Written Comment on 10th ROC Nomination on
Talc Containing Asbestiform Fibers

For the
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Submitted by
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SUMMARY

NTP has determined that talc containing asbestiform fibers is known (RGI Review) or reasonably anticipated (RG2) to be a human carcinogen. This determination is based on (moderate) increases in lung cancer and mesothelioma mortality among talc miners and millers. The epidemiology studies cited to support these determinations are (Kleinfeld et al, 1974; Brown et al, 1979; Dement et al, 1980; Lamm et al, 1988).

Such a determination is **not** supported by the weight of evidence, and NTP has not presented a scientifically credible argument to support this classification. For example, the studies cited by NTP have been superseded by more relevant studies with more cases, longer follow-up, analyses by exposure and adjustments for confounding (Brown et al, 1990; Gamble, 1993; Delzell et al, 1995). Two of these studies were not even cited in the documentation. The rationale for opposing the NTP classification is based, in part, on the following arguments.

1.) NTP should provide a functional definition of asbestiform fibers, and clearly demonstrate that Vanderbilt talc (and NY talc as in the study by Kleinfeld et al, 1974) contains asbestiform fibers.

NTP does not provide an accurate description of the mineralogy of Vanderbilt talc in terms of cleavage fragments, asbestiform fibers, talc fibers, and asbestos. The undemonstrated presumption that Vanderbilt talc is the same as asbestos results in an expectation bias (similar to diagnostic bias) that colors (biases) the interpretation of the evidence.

2.) NTP should clearly indicate how the evidence meets the standards for assuming there is a causal association between increased risk of lung cancer and exposure to Vanderbilt talc.

The observed increases in lung cancer from mortality studies of Vanderbilt workers could be due to confounding and chance, the weight of the evidence is not consistent with a causal association, and the classification of Vanderbilt talc as a carcinogen is not supported by the data.

a) There is no gradient for the risk of lung cancer to increase with increasing years worked or increased exposure to Vanderbilt talc. This is strong evidence against a causal association.

Risk ratios with increasing exposure to Vanderbilt Talc (internal comparisons)

Cumulative Exposure	0-62 mg/m3-years	63-325 mg/m3-yrs	326-1704 mg/m3-y	1705+
Delzell et al (1995)	1.00 (referent)	0.74 (0.27-2.1)	0.68 (0.24-1.9)	0.45 (0.17-1.2)
Tenure	< 5 yrs tenure	5-15 years tenure	15-36 years tenure	
Gamble (1993) (smokers compared to smokers)	1.00 (referent)	0.50 (0.05-4.98)	1.00 (0.28-3.59)	

b) Weak associations in high exposure groups with > 20 years latency detracts from a causal association, as the risk could be due to confounding (e.g. smoking) and chance.

SMRs of Vanderbilt workers with 20 or more years latency and long tenure

Brown et al (1990)	20-36 years exposure	1.82 (0.21-6.36)
Delzell et al (1995)	5 or more years exposure	2.15 (0.86-4.42)

Strong associations in short-term workers with 20 years latency are consistent with confounding exposures. Short-term Vanderbilt workers should be at least risk if talc is a carcinogen. These associations are unlikely to be due to chance and are not coherent with a causal association.

SMRs of Vanderbilt workers with 20 or more years latency and short tenure

Brown et al (1990)	1 year or less exposure	3.64 (1.54-7.04)
Delzell et al (1995)	Less than 5 years exposure	3.71 (2.23-5.80)

c) The temporal relationships of lung cancer and exposure are more coherent with a smoking etiology than a talc exposure etiology. The latency from beginning smoking to lung cancer death is similar to that found in populations of smokers. The latency from hire date to lung cancer death is shorter than the latency for highly exposed asbestos workers, and is therefore biologically implausible.

Latencies for lung cancer attributable to smoking and asbestos compared to latencies for smoking and talc exposure for Vanderbilt lung cancer cases.

	Latency since beginning smoking		Latency for Exposures at Work	
	Liddell (1980); Wynder (1977)	Vanderbilt workers Gamble (1993)	Hi levels Asbestos: Selikoff, Dement	Vanderbilt Talc Gamble (1993)
Years latency	About 40 years	40 years	28-34 years	25 years

Does the weight of the evidence from studies of Vanderbilt workers support or detract from the hypothesis that there is a causal association between talc exposure and risk of lung cancer, and that Vanderbilt talc should be considered a carcinogen?

The evidence detracts from the hypothesis of a causal association:

+ There is no exposure-response trend.
+ The association in high exposed workers with adequate latency is weak, is not statistically significant and could be due in part or in whole to cigarette smoking.
+ The association is strong and statistically significant only in short-term workers with minimal exposure but long latency and there is evidence against very high exposures in their short employment.
+ The temporal relationships are coherent with a smoking etiology, and inconsistent with a talc exposure etiology.

