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A review of the mesotheliogenic potency of cleavage fragments found in talc

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Abstract

It has long been recognized that amphibole minerals, such as cleavage fragments of tremolite and anthophyllite, may exist in some talc deposits. We reviewed the current state of the science regarding the factors influencing mesotheliogenic potency of cleavage fragments, with emphasis on those that may co-occur in talc deposits, including dimensional and structural characteristics, animal toxicology, and the most well-studied cohort exposed to talc-associated cleavage fragments. Based on our review, multiple lines of scientific evidence demonstrate that inhaled cleavage fragments associated with talc do not pose a mesothelioma hazard.

Keywords

Mesothelioma, talc, non-asbestiform, amphibole minerals, cleavage fragments, tremolite

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Introduction

Talc is a hydrated silicate magnesium mineral that has been used extensively in a wide variety of industrial products, pharmaceuticals, and cosmetics (ACGIH 2010). It has long been recognized that amphibole minerals, such as tremolite and anthophyllite, may exist in some talc deposits. Early studies on the composition of both cosmetic and industrial talc did not determine the mineral habit of the talc-associated amphibole minerals (Cralley et al., 1968; Rohl et al., 1976; Snider et al., 1972). That is, the presence of asbestiform or non-asbestiform amphiboles was ambiguous. Other early studies claimed to have observed asbestos minerals in the asbestiform habit in talc when the analytical methods used were insufficient to make such a determination, or the determination was solely based on particle dimension, specifically meeting the regulatory definition of a "fiber" (≥5 µm in length with an aspect ratio ≥3:1) (NIOSH 1980; Rohl et al., 1976; Snider et al., 1972). This lack of detail on mineral habit or the use of inadequate analytical methodology has ultimately led to confusion and debate on the presence or absence of asbestiform minerals in talc (Cralley et al., 1968; Lamm et al., 1988; Price 2010; Rohl et al., 1976; Rohl and Langer 1979; Wergeland et al., 2017). Compounding the issue is the fact that non-asbestiform amphiboles may preferentially split along planes of structural weakness into smaller particles, termed "cleavage fragments," when they are finely ground or crushed (Campbell et al., 1979; Mossman 2008; NRC 1984). As a result, these cleavage fragments may be microscopically misidentified as asbestiform fibers because these particles can have dimensions that are consistent with regulatory fibers (ATS 1990; Campbell et al., 1977; OSHA 1992). Furthermore, there remains debate regarding the carcinogenicity or lack thereof of inhaled cleavage fragments (Goodman et al., 2023; Ilgren 2004; Militello et al., 2021; Steffen et al., 2018).

The objective of this review was to assemble and present, in a stepwise manner, the current state of the science regarding the potential mesotheliogenic

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potency of cleavage fragments, with emphasis on those from amphibole minerals that may co-occur in talc deposits, such as tremolite and anthophyllite. Given the commercial importance of talc and its frequent feature in public health discussion, this review will serve as a scientific resource for the various stakeholders engaged in risk assessment and risk management of talc.

Methods

Both length and width are well-recognized to influence the inhalation, deposition, and, in turn, carcinogenicity of asbestos fibers. Thus, by analogy, it follows that the exposure and risk science of inhaled cleavage fragments should be guided by these dimensional parameters. Given this, we first identified and summarized peer-reviewed, published literature discussing the impacts of fibers on mesotheliogenic potency. Next, we summarized the available information regarding the dimensions of cleavage fragments and compared these dimensions to those understood to be associated with mesothelioma risk. We then reviewed and summarized the findings of animal studies evaluating the toxicology of cleavage fragments. Lastly, as an illustrative example at the population-level, we summarized in chronological order the key epidemiologic findings regarding the health experience of the upstate New York industrial talc miners and millers, including those employed by the Gouverneur Talc Company, which are the most thoroughly studied populations known to have been exposed to talc-associated cleavage fragments.

Results

Overview of the general dimensions of cleavage fragments

Cleavage fragments are particles formed through the crushing or weathering of non-fibrous amphibole minerals (ATSDR 2001; Korchevskiy and Wylie 2022; Price 2010; Wylie 2016). The crushing mechanisms by which cleavage fragments are formed provide them with structure, size, and shape that are distinct from asbestiform fibers, which are formed through crystallization.

