A Review of Talc Dust
Dose, Cancer of the Respiratory System and
The NTP Technical Report on the Toxicology
and Carcinogenesis Studies of Talc in
F344/N Rats and B6C3F Mice
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INTRODUCTION

It has been noted in several critiques of the talc NTP rodent inhalation study that the increased incidence of alveolar/bronchiolar adenoma, carcinoma and combined tumors observed in female rats was likely the result of particle overloading rather than talc carcinogenicity (see BEC critiques). Lapses in the study design such as the absence of positive and negative controls, biological observations such as the inflammatory process noted in all animals tested and the totality of health literature on talc, support this view. Researchers involved in the NTP study recognized these limitations and cautioned against the extrapolation of these animal data to man.

In recent years, scientists have come to better understand the effects of particle overloading on the pulmonary clearance system. Such effects are linked to proliferative or epigenetic cellular responses versus genotoxic cellular responses. Such epigenetic responses support the role of exposure level or dose as the key variable in the carcinogenic potential of many substances. Some researchers report that as many as 50% of all substances tested for carcinogenicity using massive dosages show some positive carcinogenic response - including substances found in most supermarket foods. Clearly, for most of these substances, there must be a "no effect" level.

Dose or exposure is therefore a key variable in determining real world cancer risk for many if not most substances. When clearance mechanisms are adversely effected no "downward" extrapolations can be made to risk at lower dosages where clearance systems are functional. The NTP inhalation study places talc in this dose dependent category. The question is, are typical talc exposures above or below this "no effect" cancer level!
DOSE COMPARISON

Contrary to NTP's assertion, there is considerable health data available on talc. It is true that these data vary widely in quality and cover a variety of health effects besides cancer of the pulmonary system. More often than not talc dust exposure information is incomplete in terms of both dust concentration levels and dust characterization. It is also problematic to compare one study with another given the numerous variables involved (i.e. rate and type of exposure, differences in biological systems, study durations, etc.).

Enough experimental data and human cohort studies have been conducted on talc, however, to provide reasonable insight into this dose/response issue. We do have exposure information on occupational groups exposed to talc and we do know the health experience of some of these groups (cohorts) relative to lung cancer and mesothelioma. Reasonable estimates of "worst case" dusting from consumer use of cosmetic talc are also available and this information may be compared to dosages employed in the NTP inhalation study as well as to occupational exposures and carcinogenic experience.

Section I outlines available dose information relative to animal and human talc dust inhalation exposures and to the occurrence of respiratory system cancer (or lack thereof). Dose information for these studies is reflected on Figures 1 and 2. For comparative purposes, dose data has been converted into 8 hr. Time Weighted Averages (TWA) for respirable dust expressed in milligrams of dust per cubic meter of air (mg/m³).

Section II contains an outline of additional respiratory system cancer studies involving talc. These studies include in-vivo testing and a discussion of controversial talc studies relative to lung cancer in man and animals. These studies are included to more fully address the issue of talc and cancer of the respiratory system. Other biologic systems and possible talc related risks are not addressed.
ANALYSIS

Available data suggests the level of respirable dust associated with the animal excess lung tumor observation is 7 times greater than the current occupational standard (2 mg/m$^3$), 13 times greater than average occupational exposures and 2,700 times greater than maximum consumer exposures (see Figure 1). Since no animal or human respiratory system cancer excess is recorded below this NTP dose, a cancer "no effect" level is indicated. This gross analysis further supports the position that the NTP carcinogenic results observed in female rats is more likely a dust overloading phenomena than a genotoxic effect.

This gross comparison does not take into account important biologic mediating factors such as: cumulative lung burden (i.e. a 700 fold multiplier for human lung burden versus rats is often applied), clearance rates (i.e. a 4 fold faster rate in rats is reported in the literature) and differences in deposition sites (likely related to differences in respiratory system architecture). Variances in dust exposure such as particle size are also not considered. There does appear to be differences of opinion as to whether such variables (particularly biologic) might narrow or expand differences in exposure impact between the rat and man.