INTRODUCTION

NTP has determined that talc containing asbestiform fibers is known (RGI Review) or reasonably anticipated (RG2) to be a human carcinogen. This determination is based on (moderate) increases in lung cancer and mesothelioma mortality among talc miners and millers. The studies cited to support these determinations are (Kleinfeld et al, 1974; Brown et al, 1979; Dement et al, 1980; Lamm et al, 1988).

Unfortunately, NTP does not provide the rationale that these increases in mortality constitute causal associations. The 1964 Surgeon Generals Report on smoking and lung cancer provides an early example on how a science-based determination of causality should be conducted. Such an approach is a generally accepted requirement in epidemiology in making determinations of the carcinogenicity of any substance.

The evidence cited by NTP is incomplete as appropriate studies are not part of the documentation, similar studies are inappropriately counted more than once, and the standards for determining causality are not supported by the evidence. Thus, the basis for their conclusion is of necessity hidden in speculation. I will outline causal criteria and suggest the weight of the epidemiologic evidence does not satisfy these criteria, and the evidence does not support the conclusion of NTP.

ASBESTIFORM TALC: What is it? What is the evidence that Vanderbilt talc contains asbestiform fibers? What is the evidence that asbestiform talc is a surrogate for asbestos? (Vanderbilt talc is the term used to describe the talc at issue since all the epidemiology studies are of Vanderbilt workers with the exception of Kleinfeld et al (1974).

The case has not been made that Vanderbilt talc contains asbestiform fibers.

A primary issue in the carcinogenic classification of asbestiform talc is a correct definition and characterization of the product being labeled. The product "talc containing asbestiform fibers" must be correctly described and the evidence presented making the case that Vanderbilt talc actually contains "asbestiform fibers" in sufficient quantities to be so characterized. If experimental evidence of asbestos studies is included to assess biological plausibility, then it is essential that all the evidence for and against the similarity of asbestos and Vanderbilt talc be presented.

An adequate description of Vanderbilt talc has not been provided sufficient to demonstrate that it is a "surrogate of asbestos." There is little to no discussion of particle dimensions, aspect ratios, regulatory versus mineralogical definitions, asbestiform versus nonasbestiform habits of minerals. NTP uses the descriptions of Vanderbilt talc found in Dement and Zumwalde (1979), but does not cite more complete descriptions that are inconsistent with those used by NTP. For example, Campbell et al (1979) visually show the differences between nonasbestiform tremolite (called blocky, acicular and fibrous tremolite) compared to tremolite asbestos. Approximately 50 percent of particles in fibrous tremolite were regulatory fibers (length 5 um or more, diameter 3 um or less, aspect ratio 3:1 or greater), but there were no particles with the very high aspect ratios (> 50:1) and small diameter characteristics of tremolite asbestos. The long, thin, durable fibers characteristic of tremolite asbestos that range upward to several hundred um or longer in length and diameters ranging down to 0.1-0.2 um in diameter were not observed in the samples of nonasbestiform tremolite. About 35% of regulatory fibers in tremolite asbestos have aspect ratios greater than 20:1, and about 60% greater than 10:1. Fibrous nonasbestiform tremolite had less than 1% (1 fiber out of 200) with an aspect ratio > 20:1 and 6% greater than 10:1. Unfortunately the description of Vanderbilt talc cited by NTP (Dement and Zumwalde, 1979) does not provide the distribution of fibers by aspect ratio. Kelse and Thompson (1989) demonstrated that the amphibole particles found in Vanderbilt talc do not show the characteristic long thin fibers of tremolite asbestos, and so by this criteria would not be classified as talc containing asbestiform fibers.

To incorrectly label a product as asbestos (or a surrogate of asbestos) can result in an expectation bias in the interpretation of study results. Expectation bias is analogous to diagnostic suspicion bias, where knowledge (or in this case incorrect knowledge) of occupation or exposure may influence the diagnosis and /or the search for a putative cause (Sackett, 1979; Gamble, 2000).

EPIDEMIOLOGY STUDIES OF NEW YORK TALC WORKERS:

Whatever the true nature of the talc, the correct classification ultimately rests on studies of exposed workers. To classify Vanderbilt talc as a carcinogen it must be shown that worker exposure to Vanderbilt talc increases the risk of lung cancer. The weight of evidence should support a causal association (e.g. be consistent with causal criteria including biological gradient, temporal relationships, moderate to strong association). If there is an association it should not be due to chance, bias and confounding exposures.

I will briefly discuss the epidemiology evidence regarding risk of lung cancer among workers exposed to NY and Vanderbilt talc.