During cleavage, minerals typically "fracture along sets of systematic planes" (Van Orden et al., 2008), predominantly resulting in short particles that lack the fibrous structure of asbestos (Mossman 2008; Price 2010; Van Orden et al., 2008). Cleavage fragments can be "blocky" (Belluso et al., 2017) or "irregular" (Goodman et al., 2023) in shape and "may appear as thick, short fibers" (Mossman 2008) with asymmetrical ends and a "ragged or irregular" (Van Orden et al., 2008) surface appearance (Belluso et al., 2017; Gamble and Gibbs 2008; Goodman et al., 2023; Korchevskiy and Wylie 2022; Mossman 2008; Van Orden et al., 2008).

Because of their low tensile strength and brittle nature, cleavage fragments generally fracture "horizontally across their length rather than along it", resulting in short, thick particles, that may meet the regulatory dimensional definition of a fiber (lengths ≥5 µm and aspect ratios >3:1) (Ilgren 2004). Typically, cleavage fragments have diameters "much larger than those of asbestos fibers of the same length" (Gamble and Gibbs 2008) and are shorter than 10 µm in length (Gamble and Gibbs 2008; Goodman et al., 2023; Ilgren 2004; Mossman et al., 2007). Gamble and Gibbs (2008) reported that cleavage fragments "rarely" have diameters less than 0.25 µm, concluding that few if any cleavage fragments over 8 µm long have a diameter less than 0.25 µm. Cleavage fragments thinner than 0.3 µm and longer than 15 to 20 µm have been reported to be "very rare, if they exist at all", such that nearly all cleavage fragments longer than 5 µm have a width of at least 0.3 µm (Ilgren 2004).

In 2008, Addison and McConnell noted that, the increased thickness and relative short length of cleavage fragments tend to render lower and more narrowly distributed aspect ratios compared with asbestos fibers. Specifically, cleavage fragments have broader width distributions since the width of cleavage fragments increases along with length. Conversely, width is "largely independent of length" for asbestos fibers (Addison and McConnell 2008). In fact, for fibers of a given length, cleavage fragments "are roughly twice as thick as asbestos fibers" (Addison and McConnell 2008). Indeed, Gamble and Gibbs (2008) reported that few cleavage fragments have aspect ratios greater than 10:1 (Gamble and Gibbs 2008). In contrast, asbestiform amphibole fibers tend to be long and thin, which "generally" (Mossman 2008) renders aspect ratios of 20:1 or higher in fibers longer than 5 µm (Goodman et al., 2023; Mossman 2008).

The distinction between the physical characteristics of cleavage fragments and asbestos fibers was emphasized in 1992 when the United States Occupational Safety and Health Administration (OSHA) issued their final standard for regulating occupational exposure to

asbestos in general industry and in construction (OSHA 1992). In this rulemaking, OSHA stated that "the discussion indicates that populations of fibers and populations of cleavage fragments can be distinguished from one another when viewed as a whole. For example[,] one can look at the distribution of aspect ratios or even widths for a population of particles and can then generally identify that population of particles as being asbestiform or nonasbestiform" (OSHA 1992). Similarly, the United States Environmental Protection Agency (EPA) has outlined how a population of particles occurring in the asbestiform habit can be differentiated from their non-asbestiform analogs. That is, a population of asbestiform fibers have mean aspect ratios ranging from 20:1 to 100:1 or higher (for fibers >5 µm), are very thin, have widths generally less than 0.5 µm, and exhibit two or more of the following characteristics: parallel fibers occurring in bundles; fiber bundles displaying splayed ends; matted masses of individual fibers; and/or fibers showing curvature (EPA 1993).

Key differences in physical properties between cleavage fragments and asbestiform fibers have significant influence on the potential health risks posed by each agent and have been discussed in detail at two recent conferences on elongate mineral particles (EMPs) (Goodman et al., 2023; Weill 2018).