Beyond these mediating factors, however, a dose dependent lung cancer effect is demonstrated in the NTP study itself (even at the elevated dosages employed). Coupled with the historical record and the likelihood that most talc aerosols contain particles as fine as those found in the NTP test talc, these variables do not appear significant enough to support an animal to man risk assessment utilizing the standard Armitage-Dole multistage linear model. Such an exercise using any model, in fact, would seem unnecessary.

CONCLUSION

Considering the weight and strength of evidence a risk to humans of respiratory cancer from talc exposure appears highly unlikely. In terms of consumer use of cosmetic grades, the risk appears nonexistent. Further, given the direct human and animal data available, a risk modeling exercise utilizing the NTP data appears unnecessary. Certainly application of the standard "no threshold" linear model typically applied in animal to man carcinogenic risk assessment is inappropriate.
SECTION I

CANCER OF THE RESPIRATORY TRACT
TALC DUST EXPOSURES REVIEW

Existing OSHA and ACGIH PEL and TLV for Talc Dust

2 mg/m³ Respirable Dust
8 hr. Time Weighted Average (TWA)

The term "respirable" has been more carefully defined in recent years as particles capable of deposition in the gas exchange region of the lung. Such particles exhibit a median aerodynamic diameter of 3.5 μm ± 0.3 μm. Historically the term has generally referred to those particles collected through a 10 mm nylon cyclone pre-filter operating at 1.7 liters per minute (Lpm) in a workplace setting. Depending on flow rate and a variety of other factors, the collection efficiency at which particles from 3.5 μm to 10 μm in diameter are collected (based upon a 50% cut size) can be quite variable. However, this respirable dust collection technique is said to reasonably duplicate human respiration. For the purpose of this comparison the term "respirable" shall therefore mean those particles typically collected through the 10 mm nylon cyclone at 1.7 Lpm.
CONSUMER COSMETIC TALC EXPOSURES
(Considered "Worst Case")

<table>
<thead>
<tr>
<th></th>
<th>Average Resp. Dur.</th>
<th>Single Exp. Duration</th>
<th>Daily Freq. of Activity</th>
<th>Equivalent Resp. Dust Mg/m³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dust Mg/m³</td>
<td>(Minutes)</td>
<td></td>
<td>8 hr. TWA Resp. Dust Mg/m³</td>
</tr>
<tr>
<td>Aylott, et al Ref. 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Adult Face Dusting</td>
<td>0.48</td>
<td>0.50</td>
<td>1</td>
<td>0.0005</td>
</tr>
<tr>
<td>Adult Body Dusting</td>
<td>1.13</td>
<td>1.00</td>
<td>1</td>
<td>0.0020</td>
</tr>
<tr>
<td>Baby Dusting</td>
<td>0.21</td>
<td>0.50</td>
<td>5</td>
<td>0.0010</td>
</tr>
<tr>
<td>(Most particles 2 to 5 µm size)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Russell, et al Ref. 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult Body Dusting</td>
<td>2.03</td>
<td>1.23</td>
<td>1</td>
<td>0.0050</td>
</tr>
<tr>
<td>Baby Dusting</td>
<td>0.19</td>
<td>0.52</td>
<td>5</td>
<td>0.0010</td>
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</table>
INDUSTRIAL TALC EXPOSURES AND LUNG CANCER

