Duke University Medical Center
Department of Community & Family Medicine
Division of Occupational & Environmental Medicine
Box 3834
Durham, NC 27710
December 1, 2000

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Tel: 919-286-5744
FAX: 919-286-5647

Dr. Mary S. Wolfe
National Toxicology Program
Board of Scientific Counselors
Report on Carcinogens Subcommittee
NIEHS, A3-07
Research Triangle Park, NC 27709

Re: Comments on the Subcommittee's Consideration of Listing Talc in the 10th Report on Carcinogens

Dear Dr. Wolfe:

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 your draft Report on Carcinogens: Background Document for Talc. Asbestiform and Non-Abestiform. These comments are offered to your Report on Carcinogens Subcommittee with the expectation that this report can be strengthened if it addresses certain issues in more detail. I will comment on both on studies concerning both asbestiform and non- asbestiform talc.

Asbestiform Talc

Definition: Your draft report discusses the definition of asbestiform fibers. It would be strengthened if it includes NIOSH's definition of these fibers:. NIOSH (Kullman, et al. 1995) defines asbestiform habit as:

"a specific type of mineral fibrosity in which the growth is primarily in one dimension and the crystals form naturally as long, flexible fibers. Fibers can be found in bundles that can be easily separated into smaller bundles or ultimately into fibrils."

This definition is important since many of the fibers in asbestiform talc are cleavage fragments. NIOSH' definition for asbestiform habit contrasts with there definition for the nonasbestiform habit :

"These minerals have ... crystal habits where growth proceeds in tow or three dimensions instead of one dimension. When milled, these minerals do not break into fibrils but rather into fragments

resulting from cleavage along the two or three growth planes. Particles formed by the comminution of these minerals are referred to as cleavage fragments."

Respirable fiber size: Although the draft report notes that a respirable fiber has a diameter of 3-4 μm this is for fibers with a density of 1. Talc has a specific gravity of 3 and, consequently the equivalent aerodynamic diameter of respirable talc fibers would be 1/3 of this, on the order of 1 μm (Wylie, et al. 1993). This finding is particularly important in that the fibers in asbestiform talc are primarily wider than 1 μm with only 10-11% of fibers in commercial talcs being <1 μm in diameter.

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 nonasbestiform 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. There 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.

Animal Studies: 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. 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 form 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.

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, were negative in his model.

Wylie, et al. (1997) studied the FD14 talc from the Smith et al. study in an in vitro system. It did not induce either cell proliferation. Talc samples not containing quartz were not cytotoxic where as 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, tuberulosis. 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:

	Pre-1945		1945-1965	
	mppcf	Qartz ($\mu g/m^3$)	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 the mine and mill, to result in the pneumoconioses cases described. Respirable quartz is a known human lung carcinogen, 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 GTC workers. This 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). 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 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) study in which the occupational history of workers dying of lung cancer was presented. 8 of 11 workers who died of lung cancer worked in the mine and 8/11 had worked in other than talc mines or quarries elsewhere. 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.

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 and 17 had been miners prior to working at GTC. Such work 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) 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 concerns expressed about prior studies focused on the lack of 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 dusts (other than talc) or radon being likely contributors to the risk.

Non-asbestiform Talc

Lung overload: Your Committee's concern with cancer risk from exposure to non-asbestiform talc rests in part on the finding of lung cancers in female rats exposed to greater than 18 mg/m^3 of platy talc in an NTP assay. This assessment would be strengthened with a more complete discussion of overload of alveolar macrophage clearance (lung clearance) that can contribute to both lung cancer risk in rats and lung inflammation as seen in this study.

When there is overload by inert particles of lung clearance, irreversible inflammation and even an increased cancer risk occurs. This has been documented in rat exposure studies involving carbon black, diesel soot, titanium dioxide, toner and PVC spheres (Oberdorster, 1995a). Such effects occur when particle deposition is such that AM can no longer keep the particle lung burden constant at a given dose. With sufficiently high exposures, lung clearance inhibition, and associated lung inflammation, is irreversible, even after exposure ceases (Bellman, et al, 1992). Inhibition of lung clearance and associated inflammation results in DNA and sister chromatid changes in lung epithelial cells.