The influence of fiber dimensions on mesotheliogenic potency

It has long been understood that the dimensions of mineral fibers are key determinants of mesotheliogenic potency. Dating back to seminal experiments performed in the 1970s, the weight of the scientific evidence has overwhelmingly indicated that the risk of mesothelioma varies by fiber length (Barlow et al., 2017; Berman and Crump 2003; Bernstein et al., 2013; Lippmann 1988, 1994; Oehlert 1991; Platek et al., 1985; Stanton 1973; Stanton et al., 1977, 1981; Stettler et al., 1988; Wagner 1990; Wylie and Korchevskiy 2023). Numerous groups, including several sponsored by the U.S. federal government, have concluded that fibers <5 µm in length were unlikely to cause mesothelioma (Roggli and Brody 1984; Platek et al., 1985; Davis et al., 1986; Davis and Jones 1988; Berman et al., 1995; ATSDR 2002; ERG 2003a, b; Stettler et al., 2008; Roggli 2015; Barlow et al., 2017). Indeed, in 2002, the Agency for Toxic Substances and Disease Registry (ATSDR) convened an expert panel to discuss "health effects associated with asbestos… especially those of less than 5 microns in length" (ATSDR 2002). According to the expert panel report, based on their review of the available epidemiological studies, animal studies, in vitro studies, and the physiological fate of asbestos in the human body, it was concluded that "asbestos and [synthetic vitreous fibers] shorter than 5 µm are unlikely to cause cancer in humans" (ERG 2003a). In addition, a 2003 working group convened by the EPA concluded that, based on the available literature, "the optimum cutoff for increased potency occurs at a length that is closer to 20 µm than 10 µm" (Berman and Crump 2003). Based on modeling results, the panel concluded that the "risk for fibers less than 5 µm in length is very low and could be zero" (ERG 2003b). These results were consistent with research published by the National Institute for Occupational Safety and Health (NIOSH), in which both rats and monkeys were exposed to Grade 7 chrysotile (median fiber length of 0.67 µm) at a concentration of 0.79 f/cc (fibers >5 µm) for 7 h/day, 5 days/week, for 18 months and observed for up to 11.5 years; at the end of the observation period, "[n]o lesions attributable to the inhalation exposure were noted" in the exposed animals (Platek et al., 1985; Stettler et al., 2008). More recently, using a statistical model, Wylie and Korchevskiy (2023) evaluated the relationships between mesothelioma risk and fiber dimensions, including length; they confirmed that "particles shorter than 5 µm [did] not contribute to mesothelioma risk" and that fibers >20 µm were most correlated with potency for mesothelioma.

This differential risk by fiber length is believed to be a function of biological mechanisms in the lung, such as phagocytosis by alveolar macrophages or the mucociliary escalator (Barlow et al., 2017; ERG 2003a). The rate of clearance by phagocytosis is understood to vary with fiber length, in that clearance mechanisms are more efficient for short fibers compared with longer fibers (ERG 2003a). The diameter of human alveolar macrophages has been reported by various entities to range between 10 and 20 µm, with most reported estimates falling between 14 and 20 µm (Timbrell 1982; Krombach et al., 1997; ATSDR 2002; Berman and Crump 2003; ERG 2003a, b; Dewhurst et al., 2017). Consequently, alveolar macrophages are able to fully engulf shorter fibers and clear them from the lung but are incapable of fully engulfing fibers longer than their own diameter (i.e., fibers >14–20 µm in length) (ERG 2003a). The inability of pulmonary macrophages to engulf longer fibers may, therefore, lead to a process called frustrated, or incomplete, phagocytosis, resulting in increased phagocyte

recruitment into the alveoli and sustained cellular oxidative stress (Barlow et al., 2013, 2017). This may also lead to an increased biopersistence of these fibers and chronic inflammatory conditions, ultimately resulting in disease (Barlow et al., 2017; Roggli and Brody 1984). Thus, it is unsurprising that fibers >20 μm in length are more associated with the development of mesothelioma compared to shorter fibers. Moreover, given that cleavage fragments are typically <10 μm in length and that airborne cleavage fragments have been observed to be closer to 3.5 μm in length (Gamble and Gibbs 2008; Goodman et al., 2023; Ilgren 2004; Mossman et al., 2007), if respirable, they are likely to be rapidly cleared from the lungs by alveolar macrophages upon inhalation and, thus, unlikely to cause disease.

