

Asbestos in commercial cosmetic talcum powder as a cause of mesothelioma in women

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Background: Cosmetic talcum powder products have been used for decades. The inhalation of talc may cause lung fibrosis in the form of granulomatous nodules called talcosis. Exposure to talc has also been suggested as a causative factor in the development of ovarian carcinomas, gynecological tumors, and mesothelioma.

Purpose: To investigate one historic brand of cosmetic talcum powder associated with mesothelioma in women.

Methods: Transmission electron microscope (TEM) formvar-coated grids were prepared with concentrations of one brand of talcum powder directly, on filters, from air collections on filters in glovebox and simulated bathroom exposures and human fiber burden analyses. The grids were analyzed on an analytic TEM using energy-dispersive spectrometer (EDS) and selected-area electron diffraction (SAED) to determine asbestos fiber number and type.

Results: This brand of talcum powder contained asbestos and the application of talcum powder released inhalable asbestos fibers. Lung and lymph node tissues removed at autopsy revealed pleural mesothelioma. Digestions of the tissues were found to contain anthophyllite and tremolite asbestos.

Discussion: Through many applications of this particular brand of talcum powder, the deceased inhaled asbestos fibers, which then accumulated in her lungs and likely caused or contributed to her mesothelioma as well as other women with the same scenario.

Keywords: Asbestos, Talcum powder, Chamber test, TEM, SEM, EDS, SAED, Mesothelioma

Introduction

Malignant mesothelioma occurs in both the peritoneum and in the lung pleura.¹ Mesothelioma cases have been attributed to direct occupational exposure, indirect exposure and secondary exposure.¹ A higher rate of “idiopathic” mesothelioma has been reported in women, as no link between asbestos exposure and patients has been identified.² Previous research suggests that ovarian cancer and peritoneal mesothelioma may be directly attributed to the use of talcum powder contaminated with asbestos or from exposure to partners occupationally exposed to asbestos.^{3–7} Using talcum powder in closed spaces may increase the likelihood of inhaling the powder laced with asbestos. Repeated applications increase the opportunities for inhalation and the asbestos could become concentrated in the peripheral airways and alveoli of the lungs of the talcum powder users. This has been supported by the presence of granulomas in the lungs of some talcum powder users.⁸

In 1976, Rohl and Langer tested 20 consumer products labeled as talc or talcum powder, including body powders, baby powders, facial talcums, and a pharmaceutical talc.⁶ Of the 20 products tested, 10 were found to contain tremolite and anthophyllite, principally asbestiform. The product with the highest asbestos content was the same product tested in this study. Both asbestiform anthophyllite and asbestiform tremolite were found in the Rohl and Langer tests. Given that asbestos has been determined as the primary cause of mesothelioma, it is important to note that cosmetic talc contained asbestos in the past.⁶ The contamination results from the mining process, since ore specimens taken directly from the mines have repeatedly been tested and shown to contain asbestos, most often anthophyllite and tremolite but also serpentine chrysotile asbestos.^{6,9,10}

In part from the review of corporate documents and the sworn testimony of those responsible for the sourcing of talc used in the products studied here, it was determined that three mines provided the raw material for use as talcum powder. The talc used by this cosmetic company that manufactured and

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distributed the talcum powder was from three distinct regions: the Willow Creek mine in Southwest Montana, the Regal mine near Murphy, North Carolina, and imported talc from the Val Chisone region of the Italian Piedmont.^{11–16} The specific geology of talc is an important indicator of whether a talc source may be contaminated with asbestos. These three mines all contained asbestos fibers; anthophyllite, and tremolite.^{11–18} The Val Chisone talc from Italy was studied by Pooley in 1972.¹⁸ Mine sample had intergrowths with serpentine-type, chrysotile asbestos along with tremolite and anthophyllite asbestos. The talc from Italy was named ‘American Ground Italian’ and designated as AGI 1615.^{19–21} This talc was diluted with a talc from another source to make it acceptable based on X-ray diffraction (XRD) protocols. However, it contained asbestiform tremolite and anthophyllite.²²

In this study, three laboratories analyzed a specific brand of talc from more than 50 containers of this cosmetic talcum powder product of different sizes and colors, produced over a 50-year time span to determine the presence of asbestos. The authors conducted independent product testing in unassociated laboratories in North Carolina, Georgia, and New York. A fourth laboratory, which also tested this product, will herein be referred to as Laboratory D. The lung and lymph node tissues from a woman who died from mesothelioma and testified to only using this specific brand of talcum powder were analyzed for the presence of asbestos and talc. This is the first report that explores the hypothesis that a specific brand of talcum powder coming from asbestos contaminated mines can find its way into the finished product that can be inhaled during use and cause or contribute to the development of mesothelioma

Materials and Methods

Laboratory A: product testing

In Laboratory A, over 50 containers of this particular brand of talcum powder were acquired from a variety of sources for bulk testing. Some of the containers were purchased online, while others were provided directly from the manufacturer. All of the containers were verified to be the correct brand and product.

Laboratory A tested talcum powder from each of the 50 samples using transmission electron microscope (TEM) methods. The procedure for testing by Lab A was as follows: 0.01 g of talcum powder was removed from its vial and suspended in 1 ml of distilled water with one to two drops of ethanol by brief sonication. From this suspension, 10 µl aliquots were removed and placed on a series of five formvar-coated nickel grids (100 grid openings each). In some cases, it was necessary to prepare additional sets of

five grids from the same 0.01 g sample of powder. The drops were allowed to dry in a covered Petri dish. The grids were then examined and analyzed with a Hitachi H-7000 STEM equipped with an Evex energy-dispersive spectrometer (EDS), for elemental composition and relative amounts of elements. The microscope was equipped with a tilt stage and a rotary specimen holder, which was employed with selected-area electron diffraction (SAED) analyses, as described below. Structures seen as fibers measuring at least five micrometers in length with aspect ratios of 5:1 or greater were analyzed to determine if they were regulated asbestos mineral fibers. We used EDS to chemically establish the presence of asbestos fibers and the crystalline structure was assessed using SAED. All 100 grid openings were observed and analyzed on each of the five grids for each product sample (at least 500 grid openings per sample analyzed).

Analyses were performed using a modification of the techniques described by Yamate *et al.*, and similarly adopted techniques used by the Environmental Protection Agency (EPA), American Society for Testing and Materials (ASTM), and International Organization for Standardization.^{23–26} All techniques required the use of a TEM equipped with an EDS system. Only in Yamate level III is the tilt and rotary stage optional to perform advanced SAED zone axis analysis. Yamate *et al.* stated that zone axis diffraction analysis is useful in differentiating between otherwise unidentifiable fibers.²³ In the Laboratory A analysis, zone axis analyses were not necessary as the identified amphiboles clearly demonstrated that they were asbestiform tremolite and anthophyllite confirmed by morphology, EDS chemistry, and characteristic 5.3 Å inter-row repeats on diffraction without tilting. Both asbestiform and non-asbestiform particles and fibers were present. However, in most cases this manuscript will refer to asbestiform fibers and state when they are tremolite, anthophyllite, or chrysotile type asbestos. A non-asbestos tremolite, anthophyllite will not be referred to as asbestos.

To calculate the fiber concentrations per gram of talcum powder, we first determined the number of asbestos fibers on average per grid opening. This number was multiplied by 552. The product of that equation was multiplied by 100, and then divided by 0.01 to yield the fibers/gram talcum powder value. The constant, 552, is the number of grid opening areas on the entire grid. One hundred is the number of 10 µl drops in 1 ml that the talcum powder was dispersed and the 0.01 was the weight of the talcum powder dispersed. Quality control procedures, which included testing of blanks from water, working in a clean hood environment, and working with only one



Figure 1 Pouring of powder into hands in glovebox.

sample at a time ensured that no laboratory contamination of samples.

Laboratory B: asbestos releasability testing

To determine if the user could inhale asbestos during a talcum powder application, Laboratory B assessed asbestos releasability by air sample. Air samples were generated during simulation in a glove box, consistent with normal product use in a controlled environment. These three samples included the same samples tested by Laboratory A. Environmental and personal air samples were collected using standard airborne asbestos techniques, using high-volume air pumps for environmental (stationary) samples inside and outside of the controlled area, and low-volume air pumps for personal samples taken at a distance comparable to the breathing zone of the person simulating application. Standard TEM 385 mm² effective filter area 25 mm cassettes with 0.45 µm MCE filters were used on the flow-calibrated high (7–12 l/min) and low volume (1–4 l/min) air pumps (Figs. 1 and 2).

The resulting air samples were analyzed for airborne asbestos following the analytical procedures described in the U.S. Environmental Protection Agency Code of Federal Regulations 40 CFR part 763, subpart E, Appendix A — AHERA for direct preparation of MCE filters.²⁴ All final analyses by Laboratory B were conducted on a JEOL 2000FX TEM equipped with an energy-dispersive X-ray analyzer detector and SAED at magnifications up to $\times 50\,000$, using the fiber counting criteria specified by Yamate *et al.*'s protocols.²³

Laboratory C: product bulk testing and bathroom-sized chamber releasability

Bulk methods

Laboratory C examined nine samples under an Olympus SZ-40 stereomicroscope at magnifications from $\times 7$ to $\times 40$. Portions of the particulate found in the sample were mounted in Cargille refractive index liquids for analysis by polarized light microscopy (PLM) using an Olympus BH-2 PLM with a magnification range from $\times 100$ to $\times 1000$. The PLM analysis followed the procedures for bulk analysis of building materials described by the US EPA in 1993.²⁴ Characterization of the fibers was performed using a Philips EM420 100 kV TEM equipped with an Oxford INCA EDS x-ray analysis system and capable of SAED work involving tilting of amphibole fibers. Zone axis determinations were also conducted. We used TEM asbestos fiber counting criteria of fibers greater than 0.5 µm in length with at least a 5:1 aspect ratio as described in Asbestos Hazard Emergency Response Act (AHERA) and ASTM methods: D6281, D5755,

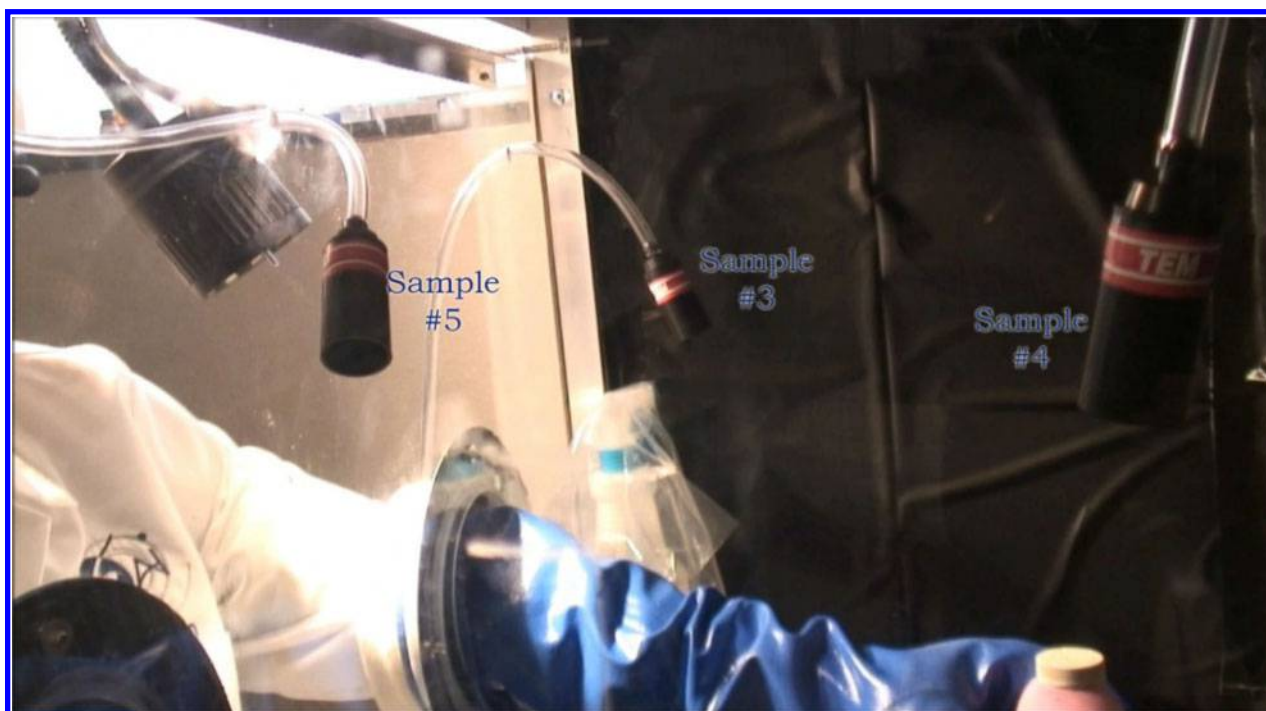


Figure 2 TEM cassettes in simulation area in glovebox.

D5756, and D648.^{24–28} Data were recorded using the ASTM D6281 format. XRD analysis was performed by an outside laboratory (DCM Science Laboratory, Inc., Wheat Ridge, CO, USA) scanning over a range of 3–45° 2 θ using 40 kV, 25 mA Cu K_{α} radiation. Mineral phases were identified with the aid of computer-assisted programs accessing a CD-ROM powder diffraction database.

Air testing

Tests to determine airborne levels of asbestos fibers resulting from application of this brand of talcum powder were performed in a testing chamber. The chamber was built to match the bathroom of the patient that used this brand of cosmetic talc. Her bathroom was measured at 7 feet, 9 inches high by 5 feet by 4 feet, 1 inch. All talc products used in these chamber tests had previously been tested in Laboratories A, B, or both.

Air test – shaker container

Using Personal Protective Equipment, a volunteer applied one of the bulk tested cosmetic talcum powders to his body using a shaker container. This particular talcum powder contained approximately 0.1% by weight and approximately 18 million anthophyllite asbestos fibers per gram. The container was weighed before and after the testing to determine the approximate weight of material applied. The talcum user wore a respirator and a bathing suit. The volunteer twisted the top of the container and shook material onto his hand. He applied the talc under his arm and around the shoulder and upper arm area. He then shook the talcum powder onto his other hand and applied it to the other underarm, shoulder and upper arm area. He shook out additional material and applied it to his neck and upper torso. He shook out and applied material two more times for a total of five applications. The total talcum application time was approximately 1 min and amounted to 0.37 g of the talcum powder. Two air samples were collected in the applicator's breathing zone at 0.5 l per minute (lpm) and two additional air samples were collected in the breathing zone at 1.0 lpm with commercial open-face air cassettes. The five-minute sampling time included the application time and a waiting period. The bystander in the test chamber had two air cassettes in his breathing zone for the five-minute period including application and the additional waiting time. The bystander wore a respirator and full protective clothing. These air samples were collected at rates of one and 2 lpm. No activities were conducted during the waiting period other than checking the pumps and cassettes. The air filters and two additional blank filters were analyzed by phase contrast microscopy (PCM) using National Institute for Occupational Safety and Health (NIOSH) Method 7400.²⁹ Two air

samples and two blanks were also analyzed by NIOSH Method 7402 via transmission electron microscopy to determine the percentage of asbestos fibers among the fibers counted by PCM.²⁹ An air sample collected from within the test chamber before the study was analyzed by a more sensitive TEM procedure following the EPA AHERA method.²⁴

Air testing puff applicator

In this test, a volunteer applied a different cosmetic talcum powder sample using a puff applicator. This particular talcum powder contained approximately 0.05% anthophyllite asbestos (approximately 70 million asbestos fibers per gram). The container was weighed before and after the testing to determine the approximate weight of material applied. The talcum user wore a respirator and a bathing suit. The talc user opened the puff container and applied the talcum powder as described above only this time with a powder puff. He then repeated the process for a total of six applications. The talcum application time was approximately 1 minute. Two air samples were collected in the applicator's breathing zone at 0.5 lpm for a sampling period of 4 minutes. One air sample was collected for a shorter period (3.3 minutes) that included the application period. Another air sample was to be collected after the application period but this sample was voided because the volunteer hit the air cassette and the cassette fell off the vacuum hose. The bystander in this test followed the same protocol as described above. Both air samples were collected at a rate of 0.5 lpm. No activities were conducted during the waiting period other than checking the pumps and cassettes. The air filters and two additional blank filters were analyzed by PCM using NIOSH Method 7400 as described above.²⁹ One air sample and two blanks were also analyzed by NIOSH Method 7402 via TEM to determine the percentage of asbestos fibers among the fibers counted by PCM.³⁰ An air sample collected from within was tested as described above by EPA AHERA method.²⁴

Human Tissue Analysis

TEM

Tissue samples from a woman with no other known exposure to asbestos other than her use of the product tested was supplied to Laboratory A. Human tissue analysis was performed according to the techniques described in Wu *et al.*²⁹ Lung and lymph node tissue was received fixed in formalin. Half of the tissue was removed from the lung and the lymph node tissue. Two grams of lung tissue were divided twice. The two halves of the lymph node weighed 0.16 g together. The two specimen types were separated throughout the study. The tissue from each was first digested in a 5% solution of potassium

hydroxide (KOH) for approximately hour at 60°C. The dissolved lung and lymph node material was then centrifuged in a high-speed centrifuge to separate the inorganic material from the dissolved organic tissue. The solute material containing the dissolved organic material and KOH was removed and distilled water was added. The inorganic material was re-suspended in the water by brief sonication. The material was re-centrifuged and the process of washing the inorganic material was performed five times. After the fifth wash, the distilled water was removed and replaced with 10 ml of fresh distilled water and the inorganic material was re-suspended by brief sonication. Ten microliter samples were removed from the suspension and placed on formvar-coated nickel grids on a metal mesh in a covered glass Petri dish to dry. Five grids were initially prepared and an additional set of five grids was prepared for each tissue type for a second analysis. The dried grids were observed with a transmission electron microscope. Four hundred grid openings on at least four grids were analyzed, and a fifth grid was used if grid openings were broken in the initial four examined grids. The fiber concentrations per gram wet weight lung or lymph node tissues were calculated from the number of fibers observed, the area analyzed, the aliquot ratio, and the total weight of the tissue sample digested.

