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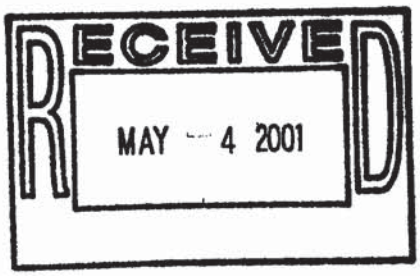
May 4, 2001



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Dr. C.W. Jameson
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Report on Carcinogens
MD EC-14
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Re: Comments on Nomination of Talc for Listing in the 10th Report on Carcinogens

Dear Dr. Jameson:

My comments are being made on the behalf of the Art and Creative Materials Institute, a non-profit trade organization that represents the major manufacturers and importers of art materials in the United States. Talc is a common component of these art materials. I would like to address several issues discussed in the *draft Report on Carcinogens: Background Document for Talc. Asbestiform and Non-Asbestiform*. I will restrict my comments to asbestiform talc.

Fiber size and cancer risk

There are excellent animal models for the relationship between fiber dimension and risk of both mesothelioma and lung cancer. For mesothelioma risk, fibers with a dimension of ≤ 0.25 μm in diameter and >8 μm long appear to present the greatest risk (Stanton, et al., 1981; Oehlert, 1991) with almost no risk presented by short fibers (Davis, et al. 1986). Most amphibole fibers in a asbestiform talc mine are shorter than 10 μm (Kelse and Thompson, 1989) and would not be expected to present a risk of mesotheliomas. Similarly, lung cancer risk also depends on fiber dimensions. Based on asbestos inhalation studies, Berman et al (1995) found that potency for lung cancer rested with fibers that were longer than 10 μm and less than 0.3 μm in diameter. Their model found that fibers that were <10 μm long and had widths from 0.3-5.0 μm were not associated with a lung cancer risk. Lippmann (1988) performed as similar analysis. He found that fiber retention drops rapidly as fiber diameter increases from 0.8 to 2.0 μm. No lung cancer risk was associated with fiber length less than 5 μm. Lung cancer risk was associated with fibers with a diameter of 0.3-0.8 μm and a substantial fraction >10 μm in length.

Although IARC considered a number of studies involving the carcinogenicity of talc in experimental animals, they did not have access to identification information concerning several of the fibrous talcs.

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This is particularly important because talcs form the Grouvenor Talc Company (GTC), the mine most studied for cancer risk, have been examined in a number of animal models and have been found to be non-carcinogenic. Stanton, et al. (1981) examined two asbestiform talcs from the Grouvenor talc district including one from GTC (Stanton talc #6) in their pleural implantation rat model. Neither of these talcs induced mesotheliomas although based on particle dimensions, a 60% incidence of mesotheliomas would have been expected with the GTC talc. Oehlert (1991) re-analyzed the Stanton data, breaking out potency assessments not only by particle size but by mineral type. When compared to asbestos, the author found that talcs were 1/135,000 as potent for causing pleural tumors. This re-analysis included both the asbestiform talcs and 5 non-asbestiform talcs studied by Stanton, et al.

Smith, et al. (1979) also studied one GTC talc (FD14) in their hamster pleural mesothelioma model. This talc, as well as another talc containing amphibole fibers, was negative in their model.

Wylie, et al. (1997) studied the FD14 talc from the Smith et al. study in an in vitro system. It was not cytotoxic and did not induce cell proliferation. Talc samples not containing quartz were not cytotoxic where asbestos was both cytotoxic and induced proliferation.

Epidemiology: non-asbestiform amphiboles

The primary components of asbestiform talcs, other than talc, are cleavage fragments of anthophyllite and tremolite. Since exposure to these cleavage fragments may be a factor in cancer risk from exposure to asbestiform talc, a review of epidemiological studies of workers exposed to nonasbestiform amphiboles is in order and will strengthen this report. Kusiak et al (1991) looked at a cohort of 54128 gold and nickel miners with potential exposure to nonasbestiform amphibole fibers. They found an excess cancer risk in pre-1945 workers but no relationship between cancer excess and exposure to mineral fibers. The concluded that the excess was probably related to exposures to arsenic and radon decay products (radon daughters). Steenland and Brown (1995) studied 3328 gold miners from South Dakota. There was no significant increase in lung cancer risk in this cohort though there was evidence of excessive quartz exposure including elevated deaths from immunological diseases, renal disease and tuberculosis. The authors suggest that a slight excess in lung cancer rates might be related to the smoking habits of miners: they smoke more then the general population. Cooper et al (1992) studied 3444 taconite miners exposed to silica and nonasbestiform amphibole fibers. The standardized mortality rate (SMR) for lung cancer was less than expected at 67 and was not related to duration of employment, exposure level or latency. When Cooper, et al. eliminated those workers with less than 3 months of employment from the analysis, the SMR for lung cancer actually decreased as duration of employment increased.