Although length has been historically emphasized in the broader discussion on the role of fiber dimension in asbestos-related disease risk, fiber width is arguably of greater importance for fibers >5 μm in length, as it is a key determinant of fiber exposure, deposition and translocation within the respiratory tract, and ultimately mesotheliogenic potency. In fact, it is generally accepted that the settling velocity of a fiber is proportional to the square of its width, such that a wider fiber will settle out of the atmosphere more rapidly than a thinner one, corresponding to a lesser probability for the wider fiber to be inhaled as a function of time (ATSDR 2001; Hinds 1999; NAS 1982; Sahmel et al., 2015; Sawyer and Spooner 1978). For example, with all other factors being equal, a fiber with a diameter twice that of another fiber will settle four times more quickly.

Furthermore, an understanding of regional and local fiber deposition is of great significance, as particle toxicity is more dependent upon the quantities deposited at specific sites rather than the total quantity inhaled (Sussman et al., 1991). Of the mechanisms involved in respiratory tract deposition, impaction and sedimentation are most relevant to fibers and are governed by aerodynamic diameter, which is approximately three times fiber width for commercial asbestos fibers (Lippmann 1990; Timbrell 1965). Inhaled fibers with widths ≥3 μm are deposited onto the surfaces of the head airways and readily cleared by sneezing or nose blowing, or transported via the mucociliary escalator to the pharynx and subsequently swallowed, entering the gastrointestinal tract, a process that requires approximately 1-2 days (ACGIH 2001; ATSDR 2001, 2004; Donaldson et al., 1993; Lippmann 1990; NIOSH 2011). For fibers that penetrate beyond the head airways, only a "few fibers" with widths >0.7 μm and "virtually none" with widths >1.5 μm are anticipated to reach the pulmonary region of the lungs (Berman and Crump 2003: p. 6.58). Thus, it is not surprising that non-respirable fibers "are not considered carcinogenic to humans" (ACGIH 2001: p. 6). Recently, at the 2023 Monticello II Conference on Elongate Mineral Particles, it was discussed that thick, short EMPs, such as cleavage fragments, are "more likely to have random orientations and, based on aerodynamics, likely result in less deposition in the deep lung." In contrast, long, thin asbestiform fibers are "more likely" to "align with the airstream" and cause "penetrat[ion] into the lung parenchyma" (Goodman et al., 2023).

For particles able to reach deeper lung regions, the ability of a fiber to translocate to the pleura "favors fiber[s] of very narrow width" (Wylie et al., 2020). For example, Lentz et al. (2003) estimated the risk of pleural plaques in a cohort of refractory ceramic fiber workers, stratifying on pulmonary dose metrics where the "critical dimension" of fibers associated with pleural plaques was defined as having a width <0.4 μm (p. 278). In their review of mesothelioma, Carbone et al. (2011) noted that "[t]he one thing all seem to agree with, is that ultrathin fibers, 0.3 μm or less in diameter, are those most frequently, if not exclusively, detected in the pleura" (p. 49). Pooley (2018) analyzed a sagittal slice of lung from an individual that was "exclusively" occupationally exposed to amosite and noted that the "average diameter of the particles detected … decreased from the central lung regions to the periphery" with those <0.2 μm identified near the pleural region (p. 19-20). Lippmann (2014) reported that it is "know[n] with reasonable certainty" that fibers <0.15 μm in width can "penetrate lung epithelia and translocate via lymphatic channels to pleural surfaces" (Lippmann 2014: p. 687). Thus, the weight of the evidence indicates that the inability for relatively thick fibers to translocate from the lung to the pleura translates to an observed effect modification in mesothelioma risk by fiber width.

Recently, Wylie et al. (2020) developed predictive models for mesothelioma potency using two-dimensional parameters of exposure to elongate amphiboles, the results of which indicated that the presence of fibers >5 μm in length and ≤0.15 μm in width "appears to be a very sensitive indicator of risk for mesothelioma, with mesothelioma potency rising rapidly with only small increases in the proportion of this fine fiber in the dose" (Wylie et al., 2020: p. 521).