Light microscopy

Tissue sections

Small lung tissue samples were put into 10% phosphate-buffered formalin and processed for embedding in paraffin. Five micrometer paraffin sections were cut, mounted on glass slides and stained with hematoxylin, eosin, and an iron stain. The tissue was evaluated for the presence of altered morphology and/or ferruginous bodies; two characteristics often seen in lung tissues that are a byproduct of iron-rich protein deposits on asbestos fibers resulting from macrophage frustrated phagocytosis.

Digested lung and lymph node tissue

Two hundred and fifty microliters of digested lung and lymph node material suspension used for TEM analyses was placed in a cytocentrifuge and the slides were cover slipped and observed by phase contrast light microscopy. The entire area was counted for ferruginous bodies and calculated back to the weight of the tissue to determine the concentration of bodies per gram of wet weight tissue.

Scanning electron microscopy (SEM)

SEM samples were prepared by taking 250 µl of the suspended inorganic material used for the TEM and light microscopy analyses and placed on a 0.1 µm pore size Nucleopore filter mounted on a carbon planchette on an aluminum SEM stub. The material

was allowed to dry in a covered Petri dish. The stub was then coated with vaporized carbon and observed with a Hitachi S-4300 field emission scanning electron microscope equipped with an Evex EDS system. The entire filter sample surface was scanned for fibers and asbestos bodies.

Results

All three laboratories confirmed in multiple tests the presence of asbestiform anthophyllite and asbestiform tremolite in the talcum powder products, just as had been found and described by Rohl and Langer over three decades ago.⁶

Initial bulk analyses of 50 samples of this product in Laboratory A showed that all of the samples contained asbestos fibers. Eighty percent contained only anthophyllite asbestos, 8% only tremolite asbestos, 8% anthophyllite and tremolite asbestos and 4% anthophyllite, tremolite, and chrysotile asbestos. The range in asbestos concentrations of fibers >5 µm in length were calculated to be, at a minimum, between 1840 and 1 104 000 fibers per gram of talcum powder. More than 80% of the tested cans and plastic containers contained over 10 000 asbestos fibers/gram of talcum powder. Four of the containers had less than 5000 fibers per gram and six containers had more than 250 000 fibers per gram. However, it should be noted that there were many asbestos fibers that also had aspect ratios less than 8:1. These fibers were generally found to be shorter than 5 µm and were noted, but not counted in the original product testing or in the lung and lymph node tissue testing by Laboratory A. There were also a number of fibrous talc particles that were easily distinguishable from asbestos by morphology. If there was a question regarding their identity, both EDS and SAED were employed to recognize such fibers as talc. All the fibers that were actually counted in bulk and tissue preparations were 5 µm or greater in length, with aspect ratios for the most part greater than 10:1. The majority of asbestos structures counted demonstrated aspects ratios >15:1, with many >20:1. A minimum of four fibers was identified in each sample, making the concentration determinations of asbestos statistically significant and reproducible.

Laboratory C. using PLM, TEM, and XRD, tested nine samples of the specific brand of talcum powder described above. Generally, the PLM analysis showed that the samples contained both platy and fibrous talc, less than 1% by volume of the PLM visible amphibole fibers and some quartz. The majority of the PLM amphibole particles had low aspect ratios (length to width) but some were >10:1. By XRD, one of the talcum powder samples was found to contain 4% anthophyllite. No amphibole



Figure 3 Application of powder from shaker in bathroom-sized chamber.

minerals were detected in the other eight samples by XRD. The XRD detection limit was approximately 2% by weight. In TEM analysis, all nine samples were positive for amphibole asbestos (primarily anthophyllite), and were confirmed with zone-axis electron diffraction measurements. At least five asbestos fibers per sample were recorded in each sample, with concentrations ranging from 0.004 to 0.9% by weight and from 3 to 200 million asbestos fibers per gram of fibers greater than 0.5 μm in length with at least a 5:1 aspect ratio.

Air monitoring

Releasability of asbestos into the air from the products was assessed by glove box simulation testing by Laboratory B, and by full chamber testing by Laboratory C. In a manner consistent with methods used by the EPA, NIOSH or ASTM, study product body powders and dusting powders were applied hand to hand and hand to arm. Consistent with bulk testing results, anthophyllite and tremolite asbestos was repeatedly found in the air tests resulting from these simulations (Figs. 6–8).

Shaker container test

The shaker application test used 0.37 g of talcum powder (Fig. 3). For the talc user, the average PCM fiber concentration in his breathing zone during application was 4.8 F/cc (3.1, 7.3, 3.9, and 4.9 F/cc). The asbestos to total fiber percentage as determined by TEM was 40%. Therefore, the asbestos concentration in the breathing zone of the talc user during application was 1.9 F/cc. For the bystander the PCM fiber concentration was 1.35 F/cc (0.9 and 1.8 F/cc) and the TEM derived percentage of asbestos was 35%, which results in a bystander asbestos concentration of 0.5F/cc. No asbestos fibers were found in the sample collected in the chamber before the testing or in the blank filters.

Puff application

The puff application test used 6.25 g of talcum powder (Figs. 4 and 5). For the talc user, the average



Figure 4 Application with powder puff in bathroom-sized chamber.

PCM fiber concentration in his breathing zone during the 5-minute sampling period was 20 F/cc (23.6 and 16.5 F/cc). The asbestos to total fiber percentage as determined by TEM was 21%. Therefore, the asbestos concentrations in the breathing zone of the talcum powder user were 5 and 3.5 F/cc. The short term sample in the breathing zone of the applier had a PCM value of 60 F/cc. Using the TEM-derived percentage of asbestos of 10%, result for the short-term sample was an asbestos concentration of 13 F/cc. For the bystander, the PCM fiber concentration was 11.7 F/cc (13.7 and 9.7 F/cc). Using the minimum TEM-derived percentage of asbestos of 36% results in a bystander asbestos concentration of 4.9 and 3.5 F/cc. No asbestos fibers were found in the sample collected in the chamber before the testing or in the blank filters.

The tests performed independently by Laboratory C using a bathroom-sized room confirmed the findings for asbestos fiber release found by Laboratory B's glovebox testing. Samples showed that significant concentrations of anthophyllite, tremolite, and occasionally chrysotile asbestos were released in the simulated application of several iterations of the products. This confirmed not only



Figure 5 Application with a powder puff in bathroom-sized chamber.

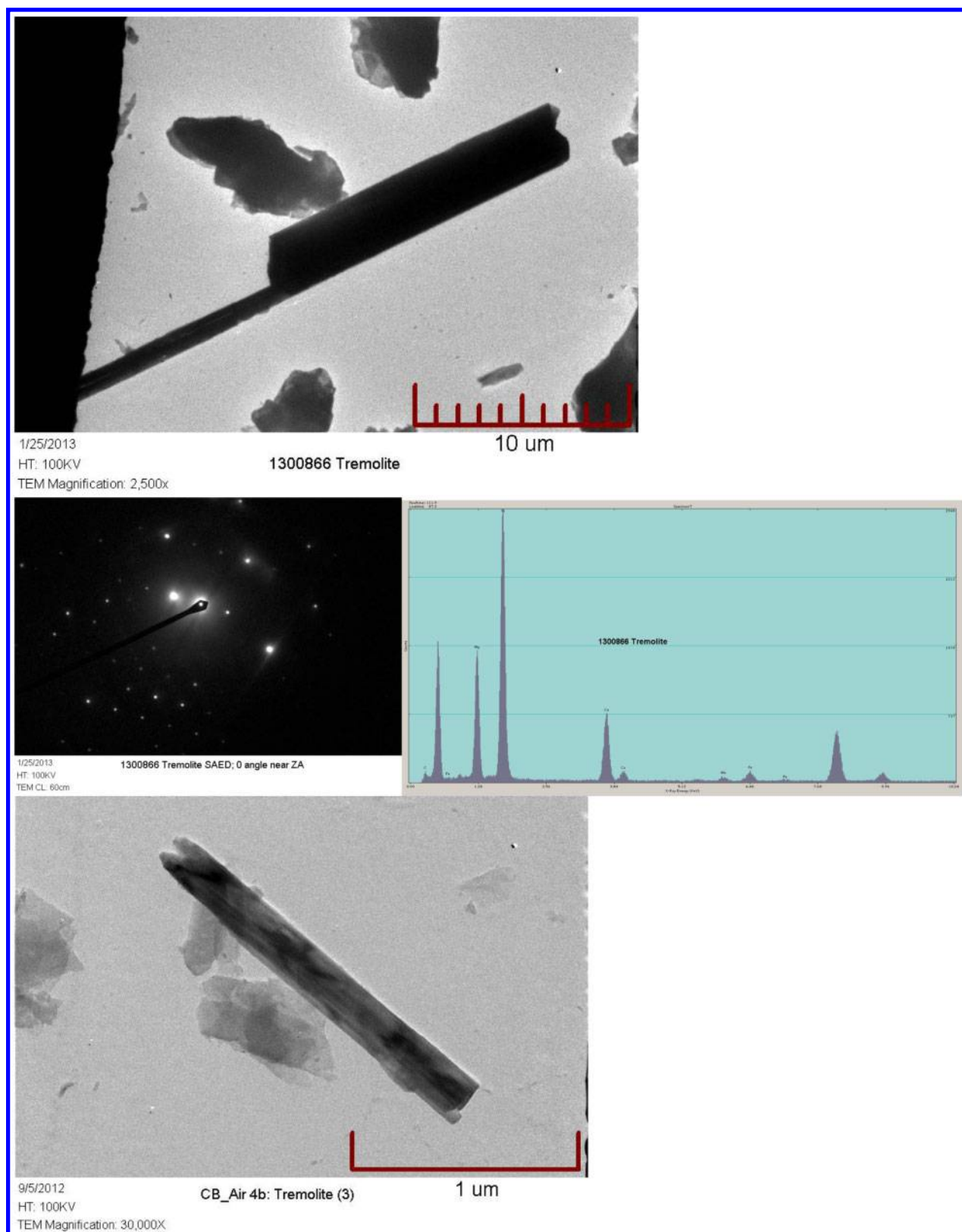


Figure 6 Tremolite asbestos from TEM analysis of releasability air testing of product (images, EDS, and SAED).

the presence of asbestos in the talcum powders, but also that the asbestos contained in the friable powders was easily aerosolized in a manner consistent with the products intended use; confirming the hypothesis that the cosmetic powders are capable agents of exposure to asbestos

Human tissue analysis

Electron microscopic analysis of the lung tissue revealed amphibole type asbestos fibers in a calculated concentration of 1380 and 4150 fibers per gram wet weight, respectively, with a limit of detection of 690 fibers per gram wet weight. All fibers counted

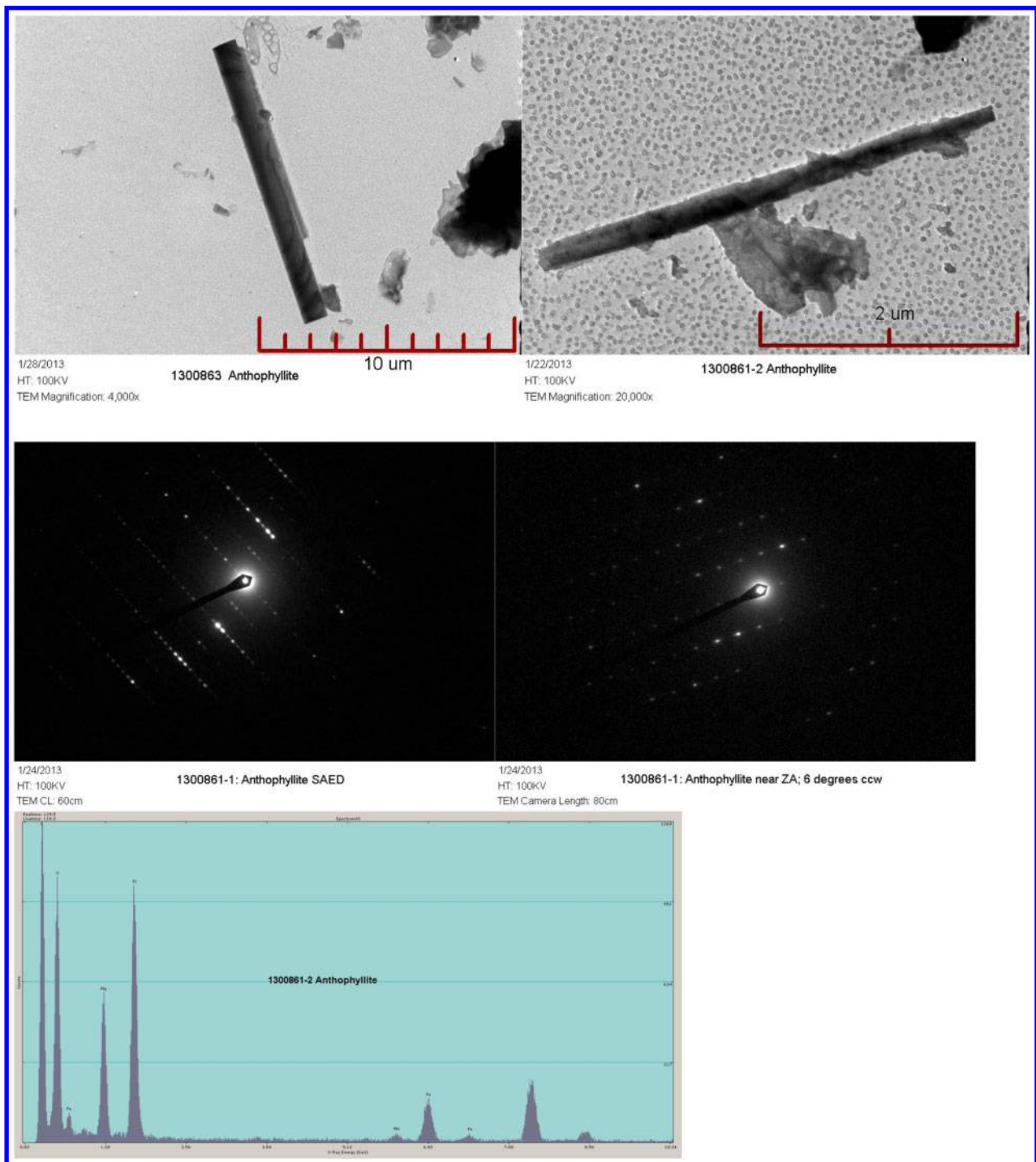


Figure 7 Anthophyllite asbestos from TEM analysis of releasability air testing of product (images, EDS, and SAED).

were 5 µm or greater in length and had aspect ratios of 20:1 or greater. The amphiboles were identified by EDS and SAED analysis as anthophyllite (Fig. 9) and tremolite (Fig. 10) asbestos. The asbestos fibers were seen in a ratio of 1:1 and 2:1, respectively (anthophyllite/tremolite). There were many anthophyllite and tremolite asbestos fibers less than 5 µm in length that were not counted. The majority of these smaller asbestos fibers were of the anthophyllite type. Light microscopic analysis of the cytocentrifuge preparation revealed a calculated concentration of 140 asbestos bodies per gram wet weight of lung

tissue by phase contrast light microscopy in both samples.

Electron microscopic analysis of the lymph node tissue revealed amphibole asbestos fibers in a calculated concentration of 12 738 fibers per gram wet weight, with a limit of detection of 2123 fibers per gram wet weight. All counted fibers were at least 5 µm in length with aspect ratios of 10:1 or greater. The amphiboles were identified by EDS and SAED analysis as anthophyllite and tremolite and they were seen in a ratio of 5:1 anthophyllite/tremolite. There were many anthophyllite and tremolite fibers less

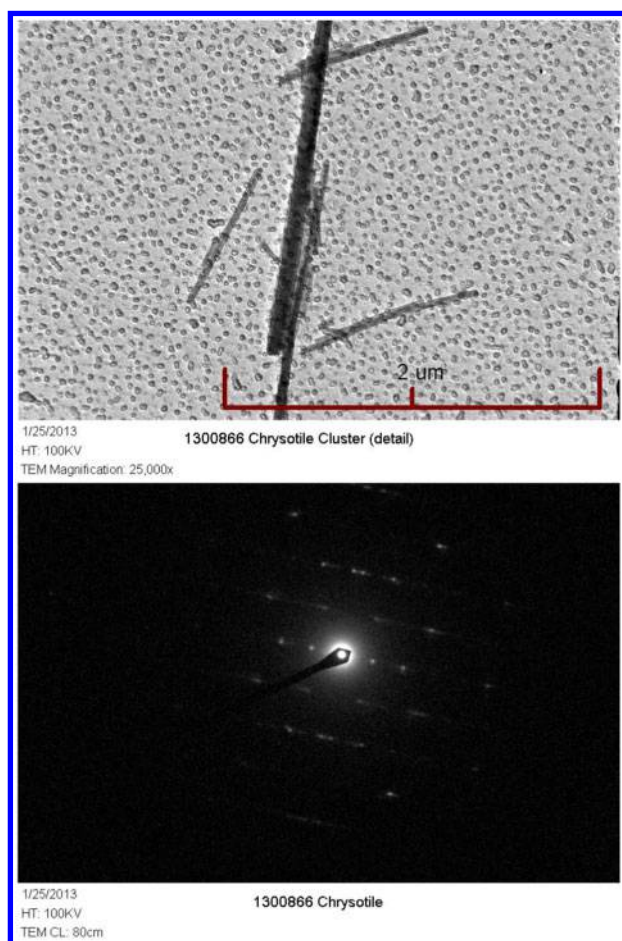


Figure 8 Chrysotile asbestos from TEM analysis of releasability air testing of product (image and SAED).

than 5 µm in length that were not counted. We also observed but did not count tremolite cleavage fragments. Light microscopic analysis of the cytocentrifuge preparation revealed a calculated concentration of 92 asbestos bodies per gram wet weight of lymph node tissue by phase contrast light microscopy (Fig. 11).