The talc that NTP identifies as containing asbestiform fibers is NY state talc. The most relevant studies identified by NTP are SMR and case-control studies of Vanderbilt talc workers. There are five cohort mortality studies of Vanderbilt workers and one lung cancer case control study. Two of these studies (Brown et al, 1990; Delzell et al, 1995) are not cited by NTP. Kleinfeld et al (1974) is an early PMR (proportionate mortality ratio) study of NY state miners and millers. The characteristics and some results from these studies are summarized in Table 1.

Table 1: Summary of 6 cohort studies and 1 case control study of Vanderbilt workers

Reference	Inclusion Criteria	Follow-up	Lung Cancer Obs: RR	Lung Cancer: > 20 yr. Latency ≤ 1 yr. tenure	>1 yr. Tenure
Kleinfeld et al (1974)	260 miners/millers >15 yrs 1940-1969	1940-1969	13/6.08= 2.14 (1.14-3.66) PMR	-----	-------
Brown (1980); Dement (1979)	Worked 1/1/47-12/31/59; N=398	1947-6/30/75	9/3.3 = 2.73 (1.25-5.18)	N=5 Not analyzed by tenure	
Stille & Tabershaw (1982)	1947-12/31/77; N = 655 (Stille);	1947-12/31/78	10/6.37 =1.57 (0.75-2.89)	Not stratified by latency	
Lamm et al (1988)	N= 705 (Lamm)		12/5 = 2.40 (1.24-4.19)	6/0.89 = 6.74 (2.47-14.7)	2/1.48 = 1.35 (0.16-4.88)
Brown et al (1990)	Worked 1947-12/31/77; N=710	1947-12/31/83	17/8.21 =2.07 (1.21-3.31)	8/2.20 = 3.64 (1.54-7.04)	5/2.79 = 1.79 (0.58-4.16)
Gamble(1993): case control	N=22 cases		22cases/66 controls	10/23 = 1.00	8/30 = 0.61 (0.21-1.80)
Delzell et al (1995)	White males 1948-1989; N = 818	1948-1989	31/12 = 2.54 (1.73-3.61)	Latency not considered 17/4.8 =3.52 (2.05-5.64)	14/7.4 = 1.90 1.04-3.19)

Kleinfeld et al (1974) is a proportional mortality study of 260 miners with 15 or more years exposure. There were 108 total deaths, with 13 lung and pleural cancer observed deaths. There is confusion about the actual PMR for lung and pleural cancer. Kleinfeld et al (1974) indicated 12% observed and 3.7% expected, "approximately 4 times that expected." The ratio of these numbers is 3.24, which IARC (1987) more

correctly characterizes as a "three-fold overall increase" with one "peritoneal mesothelioma." Recalculating from Table 2 of Kleinfeld et al (1974) yields 13 observed cases and 4.48 expected cases, for a PMR of 2.91 (Table 2).

Table 2. Recalculation of PMRs for Carcinomas of the Respiratory Tract stratified by age from Table 2 of Kleinfeld et al (1974)

Age Group	Total Deaths	Observed: % obs	Expected* : % exp	PMR (95% CI)*
< 40	3	0 : 0%	0.05: 1.6%	0
40-59	47	4: 8.5%	2.44: 5.7%	1.64 (0.45-4.20)
60-79	54	9: 16.6%	1.94: 3.6%	4.64 (2.12-8.81)
80-84	4	0: 0%	0.044: 1.1%	0
Total	108	13: 12%	4.47: 4.83%	2.91 (1.55-4.97)

* = Calculated values.

Calculation of the PMRs from Table 4 of Kleinfeld (1974) yields 13 observed cases and 6.08 expected, for a PMR of 2.14. These expected proportions of respiratory cancer increased monotonically from 2% in 1940-4 to 7.7% in 1965-9. The expected numbers are based on the median of each of the 5-year periods rather than the 1955 rates in Table 2. The PMRs using expected numbers from the midpoint of the 5-year intervals are the most precise, so the most valid PMR for these workers with 15 or more years exposure is 2.14 (1.14-3.66). (See Table 3 for calculations.)

Table 3. Recalculations of PMRs for cancers of the lung and pleura stratified by calendar time from Table 4 of Kleinfeld et al (1974).

Calendar time	Total Deaths *	Observed: % obs	Expected*: % exp	PMR (95% CI)*
1940-44	7	0: 0%	0.14: 2.0%	0
1945-49	17	2: 11.7%	0.53: 3.1%	3.77 (0.46-13.6)
1950-54	8	1: 12.5%	0.34: 4.3%	2.94 (0.07-16.4)
1955-59	25	5: 20.0%	1.42: 5.7%	3.52 (1.14-8.30)
1960-64	28	3: 10.7%	1.88: 6.7%	1.60 (0.33-4.66)
1965-69	23	2: 8.7%	1.77: 7.7%	1.13 0.14-4.10)
Total	108	13: 12.0%	6.08: 5.6%	2.14 (1.14-3.66)

* = Calculated values.