Notably, the mesothelioma potency was "not significant" for EMPs with a length >5 µm and a width of ≤0.15 µm was estimated to be <1% (Wylie et al., 2020: p. 515). Korchevskiy and Wylie (2021) extended this analysis and similarly found that "[f]or particles longer than 5 µm, the highest correlation with mesothelioma potency was achieved for width <0.22 µm" and "[t]he statistical power of the correlation was observed to lose significance at a maximum width of 0.6-0.7 µm" (Korchevskiy and Wylie 2021: p. 244). An ensuing review by this research team revealed several overarching themes salient to this topic, two of which were the "width of elongate mineral particles is a strong predictor of carcinogenicity" and "short and thick non-asbestiform particles have negligible cancer potency" (Wylie and Korchevskiy 2023: p. 114688).

It is notable that fiber width has been shown to vary by geography within commercial asbestos deposits, as differences in mesothelioma incidence between mining and milling cohorts have been observed between locations. In association with the U.S. Bureau of Mines, Shedd (1985) assessed the dimensional variation of crocidolite fiber samples from the four global regions where crocidolite has been commercially mined: the Cape and Transvaal Provinces in South Africa, the Hamersley Range of Western Australia, and Bolivia. Shedd (1985) reported that "the Cape Province and Western Australian crocidolites are distinguished from the Transvaal Province and Bolivian crocidolites by a higher percent of thin fibers" (Shed 1985: p. 15). Specifically, fibers that were ≥8 µm in length and ≤0.25 µm in width comprised 67%–88% (mean: 79%) of those from the Cape Province and Western Australia, whereas 6%–54% (mean: 24%) of the fibers from the Transvaal Province and Bolivia met the same dimensional criteria. Not surprisingly, the pathological responses of animals (Botham and Holt 1972), as well as risk of disease in humans (White et al., 2008) appeared to differ based on origin of crocidolite. For example, while published studies have shown that the risk of mesothelioma in those exposed to crocidolite from the Cape Province and Western Australia was significantly increased (Hansen et al., 1997; Hobbs et al., 1980; McDonald et al., 1978; Reid et al., 1990; Wagner et al., 1960; Wagner and Pooley 1986), no such relationship was observed in those exposed to crocidolite from the Transvaal Province (Harington 1981; Harington et al., 1971; Timbrell 1973).

Taken together, the evidence suggests that only inhaled fibers <0.7 µm in width can reach the pulmonary region of the lungs and of those fibers, only those <0.1–0.4 µm in width can translocate to the pleura. While some portion of cleavage fragments may be respirable, few if any cleavage fragments >5 µm in length would be thin enough to translocate to the pleura.

Additional properties that may influence mesotheliogenic potency

Cleavage fragments are inflexible, brittle, and have low tensile strength due to cracks and defects present along their surfaces; this starkly contrasts with asbestos fibers, which are characterized by their flexibility and high tensile strength (Gamble and Gibbs 2008; Ilgren 2004; Mossman et al., 2007; Price 2010; Van Orden et al., 2008; Wylie et al., 2022). In their 1984 report on nonoccupational health risks of asbestiform fibers, the National Research Council noted that "[c]leavage cannot produce the high strength and flexibility of asbestiform fibers" and estimated that cleavage fragments instead have strength and flexibility "approximately the same as those of single crystals" (NRC 1984). Gamble and Gibbs (2008) estimated that the "tensile strength of amphibole asbestos fibers is 20–115 times greater than the non-asbestiform amphibole variety" making them far more durable than their non-asbestiform counterparts (Gamble and Gibbs 2008). In addition, surface characteristics related to the underlying structure of asbestiform and non-asbestiform minerals also lead to significant differences in bio-durability, such as a high density of surface defects. These surface defects, characteristic of cleavage fragments, are preferred sites for dissolution as the result of acidic environments encountered in phagocytosis (Gamble and Gibbs 2008; Ilgren 2004).

Toxicology of cleavage fragments: overview of animal studies

Several animal studies have evaluated the carcinogenic potential of non-asbestiform tremolite, including cleavage fragments from talc deposits. Treatments were administered by injection or implantation, which are non-physiologic routes of exposure, particularly for cleavage fragments as they are generally not respirable. It is understood that, for injected mineral particles of any type, tumor rates less than 10% are considered to be within background (Addison and McConnell 2008).