Histological sections of the tissue showed focal areas of mild parenchymal fibrosis and a more generalized pleural fibrosis. Although many ferruginous bodies were identified in the cytocentrifuge preparation, most were relatively small and not seen in the H&E-stained paraffin sections. These macrophages were clustered and contained a combination of fibrous and platy talc and small asbestos bodies.

In addition to the fibrous and platy talc described above, other inorganic materials were seen. Aluminum silicates and magnesium aluminum silicates in both fibrous and platy form were identified. We elected not to count these fragments. Their presence supports the hypothesis that the lung and lymph node samples match findings from the tested talcum powder.

The two analyses performed on the lung tissue were from two separate tissue digestions. The second was prepared with tissue not previously analyzed, but

saved from the original half of the tissue retained by Laboratory A. The results proved to be completely reproducible with no finding of any additional fiber types other than those reported above.

Confirmation of interlaboratory analyses

After several years of independent testing in separate laboratories, the authors became aware of one another's work through litigation. The finding that this historic brand of cosmetic talcum powder contained asbestos fibers with generally the same morphological and chemical assemblage was confirmed. A fourth laboratory (Laboratory D) tested many of the same samples, but did not report asbestos findings. Owing to the inconsistency with the other laboratories, re-examination of results from Laboratory D was warranted.

Two of the three authors of this study went to the Laboratory D and were supplied with the prepared filters on TEM grids or SEM stubs previously analyzed by Laboratory D. They were also supplied with both TEM and SEM microscopes to re-analyze the specimens, along with data and locator sheets, allowing for the same grid openings and areas to be observed as in the initial analyses.

Reanalysis of subject product samples

One author re-analyzed the TEM preparations of 20 study products of talcum powder prepared by Laboratory D. Asbestos structures were found in the re-analysis, some of which were named in the original analysis as cleavage fragments, intergrowths, or fibrous talc rather than as asbestos. Although the author-reviewer agreed with many of the non-asbestos fibers identified, he concluded the original analyses were incomplete. Additional analyses by the author-reviewers showed some of the incompletely analyzed fibers to be asbestos. In other cases, asbestos found on re-analysis was located on areas of the filter where no fibers were recorded in the original bench sheets or reports. In some instances, the overall distribution of particulates on the preparations was inhomogeneous, in contrast with the method of choosing grid openings for the original analysis by skipping every other opening in a "checkerboard" fashion. Furthermore, the methods named on the analytical count sheets were not the same as the methods cited in the reports from Laboratory D.

Laboratory D reported no asbestos fibers in the 20 samples analyzed. In contrast, asbestos fibers were identified in all 20 of the same products in Laboratory A and in 16 of 20 products tested by Laboratory B. In the re-analysis of those same 20 samples originally analyzed by Laboratory D via TEM, eight were found to contain asbestiform anthophyllite, six asbestiform tremolite, and two were found to contain chrysotile fibers. These findings were significant because re-analysis was not a

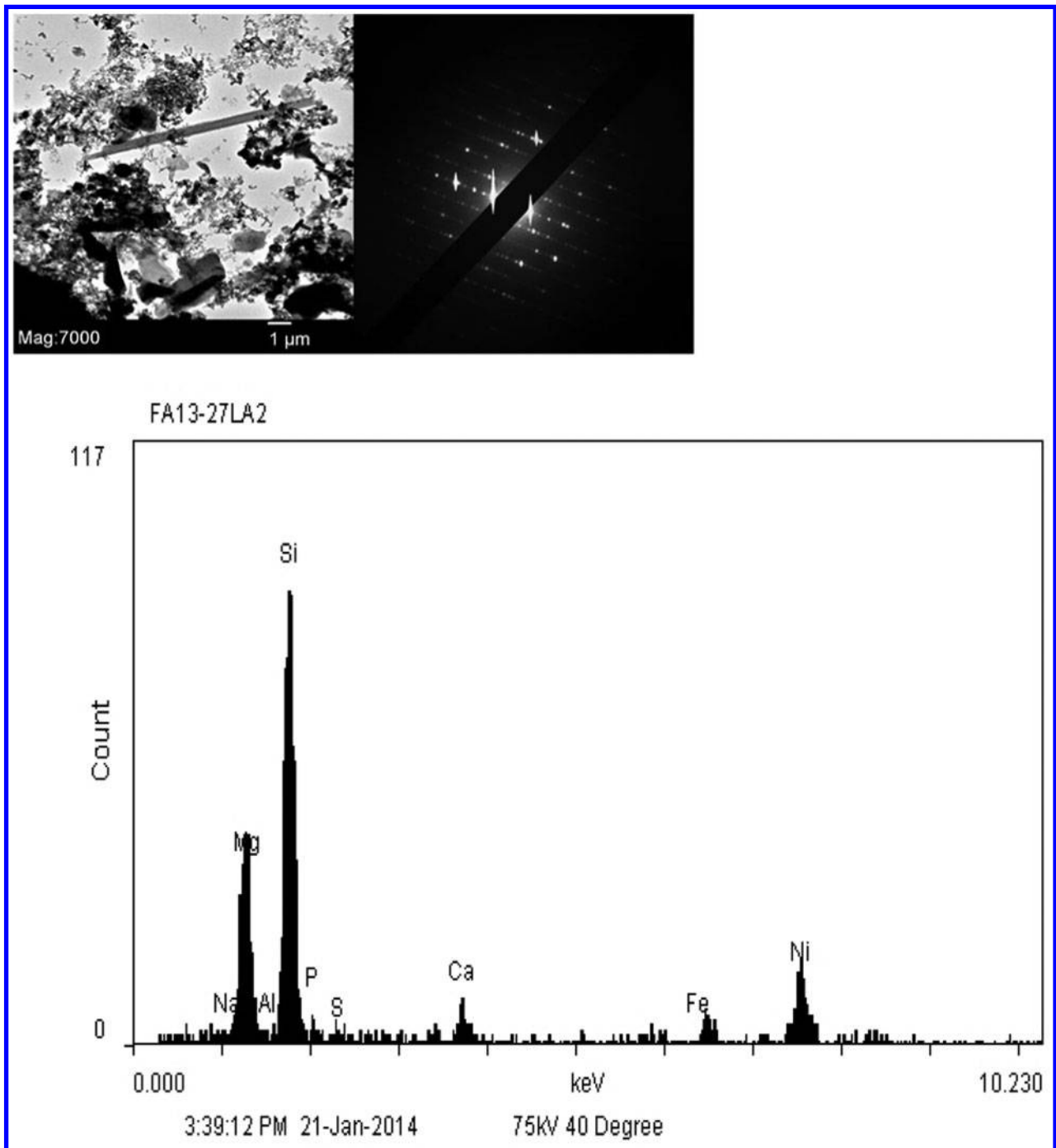


Figure 9 This asbestos fiber is a representative sample removed from the lung tissue of the patient exposed to cosmetic talcum powder. Anthophyllite asbestos fiber is observed and its SAED pattern is demonstrated beside it with the EDS spectra.

complete replication of the original analysis due to time constraints, damage, or unsuitable preparations. It was apparent that the technicians in Laboratory D missed fibers and misidentified asbestos fibers as non-asbestos.

Re-analysis of human tissue

Laboratory D also performed fiber burden analysis on human tissue with differing results than the study of the authors. Similar to the re-evaluation of bulk analyses, two author-reviewers analyzed the human tissue sample preparations of Laboratory D together and found significant differences in their analyses compared to the technicians who originally analyzed

the grids and stubs. We determined that the technicians misidentified anthophyllite asbestos fibers that had been coated with iron and protein (anthophyllite asbestos bodies) as either cleavage fragments or as amosite fibers (Fig. 12). Furthermore, it is the authors' consensus that there are no generally accepted criteria to classify individual fibers as cleavage fragments by TEM when the sample contains attributes of an asbestos fiber or countable structure. When Laboratory D technicians initially looked for asbestos bodies to determine the fiber core, they concluded that most were amosite. However, when the two author-reviewers examined

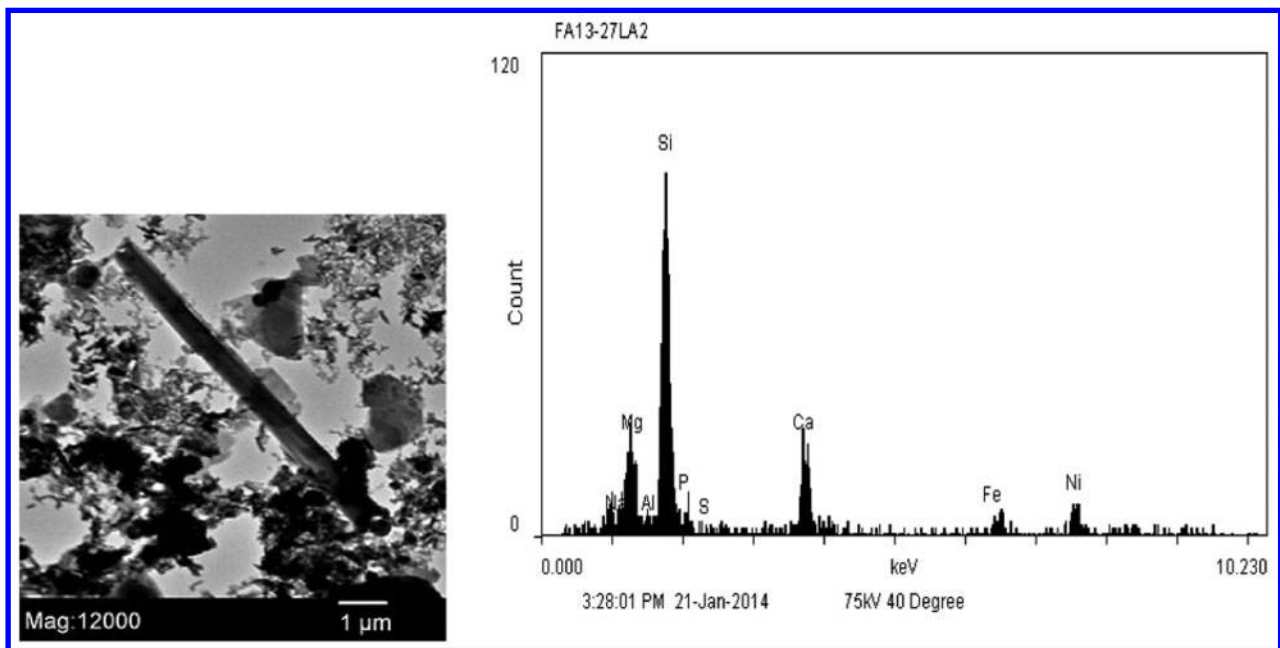


Figure 10 This asbestos fiber is a representative sample removed from the lung tissue of the patient exposed to cosmetic talcum powder. Tremolite asbestos fiber with its corresponding EDS spectra.

the same structures, it was clear that the cores were either anthophyllite or could not be determined because there was exposed fiber core. In previous studies of human tissue having anthophyllite and anthophyllite bodies (Fig. 11), it was common to find that the entire anthophyllite core, even if quite long, was completely coated.

Zone axis confirmation in bulk, tissue, and air
 Laboratories A, B, and C confirmed original amphibole asbestos structures by zone axis diffraction. Laboratories A, B, C, and D re-analyzed archived preparations with the intent of confirming amphiboles by zone axis diffraction. In all four sets of re-analyzed preparations, anthophyllite and tremolite asbestos were consistently

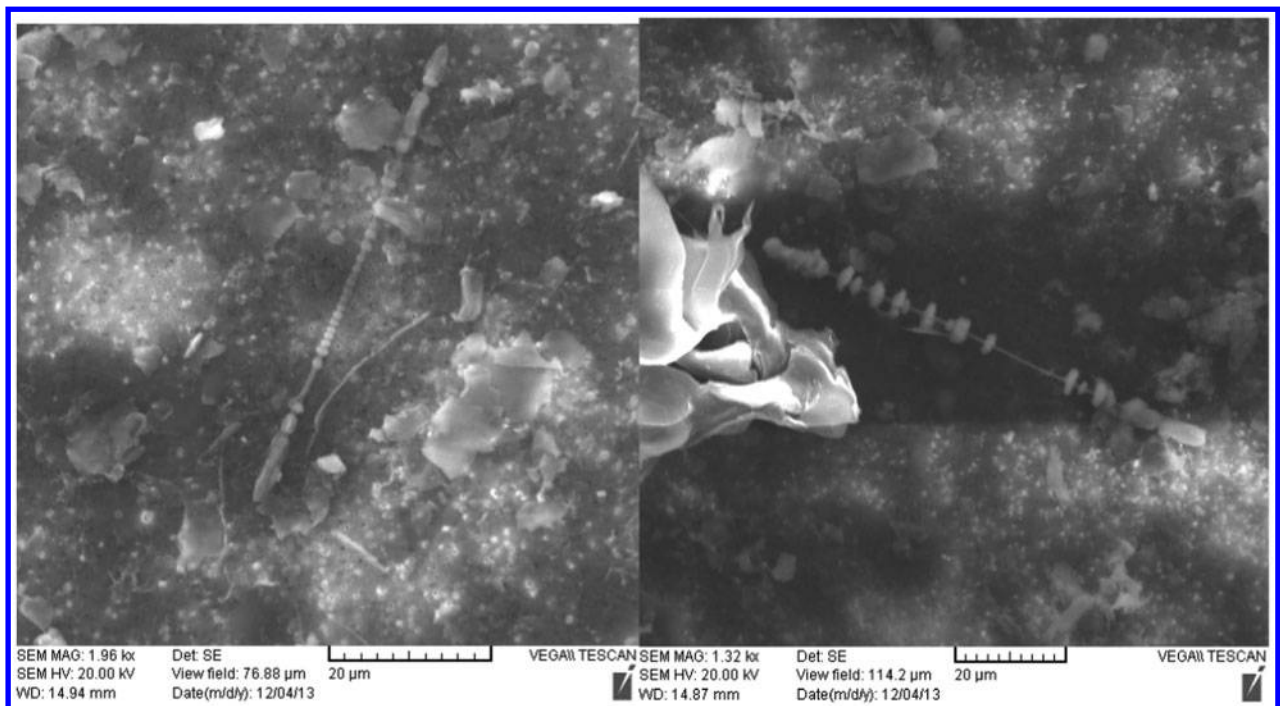


Figure 11 These are asbestos bodies from the patients lung tissue taken by SEM. It is possible to see in the one to the left that the fiber is almost completely covered by the iron protein coating. This is compared to the one at the right which appears to have much more fiber exposed. However, upon EDS testing, it was determined that in both cases, these were anthophyllite fibers and they were both entirely coated, although much thicker in some areas as opposed to others.

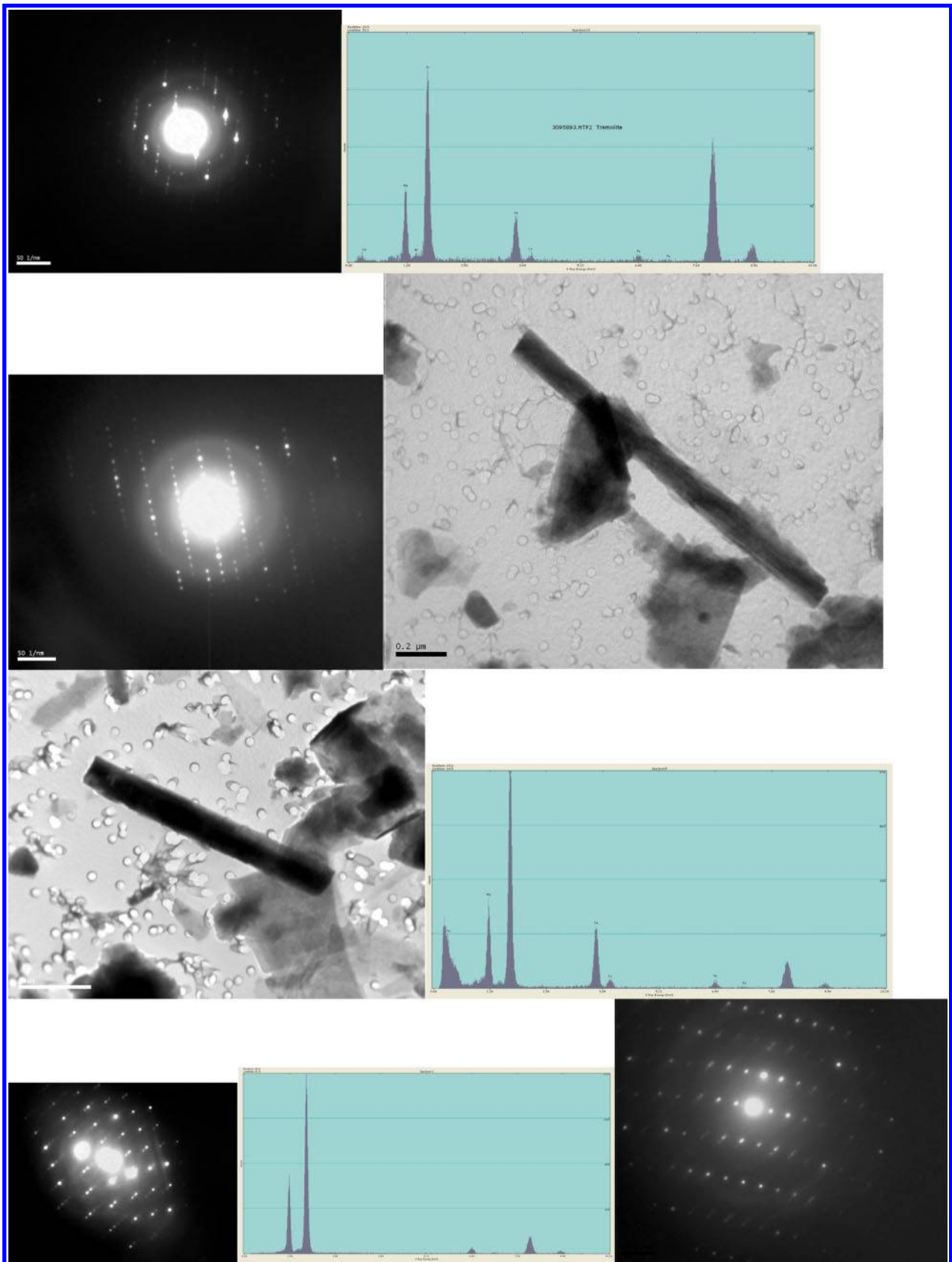


Figure 12 Tremolite and anthophyllite asbestos from re-analyses of 'Lab D' preparations (images, EDS, and SAED).

confirmed by zone axis diffraction pattern measurements. This included confirmation of asbestiform amphiboles, including anthophyllite and tremolite asbestos

from the original product testing, from the releasability air tests, and from TEM preparations of lung and lymph node tissues.