IARC (1987) noted that no data were available on smoking or on cumulative exposure. Kleinfeld et al (1974) also comment that without smoking data it is not possible to account for the role of smoking "in accounting for the differences in the occurrences of malignancies" with asbestos insulators and anthophyllite asbestos miners.

Vanderbilt Talc Studies.

The remainder of the studies are of Vanderbilt workers. A few of the workers from Kleinfeld et al, (1974) are included in these cohorts.

Dement et al (1979) and Brown et al, (1980) are the same study, with analysis only by latency. Stille and Tabershaw (1982) and Lamm et al (1988) are the same cohort of Vanderbilt workers. Lamm et al (1988) got information on missing dates of birth to increase cohort size from 655 to 705 white males. Both studies analyzed only by $\pm$ 1-year tenure, but Lamm re-analyzed by latency and tenure for the OSHA hearings. Brown

et al (1990) is the same cohort as Lamm et al (1988) but with an additional 5 years of follow-up with analysis by both latency and tenure. Gamble (1993) is a case control study nested in the cohort of Brown et al (1990) with consideration of other occupational exposures and smoking. Delzell et al (1995) is the same cohort as Lamm et al (1988) but employees hired through 1989, adding 108 more men to the cohort with follow-up through 1989.

The most relevant studies of Vanderbilt workers are Gamble (1993) because of adjustments for latency, smoking and other exposures, and Delzell et al (1995) because of largest number of cases and quantitative estimates of exposure. These are the most important studies and should form the epidemiological basis for a carcinogenic classification of Vanderbilt talc. The reasons for this conclusion are as follows:

* The references to Brown et al (1979) and Dement et al (1980) are the same study published in two different places. This first NIOSH study has no analysis by exposure or tenure, no adjustments for potential confounding from other exposures and smoking, and the number of lung cancer cases is very small (n=9).

* The studies by Stille and Tabershaw (1982) and Lamm et al (1988) are of a larger cohort of Vanderbilt workers at the same plant. The study of Stille and Tabershaw (1982) is subject to selection bias. Lamm et al (1988) analyze by tenure but not latency with some consideration of other exposures. An unpublished version includes an analysis by latency and tenure. The number of lung cancer cases is increased but still small.

* Brown et al (1990) added 5 more years follow-up to the cohort of Lamm et al (1988), analyzed by both latency and tenure, and had 17 lung cancer cases. There is no adjustment for potential confounders. This study was not cited by NTP, but should supersede the previous cohort analyses of Vanderbilt workers. .

* Gamble (1993) is a case control study nested within Brown et al (1990). The number of lung cancer cases was increased to 22, and there was adjustment for potential confounding exposures for smoking, other talc exposures, and occupational exposure to carcinogens. Analysis was by latency and tenure and by smoking status.

. * Delzell et al (1995) increased the size of the cohort to 818 white men, 31 lung cancer deaths, and added individual-level estimates of dust exposure for a latency by exposure-response analysis. This study should supersede all the other cohort studies. It is the largest study of Vanderbilt workers with longest follow-up, analyses by latency and exposure with exposure variables of both tenure and cumulative dust exposure (in mg/m3-years).

EVALUATING WHETHER THERE IS A CAUSE-EFFECT ASSOCIATION.

IARC has suggested three criteria useful for assessing causality. To determine whether there is a causal association it "is necessary to take into account the possible roles of bias, confounding and chance in the interpretation of epidemiological studies." (IARC, 1997) These criteria will be discussed with regard to individual studies.

Then criteria of temporality, biological gradient, and strength of association that are useful for assessing causality will be discussed.

Following the discussion of causal criteria I will return to the question of whether confounding is a reasonable explanation for the elevated risks of lung cancer.

STUDY CRITERIA: What are the Primary Human Studies to Determine Whether Asbestiform Talc is Carcinogenic? The criteria that must be taken into account in evaluating both individual studies and the weight of evidence with regard to the causal criteria of strength of association and biological gradient are bias, confounding and chance.

* The presence of identifiable or apparent bias may lead erroneously to an association that in fact does not exist. Selection bias is possible in Stille and Tabershaw (1982) due to exclusion of 12.5% of the cohort because of missing data. Causes of death are not independent in a proportional mortality (PMR) study, as a deficit (or excess) in one cause will result in an excess (or deficit) in another. Kleinfeld (1974) is the only PMR study of NY talc workers under consideration.

