theories about the way silica dust acted in the lungs, the idea that one could encapsulate whatever the problem was by the aluminum oxide; the second was based on some very preliminary animal studies. Those studies were discredited within, I think, about 10 years, but nevertheless, based on the very preliminary work, the underground mining industry and a lot of foundries adopted this procedure. Many underground miners and foundry workers spent the last half hour or 15 minutes of their work day, depending on how it was done, breathing aluminum dust.

Some of those people may have long-term lung disease from that therapy, which was proven not to protect them against silicosis. That has been very well documented. As a result, the method was scientifically discredited by the late 1950s. In 1978 we discovered several mines in Northern Canada that were still using the therapy and we stopped it very quickly. And there may be more people out there who are still using it.

The point I am trying to make is that it is very easy to jump to conclusions about the effectiveness of a particular detoxification process, and there may be some who would do that as an alternative to cleaning up the work place. I am not saying this to discourage your research. I am saying it to discourage the too-rapid adoption of a method that is not yet proven. And I think if I were questioned by one of the workers who I represent, I certainly would not, at this point, say that treated asbestos should be considered any safer than untreated asbestos. Maybe with more research, but I think that will take a lot of additional work.

REMARK (Dr. Flowers): I agree with just about everything you said, although I cannot confirm your experience regarding aluminum oxide as therapy in prevention of silicosis. But I tried to be fairly careful in how I characterized the results of our initial biological tests. In my summary, I indicated that it is successful in some rather extensive additional biological <u>in vitro</u> and <u>in vivo</u> tests.

A 10548

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ACL Doc 16408 · Page 11 of 16 asbestosclaims.law/library/16408/11

Also, if through process engineering and economics, we find that the material retains the desirable physical properties and will work in various industrial processes, then it could be accepted as a process for chemical treatment and detoxification of asbestos. From an economic and biological point of view I think that iron oxide, or various forms of it, is the only real treatment that will be acceptable.

There was somewhat of a chemical academic interest to extend the treatment to chromium or other transition metals to show that this is a general reaction across the transition metal group and also with amphoteric materials.

I agree that a lot more work needs to be done. In our communications with the EPA, they say that the tests, particularly the biological data, will have to be very persuasive for them to accept such a substitute. And that is not only for our material, but also for all the 60 or so materials that have been proposed as substitutes here over the last few days.

REMARK (Mr. Wright): I would like to make one final comment, not about what you presented, which I have no quarrel with, but about iron oxide. There are some questions about iron oxide itself being a cocarcinogen based on two things. One is some work that Saffiotti and others did, exposing, I think, Syrian golden hamsters simultaneously to iron oxide and a carcinogen. This showed a greater response when the iron oxide was administered along with the carcinogen than when the carcinogen was administered alone, even though iron oxide alone did not give any increased carcinogenic response.

Also there have been some epidemiologic studies in gray iron and steel foundries indicating an increased risk of cancer in those work places. We do not know what that is caused by, but one hypothesis is iron oxide, so you have to be careful.

REMARK (Dr. Flowers): Iron oxides are a normal waste product of oxidated metabolism in cells. The ferric hydroxide is sometimes viewed as the brown gelatinous amorphous material floating around in the cells, so essentially, the iron is something like that amorphous gelatinous material. However, from our X-ray defraction data, we have prepared a highly ordered form of this material, using the asbestos surface as template for its precipitation and formation.

QUESTION (Dr. Patel): I am from the New Jersey State Department of Health. I have three questions. One is what happens in your lung cell tests beyond 72 hours after treatment. The other is what happens to the acoustic properties of asbestos. Finally, is this process useful only in the manufacturing aspect of asbestos or could it be used after the product has already been manufactured, for example, in school ceilings? Can you treat the manufactured product so that it will penetrate further and not only remain on the surface?

A 10549

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ACL Doc 16408 · Page 12 of 16 asbestosclaims.law/library/16408/12

ANSWER (Dr. Flowers): We do not know what happens after 72 hours because the test protocol stops after 72 hours. This is a short-term assay to evaluate the initial biological response.

We do not look at acoustic properties. Ontario Research can make test panels and measure the acoustic properties, but that was one test we did not look at.

The process is essentially a technique for contacting the asbestos surface with a solution of treatment chemicals. Depending on your degree of imagination, you could contact the exposed asbestos at the mine with the treatment chemical. I claim that you could develop devices for contacting asbestos wherever you find it, including those asbestos fibers which are already present in the lungs of people who have been exposed, thereby providing a synthetic process for deriving a synthetic ferruginous body from an exogenous source of ferric salts.

REMARK (Dr. Cooper): I am from Berkeley. I wanted to make a comment on the remarks of the Steel Workers' representative. I certainly agree with him and with Dr. Flowers that something like this has to be studied and approached very cautiously and certainly is not a substitute for industrial hygiene.

I do not think that the analogy with aluminum and silicosis is quite applicable here. There is very good biologic evidence that aluminum and iron do modify the fibrogenic potential of silica; that has not been, shall we say, discredited. The thing that has been discredited is the inappropriate application of aluminum and iron to the prevention of silicosis. Substituting the addition of inhaled aluminum powder for adequate dust control has been justifiably discredited. Since it was clearly impossible to coat with aluminum the quartz particles that resulted from drilling a hole in a hard-rock mine, the effort was made to coat them after they got into the body. Although I think it is a difficult path that has to be followed to establish these things, I do not think that that analogy should be used to discredit this type of approach.

QUESTION (Mr. Wilkin): I am with Dresser Industry. The three criteria that you provide for detoxifying the fibers are: removing the magnesium oxide surface, ensuring the surface is stable to alkaline conditions, and maintaining the same strength and flow properties of the resultant material. Do you have any comments on the other methods of doing this, such as the acid leaching and organosilane or sodium silicate treatments that are currently patented?