Discussion

Historically, many mesotheliomas, particularly abdominal mesotheliomas in women, have been labeled idiopathic due to a lack of an identifiable source for asbestos exposure. Further, there has been an increase in the number of idiopathic pleural and abdominal mesotheliomas in women using this specific brand of talcum powder. There have been a few studies that have examined talcum powder and its potential to cause ovarian tumors.^{3–5} The studies were inconclusive, but suggested that talc, asbestos, or both may cause these cancers through vaginal exposure.⁴ These studies attributed asbestos found within the women's lesions to result from contact with their partners. There was no consideration for the potential of the asbestos being a contaminant in the women's talcum powder.^{3,4} However, it has been reported that cosmetic talcum was contaminated with asbestos, and that asbestos was found in the mines from which the talc originated.^{6,9} Our findings indicate that historic talcum powder exposure is a causative factor in the development of mesotheliomas and possibly lung cancers in women.

Talc has been identified as a causative for mesotheliomas in New York talc miners.³¹ In recent years, more than 10 women developed mesothelioma and their only source of asbestos exposure was the use of one brand of talcum powder. This study demonstrates that the brand of talcum powder tested contained asbestos. Furthermore, we have traced the asbestos in the talc to the mines from which it originated, into the milled grades, into the product, and finally into the lung and lymph nodes of the users of those products, including one woman who developed mesothelioma.

Based on the testing and re-testing conducted by the authors, it is evident that this product line has been consistently contaminated with asbestos tainted talc derivatives. The amount of asbestos was variable based on the time of manufacture and the talc source. There have been numerous publications that have indicated that the talc in many talc deposits had asbestos contamination.^{32–35} The most common types of asbestos were tremolite and anthophyllite. These are the same asbestos fiber types found in the autopsied lungs and lymph nodes tested here for asbestos presence. In a few containers tested in this study, chrysotile was also found, consistent with the source ore geology.

Most, if not all, testing of cosmetic talc was performed using techniques designed for light microscopy, PLM, or by TEM criteria designed to test air and water samples. Testing determined if asbestos levels were above the EPA standards under AHERA or the Occupational Safety and Health Agency standards. These protocols are based on the parameters described

in the Yamate method.²³ There are significant limitations to these methods. PLM analysis misses small fine asbestos fibers or fibrils because the limits of the resolution are approximately 0.2–0.5 μm for different forms of light microscopy. Based on our findings, approximately 90% of the fibers identified fall into this category. Determining the number of TEM grid openings to be counted during the analysis requires stopping factors, or limits on the quantity of analysis to be performed. The Draft Yamate method (1984) gives the guidelines of “100 fibers or 10 grid openings, whichever is first.”²³ This counting rule was instituted for cost limitation purposes. The Draft Yamate method describes that while this guideline of using 10 full-grid openings represents a judicious compromise between a reasonable experimental effort and a fairly low value of the detection limit, the analysis of additional TEM grid openings reduces the detection limit and improves the precision of the estimates. In the talc study described here, a very low level of detection was desired and therefore, in some cases, as many as 500 plus grid openings were analyzed to reduce the detection limit and improve sensitivity of the test. TEM testing has been adequate for evaluating building material asbestos abatement projects, local air sampling, and potential water contamination with asbestos.²³ However, these criteria are not acceptable for assessing asbestos fiber burden analyses in human tissues and for low asbestos content products that are used intermittently in small quantities over long periods of time, such as cosmetic talcum powder.³⁶ Talc related asbestos exposures can be heavy at times, above 4000 F/cc. The inhaled asbestos fibers are extremely variable in the causation of asbestos related tumors and fiber burdens found in the deceased woman were within the reported ranges for amphiboles to be causative factors in the development of such a tumor.³⁷

Therefore, it is imperative to analyze products such as talcum powder for small amounts of asbestos fibers. This requires that the limits of detection be lower than levels required in a typical Yamate analysis. The author-reviewers observed that the Laboratory D analyses were done using Yamate methodology and no more than 10–25 grid openings on bulk TEM grid preparations were observed.²⁴ Based on Laboratory D's protocols for testing, millions of fibers/gram of talc would have to present in order to find fibers. Lower concentrations in the ranges found by Laboratories A, B, and C demonstrated that fibers were detectable and present at levels sufficient to cause mesotheliomas.

Although long narrow asbestos fibers are highly carcinogenic, shorter, narrow fibers are also dangerous.^{36–38} It is now more common to find shorter narrow fibers in human tissue digestions than long narrow fibers, especially for chrysotile.³⁹ This

study provides evidence that low concentrations of asbestos in raw materials do not necessarily correlate to low health risk.^{38,39} Examples of recent studies of low asbestos content producing significant airborne concentrations in simulated activity include activity-based monitoring of asbestos as it naturally occurs in several sites, as conducted by the EPA and Agency for Toxic Substances and Disease Registry, and vermiculite-containing attic insulation studies.⁴⁰ These studies have repeatedly shown that substantial airborne concentrations could be derived from materials with only a fraction of a percent asbestos content.³⁶ This has been especially true when a product was in a friable state, or where the obvious use of material intimates aerosolization of fibers. Significant airborne concentration can be easily generated from such conditions when asbestos is a constituent.^{40–43}

The talc application studies were simulations of exposures to talc used by a deceased woman who had mesothelioma. The air volume in the testing space was 158 cubic feet. This is in the range of the chamber sizes used by talcum powder manufacturers in the 1970s in their studies of the quantity of talcum powder used in normal application. The space used by Russell was 171 cubic feet and the space used by Aylott was between 152 and 163 cubic feet. The amount of material used in the shaker test was 0.37 g. The amount used for the puff applicator test was 6.25 g.^{44,45} The shaker test was a light application and the puff a heavy application. However, the heavy application was within the ranges published by Russell of 8.84 ± 8.32 g and Aylott of 2.5 ± 12.5 g. The “talking times,” or the duration of talcum powder application, were approximately 55 seconds for the shaker test and approximately 57 seconds for the puff applicator test.^{44,45} These were within the ranges published by Russell of 83 ± 33 seconds and Aylott of 28–78 seconds for adult dusting.^{44,45} Laboratories A and B determined that the contaminated talcum powder released inhalable asbestos into the air.

Another issue in this study was the documentation and identification of cleavage fragments. The scientific community has not generally adopted cleavage fragment differentiation criteria.⁴⁶ It is unclear how to identify a cleavage fragment once the stone or material has been finely ground. Two criteria for distinguishing cleavage fragments from asbestos fibers have been proposed. The first is that the ends of cleavage fragments have oblique angles and second is that the aspect ratios are all less than 20:1. The ends criterion has not been validated with known asbestos/cleavage fragment standards and while an aspect ratio of 20:1 suggests that a fiber is likely to be an asbestos fiber, some fibers with aspect ratios below

20:1 are also asbestos. As the fiber aspect ratio increases, the percentage of asbestos fibers versus cleavage fragments also increases.⁴⁷ However, this criteria falls short when the fiber is extremely thin and is the smallest unit of diameter of a fiber. When these small fibers are removed and analyzed from human tissue, these criteria have to be discarded because enzymes with basic and acidic molecules within cells can leach elements from the surface, causing a breakdown of the fibers, especially when thin in diameter. van Orden *et al.* propose criteria to identify cleavage fragments by SEM.⁴⁶ The criteria are based on surface contours which identify a cleavage fragment.⁴⁶ However, this method has not been verified and is not generally accepted. There were no photographs of TEM or high-resolution high-magnification SEM provided by Laboratory D, which classified potential asbestos fibers as cleavage fragments

In conclusion, we found that a specific brand of talcum powder contained identifiable asbestos fibers with the potential to be released into the air and inhaled during normal personal talcum powder application. We also found that asbestos fibers consistent with those found in the same cosmetic talc product were present in the lungs and lymph node tissues of a woman who used this brand of talc powder and developed and died from mesothelioma.

Disclaimer Statements

Contributors All authors did studies relevant to the manuscript and all contributed and accepted all the writing.

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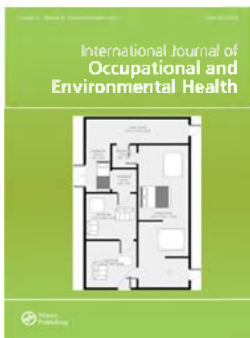
Conflicts of interest Funding for all Labs was provided as part of litigation. No funds were for writing this article. Laboratories are available for defense or plaintiff litigation.

Ethics approval Ethical consent was not needed.

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Asbestos in commercial cosmetic talcum powder as a cause of mesothelioma in women

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Asbestos in commercial cosmetic talcum powder as a cause of mesothelioma in women

R Gordon, S Fitzgerald, J Millette

Volume 20, Number 4, pp. 318–332.

Page 319 Column 1. “The Val Chisone talc from Italy was studied by Polley in 1972.¹⁸” **should have read** “The Val Chisone talc from Italy was studied by Polley in 1972.¹⁷”

Page 318 Column 2. “Analyses were performed using a modification of the techniques described by Yamate et al., and similarly adopted techniques used by the Environmental Protection Agency (EPA), American Society for Testing and Materials (ASTM), and International Organization for Standardization^{23–26}.” **should have read** “Analyses were performed using a modification of the techniques described by Yamate et al., and similarly adopted techniques used by the Environmental Protection Agency (EPA), ASTM-International (formerly American Society for Testing and Materials (ASTM)), and International Organization for Standardization (ISO).^{22,24–27,48}”

Page 319 Column 2. “Yamate et al. stated that zone axis analysis is useful in differentiating between otherwise unidentifiable fibers.²³” **should have read** “Yamate et al. stated that zone axis analysis is useful in differentiating between otherwise unidentifiable fibers.⁴⁸”

Page 320 Column 2. “The resulting air samples were analyzed for airborne asbestos following the analytical procedures described in the U.S. Environmental Protection Agency Code of Federal Regulations 40 CFR part 763, subpart E, Appendix A – AHERA for direct preparation of MCE filters²⁴.” **Should have read** “The resulting air samples were analyzed for airborne asbestos following the analytical procedures described in the U.S. Environmental Protection Agency Code of Federal Regulations 40 CFR part 763, subpart E, Appendix A – AHERA for direct preparation of MCE filters²².”

Page 320 Column 2. “All final analyses by Laboratory B were conducted on a JEOL 2000FX TEM equipped with an energy –dispersive X-ray analyzer

detector and SAED at magnifications up x50000, using the fiber counting criteria specified by Yamate et al.’s protocols.²³” **should have read** “All final analyses by Laboratory B were conducted on a JEOL 2000FX TEM equipped with an energy –dispersive X-ray analyzer detector and SAED at magnifications up x50000, using the fiber counting criteria specified by Yamate et al.’s protocols.⁴⁸”

Page 320 Column 2. “The PLM analysis followed the procedures for bulk analysis of building materials described by the US EPA in 1993.²⁴” **should have read** “The PLM analysis followed the procedures for bulk analysis of building materials described by the US EPA in 1993.²³”

Page 321 Column 1. First line: “D5756, and D648.^{24–28}” **should have read** “D5756, and D6480.^{22,24–27}”

Page 321 Column 1. Bottom: “The air filters and two additional blank filters were analyzed by phase contrast microscopy (PCM) using National Institute for Occupational Safety and Health (NIOSH) Method 7400.²⁹” **should have read** “The air filters and two additional blank filters were analyzed by phase contrast microscopy (PCM) using National Institute for Occupational Safety and Health (NIOSH) Method 7400.²⁸”

Page 321 Column 2. “An air sample collected from within the test chamber before the study was analyzed by a more sensitive TEM procedure following the EPA AHRA method.²⁴” **should have read** “An air sample collected from within the test chamber before the study was analyzed by a more sensitive TEM procedure following the EPA AHRA method.²²”

Page 321 Column 2. “The air filters and two additional blank filters were analyzed by PCM using NIOSH Method 7400 as described above.²⁹ One air sample and two blanks were also analyzed by NIOSH Method 7402 via TEM to determine the percentage of asbestos fibers among the fibers counted by PCM.³⁰ An air sample collected from within was tested as described above by EPA AHERA method.²⁴” **should have read** “The air filters

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and two additional blank filters were analyzed by PCM using NIOSH Method 7400 as described above.²⁸ One air sample and two blanks were also analyzed by NIOSH Method 7402 via TEM to determine the percentage of asbestos fibers among the fibers counted by PCM.²⁹ An air sample collected from within was tested as described above by EPA AHERA method.²²

Page 321 Column 2. "Human tissue analysis was performed according to the techniques described in Wu et al."²⁹ **should have read** "Human tissue analysis was performed according to the techniques described in Wu et al."³⁰

Page 330 Column 1. "There have been numerous publications that have indicated that the talc in many talc deposits had asbestos contamination."³²⁻³⁵ **should have read** "There have been numerous publications that have indicated that the talc in many talc deposits had asbestos contamination."³²⁻³⁴

Page 330 Column 2 First line: "in the Yamate method."²³ **should have read** "in the Yamate method."⁴⁸

Page 330 Column 2. "The Draft Yamate method (1984) gives guidelines of "100 fibers or 10 grid openings, whichever is first."²³ **should have read** "The Draft Yamate method (1984) gives guidelines of "100 fibers or 10 grid openings, whichever is first."⁴⁸

Page 330 Column 2. "TEM testing has been adequate for evaluating building material asbestos

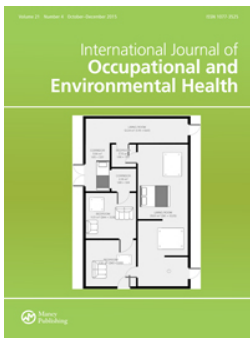
abatement projects, local air sampling, and potential water contamination with asbestos."²³ **should have read** "TEM testing has been adequate for evaluating building material asbestos abatement projects, local air sampling, and potential water contamination with asbestos."²²

Page 330 Column 2. "The author-reviewers observed that the Laboratory D analyses were done using Yamate methodology and no more than 10-25 grid openings on bulk TEM grid preparations were observed."²⁴ **should have read** "The author-reviewers observed that the Laboratory D analyses were done using Yamate methodology and no more than 10-25 grid openings on bulk TEM grid preparations were observed."⁴⁸

Page 330 Column 2. "Although long narrow asbestos fibers are highly carcinogenic, shorter, narrow fibers are also dangerous."³⁶⁻³⁸ **should have read** "Although long narrow asbestos fibers are highly carcinogenic, shorter, narrow fibers are also dangerous."^{37,38}

Page 332 Column 1. In reference 25 "ASTM D5756" **should have read** "ASTM D5755"

Page 332 Column 2. This is an additional reference, number 48 Yamate G, Agarwal S, Gibbons R. Methodology for the measurement of airborne asbestos by electron microscopy. Draft EPA Report on Contract 68-02-3266. 1984.



Asbestos in commercial cosmetic talcum powder as a cause of mesothelioma in women

Richard Lee & Drew Van Orden

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Letter to the Editor

Asbestos in commercial cosmetic talcum powder as a cause of mesothelioma in women

Richard Lee, Drew Van Orden

RJ Lee Grop, Inc., Monroeville, PA, USA

Dear Editor:

The role of a scientific journal is to publish papers that contribute to the body of scientific knowledge, are technically correct, and appropriately reviewed and edited. The role of the editor is to ensure that the content, writing, format, and references meet the standards of the journal. The role of the peer reviewers is to assess whether the work is new and contributes to the knowledge in the field, ensure that the writing fairly represents the current knowledge in the field, and that the citations are accurately cited. The role of the authors is to provide a full disclosure of their work, including sufficient detail about data and methods so that independent investigators can assess the credibility of their work. The reader relies on the journal editor and his/her selection of reviewers to ensure these standards are met. In the matter of the subject paper, the editor, the reviewer(s), and the authors, failed to meet these standards, resulting in the publication of a paper that is scientifically unacceptable.