* The presence of substantial confounding may also produce an erroneous association. Several potential confounding exposures have been suggested to explain the elevated risk of lung cancer in the cohort studies. These potential confounders include smoking, other talc exposures and other occupational exposures (and are discussed further below). Lamm et al (1988) considered other talc exposures posed a significant risk, but the data were from personnel records and may be incomplete. They had no data on smoking or other occupational exposures. Gamble (1993) found that smoking was a significant confounder that appeared to explain the elevated risks of lung cancer in the cohort studies. Other occupational exposures (both talc and non-talc) did not increase the risk of lung cancer in the case control study, and so therefore are not considered to be confounders. Delzell et al (1995) conducted internal exposure-response analyzes which reduced potential confounding effects due to smoking. None of the other studies had data or analyzes to adjust for confounding.

* Could the results be due to chance? All studies considered statistical significance. None of the studies showed statistically significant excess risk of lung cancer among workers with 20 or more years latency and 1 or more years tenure. Thus among the high exposure (high risk) group the elevated risk ratios could be due to chance.

IARC considers lack of clarity in any of these aspects of a study to "decrease its credibility and the weight given to it in the final evaluation." The greatest clarity on these issues comes from the case-control study (Gamble, 1993) and the largest cohort study (Delzell et al, 1995). These are the studies that should be given greatest weight in assessing whether the weight of evidence is consistent with a causal association.

CAUSAL CRITERIA: The question being addressed in this section is under "what circumstances can we pass from this observed association to a verdict of causation?" (Hill, 1965) Temporality can exclude a causal association if the putative cause does not come before the effect. Otherwise, none of the causal criteria "can bring indisputable evidence for or against the cause-and-effect hypothesis." (Hill, 1965). Further discussion of the causal criteria are found in Hill (1965), 1964 Surgeon General Report on Cancer

and Smoking, Rothman and Greenland (1998), Susser (1973) and IARC among many others. The more of these criteria that are satisfied the greater the weight of evidenced that observed associations are likely to be causal.

The causal criteria of temporality, biological gradient (or exposure-response trends), and strength of association are discussed. The causal criteria of consistency and biological plausibility will not be discussed. Since only Vanderbilt talc is described as containing asbestiform fibers, there is essentially only one cohort of exposed workers (albeit several studies). Although it is important, biological plausibility will not be discussed in this submission. Plausibility refers to the biological plausibility of the hypothesis, which is often based on the experimental animal data and *in vitro* experiments, and is a major part of the NTP documentation. For the weight of evidence to support plausibility, two requirements must be satisfied. One, a clear case must be made that Vanderbilt is morphologically like the asbestos in the studies used to support plausibility. That has not yet been done. Second, all the *in vitro* and *in vivo* studies of Vanderbilt talc must be included as part of the evidence. This also has not been done. Until this evidence is included in the case being made, there is no scientific justification for concluding that the criterion of biological plausibility has been satisfied.

As shown below, the weight of the evidence does not support the causal criteria, so the epidemiology studies DETRACT from the hypothesis that Vanderbilt talc is carcinogenic.

+ Temporality criterion. The exposure must precede the effect. For lung cancer the exposure should precede the diagnosis of lung cancer by 20 or more years (Brown and Dement, 1982). If the latency is less than 20 years or so, then it is unlikely that the exposure caused the disease. By this criterion there are 6 lung cancer cases in Brown et al (1980), 13 in Brown et al (1990), 18 in Gamble et al (1993) and 26 in Delzell et al (1995) where the lung cancer might be caused by Vanderbilt talc exposure.

Table 4. Lung cancer cases with 20 or more years of latency.

	Kleinfeld et al (1974) > 15 yr	Brown et al (1980)	Brown et al (1990)	Gamble (1993)	Delzell et al (1995)
Cases > 20 yrs latency	13/6.08 = 2.14 (1.14-3.66)	6 /1.3 =4.62 (1.69-10.1)	13/2.83= 2.60 (1.37-4.4)	18 smokers + exsmokers	26/8.4 = 3.09 (2.02-4.54)

The temporality criterion is discussed below with regard to whether the time since starting smoking or the time since talc exposure began is more coherent with our knowledge of the natural history of lung cancer.