<table>
<thead>
<tr>
<th>References</th>
<th># Samples</th>
<th>Sample Range</th>
<th>Average 8 hr. TWA Resp. Dust Mg/m³</th>
<th>Lung Cancer</th>
<th>Obs./Exp.</th>
<th>Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Selevan Ref. #3 and Boundry Ref. #4 -</td>
<td>192</td>
<td>0.5-2.9</td>
<td>1.39</td>
<td></td>
<td>6/6.28</td>
<td>No</td>
</tr>
<tr>
<td>Vermont Talc Millers*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cosm grade - Trace SiO₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort #225, &gt;1 yr. worked, covers 1940 to 1969</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No mesothelioma linked to exposure.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Lamm Ref. #5 and NIOSH Ref. #6 -</td>
<td>36</td>
<td>0.16-2.9</td>
<td>0.90</td>
<td></td>
<td>1/1.4</td>
<td>No</td>
</tr>
<tr>
<td>NY Talc Millers*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremolitic talc - Trace SiO₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Approximately 50% amphibole, 30-40% talc</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort #250, &gt;1 yr. worked, covers 1948 to 1977</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No mesothelioma linked to exposure.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>• Wergeland Ref. #7</td>
<td>unknown</td>
<td>unknown</td>
<td>unknown</td>
<td></td>
<td>4/5.2</td>
<td>No</td>
</tr>
<tr>
<td>Norway Talc Millers*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cosmetic grade - Trace SiO₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort #295, &gt;2 yr. worked, covers 1935-1972</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No mesothelioma linked to exposure.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Rubino Ref. #8</td>
<td>unknown</td>
<td>unknown</td>
<td>unknown</td>
<td></td>
<td>9/19.7</td>
<td>No</td>
</tr>
<tr>
<td>Italian Talc Miners &amp; Millers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cosmetic grade - Trace SiO₂</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cohort #1514 miners, 478 millers, &gt;1 yr. worked, covers 1921-1950.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No mesothelioma linked to exposure.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Leophonte Ref. #9</td>
<td>unknown</td>
<td>unknown</td>
<td>unknown</td>
<td>compared to No</td>
<td></td>
<td></td>
</tr>
<tr>
<td>French Talc Miners and Millers</td>
<td></td>
<td></td>
<td></td>
<td>regional pop.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cosmetic Grade - Trace SiO₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort #470, &gt;1 yr. worked, those who left employment 1945 to 1981.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No mesothelioma linked to exposure.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Gamble Ref. #10</td>
<td>275</td>
<td>0.07-2.54</td>
<td>0.97 mills</td>
<td>Not reported</td>
<td></td>
<td></td>
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<tr>
<td>Montana, Texas, North Carolina Talc Mines and Mills</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Essentially Cosmetic talc - trace SiO₂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fine Ref. #11</td>
<td>48</td>
<td>0.59-3.55</td>
<td>1.0</td>
<td>Not reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Various Rubber Processing Plants</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Essentially Cosmetic talc - trace SiO₂</td>
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</tbody>
</table>

* When possible only talc miller experience was reflected although data for the whole mining cohort exists. Dust exposure is considered higher for millers than miners and better represents consumer talc exposure.
ANIMAL TALC INHALATION STUDIES
EXPOSURES AND LUNG CARCINOGENICITY

• Wagner 1977 Ref. #12

Dose - 10.8 mg/m³ - 7 hrs./day - 5 days/week, for 6 months and 12 months
8 hr. TWA Equivalent: 9.45 mg/m³

Talc Type - Cosmetic grade - mean particle size 25 µm - 92% talc 0.5-1% SiO₂
Test Group - 24 male and 24 female Wistar rats
Results - no lung carcinogenicity (1 nonmalignant tumor - 12 month group)

Critique - Limited number of animals allowed to survive >1 year.

• Wehner 1979 Ref. #13

Dose - 8.1 and 9.8 mg/m³ - 3, 30 or 150 min. day - 5 days/week, for 30 days & 300 days
8 hr. TWA Equivalent - Highest dose: 3.06 mg/m³

Talc Type - Cosmetic baby/body dusting powder - mean particle diameter 4.9 µm to 6µm
Test Group - 50 male and 50 female Syrian hamsters
Results - No lung carcinogenicity (any hamster, any dose)

Critique - Short survival time allowed ≤300 days.

• NTP 1986 Ref. #14

Dose - 6 or 18 mg/m³ - 6 hrs. day - 5 days/week, for 113-122 weeks rats 103-104 mice
8 hr. TWA Equivalent - 4.5 mg/m³ and 13.5 mg/m³ (6 & 18 respectively)

Talc Type - Fine Cosmetic grade - trace SiO₂, mean particle size 2.7 to 3.6 µm
Test Group 47 to 50 per group male and female rats and mice
Results - No lung carcinogenicity for male and female mice and male rats both dosages.
Significant lung tumors female rats at 18 mg/m³ only.