Gordon *et al.*¹ undermine the scientific method, the integrity of the scientific peer-review process, and the ASTM Standardization process. The subject matter of the paper is at issue in on-going litigation where the authors have been retained by plaintiffs and Lab D (the undersigned) by defendant. All laboratories found the samples to consist primarily of platy talc particles characteristic of cosmetic grade talc. However, the authors made multiple errors leading to the misidentification of trace levels of accessory minerals as asbestos in the talcum powder. The authors presumed that they could use visual pattern recognition to identify selected area electron diffraction (SAED) patterns as a particular mineral, without performing any tests on minerals that were likely to pose interferences to establish the reliability of their method. The authors presumed that the particles they counted by transmission electron microscopy (TEM) were regulated amphibole asbestos, even though they found no evidence of asbestos by polarized light microscopy (PLM), and in the face of contradictory findings by Lab D. The authors failed to compare and contrast their interlaboratory

results, which varied dramatically. For example, in one bulk sample that Lab C analyzed three times, the results varied from nondetect to 202 million fibers per gram on a single sample. In the same bulk sample, Lab A found a single fiber only after analyzing between 400 and 500 grid openings, which Lab A extrapolated to 11 400 fibers per gram on the same sample. They left the reader with the mistaken impression that “three independent laboratories” had validated each other’s work.

The paper does not disclose key portions of Lab B’s methodology – that it attempted to extrapolate to exposure using indirect preparation methods – or the fact that the analysis of glove box air samples Lab B prepared by direct preparation yielded statistically insignificant fiber concentrations. Moreover, the authors misrepresented the work performed by the laboratories. The authors suggest that the identity of the product was verified, but in reality the samples were collected from a variety of sources and none were in as-manufactured condition. Contrary to what is written in the paper, both Lab A and Lab C analyzed samples for which they found no countable structures. Lab B made no independent bulk analysis as implied in the paper, but reported no asbestos in four of the 20 Lab D samples reviewed. Lab A never did releasability testing or quantitative SAED as claimed in the paper.

The authors criticize the work of Lab D, arguing that Lab D’s definition of cleavage fragment is not generally accepted, ignoring the fact that these same definitions are part of the literature and methods they cite. They claim that Lab D’s definition of asbestiform is incorrect, ignoring the fact that the method was accepted by EPA and was, in fact, published in a peer-reviewed journal. The authors claim that Lab D’s analyses were in error, but base their argument on a “consensus” among themselves, not on analytical data, and give no indication of the error rate they attribute to Lab D. The authors also incorrectly quote or ignore relevant peer-reviewed literature, including their own and that of RJ Lee Group (RJLG).²⁻⁴ In short,

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their paper misstates the facts, and misrepresents their own work, the conclusions of the references cited, and the work by Lab D (RJLG).

ASTM is a developer and provider of consensus-based standards. ASTM developed testing methods that are a critical part of the means by which the scientific community ensures that test results are reliable and repeatable. The authors, two of whom are members of the ASTM committee charged with developing methods for asbestos analysis, claimed to have used methods developed by the committee, but failed to perform critical steps required by ASTM in the identification of amphiboles. They also ignore the fact that the same ASTM committee has a draft method for the identification of asbestos in talc under development. This method provides a means for separating asbestos from nonasbestos because of the complex mineral assemblage encountered that could have been used in their analysis. Producing results which are purported to have been performed according to a standard method, but not following critical portions of the method undermines the integrity of the process.

The primary issues in the underlying litigation are determining whether cosmetic talcum powder is contaminated with asbestos and deciding whether exposure to cosmetic talc was the causative factor for the mesotheliomas at issue. The authors claim to have shown that exposure to asbestos-contaminated talc is that causative factor, but support their argument with incorrect methodology and faulty data. They also ignore the science, as expressed by IARC,⁵ which did not identify a causative link between exposure to talc, free of asbestiform minerals, with lung cancer or mesothelioma. Cosmetic talc, including the source mines at issue, has been recognized as being free of asbestos.^{5,6} Finally, the authors ignore the presence of amosite, found by Lab D (RJLG) in the TEM analysis of the diseased lung tissue. Amosite, a commercial asbestos fiber, has never been found to be a contaminant of cosmetic talc, but is a well-recognized causation agent for mesothelioma. A conclusion contrary to the existing body of knowledge requires a detailed analysis with well laid-out experimental procedures, measurements, and statistics, and not hand-waving arguments.

The authors and Lab D (RJLG) have been investigating the potential occurrence of asbestos in cosmetic talc in a series of cases in which the plaintiffs argue that usage of cosmetic talc led to the induction of mesothelioma. The interlaboratory debate boils down to whether the laboratories accurately identified the amphiboles they claimed to and if so, whether those amphiboles were asbestiform. It is well recognized that elongate mineral fragments do not have the same biological activity as asbestos fibers.^{7,8} The known elongate minerals found at trace levels in cosmetic talc include a mixture of magnesium silicates (e.g. sepiolite), including talc fiber (some of which are talc plates viewed on edge), transitional intergrowths of talc and anthophyllite, nonasbestos tremolite, and nonasbestos

anthophyllite. The issue is whether the authors establish the presence of anthophyllite asbestos and to a lesser extent tremolite asbestos, as claimed in the paper, given these acknowledged background interferences.

The first issue is whether the analytical methods, as the authors used them, were reliable for the purpose and used properly. One of the authors claimed to have followed a modified Yamate⁹ protocol, but had no record of which grids were analyzed, and recorded no fiber count data sheets showing the grid opening in which a fiber was found or TEM grid maps as required by the method. Another claimed to have followed Yamate as well, but provided no record to relate the individual particles counted to the corresponding analytical data. The third claimed to have followed D6281,¹⁰ a method for identifying asbestos in air in locations, but which acknowledges that nonasbestos amphiboles may be included in the fiber count. The authors write that they did not need to perform quantitative zone axis identification, suggesting that Yamate says it is “optional” and “useful,” when, in fact, it is expressly required by both Yamate Level III and D6281.

Because of the extensive milling in cosmetic talc, amphibole minerals are often found as particles having elongated aspect ratios (>5:1) and parallel sides thus requiring a detailed characterization to properly define them as either asbestos fibers or nonasbestos fragments. The characterization must comply with accepted definitions of what is asbestos and what is not asbestos. Of the methods supposedly used by the authors, only EPA 600/R-93/116¹¹ (R-93) has an explicit analytical definition of asbestos. This definition is consistent with other published work.^{2,12-15} Under R-93, if most of the individual fibrils are thick (i.e. >0.5 µm in width), the population is not asbestos. Also, per R-93: “If a sample contains a fibrous component of which most of the fibers have aspect ratios of <20:1 and do not display the additional asbestiform characteristics, by definition the component should not be considered asbestos.” In this case, the PLM optical data from Lab C and the data from Lab D (RJLG), both using R-93, conclude that the amphibole particles present are not asbestos. This last fact alone should have led the authors to reconsider their findings since 90% of all the particles identified in the talc samples were optically visible, and if asbestiform, should have been observed in the optical analysis.¹⁶

The authors cite a lack of accepted procedures for identifying asbestos fibers from nonasbestos fragments by electron microscopy. In fact, a review of the literature, including Van Orden *et al.*¹² and Wylie,¹⁶ shows that there are well-defined characteristics of asbestos that differentiate it from the nonasbestos mineral fragments in the TEM. The authors claim that Van Orden’s method is a scanning electron microscopy (SEM) method that was not validated for the purpose of distinguishing between asbestiform and cleavage populations. As seen in Van Orden *et al.*, the method was validated, and is a TEM – not an SEM – method as stated in their paper.

Asbestos is identified by its habit by looking at a population of particles. If most of the particles in a population of particles longer than 5 μm have an aspect ratio less than 20:1, or if the average aspect ratio is less than 20:1, it should be classified as nonasbestos.^{2,11,15,17} “Elongated particles [...] that did not come from a population of asbestos fibers are sometimes called cleavage fragments.”¹⁸ Lab A did not report dimensional data for the particles counted, but the paper indicates that the majority of its counted fibers had aspect ratios less than 20:1. The particles Lab C identified in the bulk talc as anthophyllite had average aspect ratios less than 20:1 in samples with four or more particles. The aspect ratio of the tremolite particles reported by Lab C were greater than 20:1, but only four particles were identified as tremolite of the 13 bulk samples analyzed. In no sample were a sufficient number of tremolite particles identified to characterize as a population. Moreover, review of the images provided indicates one of the particles fall in the category of particles which cannot be identified as asbestiform or cleavage based on a single particle and the other three are nonasbestos cleavage fragments. The particles identified as anthophyllite by the author–reviewer, during the review of Lab D bulk analysis, had higher aspect ratios but proved to be fibrous talc or clay upon reexamination. Four of the five particles illustrated in their paper had aspect ratios less than 20:1. The upper image in Fig. 6 is unambiguously a cleavage fragment. Thus, the authors have not demonstrated that an asbestiform amphibole population was present in the talc.

The authors premise their conclusions on visual inspection of SAED patterns to identify amphiboles with (0.53nm) row spacing as is permitted by Yamate Level II for environments known to contain asbestos. The major analytical problem with this approach is that magnesium silicates, talc fibers, and mineral intergrowths found in talc can have SAED patterns with row spacing (0.53nm), or other patterns, that are very similar to those produced by anthophyllite or tremolite. This gives rise to significant interferences. In order to unambiguously identify such particles, it is necessary to tilt the fibers to multiple orientations, record the SAED patterns, and make quantitative measurements of the d-spacings and angles constituting the basis vectors in the pattern.^{9,10} These measurements should then be compared not only with the suspected mineral but also with potential interferences by other amphibole and nonamphibole minerals. Two of the authors, after repeated criticism, produced a number of zone axis SAED patterns measurements that they compared with zone axis data for anthophyllite and tremolite. They reported matches in a number of cases. Our independent re-analysis of their claimed anthophyllite pattern measurements indicate that a number of other minerals, including talc and clays, have a comparable or better fit.

The authors criticize Lab D’s (RJLG) analysis, suggesting that they missed or ignored countable asbestiform structures and misidentified amphibole structures as talc

or transitional minerals. To support their argument, they provide pictures, SAED patterns, and EDS spectra from particles they found in their re-analysis of Lab D grids in Fig. 12. Typical of the data from Labs A and B, in Fig. 12, there are four unlabeled and unindexed SAED patterns, three unlabeled EDS spectra, and two unlabeled images, making it impossible to relate the pieces of data. The particles in Fig. 12 have aspect ratios of about 10:1, not characteristic of asbestiform structures. The EDS spectra do not match the EDS spectra of particles found in the lung. There is indication in the SAED patterns (left center in Fig. 12) that at least one of the particles is multiphase or transitional. The morphology of the exemplar particles is not asbestiform, nor does the data provided support the claimed identification. Their exemplars do not provide evidence that Lab D (RJLG) was incorrect or that the particles in the lung match the particles in the talc.

We have examined the TEM grids prepared by the authors, as they did ours. Except where the documentation was nonexistent (Lab A), we have successfully relocated most of the particles greater than 5 μm in length in Lab B and Lab C samples. We did confirm the presence of non-asbestos tremolite identified by the authors in some cases, but in others found that the particles were intergrowths with talc. With minor exception, however, their identifications of anthophyllite have been incorrect. When subjected to quantitative zone axis SAED analysis, the particles identified by the authors as anthophyllite have proven to be talc, talc/anthophyllite intergrowths, or amorphous clays. Thus, the authors have not provided the requisite analytical data, required by the protocols used, to demonstrate the products analyzed contained the minerals they claim to have found.

We also searched for and relocated particles for which data were provided from the authors’ reevaluation of Lab D grids. We were able to relocate the upper particle in Fig. 12. It is not a fiber overlapped by other particles but a single coherent intergrowth between talc and tremolite and should not be treated as a respirable particle or asbestiform fiber. The authors reviewed 20 samples originally analyzed by Lab D. In most of those, the reviewers either explicitly agreed with the analysis or identified no particles within the area analyzed by Lab D that they believed were incorrectly identified. Of the six particles he reported that had been analyzed by Lab D, the reviewer agreed with the identification of five. We have been unable to relocate eight particles analyzed by the reviewer because no map was provided. The remainder, those outside the Lab D analyzed areas, but for which location data were provided, we were unable to locate two, but eight (four claimed anthophyllite, two claimed chrysotile/antigorite, and two claimed tremolite) were relocated and quantitatively analyzed. Only one (nonasbestiform) tremolite particle was found to be correctly identified by the reviewer. The remainder of the particles were intergrowths, talc, or clay fibers. The authors have not demonstrated that Lab D’s mineral identifications were incorrect as claimed in the paper.

In attempting to link cosmetic talcum powder to mesothelioma, the authors argue that the asbestos bodies found in the lung tissue are derived from the talc; yet, the morphology of the particles in the talc was not consistent with the morphology of the asbestos bodies found in the lung. The two asbestos bodies in Fig. 11 have aspect ratios over 100:1, are less than a micrometer in diameter, and have highly parallel sides. They have a dramatically different morphology than the five particles used by the authors to illustrate their product testing findings. In fact, very few if any, of the 1000 plus particles characterized by the four laboratories during product testing have the morphology of the asbestos bodies found in the lung by Lab D or the two asbestos bodies shown in the paper. Finally, in drawing the causative link between allegedly contaminated talc and causation of mesothelioma, Gordon *et al.* ultimately relies on the identification of the mineral core of an asbestos body in the lung tissue. They ignore any possible iron content of the mineral fiber, instead assigning that to the iron coating on the fiber. But they fail to recognize the large number of uncoated amosite fibers that were also present in the lung tissue as possibly causative of the disease or that these fibers are dimensionally and morphologically similar to those that are coated in the asbestos bodies. Thus, contrary to the claims in the paper, the authors have not established the connection between the talc samples and asbestos disease in the lung tissue.

The authors cite a number of publications supposedly supporting their claims that consumer cosmetic talc usage has been linked to the occurrence of malignancy. Citations as to causation of mesothelioma are used to support the arguments of the authors, but these studies¹⁹ – for which Gordon was one of the authors – showed no relationship between talc exposure and the presence of asbestos in ovarian tissue, even though more than 60% of those studied had known exposures to talc. In 74 of the 75 ovary samples studied in their references, any asbestos found in the ovaries was identified as chrysotile, amosite, and/or crocidolite¹⁹ (see also Refs. 4 and 5 in the paper) – not anthophyllite or tremolite as characterized in this study. Tremolite was reported in one sample. Thus, the findings of the references cited as a basis for claiming that asbestos in cosmetic talc has been related to ovarian cancer or mesothelioma in the past are misrepresented.

Gordon *et al.* cite several books and other studies to suggest that talc ore deposits are known to be contaminated with asbestos fibers. However, the cited references^{20,21} do not report asbestos in any talc ore sample. As noted by Rohl and Langer: “because no methods exist to distinguish between possible differences in fiber surface, we do not refer to anthophyllite and tremolite fibers in these talcums as asbestos. Instead they are referred to as asbestiform.”²⁰ Pooley’s study of northern Italian talc²¹ indicates that tremolite does not occur in the talc ore, but in the surrounding country rock and when crushed, the tremolite is shorter and thicker than asbestos. Berg²² was clearly aware of the

potential significance of asbestos, noting that the communities are sensitive to asbestos issues, but in none of his analyses of Montana talc ore samples did he report any asbestos fibers. The other references cited make no mention of asbestos in cosmetic talc ores. Thus, these citations do not support the premise that the mines from which the products analyzed were produced contain asbestos anthophyllite or tremolite.

There are a number of additional errors in this paper that should have been caught by the editors. For example, the Yamate protocol is extensively discussed, but never formally referenced in the paper. On a number of occasions, a citation is made that is incorrect: Pooley study as Reference 18 when it is actually 17 in the published paper; Reference 22, an analytical method, is cited to indicate that the talc is contaminated with asbestos; Reference 8 is a study of industrial grade talc miners and has nothing to do with cosmetic grade talcum powder users as described in the paper. No quantitative comparison of the data from Labs A, B, and C was presented.

In summary, this paper purports to demonstrate a causal link between the usage of cosmetic talc as a personal care product and the incidence of mesothelioma. This would be a significant finding if the underlying data and arguments were to withstand scrutiny and their results able to be replicated. In this case, neither the underlying data nor the references support the arguments of the authors. The authors contradict prior writings and testimony without explanation. As a result, the editors should require the paper be withdrawn.

Disclaimer statements

Contributors - Both authors did studies relevant to the letter. Each contributed to and accepted all of the writing.

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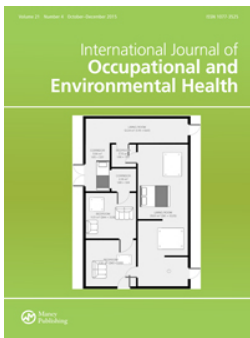
Conflicts of interest - Both authors have participated in talc litigation.

Ethics approval - Ethical consent was not needed.

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Letter to the Editor

Response to RE: Gordon R, Fitzgerald S, and Millette J. Asbestos in commercial cosmetic talcum powder as a cause of mesothelioma in women. *Int J Occup Environ Health*. 2014;20(4):318-332

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Dear Editor:

Thank you for the opportunity to reply to the letter you received from by Dr. Lee and Mr. Van Orden.¹ It is clear that Dr. Lee and Mr. Van Orden have no idea of what constitutes a true academic journal submission. As you are well aware, this manuscript² was submitted online and reviewed by at least two reviewers and at least two editors. The authors have included references or discussion of all methodology used in the studies performed. Further, the original paper represents a unique presentation of data documenting the presence of asbestos from the talc mines to a particular brand of talcum powder product. The original paper further demonstrated that similar types of asbestos were found in a patient using this brand of talcum powder and shows exactly how the patient was able to inhale the asbestos. The patient developed mesothelioma and ultimately died from this cancer. This manuscript confirms that the asbestos findings in prior testing of the talcum powder product and documents the presence of asbestos in the mines from which the talc for this product was sourced. The fact that the authors of the letter claimed that they had not found any asbestos based on their cursory testing of the talcum powder does not make the published manuscript scientifically unacceptable. In fact, it is their methodologies that are scientifically unacceptable. The authors of the article in question and their asbestos analysts are all very familiar with the analysis of asbestos-forming minerals and their potential interferences. In fact, all three authors are well-known recognized authorities on the identification and science of asbestos analysis with decades of asbestos laboratory experience

and dozens of contributions to the peer-reviewed body of literature on the subject. In this letter to the editor, the writers openly admit their identity as the outlier of the four laboratories that analyzed this material. Their laboratory was the only one that did not identify asbestos in the products, and the missive constitutes a blatant attempt to create doubt in the results of the other three laboratories by evoking inadequate, sometimes antiquated methods. This letter to the editor provides intentionally misleading information.