+ Biological Gradient criterion. A strong indication of causality is when the risk of disease increases with the amount of exposure. Tenure and cumulative exposure to dust (mg/m3-years) are the measures of exposure. A strong indicator of causality occurs if the risk of lung cancer increases as tenure/cumulative dust increases. **The lack of biological gradients in the studies of talc workers detracts from the hypothesis that Vanderbilt talc is carcinogenic.**

Table 5. Exposure-response relationships for lung cancer (20 or more years latency except for cumulative exposure (Delzell et al, 1995)

	Lamm and Starr	Brown et al (1990)	Gamble (1993)	Delzell et al (1995)
> 20 years latency	(8) 3.38 (1.45-6.65)	(13) 2.60 (1.37-4.41)	Smokers + exsmokers	(26) 3.09 (2.02-4.54)

> 1 year tenure < 1 year tenure	(2) 1.35 (0.16-4.88) (6) 6.74 (2.47-14.7)	(5) 1.79 (0.58-4.16) (8) 3.64 (1.54-7.04)	8/21 0.65 (0.21-2.0) 10/17 1.0	
15-36 yrs tenure 5-15 yrs tenure < 5 yrs tenure			**5/10 1.00(0.28-3.59)** **0.50(0.05-4.98)** **12/24 1.0**	(7) 2.15 (0.86-4.42) (19) 3.71 (2.23-5.8)
1705+ mg/m3-yrs 326-1704 63-325 0-62 mg/m3-yrs				**(7) 0.45(0.17-1.2)** **(6) 0.68 (0.24-1.9)** **(6) 0.74 (0.27-2.1)** **(10) 1.0**

All of the studies showed that more than a majority of the lung cancer cases had short (< 1 year) employment histories, and the short-term workers had higher risks than the longer-term workers. The risk of lung cancer among longer- term workers was not statistically significant, although the number of cases was small. The case control study showed an inverse relationship with tenure in an internal comparison comparing smokers + exsmokers with smoker + ex-smoker controls. Delzell et al (1994) showed an inverse relationship with dust exposure in an internal comparison (with 3 cases having < 20 years latency). These studies suggest there is an inverse biological gradient, a strong indication against causality.

Delzell et al (1995) also assessed risk of lung cancer by work area. Mill workers and mine workers had similar cumulative dust exposure, but the excess risk was concentrated in the miners with an SMR of 4.73 (2.80-7.47) and unexposed workers with an SMR of 4.33 (0.87-12.64). Mill workers had an elevated SMR of 1.50 (0.60-3.09 that is consistent with random variability.

These comparisons by work area and the inverse relationships with exposure indicate Vanderbilt dust *per se* is not producing the excess risk of lung cancer, and is strong evidence against the hypothesis that Vanderbilt talc is a carcinogen.

Brown et al (1980) suggest that increasing risk with increasing latency is consistent with an occupational etiology. However, an analysis by latency alone includes workers that do not meet the temporality criterion and there is coincident latency from smoking. The question of smoking is discussed further below. The consistent lack of exposure-response trends clearly provides more clarity and weight than the analysis by latency alone. The internal exposure-response analyses also tend to reduce the potential for confounding because the comparison is between workers from the same cohort.

+ Strength of Association criterion. A large relative risk is more likely to indicate causality than a weak association is. A weak association is more susceptible to bias and confounding in producing an erroneous association. A weak association is generally considered to be less than about 2-fold.

The most appropriate category to assess strength of association is in the high exposure group with 20 or more years latency. In Brown et al (1990) the SMR is 1.82 (0.21-6.36) for lung cancer cases with 20-36 years tenure, and 1.79 (0.58-4.16) for cases with more than one year of tenure. The corresponding ORs is 1.00 (0.28-3.59) for smokers + exsmokers with 15-36 years tenure and 0.65 (0.21-2.0) for cases with 1 or more years tenure. Delzell et al (1995) in the group with 5 or more years tenure had a nonsignificant elevated SMR of 2.15 (0.86-4.42). The risk ratio in the cases with highest cumulative exposure was less than one, 0.45 (0.17-1.2) compared to cases with minimal cumulative dust exposure.

The strength of association in the highest exposed groups is generally weak in external comparisons and nonexistent in internal comparisons. The increased risk ratios could be due to random variability. These findings do not support the hypothesis that Vanderbilt talc is a carcinogen.

MORE ON QUESTION OF CONFOUNDING

Now that the relevant studies have been reviewed to assess temporality, biological gradient and strength of association, the important question of confounding will be addressed more directly.

The evidence is supportive that the increased risk of lung cancer in these studies can be explained in part or wholly as due to confounding from smoking. Other hypothetical risk factors do not appear to be important confounders.

Brown et al (1990) comment that the high risks of lung cancer are in part due to exposure to Vanderbilt talc, although cigarette smoking and other occupational exposures may also have contributed. They speculate that the high lung cancer mortality among short-term workers might be explained by:

1) Employment in other NY talc mines;

2) Exposure to lung carcinogens from employment prior to Vanderbilt and including other NY talc mines and mills;

3) Very high exposures in their short employment at Vanderbilt, especially in the early years of the mining operation;

4) Cigarette smoking.

Each of these issues were addressed in the case control study (Gamble, 1993).