Smith et al. (1979) performed intrapleural injections of 10 mg and 25 mg of five samples of "tremolite" in hamsters. Sample FD-14 was characterized as "fibrous talc from New York State," which contained 50% tremolite, 35% talc, 10% antigorite, and 5% chlorite and was only tested at the high dose (Smith et al., 1979). According to Smith et al. (1979), the average diameter of "fibrous-shaped particles" was 1.6 µm. Sample 275, which was "isolated from a sample of tremolite taken from a tremolitic talc ore body similar to those from which FD-14 was produced", consisted of 95% tremolite, for which the average width was 0.4 µm (p. 336). Intrapleural injection of 25 mg of FD-14 resulted in no tumor formation and no tumors were observed in animals administered 10 mg or 25 mg of Sample 275. It was concluded that both FD-14 and Sample 275 were "non-carcinogenic" (p. 336, 338).

Sample 31, which was described by Addison and McConnell (2008) as "possibly asbestiform," was tremolitic talc from the Western United States that consisted of a combination of particles with parallel sides and others, although elongated, that were roughly shaped acicular fragments. The overall tremolite content of this sample was 90%, which consisted of "many long, thin particles" and the average diameter was reportedly 0.5 µm. The remaining two samples (72 and 72N) were asbestiform tremolite preparations, that consisted of numerous long, thin fibers with parallel sides. The samples were characterized as 95% tremolite, and the average diameter of the fibers was 0.4 µm and "many" of the fibers were longer than 20 µm (p. 339). Tumors were observed following injections of Sample 31; however, the incidence of tumors only exceeded 10% in the 25-mg dose group. For Samples 72 and 72N, tumors were observed in a dose-dependent manner. The authors concluded that sample 31 was "less carcinogenic" than sample 72 (p. 336). Further, pleural fibrosis was "extensive" in animals administered sample 72, and less fibrosis occurred following treatment with sample 31, such that "[t]he fibrogenicity of these samples … paralleled their carcinogenicity" (p. 336). The authors reported that they could not conclusively attribute the positive results for Samples 72 and 31 to tremolite content since they contained at least 5% of other material. If one were to assume that the carcinogenic activity of Samples 72 and 31 were due to tremolite, "then the experiments indicate[d] that appropriately high doses of long, thin particles of tremolite induced tumors, whereas high doses of shorter particles did not" (p. 338). In conclusion, Smith et al. (1979) reported that the experiments showed that "consideration must be given, not merely to the amount of tremolite, but also to other factors, such as the morphologic characteristics of the mineral" (p. 338).

Stanton et al. (1981) performed 72 experiments in which various minerals across size categories, including in the "index size range" (>8 µm, and <0.25 µm) were implanted in the pleura of rats to better understand how fibrous dimensions relate to carcinogenicity. In the experiments for the different minerals, a 40 mg dose of particles dispersed in hardened gelatin was applied via open thoracotomy to the left pleural surface of rats. Thirty to 50 rats were treated and followed for 2 years for each experiment. The occurrence of pleural sarcomas that resembled human mesenchymal mesotheliomas after the first year were considered a positive response in the study. Stanton et al. (1981) evaluated three types of control animals in their experiments, which included untreated rats, rats that received thoracotomies but no pleural implants, and rats that received pleural implants of nonfibrous material. Multiple fibrous materials were evaluated by Stanton et al. (1981), including two asbestiform tremolite asbestos samples, and seven talc samples. The two asbestiform tremolite samples were reportedly from the same lot of asbestos from California and "were in the optimal range of size for carcinogenesis" (Stanton et al., 1981: p. 971; Wylie et al., 1993). The seven talc samples were characterized as "refined raw materials for commercial products," and it was reported that each talc sample "was from a separate and diverse source and selected to include all extreme ranges of dimension" (p. 966). While the origins of the talc samples were not reported by Stanton et al. (1981), it has since been reported that Talc 6 and 7 were tremolitic talc samples from the Gouverneur mine in New York State and contained 40%–50% tremolite cleavage fragments (Addison and McConnell 2008; Gamble and Gibbs 2008; Wylie et al., 1993).