Epidemiology: asbestiform talc

The association between exposure to asbestiform talc and lung cancer risk is primarily based on the findings of increased cancer risk in workers exposed to asbestiform talc in the Grouvenor talc district (GTD) of upstate New York. A more detailed description of these studies, as well as inclusion of the latest (Dezell et al, 1995) study would be in order. Kleinfeld, et al. (1967, 1974) found a 10 pulmonary and pleural tumors among a study of all GTD workers. All cases occurred in workers who were exposed prior to the introduction of exposure control measures ca. 1945. Twenty-nine of the workers died of pneumoconioses, including 5 who died of a complication of quartz exposure, tuberculosis. This study had the short coming that it did not take into account exposures other then to talc, did not take into account smoking history and did not relate exposure levels to outcome. Recent data developed by

NIOSH (1980) can be used to estimate respirable quartz exposures to workers in this study. NIOSH found that for the average dust exposure of 2.9 million particles per cubic foot (mppcf) in GTC mills, the average respirable quartz exposure was 11 $\mu g/m^3$ and that for the average dust exposure of 8.1 mppcf in the GTC mine the average quartz exposure was 12.4 $\mu g/ m^3$. Dust exposure measurements were made for GTD mines and mills in the Kleinfeld, et al. study. These exposures can be translated to average respirable quartz exposures as follows:

Estimated quartz exposures at asbestiform talc mines

	Pre-1945		**1945-1965**	
	Mppcf	Quartz ($\mu g/m^3$)	Mppcf	Quartz ($\mu g/m^3$)
Mines: drilling	818	1250	5	8
Mines: other	129	190	5-9	8-14
Mills	69-278	260-1050	27-37	102-140

Exposure levels prior to 1945 were sufficiently high, in both mines and mills, to result in the pneumoconioses cases described above with quartz levels in air as great as 10 fold higher than today's permissible exposure limit for respirable quartz of 100 $\mu g/m^3$. Respirable quartz is a known human lung carcinogen, with elevated risks particularly when exposures are sufficient to result in silicosis. That respirable quartz exposures were a concern has been confirmed by autopsy studies performed by Dr. Jerrold Abraham of 8 GTD workers. Two of the 5 workers with a history of more than 20 years of talc mining had silicosis.

The second study that has been used to implicate a risk between exposure to asbestiform talc and lung cancer is the NIOSH 1979 study of Grouvenor Talc Company workers. GTC went into operation in the late 1940's using a wet drilling method that would have suppressed exposure to respirable quartz dust as noted in the above table. The NIOSH study has been criticized because of a number of short comings. It would be important to highlight these short comings since they have been addressed in later epidemiological studies of these workers. Specific concerns with this study included its small size; inclusion of all workers, including those that had only worked days; lack of assessment of the contribution of prior exposures; no study of exposure-lung cancer relationships; and no adjustment for smoking effects (Brown, et al, 1983). Any prior mine work among GTC employees would have likely involved high level exposures to quartz dust. Stille and Tabershaw (1982) were able to nearly double the size of the cohort. They found that the SMR for lung cancer among workers who had only worked at GTC was less than expected (76) and that tuberculosis, a disease associated with silicosis, was a significant finding (SMR 680). This study did not correct for smoking history, exposure or identify non-GTC exposures that many have been a concern.

Lamm, et al. (1988) presented a re-analysis of the Stille and Tabershaw (1982) data set in which the occupational histories of workers dying of lung cancer were presented. 8 of 11 workers who died of lung cancer had worked in mines other than talc mines or in quarries elsewhere than at GTC. The SMR for lung cancer in mill workers was 72 for those workers who had worked at least one year at GTC. For those for workers who worked less than one year and had first worked to GTC 20-24 years prior to their death, the SMR for lung cancer was 1111. The latter group would have included workers with prior exposures to mine dust prior to the putting in place of dust control technologies.