1) Potential Confounding from Non-talc employment: A complete work history was obtained for each case and control. Non-talc jobs were ranked as "probable,' 'possible,' and 'none' for risk of lung cancer. **There was no trend for risk of lung cancer to increase with non-talc exposure,** so there was no apparent confounding from this variable and no adjustment for this variable was made in the analyses.

Table 6: Analysis of potential confounding from non-talc employment (Gamble, 1993)

Score: (panel score X years worked)	Cases	Controls	Odds Ratios (95% confidence intervals)
221-533	3	13	0.55 (0.12-2.46)
121-220	6	13	1.10 (0.31-3.91)
51-120	5	21	0.56 (0.16-2.03)
0-50 (Referent)	8	19	1.00

2) Potential Confounding from Other Talc (non-Vanderbilt) exposure: Non-Vanderbilt talc employment added little to Vanderbilt employment for either cases or controls: 1.1 year to 6.6 years for cases and 0.7 years to 9.2 years for controls. **There was no significant trend for the risk of lung cancer to increase as years of total talc employment increased among smokers + exsmokers with 20 or more years latency.**

However, smokers + exsmokers with more than 15 years total talc exposure had a nonsignificant elevated OR.

Table 7: Analysis of potential confounding from other talc exposures (Gamble, 1993)

Total Talc years: > 20 yrs latency	Cases: Smokers + Exsm	Control: Smoker + Exsm	Odds Ratios (95% CI)
15-41 years tenure	6	10	1.42 (0.41-4.87)
5-15 years tenure	1	4	0.59 (0.06-5.90)
<5 years tenure	11	26	1.0

Exposure at non-Vanderbilt mines appears to be considerably higher than in the Vanderbilt mine and mill. Dement and Zumwalde (1979) reported dust counts collected at Vanderbilt in the mid-1970s while Kleinfeld et al (1967) summarized dust counts in surrounding mines and mills from before 1945 to the 1970s. Mill concentrations in surrounding mills were 10-300 times higher than in the Vanderbilt mill, while mine concentrations were roughly similar except prior to 1945. Six (27%) of the cases had worked at surrounding mines and mills, mostly in the 1940s. Fourteen (21%) of the controls had worked in surrounding facilities in approximately the same time period, although three had worked in the late 1930s.

Concentrations in mppcf: range	Dement and Zumwalde (1979)	Kleinfeld et al (1974) Mines and Mills in Upper NY State around the Vanderbilt mine and mill		
	Late 1970s	1972(range of avg)	1946-65	Pre-1945
Mine	1.5-15.8 (1.0)	3-7 mppcf (0.6)	9-19 mppcf (1.6)	120-818 (54)
Mill	0.5-3.6 (1.0)	7-36 mppcf (10)	28-43 mppcf (17)	69-1227 (324)

The lack of a gradient with total talc tenure among smokers + exsmokers detracts from the hypothesis that talc exposure is associated with increasing risk of lung cancer.

3.) Very High Exposures for Short-term workers in Early Years of Work.

Gamble (1993) matched controls on date of hire. The match was quite good, as mean date of hire for both cases and controls was 1949. **Matching on date of hire indirectly accounts for intensity of exposure and increases the likelihood of similar exposures for cases and controls.** There is no evidence that cases were preferentially placed in very high exposure jobs; when workers were hired there was no way to predict who would be cases or controls, long-term or short-term workers. Assuming workers were hired more or less at random, then cases and controls have equal opportunity to be assigned high and low exposure jobs. **Thus there is evidence against the hypothetical explanation of high risk among short-term workers because of very high intense exposures.**

4) Confounding by Smoking.

The NIOSH investigators (Brown et al, 1980, 1990) have suggested smoking is an unlikely explanation for the elevated lung cancer risks. To address this question in the cohort studies one must determine what increased risk has to be explained. The overall SMR of 2.73 (1.25-5.18) in the first NIOSH study was said by Brown et al, (1980) to be

too high to be explained by smoking. In a heavy smoking population they estimate "smoking alone would increase the expected lung cancer mortality risk by no more than 49 percent," (a risk ratio of 1.49). Thus Brown et al (1980) suggest cigarette smoking *per se* is unlikely to account for the 2.73-fold increased risk of lung cancer among the 9 talc miners and millers." However, the actual SMR lies somewhere between 1.25 and 5.18. And when the actual smoking patterns of the cases and controls are used in an Axelson-type adjustment, smoking alone can explain about a two-fold risk. Since the hypothetical figure of 1.49 is above the lower confidence of 1.25, the idea that smoking could be a cause of the elevated risk cannot be excluded.