Although your Report discounts lung clearance as a mechanism for the finding of lung cancer in female rats in the NTP study, this overlooks the strong likelihood that lung overload was involved in the noted outcome. Oberdorster (1995b) found that lung clearance was markedly inhibited in both rats and mice in this study. Based upon the expected particle retention half life, talc lung burden in rats was increased by a factor of 5-6.5 fold and in mice by a factor of 9.4 to 21.6 fold at 24 months. Bronchiolar lavage studies done by NTP at this time confirmed the level of inflammation was what would be expected from the effects of lung clearance overload, not a specific toxic effect such as seen with respirable quartz. Goodman (1995) a member of the Scientific Board of Counselors evaluating this chronic talc inhalation study concurred with Oberdorster that the maximum tolerated dose for this study was exceeded. He noted that platy talc was not genotoxic (Endo-Capron et al., 1990) and that the chronic toxicity and inflammation in female rats was substantially higher than in males (or mice) where no tumors were noted.

Animal studies: The NTP talc study is not supported by other studies of the carcinogenic potential of talc in experimental systems. Stenback et al (1978) injected USP platy talc into the treachea of hamsters and found no respiratory tract tumors. Lesions seen were similar to those seen with treatment with iron dust. Endo-Capron, et al. (1990) injected fiber-free talc into the pleural space of 52 Sprague-Dawley rats. No pleural tumors occurred during their life span. Asbestos served as a positive control. Stanton, et al. (1981) examined the carcinogenicity of 7 talcs in their rat intrapleural assay. None of these talcs caused a higher frequency of tumors than seen in the study's control population. 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.

Epidemiological studies: Your report discounts the follow up study of patients treated intrapleurally with talc (Research Committee of the British Thoracic Association and the Medical Research Council Pneumoconiosis Unit, 1979) because the talc was not identified and follow up intervals were less than 15 years. 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. Selvan, et al. (1979) found that the relative risk of lung cancer among millers exposed to platy talc was 1.0 but elevated in miners. They discounted this association because miners can be exposed to radon daughters. Wergeland, et al. (1990) also found that cancer risk among talc millers working with fiber-free talc was not elevated.

They also explained a slight increase in lung cancer risk among miners as likely secondary to radon daughter exposure. Radon daughter exposure level in the studied mine was 10 fold higher than in the talc mine in the Selvan, et al. study.

In summary, your assessment of cancer risk of asbestiform cancer can be strengthened by:

- Addressing issues of risk associated with fiber size. 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) this relationship is particularly important for assessing the exposure-effect relationships in the cohort studies on which your Committee bases there cancer risk concern.

- Including information on talc source in your description of animal studies with talc. A number of studies have been made of the GTD 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.

- Including in your assessment a review of epidemiological studies of lung cancer risk associated with exposure to nonasbestiform fibers. This is particularly cogent since the major fiber burden in GTD talcs is from such fibers.

- Including a discussion of exposure-effect relationships in your epidemiological assessment of asbestiform cancer risk. This is particularly pertinent since there is major confounding in the worker segment with lung cancer from smoking and exposures to non-talc dusts (respirable quartz) which have been associated with human lung cancer risk. A detailed assessment of exposure has not found a relationship between asbestiform talc exposure and increased lung cancer risk.

- Including in your assessment a more detailed discussion of confounding by lung overload in the NTP talc inhalation study. Lung overload with inert particles is associated with lung inflammation and cancer risk. Significant lung overload occurred in both rats and mice in this study associated with both inflammation and lung cancer at the highest exposure level. That the cancer risk was likely associated with lung overload-related mechanisms needs to be addressed.

- Comparing the potency of talc to asbestos in animal models. An updated assessment of the Stanton, et al. study of talcs in their rat model found that abestos was 135000 fold more potent that talc. Although asbestiform talc contains fibers, these do not appear to behave like asbestos. Similarly this animal model does not provide biological support for the NTP study findings.

- Addressing the similarities between human talc pleurodesis and the rodent pleural implantation model. The finding of no tumor risk in long term follow up of patients treated with pleurodesis lends support to the negative findings with talc implantation in the animal model.

Respectfully submitted,

Woodhall Stopford, MD, MSPH

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