ANSWER (Dr. Flowers): I was very interested in the Dow patents, for example, involving the molybdate and tungstate treatment. They used a Grade 7 chrysotile and showed that hemolytic activity could be decreased up to 100 percent by treating the surface with the molybdate and the tungstates. They used a wet process. I think they

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ACL Doc 16408 · Page 13 of 16 asbestosclaims.law/library/16408/13

also removed some of the brucite or the magnesium oxide associated with the surface. The metallic tungstate and molybdate salts are alkaline resistant, so I think it does not violate the three principles that I have enunciated.

The heat treatment of asbestos actually drives off hydroxide by hydroxide reaction or oxidation with oxygen. This gets rid of hydroxyl groups. I think that when you hydrate or rehydrate silicate bonds you may have some problems once they are deposited in a physiological system.

One other treatment used is the removal of magnesium oxides and other metals by moderately strong acid treatment of the surface. According to the paper presented in May, by Marcelle Cahette, at the Fourth International Conference on Asbestos in Italy, they have successfully demonstrated decreased cytotoxicity and decreased release of enzymes from membranes and also decreased hemolytic action of the chrysotile asbestos, which had been subjected to the moderate acid treatment.

So, yes, there are other approaches. My approach was to mimic what I consider to be a detoxification attempt by the body and to make a synthetic ferruginous body.

QUESTION (Mr. Wilkin): Would your studies also include the possibilities of detoxification by the reaction of the surface with an organosilane to make the surface hydrophobic?

ANSWER (Dr. Flowers): I cannot comment on that one way or the other, but I really have not given any thought to that particular process.

REMARK (Mr. Wilkin): There are a few applications for asbestos that would probably best be served by a hydrophobic coating rather than a hydrophilic coating.

REMARK (Dr. Flowers): I do not want to make my process mutually exclusive of other processes. I think there is probably room in the substitute field for many products.

REMARK (Dr. Gross): I am with the Industrial Health Foundation. If phagocytosis to these treated fibers does take place, then we are up against another facet that contradicts the present theory of the pathogenicity of asbestos, namely, the theory that incomplete phagocytosis of the asbestos fiber causes leakage of intracellular enzymes into the surrounding medium and, consequently, into the surrounding tissues. The leakage of these intracellular enzymes would then cause tissue damage and, ultimately cancer.

If your demonstrated lack of cytotoxicity by the treated asbestos fiber takes place in spite of phagocytosis, then this theory falls into the ash can, and we do not have a viable theory for the pathogenicity of asbestos. Our concern for the substitutes for asbestos,

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ACL Doc 16408 · Page 14 of 16 asbestosclaims.law/library/16408/14

like man-made vitreous fibers, also should be abated because this concern is based on the theory that the geometry of the fiber in great part is responsible for the pathogenicity of fibers.

It is agreed that the geometry of a fiber is responsible for the fiber landing at the target site, but if this theory about leakage of intracellular enzymes into incomplete phagocytosis is destroyed, then we should not have any concern for the pathogenicity of manmade fibers.

QUESTION (Dr. Bernstein): I think Dr. Gross's comments are well taken. I would like to ask you, along the same lines, did you do size measurements of your fibers, and if you did, did you do it before they were treated and after they were treated, and what sizes were they?

ANSWER (Dr. Flowers): Yes, we have rather extensive data, both the light microscope and the electronmicroscope data on the size distribution of the fibers and the effect of treatment on size.

There is a slight increase in average diameter after treatment, compared to before treatment.

QUESTION (Dr. Bernstein): What were the figures?

ANSWER (Dr. Flowers): I do not have the figures with me.

QUESTION (Dr. Bernstein): What about the length? Did you look at length?

ANSWER (Dr. Flowers): No. I used Grades Triple A chrysotile, Grades 4 and 5 chrysotile, Grade 7 type purity, Grade 7 RF 99, and these go from extremely long materials to extremely short fine fibers.

REMARK (Dr. Bernstein): Well, I think it is important to point out that the effects you have shown could be explained by either a change in diameter, an increase in diameter, perhaps, or a decrease in diameter and/or length. And until that is straightened out and put on the record, it is really unfair to interpret the results.

QUESTION (Dr. Flowers): What percentage change would be significant, in your opinion?

ANSWER (Dr. Bernstein): I could not venture a guess until I saw your results and I do not know if I could venture a guess after that until I have seen the experiment.

REMARK (Dr. Flowers): There is less than about a 5 percent change in diameter and no change in length.

We mainly took pictures sufficient to count the cells, but not to evaluate whether phagocytosis was going on. So that is an omission.

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ACL Doc 16408 · Page 15 of 16 asbestosclaims.law/library/16408/15

In the protocol that we followed, we primarily were interested in seeing if we could demonstrate a decrease in cytotoxicity and that was the one issue we looked at. We did not look at some of these other issues, which now seem to be more important, or assuming more importance.

REMARK (Dr. Bernstein): Relating to Dr. Gross's comments, I think if you can demonstrate that the phagocytes are ignoring your coated fiber (and you probably could do that using the methods that we saw from the Brookhaven National Laboratory), you might be able to support your findings a lot better.

REMARK (Dr. Flowers): We do not make any claims that this is the only test that we are going to run. As a matter of fact, this afternoon I am going to talk about criteria for acceptable test protocol for evaluating proposed substitutes. This was based on an unofficial request to EPA under Section 4(g) of TSCA, as a petition for acceptable test protocols for evaluating and, subsequently, if successful, registering a product for use. We do plan more extensive <u>in vitro</u> and <u>in vivo</u> tests.

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