In the second NIOSH study the overall risk ratio for lung cancer was 2.07 (1.21-3.31) (Brown et al, 1990). Using an Axelson (1978) adjustment, Brown et al (1990) estimate that "even if 100% of the cohort were smokers, the risk for lung cancer would have been increased only by 60% or an SMR of 160." The actual value of the SMR lies somewhere between 1.21 and 3.31. The lower 95% confidence interval of the risk ratio falls well below the 1.60 suggested by Brown et al (1990). Thus smoking can explain at least some of the increased risks using the estimates proposed by the NIOSH authors.

Note that 91% of the cases were smokers and 9% were ex-smokers compared to 64% and 9% respectively for the controls (Gamble, 1993).

The risks associated with smoking are greater than the lower 95% confidence intervals of the overall risks of lung cancer. Therefore, smoking is a viable cause of at least some of the overall excess in the NIOSH studies, and random variability is also a possible explanation (Brown et al, 1980, 1990).

But these are not the most relevant risks that need to be explained, since some of the lung cancer cases have less than 20 years since first exposure to talc. Four of the lung cancer cases with less than 20 years talc latency have an average of 32 years latency (25-35 years) latency since starting smoking (from Gamble, 1993). For these cases, smoking is a more likely explanation than talc.

The more appropriate risk that needs to be explained is among the most exposed cases with 20 or more years latency. The SMR in the group with greater than 1 year tenure is 1.79 (0.58-4.16) (Brown et al, 1990). This risk could be due to random variability. An Axelson-type adjustment suggests the risks associated with smoking could be 1.29 (0.42-2.99) using actual smoking data. The SMR is 2.15 (0.86-4.42) in the high exposure category of Delzell et al, (1995) with about 1.55 (0.62-3.18) explainable by smoking. Random variation is a probable cause of the elevation.

Elevations in lung cancer risk among high exposure groups could be chance findings as they are not statistically significant. If there is a true risk, potentially all or a substantial portion of what might be an increased risk can be explained by smoking. These indirect adjustments for smoking suggest that smoking, as a causal agent cannot be excluded.

Gamble (1993) conducted a direct test of the smoking hypothesis. The smoking status of all cases and controls was determined. Since all cases were smokers or exsmokers, a comparison between cases and controls who were smokers and exsmokers was conducted. The odds of longer tenure were no greater among the cases than among the controls, a finding consistent with a smoking rather than an effect of exposure.

Another way to examine the role of smoking and exposure is to evaluate their respective latencies. The mean time from date of hire till death for chrysotile asbestos

miners and millers was about 40 years, regardless of smoking habits (Liddell, 1980). The mean years latency among asbestos workers with very high exposure and high risk of lung cancer is about 28-34 years (Selikoff et al, 1980; Knox et al, 1968; Dement et al, 1983). It is unlikely that asbestos workers exposed to true asbestos at high concentrations would have a longer latency than workers exposed to lower exposures of talc (with or without asbestiform fibers).

Mean time from beginning smoking till death from lung cancer was 40 years. Smokers have a latency of about 40 years (Liddell, 1980; Wynder and Stellman, 1977). Therefore, the criterion of temporality suggests smoking is a more plausible risk factor for lung cancer than exposure to talc for these workers.

Coincident Latencies: Temporal relationships are more suggestive of a smoking etiology than talc or asbestos etiology.

SUMMARY

The appropriate studies to assess risk of lung cancer among workers exposed to Vanderbilt talc is the last update of the Vanderbilt cohort which adds an exposure-response analysis with cumulative exposure (Delzell et al, 1996) and the lung cancer case control study nested within this cohort (Gamble, 1993) which adjusts for confounding. These studies have longer follow-up, more lung cancer cases, and an analysis by latency and tenure and cumulative exposure such that in the aggregate neither bias nor confounding compromise the validity of the studies. When elevated risks occur in high risk groups they may be the result of random variability.

These studies show that the only significant excess risk is among short-term workers and that there is an inverse exposure-response gradient using both external controls (e.g., Brown et al, 1990; Delzell et al, 1995) and internal controls (Gamble, 1993; Delzell et al, 1995). The associations are weak and not statistically significant, and smoking is a plausible explanation for the increased risk in the workers with longer exposure and adequate latency. Talc, as an etiological agent, is not coherent with the lung cancer latency shown in highly exposed asbestos workers. Smoking as an etiological agent is coherent with latency shown for smokers.

In sum, the weight of the evidence from these studies does not satisfy the criteria for a causal relationship between Vanderbilt talc exposure and risk of lung cancer. The associations are weak and elevated risks could be due to chance and confounding from smoking. There are consistent inverse exposure-response gradients where exposure variables are both tenure and cumulative talc dust. The temporality criterion is more consistent for a smoking etiology than for a talc etiology.

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