Dr. Lee and Mr. Van Orden are wrong in suggesting that the results in the published paper are biased. I am an academic who prides himself in being extremely honest and straight forward and will not manipulate data under any circumstances. I operate a pathology-based core facility laboratory at the Icahn School of Medicine at Mount Sinai, New York City, NY, USA. The laboratory has been licensed by the state and the College of American Pathologists and has never been cited on an inspection. I have been a member of that department for over 35 years and only publish work that is relevant and that adds to the scientific literature as in this case. Although the initiation of this publication was in light of testing done for legal issues, it was not the reason for the article publication whatsoever. I did not do this testing because it is the primary source of my income. I did it as a service to the institution as well as for attorneys and other clients that seek my counsel. I do not discriminate as to who can send me samples for testing. I will not manipulate data or alter methods so as to conform to what the client would like to find or not find. I use existing methodology and/or further develop that methodology to answer the demands of the project and not just employ techniques that will give only positive results, as insinuated by the letter. The work reported in this published manuscript was only an

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extension of some previous published work that reported on the gynecologic effects of talcum powder in the development of ovarian and other gynecologic tumors; disease genesis very similar in derivation to mesotheliomas. Our study also gave insight into the issues of talcum powder that we had not been aware of in previous studies. Further, the other two authors confirmed my findings of asbestos in a number of the specimens that I tested. In addition, they did testing on whether fibers could be released into the air through use of this product and detected countable asbestos structures in the breathing zone of the person using it. One of Dr. Lee's criticisms is that Lab C was not able to confirm Lab A's work, which in retrospect is just not true. Although the initial analyses of Lab C did not find asbestos fibers in a few of the bulk samples, subsequent analyses at greater analytical sensitivities did find asbestos fibers whether they were by light microscopy of bulk samples or electron microscopy, thereby confirming the findings of Lab A by Lab C.

All the work that was performed for the published manuscript was done based on accepted methodologies. The fibers were identified as asbestos fibers using morphology, elemental composition by energy dispersive spectroscopy (EDS) and crystal structure by selected area electron diffraction (SAED) as is standard confirmation of asbestos. These methods used in the published paper were all based on methods accepted by the National Voluntary Laboratory Accreditation Program, the Environmental Protection Agency, the Occupational and Safety and Health Administration, and others. Dr. Lee *et al.* stated that SAED amphibole structure confirmation was only done visually, which is not completely true. Any visual determination that was questionable was evaluated either by an overlay method with SAED from Union Internationale Contre Le Cancer controls or actually *d*-spacing measurements made to confirm. In all cases, not one fiber was ever "presumed" to be confirmed – it was confirmed. There is no evidence that Dr. Lee's Lab, R J Lee Group (RJLG), has ever reported an asbestos fiber or structure in any of the subject brand samples that he tested. When two of the authors of the published manuscript went back to the grids prepared and analyzed by RJLG, not only was asbestos observed and documented on the RJLG grid preparations but also countable asbestos structures were repeatedly found in the same grid openings (filter preparation area) examined by RJLG. Apparently, these asbestos fibers were not seen or not reported by Dr. Lee or the technicians that analyzed them. Furthermore, on review of the testing, none of the R J Lee Group (RJLG) analyses of this product were conducted by either Dr. Lee or Mr. Van Orden.

I was asked by the attorneys to determine if there was asbestos in containers of one particular brand of talcum powder and to determine if asbestos would be released into the breathing zone of users if used in a manner consistent

with product intent, as were my co-authors. It was understood that I would not be limited to relatively small samples or to a methodology that might miss shorter asbestos fibers. I looked at larger samples of the talcum powder and confirmed them to be asbestos containing. My testing included multiple testing of the same sample and different samples from the same container. The results of my analyses were expressed in terms of the number of fibers per gram of powder. It is important to report results in terms of number of fibers per gram, as it is individual fibers that will ultimately lead to development of fibrosis, lung tumors, or mesotheliomas, pleural or peritoneal. Further, this methodology has been reported in the literature by myself as well as other investigators numerous times and accepted without question.³⁻⁶ In no way was the reader deceived with regard to the validity of the work, since the number of specimens of talc that were examined by each lab was stated in the paper. In addition to finding the same types of asbestos in those specimens of talcum powder many additional specimens were looked at by laboratory B and the findings of asbestos present correlated with the initial results of Lab A. This gave the authors significant confidence that asbestos was present in all the specimens from the one producer because asbestos was found using different methods and because the results were so reproducible.

Regarding Dr. Lee's assertion that the author's "undermine the ASTM Standardization process," Dr. Lee insists that the authors should have relied upon a Draft ASTM method for asbestos in talc knowing full well that this was not the proper thing to do. Having been involved with ASTM for many years, Dr. Lee should know that Draft ASTM methods are not to be relied upon as one would rely on the authority of published ASTM Standards. As a draft, the method has not been accepted by the ASTM committee of experts and asbestos specialists, and can be changed at any time. Furthermore, in making his statement, Dr. Lee apparently either did not really know what the current ASTM Draft method on talc actually states regarding appropriateness of use, or decided to blatantly disregard the policy of use as stated, Witness the following statement found on the top of every ASTM ballot:

"This document is under consideration within an ASTM International technical committee. The revisions proposed have not received all approvals required to become an ASTM standard. You agree not to reproduce or circulate or quote, in whole or in part, this document outside ASTM Committee/Society activities, or submit it to any other organization or standard bodies (whether national, international, or other) except with the approval of the Chairman of the Society. If you do not agree with these conditions please immediately destroy all copies of all documents."

Dr. Lee did neither obtain the approval of the Chairman of the Committee having jurisdiction over the Draft method for asbestos in talc nor did he request written authorization of the President of the Society. It is Dr. Lee who is attempting to "undermine the ASTM Standardization process" by introducing an ASTM Draft method in support of his litigation opinions, not the authors.

Yes, it is true that Lab A did not do releasability testing, but it was never stated that it had. However, SAED was confirmed on every fiber that was found. Further, when analyses of these same specimens were repeated the findings of asbestos fibers were confirmed by SAED. Dr. Lee also claims that “The authors presumed the particles they counted by TEM were regulated amphibole asbestos, even though they found no evidence of asbestos by Polarized Light Microscopy (PLM), and in the face of contradictory findings by Lab D.” The authors carefully identified amphibole asbestos by TEM using acceptable methods. It is well known that asbestos fibers can be smaller than those seen by PLM. The Rohl *et al.* article of 1976⁷ concluded that for talc PLM could only be used as a screening procedure. Rohl cited earlier work by Stanley and Norwood in 1973⁸ who concluded that “light microscopy was helpful only in screening samples with large particles and high concentrations of objectionable fibers.” In fact, a negative finding of asbestos using PLM is not considered a sufficient cause to classify a number of products (e.g. floor tiles) as non-asbestos containing material. Such products must be analyzed by TEM if found negative by PLM. It is not required that asbestos be found by PLM before it can be counted by methods using other microscopes. Ironically, the PLM analyses conducted by Dr. Lee’s laboratory did identify the asbestos-forming minerals anthophyllite, tremolite, and serpentine – just not optically considered asbestiform by his analyst(s). The determination of asbestiform is a visual assessment, and low levels of asbestos content especially in talc cannot be determined as non-existent by light microscopy (PLM) alone.

In this study, three laboratories using independent techniques found asbestos in the samples of talcum powder. Their results contradicted those of lab D (Dr. Lee’s lab) because his lab uses different, novel approaches to define asbestos that have not been accepted. In fact, Dr. Lee condones the use of SEM techniques that are not supported by any governmental agency that promulgates methods for testing products or materials for asbestos. Further, there is still no convincing evidence or documentation that cleavage fragments of sizes similar to asbestos fibers do not cause disease.

The entire concept that Dr. Lee is proposing is that the original manuscript was submitted and published for the sole purpose of gaining advantage in ongoing litigation. This was not at all the reason for this study. The manuscript was submitted for publication because it provides the results of the scientific work performed by three laboratories on an important health concern related to the use of vintage talcum powder. The authors understand that Dr. Lee has a different opinion; essentially that none of the mines and none of the processed talc contained asbestos. We encourage Dr. Lee to submit his findings for peer review as the authors have. We have shown in

the manuscript beyond a reasonable degree of scientific certainty that the cosmetic talc that was tested, in fact, contained asbestos, to include anthophyllite asbestos, tremolite asbestos, or chrysotile asbestos or a combination of the above. We based our analytical procedures and asbestos criteria on approved methods including sanctioned and seasoned standards of the EPA, OSHA, NIOSH, ISO, and ASTM International.

There is significant documentation from the talc suppliers and their own employees that the mines known to be used to supply the talc for this product contained asbestos. As described in the original manuscript, the talc sources predominately used for manufacture of this product were shown to contain asbestos and the asbestos-forming minerals in or in proximity to the talc mined, consistent with the known geology and mineralogy, and confirmed in historic and contemporary testing of those source ores.

It is important to note that a number of women who used the talcum powder that is the subject of the published paper exclusively developed mesothelioma. These women, from all over the country, had no other known exposure to asbestos-containing products. While it is true that I did not and do not maintain count sheets or identify the specific grid openings in which I identify asbestos, I do document every fiber that I count by all the criteria: morphology, chemistry by EDS, and crystalline structure by SAED. Further (and much more extensively than as is the practice of the letter authors), I examine every grid opening in a minimum of five grids 10–100 times greater area of analysis than the minimum typically specified for air sampling, for example. Since I am not doing air or water sampling, those suggested guidelines are not an issue, and not necessarily sensitive enough to detect the relatively low ratio of asbestos to obfuscating talc particulate in these powders. As to the criticism that Dr. Lee’s laboratory was unable to verify my grids, it is frequently fruitless to go back to these grids in projects where I have tested talc because the carbon support film breaks. The primary reason that the replica does not store well is that my preparations are specifically designed to maximize particle load, so that I am maximizing the amount of material I am looking through for each grid. Further evidence of the fragile nature of carbon film grids was found when I looked at two grids containing filters supplied by Dr. Lee. All the grid openings were blown making it impossible to analyze.

The results of the testing of the lungs of the individual described in our original paper confirmed that asbestos fibers associated with the talc were present. There was nothing faulty about the methodology used to determine the presence of asbestos fibers and their identity. Dr. Lee believes his criteria, and unapproved SEM methodologies, which have not been accepted by any agency, the only criteria by which asbestos presence can be confirmed. He proves his ignorance of tissue-modified asbestos fibers in his claim that he found amosite in the lung tissue of the

woman in this case. In fact, I have shown by re-examination of his (or, his laboratory, as we know that none of the actual analyses were his) own preparations that it was not amosite that he identified but anthophyllite that had been coated with iron and protein, which we as clinical pathologists usually identify as asbestos bodies. We found most of these fibers and bodies in his TEM and SEM samples that we looked at in his facility (RJLG). We were able to prove that the fibers were not amosite by determining the relative peak heights for the iron. In the case of amosite, it generally has a peak height as a pure fiber of a minimum 2/3 to 3/4 of the silica peak. If it had some coating because of the biological interaction in the human lung that there would be more iron present, however, there would not be less. When we found these fibers on the RJLG TEM grids, we were able to get EDS spectra that significantly varied along the fiber length with many sites being as little as 1/3 of the silica peak or less. When we identified asbestos bodies that the RJLG report indicated were amosite bodies, we were able to find sites along the body that were less coated and we could get iron peaks that were 1/2 or less in height compared to the silica peak. We also found that the magnesium peak was larger than would be expected for amosite. These chemical variances and inconsistencies in the mineral fraction isolated from the lung tissue of the woman at issue in this case were therefore clear indicators that the dominant asbestos type in the tissue was anthophyllite, wrongly identified by the laboratory of the author of the letter to the editor as amosite.

In my opinion, there is no debate as to whether there were asbestos fibers in the subject talc – it just comes down to how much was present. The fact that only one fiber was found in a set of five grids does not constitute insignificance. Significance and correlation were determined by getting the same results in analyzing the same samples over and over again. The determination is based on reproducible findings no different than any hematologic, chemistry lab test for blood, urine, or other bodily fluid or even homogenized tissue or cells. All these test methods have been proven to be statistically accurate. Dr. Lee's methods of determining the mass of asbestos (or should I say his claim, since he never finds asbestos) are meaningless to the correlation with inhalation and disease causation in humans. It is clear that he has no understanding of the concept of the correlation of inhaled fibers and disease causation. The literature indicates a universally accepted principle that the greater the number of fibers the greater the chance of developing an asbestos related disease. For just that reason I determined and reported the number of fibers per gram of talcum powder.

Another issue for which Dr. Lee developed criteria, which not one agency has been willing to accept specifies whether particle are certain true asbestos fiber structures or cleavage fragments. As he stated,⁹ when the talc is finely ground, it becomes impossible to determine if any single fiber is an asbestos fiber or a cleavage fragment.

Further, the entire concept that an asbestos fiber is only considerable as such if it has to a length-to-width ratio of >20:1 is totally misleading. Regarding Dr. Lee's use of aspect ratios >20:1 to define asbestos, he fails to specify that the asbestos definition he is quoting to create doubt is from the Glossary of EPA 600/R-93/116 (R-93),¹⁰ which is specific to light microscopy rather than TEM.

Dr. Lee also fails to explain that the R-93 definitions and, in fact, the whole R-93 document has never been officially adopted by EPA. While there is general consensus among analysts that R-93 contains good information about how to perform polarized light microscopy of bulk samples for asbestos, it is not legally binding. In 2010, Mr. Van Orden, a senior staff member and signee of this letter of the RJ Lee Group, published a paper¹¹ with attorney co-authors where they argue that the EPA-600/R-93/116 is not a legally binding test method. Specifically, they claim: "What remains the single, legally binding test method was originally promulgated in 1982..."¹² It may be that EPA has not adopted R-93 officially, in part, because there are discrepancies in the method. Dr. Lee could have easily quoted Table 2.2 in R-93 concerning the Optical Properties of asbestos fibers where it says, in reference to anthophyllite asbestos morphology and color: "straight to curved fibers and bundles; aspect ratio typically >10:1," inconsistent with his 20:1 assertion.

Further, Dr. Lee claims that the R-93 definition of asbestos is "consistent with other published work." He cites five articles as evidence. Two of the citations are of his writing (Letter references 12 and 14) and one, reference 13, is a title of a presentation at a meeting, which has no proceedings, and therefore, has not been published. Reference 2 is the paper with the original suggestion of the mineralogical definition that was modified for inclusion into EPA R-93 and the last reference (reference 15) is an old "Absence of Asbestos" method that the U.S. Food and Drug Administration has requested be modernized.¹³ The Expert Panel charged with the task of updating the method concluded that the method, as currently written, could lead to false-negative results, which could allow talc samples with asbestos contamination to pass. In addition, the Panel further concluded the lack of identification procedures by optical microscopy could lead to false-positive results. Therefore, Dr. Lee's reference 15 is an old method under much-needed revision in order to assure that PLM analysis is not considered adequate for the determination of the absence of asbestos in talc, and cannot be considered an authoritative scientific reference.

Dr. Lee has not considered bundles of fibrils that are broken from longer fibers and have ratios <20:1. The paper by Illgren¹⁴ that was quoted by Dr. Lee as a reference makes a clear distinction between the asbestos fiber and the cleavage fragment. All of the fibers that I identified in the subject talcum powders fit the criteria Illgren claimed as asbestos in his review. Wylie makes a point about size and aspect ratio, but never requires >20:1 aspect to be

asbestiform, just that – asbestos fibers are more likely to be greater.¹⁵ The OSHA Method says “when in doubt, count.”¹⁶ I would ask of Dr. Lee, why is it acceptable to create doubt in order to not count asbestos?

In the manuscript, I reported that the majority of the asbestos fibers I identified had aspect ratios of >15:1 and many were above 20:1 to quote the article accurately. The systematic use of size alone indicates that the greater the aspect ratio the more likely it will be an asbestiform fiber not a cleavage fragment. In almost every case, the fibers I identified were asbestos fibers by both Dr. Lee’s and my criteria to the extent I can determine his criteria.

Even in 1976, McCrone stated that once talc is ground it is difficult if not impossible to see the smaller asbestos fibers by light microscopy and Electron Microscopy has to be employed. The New York State Department of Health stated that if the light microscopy is negative for some products where light microscopy has been repeatedly proven inadequate, TEM confirmation is required. It appears that Dr. Lee speaks out of both sides of his mouth. In one assertion, he claims that there has to be a population of fibers to call it asbestos. In another assertion, individual fibers are discounted as cleavage fragments. We are left with no possibility by which asbestos presence can be allowed. He quotes papers that have stated that for fibers to be considered asbestos they have to be >5 µm in length and have an aspect ratio of 20:1 or greater. However, there is no agency in this country or for that matter any country that has ascribed to a definition of asbestos where only those fibers with aspect ratios >20:1 are asbestos. Even the papers that Dr. Lee quoted indicate that if the fibers are that size and aspect ratio they are more likely to be asbestos.