Certain tumor observations in control animals needed to be factored into the assessment of carcinogenicity of experimental materials. The calculated incidence of pleural sarcomas in all three control groups combined by the life table method was 7.7 ± 4.2% (Stanton et al., 1981). Relative to the combined control group incidence, incidence of pleural sarcomas in an individual experimental group was significantly greater than the combined control group if it exceeded 30%. While tumor incidence for the two asbestiform

tremolite samples were high (22/28 and 21/28), none of the tumor incidences for the seven talc samples exceeded background, and no tumors were observed following implantation of Talc 6 or Talc 7 (Talc 1: 1/26, Talc 2: 1/30, Talc 3: 1/29, Talc 4: 1/29, Talc 5: 0/30, Talc 6: 0/30, and Talc 7: 0/29). The lack of tumor development following administration of Talc 6 was despite the fact that this sample contained more Stanton "index fibers" than Sample 2 of the asbestiform tremolite and almost as many as Sample 1 (Addison and McConnell 2008). Based on the results for the wide variety of compounds evaluated in the study, the authors concluded that their results showed "avid phagocytosis of both short fibers and large-diameter fibers but negligible phagocytosis of long, thin fibers" and acknowledged that both short fibers and thick fibers were less carcinogenic than fine, long fibers (p. 974).

Wagner et al. (1982) evaluated the biological activity of three types of tremolite through intrapleural injection in rats. One tremolite sample (Sample A) was prepared from a sample of Californian tremolitic talc, which originally contained 62% talc and 38% non-asbestiform tremolite. However, the talc in the sample was reduced by froth flotation, which produced a sample consisting of >95% tremolite and <5% talc and magnesium and calcium carbonate. Most fibers in this sample were <6 μm long and <0.8 μm wide. The second sample of non-asbestiform tremolite (tremolite Sample B) was prepared from a tremolite rock from Greenland. The sample consisted of "fibrous particles," most of which were <3 μm long and <1.2 μm wide (p. 354). Indeed, according to Gamble and Gibbs (2008) none of the particles in this sample were >10 μm in length or <0.25 μm in width. Relative to tremolite Sample A, tremolite Sample B consisted of fibers that were shorter and thicker on average. The third sample (tremolite Sample C) was asbestiform tremolite from South Korea. Size reduction for Sample C resulted in a dust that consisted of fibers up to 140 μm, most of which were <0.6 μm wide. As described by Wagner et al. (1982), the fibers in tremolite Sample C were "very much longer and finer than those in Samples A and B″ as the number of fibers ($\times 10^3$) >8 μm long and <1.5 μm wide were 1.7, 0, and 56.1 for Samples A, B, and C, respectively (p. 354). A dose of 20 mg of one of the three samples was injected into the right pleural cavity of rats. In Experiment I, Wistar rats were treated with Sample A 2 years prior to the rest of the study and rats receiving SFA chrysotile served as positive controls. In Experiment II, Samples B or C were injected into groups of Sprague-Dawley rats but with UICC crocidolite serving as the positive control. No mesotheliomas were observed following injection of Sample A (n = 31; mean survival time after injection = 644 days) or sample B (n = 48; mean survival time = 549 days). However, 14 (30%) mesotheliomas were observed following injection of Sample C (n = 47; mean survival time = 541). Wagner et al. (1982) concluded that, based on their findings, only Sample C was carcinogenic.

Davis et al. (1991) evaluated the carcinogenicity of six varieties of tremolite minerals through intraperitoneal injection in rats. The six tremolite varieties used in the study included asbestiform tremolite from Jamestown, California (Sample 1), Korean asbestiform tremolite (Sample 2), asbestiform tremolite from Swansea (Sample 3), Northern (Ala di Stura) Italian tremolite (Sample 4), tremolite from Carr Brae, Dornie, Scotland (Sample 5), and non-asbestiform tremolite from Shinness, Scotland (Sample 6). Samples 1–3 all had "a very distinctive asbestiform morphology" and were described as consisting of "polyfilamentous fiber bundles, curved fibers, fibers with splayed ends, and long, thin, parallel-sided fibers" (p. 475, 478). All three asbestiform samples also had cleavage fragments but their nonfibrous proportions were low. Italian tremolite (Sample 4) contained "mostly cleavage fragments" but also had some long, thin needle-like fibers (p. 479). Dornie tremolite (Sample 5) consisted of mostly cleavage fragments and contained a small proportion of long, thin asbestiform fibers. Shinness tremolite (Sample 6) was "almost exclusively composed of cleavage fragments," of which only a small proportion had an aspect ratio greater than 3:1 (p. 479). The number of fibers ($\times 10^5$) with ≥8 μm in length and <0.25 μm in width for samples 1–6 were 121, 8, 48, 1, 0, and 0, respectively. A single dose of 10 mg of one of the six prepared tremolite samples was injected intraperitoneally into groups of AF/Han rats that were allowed to live until showing signs of debility or tumor formation. Nearly all animals treated with asbestiform tremolite (samples 1–3) developed mesotheliomas (Sample 1: 36/36; Sample 2: 35/36; Sample 3: 32/33), Sample 4 (Italian tremolite) produced tumors in 67% of animals (24/36), and Samples 5 and 6 produced few mesotheliomas (Sample 5: 4/33; Sample 6: 2/36). Davis et al. (1991) noted that the intraperitoneal injection test was extremely sensitive, such that it was usually considered that at the evaluated dose "any dust that produces tumors in fewer than 10% of the experimental group is unlikely to show evidence of carcinogenicity