Critique - Dose variance for 7 weeks noted, both dose levels appear at particle overload levels (especially 18 mg/m³ dose).
8 HR. TWA RESPIRABLE TALC DUST COMPARISON AND RESPIRATORY TRACT CANCER

Confirmed Carcinogenic Response (lung)

- YES: Female Rats
- NO: All others

- NO
- NO
- NO

OSHA STD.
ACGIH

see Excerpt

Animal Inhalation
Industrial Exposures
Consumer Max. Exposure
0.005 Mg/m³
8 Hr. TWA

Figure 1
8 HR. TWA RESPIRABLE TALC DUST COMPARISON

INDUSTRIAL VS. CONSUMER

Excerpt

Figure 2
SECTION II

ANIMAL RESPIRATORY SYSTEM - IN VIVO TESTING

TALC CARCINOGENICITY

- **Stenback 1978 Ref. #15:**
  18 weekly **intratracheal** injections of 3 mg cosmetic talc (93.3% below 25 μm particle size) in groups of male and female Syrian golden hamsters. The animals were allowed to live out their life-span (50% survival, 46-55 weeks).

  **Results** - No respiratory tract tumor was observed in animals exposed to talc alone.

- **Bischoff 1976 Ref. #16:**
  Male Marsh mice and female Evans rats received single **intrathoracic** injections of 10 mg and 50 mg USP talc respectively and allowed to survive 18 to 21 months.

  **Results** - 5 of 47 treated mice had tumors compared to none of 48 saline-injected controls. No tumor excess above controls observed for rats. (Reported in abstract form only).

- **Wagner 1977 Ref. #17:**
  24 male and 24 females Wistar rats received single **intrapleural** injections of 20 mg of Italian cosmetic grade talc - mean particle size 25 μm. Test and control animals (saline injected) allowed to live out their lives.

  **Results** - No mesothelioma in any group, one small pulmonary adenoma in one animal who died 25 months after injection.

- **Stanton 1981 Ref. #18:**
  30-50 female Osborne-Medel rats per group received single **intrapleural** implantations of 40 mg of one of seven talcs (5 cosmetic grade, 2 New York tremolitic talc). Test and control animals allowed to live out their lives up to two years.

  **Results** - Cosmetic grade talcs showed no tumors above controls. Tremolitic talc, no tumors. Significant tumors were observed for asbestos samples similarly administered.

- **Smith 1979 Ref. #19:**
  Female and male Syrian hamsters received single **intrapleural** injections of 10 mg and 25 mg New York tremolitic talc (approx. 1/2 talc, 1/2 amphibole - trace SiO₂). Tremolite asbestos was similarly tested (note the tremolite and anthophyllite in New York talc is *nonasbestiform*). Test animals were allowed to live up to 600 days.

  **Results** - No tumors were observed at either dose for the tremolitic talc group. Tumors observed at both doses for the asbestos exposed group.
CONTROVERSIAL TALC STUDIES AND LUNG CANCER

There are four studies (two previously mentioned) which suggest a talc/lung cancer link. Each of these studies are controversial. Like all studies which suggest a carcinogenic association, these studies are often stressed or highlighted at the exclusion of "negative" studies. To put the issue of talc and respiratory tract cancer in perspective it is important to summarize these four studies and the controversy associated with each.

- N.Y. State Tremolitic Talc: 40-60% nonasbestiform tremolite, 30-50% talc, trace SiO₂.

Mortality studies of upstate New York tremolitic talc miners and millers has caused considerable confusion. Through a series of studies beginning in the 1950's by the New York State Department of Health and a mortality study in the mid-1970's by NIOSH, it was widely believed that excess lung cancers (2 to 4 fold excesses) were causally linked to the talc dust and that this talc dust contained asbestos (Ref. #20, 6). As a result of these studies fear arose that many other talcs might contain asbestos as well. Since these early studies, more rigorously conducted studies of these talc workers have found that the excess lung cancer is unlikely linked to dust exposure and that what was said to be "asbestos" was in fact not asbestos (Ref. #5, 21-28).