In the dozens of analyses of the talcum powder products in question, Lab A only counted fibers 5 µm in length or greater. Aspect ratios in those analyses were mostly 15:1, or >20:1. The majority of scientists involved in asbestos analysis consider 5:1 as a realistic aspect ratio to consider as asbestos. Further, most investigators do not ascribe to the statement in the letter to the editor regarding the letter authors’ laboratory, RJLG (Lab D), to wit: “The authors criticize the work of Lab D, arguing that Lab D’s definition of cleavage fragment is not generally accepted, ignoring the fact that these same definitions are part of the literature and methods they cite.” The key insinuation here is that Lab D’s definition of cleavage fragment is parts of the literature and parts of methods that the authors’ cite. To the contrary, Lab D’s definition is cobbled together from various methods to produce a definition that suits Lab D: a definition that consistently and repeatedly is used to refute

the obvious presence of asbestos. Finally, Dr. Lee’s arguments are totally irrelevant in light of the fact that people that inhaled the talcum powder have repeatedly developed mesothelioma.

Disclaimer Statements

Contributors Dr Gordon’s response incorporated input from Dr James Millett and Sean Fitzgerald who co-authors of the initial publication in question.

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Conflicts of interest Dr Lee and Dr Gordon are working for attorneys on opposite sides of a civil law suit.

Ethics approval Not required.

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Response to Gordon 2016

Richard Lee, Drew Van Orden & Matt Sanchez

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Letter to the Editor

Response to Gordon 2016

Richard Lee , Drew Van Orden, Matt Sanchez

RJ Lee Group, Inc., Monroeville, PA, USA

Dear Editor,

We appreciate the opportunity to respond to Dr. Gordon's comments¹ on our Letter to the Editor² concerning the weaknesses in his original paper, "Asbestos in commercial cosmetic talcum powder as a cause of mesothelioma in women."³ Dr. Gordon has misquoted his own publications and he incorrectly claims we did not identify grunerite asbestos (amosite) in a sample of lung tissue.

Gordon, Fitzgerald, and Millette (GFM) incorrectly claimed that prior work had established a link between asbestos contaminated talc and ovarian cancer. Our objection to the original paper and to the Dr. Gordon rebuttal¹ is that the scientific literature does not support a link between ovarian cancer and talc contaminated with anthophyllite asbestos as claimed by the authors. GFM (page 318, paragraph 1) state, "Previous research suggests that ovarian cancer and peritoneal mesothelioma may be directly attributed to the use of talcum powder contaminated with asbestos or from exposure to partners occupationally exposed to asbestos." GFM then cite three papers by Heller,⁴⁻⁶ of which Dr. Gordon was a co-author, and presumably was also the analyst who performed the work on which the papers were based in support of this statement. Yet, this previous research draws no such conclusions, and the implication of talc in ovarian cancer was not the point of the papers. The Heller papers documented the occurrence of asbestos in the ovaries and fallopian tubes of women who had known exposures to commercial asbestos compared to those who did not.

In reference 3 of GFM⁴, Heller *et al.* concluded "We have demonstrated that asbestos can reach the ovary and may be present even without known exposure." Heller also noted "None of the women had ovarian carcinoma. Some had a history of talc usage." The types of asbestos observed by Heller included chrysotile, crocidolite, and amosite; no anthophyllite asbestos was reported in the 21 women studied, even though some of the women were noted as having used perineal talcum powder. Heller went further, however, and excluded talcum powder as a

potential source of asbestos: "Some older talc preparations contained asbestos, but this is no longer a concern. Some of the subjects did use perineal talc, but talc and asbestos are easily distinguished by electron microscopy, so our findings truly represent asbestos."

Reference 4 of GFM,⁵ Heller *et al.* clearly compare populations of women with and without exposure to commercial asbestos: "Ovaries were studied from 13 women with household contact with men with documented asbestos exposure and from 17 women undergoing incidental oophorectomy." Heller noted "Except for one case, in which tremolite was observed, the fibers were either chrysotile or crocidolite, or both." No mention was made of anthophyllite asbestos – the vast majority of the fibers reported by GFM – even though "In addition, talc was detected in 11/13 exposed women (85%) and in all 17 controls (100%). No asbestos or talc was detected in the stillborn material."

There is more to be gleaned from reference 4 of GFM. Table 3, reproduced below, which shows the type and size of asbestos fibers found in the ovaries of thirty women as reported by Heller *et al.* According to Table 3, 78 of 80 fibers (97.5%) found in the ovaries had widths less than 0.2 μm , completely consistent with historical analysis of commercial asbestos in tissue. In contrast, of the fibers reported by GFM, 90% had diameters between 0.2 and 0.5 μm , representing a completely different population:

There are significant limitations to these methods. PLM analysis misses small fine asbestos fibers or fibrils because the limits of the resolution are approximately 0.2–0.5 μm for different forms of light microscopy. Based on our findings, approximately 90% of the fibers identified fall into this category.

In reference 5 of GFM,⁶ Heller *et al.* specifically targeted the relationship between talc usage and talc content of the ovaries. In a study of 24 women, 12 of whom had no known talc exposure, they reported,

Talc as a possible etiologic agent in the development of epithelial ovarian cancer may be related to asbestos exposure in several ways. Aside from the chemical similarities between the two, many cosmetic talcs

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Table 3 Asbestos fibers in ovarian tissues: type, number, and dimensions

Subject	No. of fibers	Fiber type	<3 μm long	3–10 μm long	>10 μm long	<0.1- μm diameter	0.1–0.2- μm diameter	>0.2- μm diameter
1 ^a	4	Chrysotile	1	2	1	4	–	–
	8	Crocidolite	1	7	–	4	4	–
3 ^a	40	Chrysotile	2	28	10	35	5	–
	40	Crocidolite	3	31	6	30	10	–
4 ^a	4	Chrysotile	–	3	1	4	–	–
5 ^a	8	Chrysotile	1	6	1	7	1	–
6 ^a	80	Chrysotile	5	62	13	71	9	–
8 ^a	32	Chrysotile	2	22	8	22	10	–
	8	Tremolite	1	7	–	–	6	2
9 ^a	1	Chrysotile	–	1	–	1	–	–
	1	Crocidolite	–	1	–	1	–	–
11 ^a	12	Chrysotile	1	9	2	8	4	–
12 ^a	20	Crocidolite	2	14	4	12	8	–
1 ^b	10	Chrysotile	1	8	1	4	6	–
	20	Crocidolite	2	18	–	17	3	–
2 ^b	8	Chrysotile	–	7	1	5	3	–
	8	Crocidolite	1	7	–	6	2	–
3 ^b	4	Chrysotile	–	4	–	3	1	–
4 ^b	4	Chrysotile	–	4	–	3	1	–
	8	Crocidolite	1	7	–	7	1	–
5 ^b	8	Crocidolite	–	8	–	6	2	–
6 ^b	80	Chrysotile	7	58	15	68	12	–

^aFrom Table 1.

^bFrom Table 2.

Reproduced from Ref. [5].

contained significant amounts of asbestos, particularly before 1976. Although tremolite asbestos has been documented as a contaminant of some talc preparations, the types of asbestos detected here are more commonly associated with an environmental (chrysotile) or occupational (chrysotile and crocidolite) exposure. The detection of talc in all the ovaries demonstrates that talc can reach the upper genital tract. However, the quantity detected in this study did not correlate well with the reported exposure. Further study is required to elucidate whether the presence of talc in ovarian tissue is pathogenic.

Again, no anthophyllite asbestos was reported in any sample included in this study.

Thus, in the studies claimed by Dr. Gordon to support his supposedly unbiased academic opinion, not one anthophyllite asbestos fiber was reported, even though in the GFM paper,

Initial bulk analyses of 50 samples of this product in Laboratory A showed that all of the samples contained asbestos fibers. Eighty percent contained only anthophyllite asbestos, 8% only tremolite asbestos, 8% anthophyllite and tremolite asbestos and 4% anthophyllite, tremolite, and chrysotile.

According to Dr. Gordon, anthophyllite asbestos was found in 92% of the bulk commercial cosmetic samples he examined. But that was not the case, not even once, in the ovarian cancer papers he cited.^{4–6}

Dr. Gordon's citations do not support the claim that talc contaminated with anthophyllite asbestos was associated with ovarian cancer. Instead, with one exception, only chrysotile, crocidolite and amosite were reported in the cited papers, all with diameters less than 0.2 μm . Moreover, these data raise serious questions about the credibility of

the GFM authors, particularly Dr. Gordon. If in 50 samples of cosmetic talc, more than 80% contained anthophyllite asbestos, how is it that no anthophyllite asbestos made it into the ovaries of the women in his prior body of work?

There is a larger deception in not identifying the fact that this is a completely novel finding. Dr. Gordon's citations describe the analysis of more than 70 samples from women's fallopian tubes or ovaries. These results were previously reported in peer-reviewed journals by Dr. Gordon as having had no anthophyllite asbestos – even though talc was found in some of the samples. By citing these analyses as support for the premise that prior research linked asbestos-contaminated talc with ovarian cancer, Dr. Gordon misled the reviewers and the readers into thinking his results were supported by prior science. Instead the prior literature points to the fact that his current findings have no basis. This is an intolerable scientific misrepresentation. Dr. Gordon's own analysis of some 70 ovaries and fallopian tube samples found only evidence of commercial asbestos exposure, not the anthophyllite asbestos he claimed to have been found in every analysis of some 50 samples.

Dr. Gordon incorrectly claims that RJ Lee Group (RJLG) misidentified anthophyllite asbestos in lung tissue as amosite. Dr. Gordon states,

These chemical variances and inconsistencies in the mineral fraction isolated from the lung tissue of the woman at issue in this case were therefore clear indicators that the dominant asbestos type in the tissue was anthophyllite, wrongly identified by the laboratory of the author of the letter to the editor as amosite.¹

Dr. Gordon based his argument that the particles were anthophyllite on the ratios of iron to silica in several particles not matching those expected for amosite. Dr. Gordon

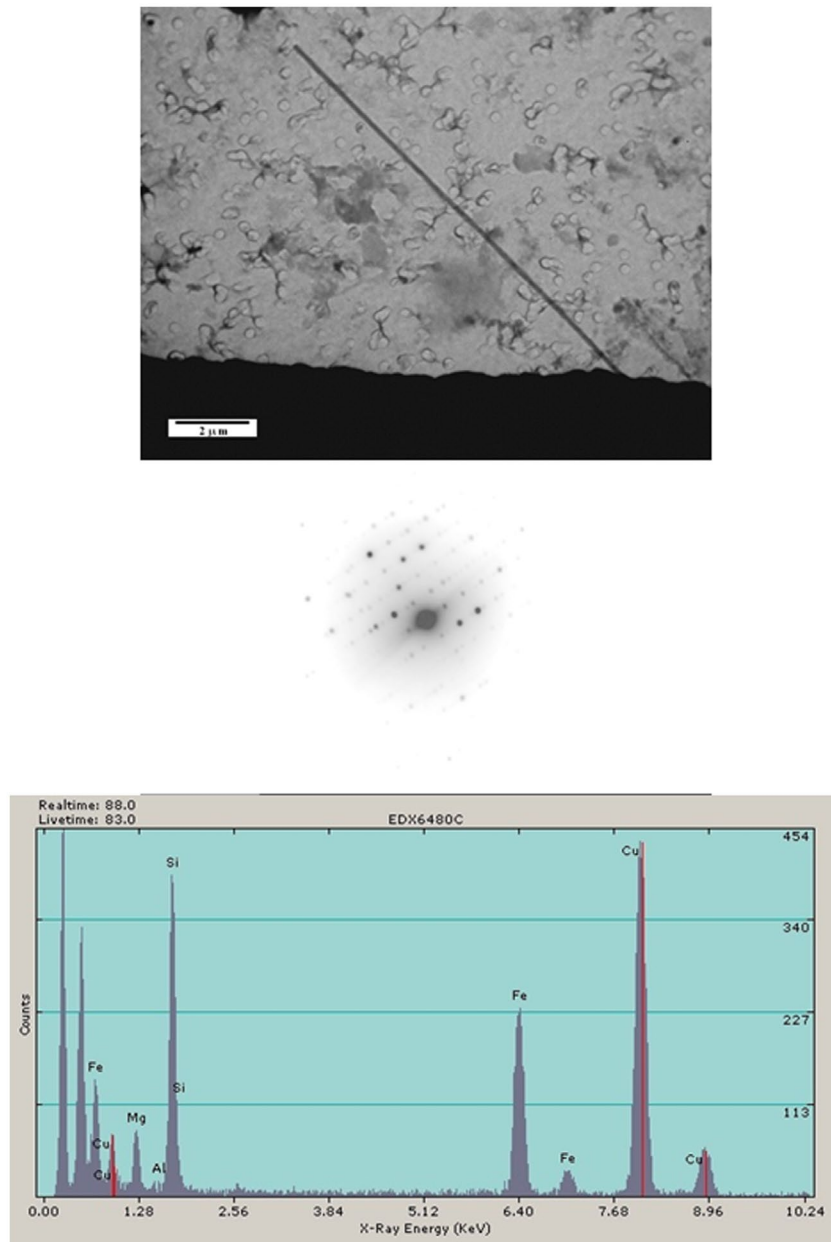


Figure 1 Photograph (top), selected area electron diffraction pattern (middle), and energy-dispersive X-ray spectrum (bottom) for an uncoated amosite fiber observed in the particulate from the lung tissue of a woman.

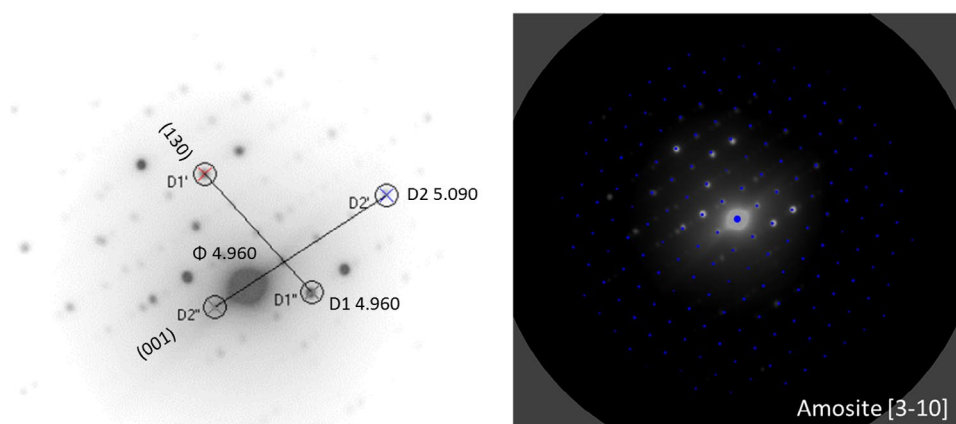


Figure 2 The Selected Area Electron Diffraction (SAED) is presented in two forms: left is the digitized pattern with the d-spacing and angle used to search for potential solutions and right has the pattern overlaid with the simulated solution derived by the search routine.

Note: The indexed SAED is a classic [310] monoclinic diffraction pattern, not an orthorhombic pattern.

missed the fact that in all cases of uncoated fibers, the magnesium (Mg) peak was smaller than the iron (Fe) peak, making the particles inconsistent with anthophyllite. Dr. Gordon showed his bias by ignoring the fact that in the same TEM grids in which he claims particles were misidentified, RJLG located 21 amosite particles which were not coated, and for which conclusive data to identify them as amosite was obtained (see figure below). In Figure 1, we show the morphology of a particle which is consistent with amosite asbestos.

The energy-dispersive X-ray spectroscopy spectra are consistent with an iron amphibole. The Selected Area Electron Diffraction pattern (SAED) is presented in two forms: Figure 2 (left) is the digitized pattern with the d-spacing and angle used to search for potential solutions, and Figure 2 (right) has the pattern overlaid with the simulated solution derived by the search routine.

The indexed SAED is a classic [310] monoclinic diffraction pattern, not an orthorhombic pattern, as would be the case if the particles were anthophyllite asbestos. Dr. Gordon exhibits bias and lack of academic integrity by claiming that he had simple, clean identification of a unique exposure when it is clear that the patient had multiple sources of exposure.

Dr. Gordon misrepresented the scientific literature, which he claimed demonstrated the presence of asbestos in historical talc. GFM,³ citing Rohl and Langer⁷ stated,

In 1976, Rohl and Langer tested 20 consumer products labeled as talc or talcum powder, including body powders, baby powders, facial talcums, and a pharmaceutical talc. Of the 20 products tested, 10 were found to contain tremolite and anthophyllite, principally asbestiform. The product with the highest asbestos content was the same product tested in this study. Both asbestiform anthophyllite and asbestiform tremolite were found in the Rohl and Langer tests. Given that asbestos has been determined as the primary cause of mesothelioma, it is important to note that cosmetic talc contained asbestos in the past.

However, in Appendix A of the Rohl and Langer article,⁷ it is clearly stated that “we do not refer to anthophyllite and tremolite fibers in these talcums as asbestos. Instead they are referred to as asbestiform.” Langer reiterated this recently in a communication to Drew Van Orden.⁸ Langer states

The appendices explain the nomenclature we used. We did not state that asbestos was present in consumer talcum but that on the TEM scale we could not distinguish between cleavage fragment and amphibole asbestos fibril when finding a single isolated particle. If we didn't know the nature of the source materials we could not (at that time) distinguish between the forms. We even had a paragraph or two in the talc paper with some attribution to grunerite and amosite. We were deep into the blue mists of Lake Superior.

Thus, Rohl *et al.* clearly understood they were not looking at asbestos, yet Dr. Gordon uses their work to conclude that cosmetic talc contained asbestos in the past. This is unethical and clearly framed to support his litigation argument.