Gamble (1993) performed a nested case control study on NIOSH's second evaluation of 710 GTC workers (NIOSH, 1990) to address concerns of confounding. They found that when using fellow GTC workers as controls, all of the excess lung cancer risk could be ascribed to smoking. When looking at past exposures they found that essentially all talc exposure could be ascribed to work at GTC. They were able to give more complete exposure histories for the lung cancer cases: 8 of the 22 cases had worked as drillers at mines or quarries other than GTC and 17 had worked in metal mines prior to working at GTC. Work in mines would have been expected to be associated with exposure to either quartz dust (exposures would have likely been even higher in metal mines than in talc mines because of quartz content of base rock) or radon daughters, a known cause of excess lung cancer risk in metal miners. That drillers may be at particular risk of quartz exposure has been noted by Rubino, et al. (1976) who found that dust generated from drilling operations my contain up to 18% quartz, even though talc itself is relatively free from quartz. In metal mines, drilling dust can contain up to 39% quartz (McDonald, et al., 1978).

Dezell, et al. (1995) further expanded the cohort to 818 workers and increased the latency time to an average of 21 years for GTC workers. They were able to address the concern that prior studies did not address incorporate an exposure-response analysis by estimating respirable dust exposures. When compared to past dust measurements, there was an excellent correlation between the two with a correlation coefficient of 0.78. They found no relationship between dust exposure at GTC and lung cancer. Increases in lung cancer were limited to workers hired prior to 1955 with deaths from non-malignant respiratory disease concentrated in this group as well. When adjusting for exposure they found an inverse relationship between lung cancer and exposure to all subjects, to those workers who were first employed prior to 1955 and to those workers who had worked at GTC for more than one year. The Gamble and Dezell, et al. studies discount the finding of an exposure-related risk of lung cancer for GTC workers with smoking and/or prior exposures to cancer-causing quartz dust or radon being likely contributors to the risk.

Talc injections into the pleura (pleurodesis) have been routinely used to treat such conditions as advanced tuberculosis. The Research Committee of the British Thoracic Association and the Medical Research Council Pneumoconiosis Unit, 1979, conducted a long-term follow up assessment of patients treated in this fashion. The pleural cavity appears to be particularly sensitive to the carcinogenic effects of minerals in the animal model. This "experiment" is, therefore, particularly cogent. Although talc types were not identified, European Pharmacopea talcs which would have likely included talcs used for this purpose, have been analyzed (Paoletti, et al, 1984) and included both fibrous as well as platy talcs. Eighty-eight of the patients where followed for 15-30 years and 75 for 30-40 years, a duration sufficiently long to have identified any cancer risk from such a procedure.

Summary

Animal and epidemiological studies of talc containing asbestiform fibers can be summarized as follows:

- Fiber-associated cancer risk is not seen with the small fiber lengths that predominate in the GTC mine and mill. Because exposures were qualitatively similar to those at other mines and mills in the region (Brown, et al. 1983), the association of talc dust exposure with lung cancer in earlier studies should be discounted.

- A number of studies have been made of the GTC talcs, all negative for cancer risk. This finding is particularly important since the positive epidemiological studies for asbestiform talc are related to exposures to talc (and other) dust from this region.

- The predominant fibrous component of talc containing asbestiform fibers are nonasbestiform cleavage fragments. Epidemiological studies have found no lung cancer risk associated with exposure to such asbestiform cleavage fragments.

- Major confounding in the worker segment of studies relating exposure to talc containing asbestiform fibers has occurred by not adjusting for risks of lung cancer from smoking and exposures to respirable quartz, both factors associated with human lung cancer risk. Smoking differences were found, in the one study that adjusted for smoking effects, to explain excess lung cancer risk.

- A detailed assessment of talc dust exposure has not found a relationship between asbestiform talc exposure and increased lung cancer risk at the GTC mine.

- An updated assessment of the Stanton, et al. study of talcs found that asbestos was 135000 fold more potent than the talcs that they studied. These talcs included both asbestiform and non-asbestiform talcs, including 2 from the Grouvenor talc district. Although asbestiform talc contains fibers, these do not appear to behave like asbestos.

- The finding of no tumor risk in long term follow up of patients treated with pleurodesis lends support to the negative findings with talc in the animal model.

Respectfully submitted,

[redacted]

Woodhall Stopford, MD, MSPH

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