The reported link between this talc and cancer of the lung was placed in doubt when it was observed that typical dose/response associations were not observed in this mining population. Most cases worked less than one year (a large proportion only days and weeks) and in traditionally less dusty activities. In contrast, the incidence of pneumoconiosis (talcosis) did follow a typical dose/response scenario. When smoking was addressed through a case-control analysis there appeared a stronger association between smoking and lung cancer than between dust exposure and lung cancer (i.e. all cases smoked, other smoking related causes of death were elevated, latency for smoking fit best, etc.). There was also no consistency in cancer results as animal studies employing this same talc caused no tumors while asbestos, tested under the same conditions, did (Ref. #18, 19). Studies of other mining cohorts exposed to similar nonasbestiform amphiboles showed no elevated lung cancer as well (Ref. 29, 30).
In respect to the "asbestos" issue, mineral scientists have made it clear that it is incorrect to call the minerals found in this talc "asbestos". The "asbestos" upon which a vast body of health literature was developed is not the same as any mineral found in this talc. Detail on this aspect of the issue may be found elsewhere (Ref. #25-29).

The mineralogical errors involved in this case were important to correct because the nonasbestiform amphiboles most at issue are common rock and soil forming minerals. These minerals (unlike asbestos) are common throughout the earth's crust and are encountered in an abundance of mineral deposits of commercial importance (iron, copper, gold, talc, aggregates, etc.). Today, all U.S. federal regulatory agencies have clarified their asbestos standards to cover only asbestos as a result of this tremolitic talc issue (Ref. #31). Confusion in this area, however, is likely to persist.

- Thomas 1987 Ref.# 32:

This study involved a cohort mortality study of 2,055 men employed at least one year between 1939 and 1966 at three plants engaged in the manufacture of ceramic plumbing fixtures. Workers were exposed to cosmetic ("non-fibrous") grade talc in combination with silica dust and to a lessor degree (shorter time) some workers were exposed to an amphibole containing talc. Elevated lung cancer (2.5 fold excess) was noted for workers exposed to cosmetic grade talc and silica but lung cancer was not significant for those only exposed to amphibole containing talc ("fibrous"). There was some increase in lung cancer incidence with increasing tenure.

This study appears to be a reasonably conducted human cohort study which associates lung cancer to cosmetic talc exposure. However, significant confounding variables remain unaddressed. It is noted that excess lung cancer exists only among those exposed to "high levels of silica dust". Thus, we do not know if talc, silica or some other workplace exposure singularly or together is responsible for the excess. Further, there is no smoking histories, direct dust exposure data or work histories.

The association suggested between cosmetic grade talc and lung cancer in this study appears tenuous at best.
Katsnelson & Mokronosov 1979 Ref. #33:

This is an extremely sketchy mortality study conducted in the U.S.S.R. of cosmetic grade talc miners and millers. Extremely elevated lung cancer deaths were reported. However, data presentation and calculations reflect serious flaws (i.e. deaths included current and past workers but only currently employed workers were used as the denominator). There are no smoking histories, no clear or reasonable dust characterization or exposure data, no work histories, no dose/response analysis, etc.

In all, this study is generally considered too weak for serious consideration.

NTP 1986 Ref. #14:

This rodent inhalation study is referenced above and extensively critiqued by Biomedical and Environmental Consultants, Inc. Briefly, it is felt this study does not demonstrate respiratory tract carcinogenicity to female rats at the highest dose employed (18 mg/m³) for cosmetic grade talc but rather a particle overloading effect similar to that observed with other particulates of low toxicity. All reviewers, including the NTP contracted researchers, feel the lung tumor excess noted in female rats at the highest dose is not correlatable to human respiratory cancer risk.
References