Similar problems are found in the references cited to support the premise that anthophyllite asbestos was found in the talc mines that supplied the talc to the cosmetic talc producer. None of these references report asbestos, let alone anthophyllite asbestos, in the talc ores in question as we pointed out in our original letter.²

Dr. Gordon's paper³ and his Letter to the Editor¹ contain two types of errors. The first, improper citations could be deemed as simply sloppy work, but because it happened repeatedly throughout his paper and was repeated in his Letter, we believe it demonstrates bias and lack of integrity. The second, the causal issues leading to the three laboratories misidentifying particles in talc as anthophyllite is a complex technical issue. The root problem is that Dr. Gordon, while very experienced in tissue analysis for commercial asbestos, was completely inexperienced in the analysis of talc and has no knowledge of mineralogy.^{9,10}

Had Dr. Gordon understood talc mineralogy, he would have known that talc deposits contain fibers which are intergrowths between amphibole and talc as well as talc fibers that are highly asbestiform. However, as pointed out by Crane of the Occupational Safety and Health Administration, these are not anthophyllite asbestos even though they produce SAED patterns that cannot be visually separated from those of amphiboles. Crane says

when viewed in the TEM, almost all of the fibers appear to be anthophyllite using the usual techniques of asbestos analysis applied to the asbestos abatement industry. The diffraction patterns are sufficiently similar that using only pattern recognition, a mistake is made. [...] The cure, in this case, is careful analysis. Pattern recognition for SAED contains a number of pitfalls which should be avoided by indexing whenever practical. Whenever general mineralogical materials might be present beyond the commercial asbestos minerals, it is very important to step beyond the short set of identification criteria and fully identify the fibers present.¹¹

Crane's memo points out the difficulty of separating these intermediate fibers in talc from amphibole asbestos. Failure to address this issue is what led to the mistakes by Dr. Gordon in the original paper.³ The problem is not confined to Dr. Gordon and his comrades. There are currently many laboratories that have been performing routine asbestos analysis for years and that are now starting to analyze samples for naturally occurring asbestos; they will find themselves in the same boat if they do not recognize and understand the complexity of the mineralogy of the system they are studying. Failure to follow appropriate analytical methods completely will continue to lead to findings of asbestos where none exists at great expense to industry and to our health professionals as they strive to understand reality.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Response to Second Letter by Lee et al. of 2016

Ronald E. Gordon

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Response to Second Letter by Lee et al. of 2016

Response to second Letter to the editor by Dr. Lee et al. OEH472 to Manuscript Entitled, “Asbestos in talcum powder as a cause of mesothelioma in women” By Gordon, Fitzgerald & Millette 2014 [1].

I would like to thank the Journal for giving me the opportunity to respond to Dr. Lee’s bizarre reply to my response to his initial criticisms.

Dr. Lee criticized my response to his opinion letter in three basic areas. The first of which is a multiple page diversion to a reference that had nothing to do with the manuscript in question but was a critique about previous publications regarding talcum powder, and ovarian and gynecologic tumor developments. The second are comments on my ability to properly analyze bulk minerals. The third is to defend his analysis of phantom fibers not at all in the tissue from the patient published in this original article based on an exhaustive analysis.

Unfortunately, we submitted errata to correct the issues created by the manuscript reviewer and editorial suggested exclusions which were missed upon the last review prior to publication. This has been corrected by the publication of a Corrigendum [2]. In every case we have not misquoted anything and our claims are reliable, easily duplicated, and highly accurate.

It is apparent that the focus of half of his letter refers to a single reference to talc in gynecologic tissues and organs in the Introduction and Discussion of our manuscript. Their premise represents a misinterpretation of the reference and the claims that our manuscript does not tell the complete story. However, that was not the focus of the published work regarding the contamination of Cashmere Bouquet talcum powder with asbestos. The purpose was clearly defined to correlate the finding of the same types of asbestos found in the containers of talcum powder given to us directly by Colgate as well as containers that were received, factory sealed, with the asbestos found in the lungs and lymph nodes of the patient that used the Colgate brand of cosmetic talcum powder. In addition, we also tested the ability to find and confirm that the use of the talcum powder confirmed the presence of asbestos by documented sampling in air testing in a glove box and a simulated bathroom conditions. The air testing confirmed that respirable asbestos could be deposited in the lungs of those using the talcum powder. The data presented in no way reflects anything in the ovaries or gynecologic tissue. To distort our work in this forum the way Lee has clearly driven by his clients or their lawyers and totally inappropriate. Lee’s goal was not to advance the science of cancer causation so that lives may be saved by sound scientific research, but rather addressed other legal issues he faces in his defense of talc which has no place in published commentary and has even less to do with our 2014 published manuscript [1] to which Lee et al. refers. Dr. Gordon will in fact address this in a new manuscript to be

written. It should be noted that the data for this manuscript was available at the time of the writing and publication of our article being criticized here.

In the references to the gynecological studies, I did not look at 70 patients at the electron microscopy level. This is a fatal flaw in Lee’s review of our work. I also did not look at the talc used by the patients for its content. Again, the authors of this letter are trying to address issues that are not presented or contained in the manuscript that they are criticizing. It may sound like science, but it is not sound science.

I will only briefly respond to the criticisms of the correlation of data previously published on gynecologic tissues. The study was initiated to study the presence of talc in these tissues to determine if these women were developing tumors related to exposure to cosmetic talcum powder. Not only did we find cosmetic talcum powder in the gynecologic tissue, we also found asbestos, a class one carcinogen. We found talc not only in the user group, but also in the control group of women that did not use the talcum powder in their perineal areas. Not reported, however, was the use of talcum powder cosmetics in other areas of the subjects’ bodies. We did find asbestos in women that had partners who were exposed occupationally to asbestos. Lee et al. indicated that we did not report anthophyllite type asbestos. This was true at the time of publication of those articles. However, as with the talcum powder and the human tissues studied, the amount of tremolite and anthophyllite was relatively small and required greater sensitivity to detect. This was the case with the studies analyzed in the Heller work [3–5]. When the manuscript is published, honest reviewers will reach their own conclusions. This should never have been addressed in this forum because it has no impact with regard to issues presented in this manuscript in question.

Talc and its effects on gynecologic tissues, will be further discussed in a future manuscript to be written by me and other concerned scientists.

Lee’s letter is a personal attack. His gratuitous and unsubstantiated use of the terms such as “sloppy” and “incompetent” is irresponsible and doesn’t negate our research or its conclusions. It may satisfy Lee’s need to get the last word, but without foundation, it is as unhelpful as it is unscientific. Like any conscientious scientist, I have no problem with critical review of our research. In fact, we welcome honest commentary and rely upon it to improve the final product, just as that final product improves the lives of its subjects by answering critical questions with practical implications for prevention. In my opinion, rebuttals and sur-replies, the likes of which are carried out by Dr. Lee only in the interest in hiding the truth and covering up facts, than it is answering the critical questions surrounding the cause of some cancers. I have personally witnessed Dr. Lee pulling the wool over the eyes of a judge to disqualify one

of the most honest and careful scientists/minerologists I know. This was done in a court proceeding when the other side was not able to question his explanations.

I have published over 200 peer reviewed manuscripts on many subjects. I know and understand the scientific method. In some analyses, I may not use the scientific method per se in testing as the Lee lab does. Our protocols are a matter of testing and the use of many protocols for testing approved by various agencies. However, in the testing of talcum powder there are no uniform testing protocols. There are suggested methods. My research and methods have increased the sensitivity of testing to find smaller amounts of asbestos by looking at more material. To do that, more material is tested by techniques dependent on a greater sensitivity. I have the same capability to test bulk samples by techniques such as PLM or PCM or XRD. However, the literature and numerous replicable test results already published reveals that such tests are inadequate in identifying asbestos in talcum powder. In other words, if one does not want to find them, he can make that happen. Using TEM techniques has the sensitivity to identify these structures provided the specimens are studied with adequate sensitivity by looking at more and more of the material. It is well documented now that even small amounts of asbestos can cause cancer and in particular mesothelioma in the pleura of the lung and in the abdomen. Tests performed and reported in our paper show that the asbestos released from talcum powder can be breathed and as a result may cause these cancers whether it stays in the lungs or is dissolved or transported out of the lung. To be sure, as with all asbestos-related diseases, the latency is very long which may be due to the level of exposure and relative size of the fibers.

Lee also claims our lab should use the Draft Yamate method [6] and criticizes our choice not to do so in these circumstances. The Draft Yamate [6] method was developed in the 1980s to meet specific criteria for the percentage of asbestos in air, water, or a bulk sample. As most earnest researchers know when a sample has very little asbestos and where the fibers are relative small, the Draft Yamate [6] method is not adequate due to sampling and sensitivity. Further, the concept that tilting or zone axis analysis is required, in SAED analysis is ridiculous since differentiating between talc and anthophyllite is clear without ever doing zone axis tilting. Millette clearly stated this in his 2015 publication, "Procedure for the Analysis of Talc for Asbestos" [7]. Talc always appears as talc even with tilting, anthophyllite, however, appears as amphibole asbestos on a flat plane, but when tilted to certain angles it can appear as talc. That is the deception promoted by the Lee lab during its documentation. In our testing of the grids that were prepared by the Lee Lab, we found significant asbestos fibers which were confirmed by SAED. Lee found tremolite and anthophyllite but called them cleavage fragments no matter what the size and what all other agencies criteria defined. An asbestos fiber by any other name is still an asbestos fiber.

The allegation that I have not been formally trained in mineralogy is absurd. I have learned all the techniques over many years of doing this work and I am more than competent in identifying asbestos fibers and typing them. I may not know how to identify all minerals, but I am well

educated in identifying asbestos type minerals. As I stated, it is more difficult when modified by a human than just looking at a mineral.

This is not a game. This public jousting serves only to sow doubt, but doubt can be the product some want. A client may not need to prove asbestos isn't in their products, they just need a lab willing to provide the reasonable doubt the company needs in court. My motivation is that sound science will show the way to cancer prevention. Prevention is the most reliable cancer cure. Talc undeniably causes granulomatous lung disease in some individuals and it is used for just that purpose with talc pleurodesis. Whether it is a carcinogen or co-carcinogen in its own right is yet to be determined. However, there is substantial evidence that talc can cause an inflammatory process. In that respect alone, it is acting as a potential cancer promoter.

Lee also claims that I have found asbestiform fibers in product testing, and that the "asbestiform fibers" are not asbestos, but are rather intergrowths or cleavage fragments. Lee is wrong, it is impossible to identify a cleavage fragment when there are single fiber identifications. Lee is wrong on the cleavage fragments vs asbestos fiber front for three reasons. First, I have identified fibers in samples that I received from Dr. Nolan tested by Drs. Rohl and Langer. I found asbestos that any laboratory would call asbestos fibers because they had an aspect ratio greater than 20:1 and in a few instances were greater than 100:1. All human health related agencies provide that if a particle is found that has the typical characteristics of a fiber, is greater than 5 μm , has aspect ratios of greater than 3:1 and fits the EDS and SAED criteria of a type of asbestos, it has to be considered an asbestos fiber. It should be noted that asbestiform is the criteria that has been used because it is clear that from a biologic standpoint there is no difference. Secondly, my work on these specimens was confirmed in two other mineralogy laboratories. Regardless of what Dr. Lee claims, Dr. Langer told him in an unsubstantiated conversation, that conversation is meaningless given he communicated the opposite to me in an email I have maintained. The laboratory they worked in was clean and there was no chance of contamination as suggested by Colgate attorneys. Langer was very careful not to contaminate his lab or the specimens. I visited Dr. Langer's Laboratory and saw how careful he was to not cross contaminate any samples. And although Dr. Langer has done some back pedaling with regard to those samples and the possibility of being cleavage fragments. Drs. Langer and Nolan were asked to reanalyze those specimens. Their report was never produced by the Colgate attorneys, a common litigation strategy when results do not support an attorney's litigation necessity. From a health perspective there is no difference. Dr. Lee et al's statements in this letter regarding the biologic effects of fragments vs fibers have been totally and unequivocally refuted by the EPA in a document dating back to 2006 [8]. I will not go any further since I do not care to personally attack Drs. Lee and Sanchez and Mr Van Orden. It is unfortunate that they do not understand where mineralogy ends and biologic effects begin or where they intersect. I offer as additional proof that other minerals not termed asbestos and have fibrous appearance have been implicated as causative in the

development of fibrosis, lung cancer, and mesothelioma, and possibly other types of cancer.

After seeing many reports on tissue fiber burden analyses and on bulk product testing, and after reading depositions related to Lee's laboratory procedures, it is apparent that Lee does not perform their testing based on their own SOP. Lee is inconsistent and picks and chooses the techniques and protocols he will use. Further, although his lab claims to use the Draft Yamate III protocol [6], I have yet to see a report among the many I have reviewed that confirms he used it. His lab frequently uses SEM as a means of analyzing for asbestos not approved by any agency. My lab protocols conversely meet suggested methodology.

Lee advocates that even if these fibers are found, regardless of size, they are cleavage fragments not asbestos fibers. Such was the testimony of Dr. Sanchez. Their position is not supported by any agency that considers human health effects. The EPA published a specific document that clearly indicates that Dr. Lee's position is totally unreliable [8]. Lee's work suffers from publication skepticism, because it in no way defines specifics of his criteria. Lee's cleavage fragment defense does not in any way allow for human tissue interactions with asbestos fragments or fibers and its consequences. In the end, all that results is confusion of the issue of what is asbestos. Lee's lab ignores the definition and criteria of every agency that provides guidance on asbestos analysis. Their criteria may suit their purposes but it is not the criteria for reliably identifying asbestos. All agencies include TEM as an optional/recommended tool when studying bulk samples for the presence of asbestos. Lee claims that cleavage fragments can be defined by SEM techniques by what criteria? All agencies require TEM analysis for the determination of Taos contaminated by those minerals. SEM is not an acceptable methodology unless one is trying not to find asbestos. When Lee's lab does find what is clearly an asbestos fiber he calls it by any other name. Cleavage fragment is Lee's favorite pseudonym for asbestos, but all the agencies indicate that when in doubt it is to be defined as an asbestos fiber. The Lee lab has taken the opposite approach, criteria be damned. The reader can be the judge as to why one who defends asbestos companies uses a technique that will not reliably find asbestos fibers in his clients' products.

Let's be clear, these mistakes alleged by Lee are mistakes of his own making, not Gordon et al. [1]. Lee claims that my expertise is with tissue digestion and not mineralogy. He questions my analysis of finding anthophyllite vs amosite based on reduced Mg ratio to iron. Lee is ignorant of what happens to these fibers in the human body over many years. They actually show a documented fiber of amosite based on their analysis. As I stated earlier, I believe that there is a good chance that whoever gave them the tissue may have contaminated it with a specimen from a patient that may have had an amosite exposure or contamination in their own lab. I looked at all the tissue, not just a representative sample of the tissue by the same technique, SEM, that was used by Lee et al. and did not find one amosite type asbestos fiber or asbestos body. Further, there is a big difference between what is determined as an anthophyllite fiber from tissue that greatly differentiates it from what a mineralogist will identify. It is well documented that the main changes

associated with human on asbestos fibers is the subtraction by the leaching of magnesium and the addition of iron. When one looks at a fiber directly from the mine or at least not in contact with human or animal cells, there is a constant and documented ratio of Mg, Si, and Iron, the same components seen in anthophyllite and in amosite. One distinguishing factor for amosite is the presence of Mn in most amosite fibers. Clearly there was none in the EDS demonstrated. Further, Mg is higher in anthophyllite. However, in the fiber produced in this letter, they show an intermediate amount of Mg. This best supports, along with our assessment, that it is anthophyllite not amosite based on reduced Mg due to leaching. The fiber is coated with iron that could not be seen in this TEM visually, but is present increasing the iron peak. This is best demonstrated when you do multiple EDS analyses along the length of the fiber. When the ratios of both iron and Mg change, it is clearly more likely to be anthophyllite than amosite just based on EDS. When at Lee's lab studying Dr. Lee's prepared grids on this case, Sean Fitzgerald did the same analyses of SAED and determined that all the fibers we were able to identify, not all due to time constraints by EDS and SAED, were found to be anthophyllite. Further, Sean Fitzgerald is a mineralogist that formerly worked in Dr. Lee's lab. All this information was contained, but ignored by Lee in my original response. Based on the size of the fiber, I refuse to believe that the SAED produced in this letter is not from the fiber represented in the photo represented by Lee in his final letter. Many of the same samples that I studied were confirmed by not one, but two mineralogists that were authors on this paper. Not only did they find it in the talc product, but they identified it in air samples from the containers by two different methods with the same results I had.

The most recent manuscripts both before and after publication clearly indicate that the criteria used by myself for identifying the fibers as asbestos and not cleavage fragments are correct. In addition, it has been stated by Lee et al. that dual axial tilting as part of identifying anthophyllite from other amphiboles and in particular talc is necessary. However, they have never described why and yet in a very recent publication by Dr. Millette, he indicated that doing such are time-consuming and do not add relevant data to the identification. Thirdly, the EPA does not recognize Lee's argument regarding the identification of cleavage fragments. He, and the lawyers who helped, encouraged, or wrote his response can continue the personal attacks, but I do not undertake talc testing for litigation purposes. I am doing it to promote our knowledge of how asbestos at various environmental levels impact the development of disease in humans. I do not only accept specimens from individuals, other pathologists and plaintiff attorneys alone, I will accept them from anyone that will send them to me for analysis.

In summary, it is clear that a couple of statements appearing in the introduction and discussion of this the manuscript at question is that this manuscript looks at pleural mesotheliomas not gynecologic tissues. The basis for Lee et al. arguments here on both product testing and human tissue demonstrate their bias not mine. We have reported our findings that they disagree with and they have expressed why and I hope that the reader will take

into account our rejection of their criticisms and our basis for such rejection. Dr. Lee et al's criticisms miss the mark. Sound science is more important than sounding like science. I encourage them to continue their review of this very important work with this in mind and thank them for their comments.

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