following administration by the more natural route of inhalation" (p. 489). The authors reported that, in general, carcinogenicity corresponded to the number of long, thin fibers as opposed to other dimensional characteristics.

In conclusion, the weight of the toxicological evidence supports that non-asbestiform tremolite, including cleavage fragments, generally do not produce mesothelioma in excess of background in animals following injection or implantation. This observation holds true for samples of talc that contain a considerable quantity of cleavage fragments that meet the dimensional criteria of a Stanton "index fiber."

Review of health effects in upstate New York industrial talc Miners and Millers exposed to cleavage fragments

Upstate New York industrial talc miners and millers, including those employed in the Gouverneur Talc Company, are the most thoroughly studied worker populations known to be exposed to talc-associated cleavage fragments. While initial studies seemed to suggest that upstate New York talc contained asbestos fibers, exposure to which resulted in an increased risk of lung cancer, the current state of the science supports that any observed risk was not associated with occupational exposures to talc, and that the amphibole minerals present within the talc deposits were in the non-asbestiform habit. A timeline of the key epidemiological studies of this cohort is presented in Table 1. Furthermore, as described herein, none of the cohort mortality studies performed on these workers supported an increased risk of mesothelioma.

Composition of New York state talc. Talc mining and milling operations by the R.T. Vanderbilt Company, Inc., in the Gouverneur Talc District in upstate New York, began in 1947, and since 1974, R.T. Vanderbilt has owned and operated the only New York State tremolitic talc mine (Kelse and Thompson 1989; NIOSH 1980). The term "tremolitic talc" or "tremolite talc" describes industrial talc that contains large quantities of the mineral tremolite (ATSDR 2001); this term provides no information on the habit of the tremolite within the talc deposit (e.g., asbestiform v. non-asbestiform).

In 1980, as part of their morbidity and mortality studies of the Gouverneur Talc Company (a subsidiary of R.T. Vanderbilt) miners and millers, NIOSH, and "independent research laboratories" evaluated bulk samples of talc for the presence of asbestos using X-ray diffraction (XRD), optical petrographic microscopy, and electron microscopy (NIOSH 1980: p. 5). Air samples were also collected in the breathing zones of miners and millers, which were analyzed by phase contrast microscopy (PCM) to determine the "TWA exposures" to fibers (NIOSH 1980: p. 5). According to NIOSH (1980), "a representative number of the individual fiber samples was randomly chosen and the samples were analyzed by electron microscopy" coupled with selected area electron diffraction (SAED) to determine the crystal structure and energy dispersive X-ray analysis (EDXA) to determine elemental composition for fiber identification (NIOSH 1980: p. 5). Based on XRD and petrographic microscopy, the authors determined that the bulk samples contained between 14 and 48% talc (by weight), 37 to 59% tremolite, 4.5 to 15% anthophyllite and 10 to 15% serpentines, which were identified as lizardite and antigorite (NIOSH 1980, Table 1). Based on PCM, "TWA exposures" (fibers >5 μm) by mining operation ranged from 1.5 f/cc for the packhouse foreman to 9.8 f/cc for the crusher operator. According to NIOSH (1980), of the fibers that were >5 μm in length, 7% were tremolite, and 65% anthophyllite. Furthermore, the median length and width of particles characterized as tremolite fibers were 1.55 μm and 0.19 μm, respectively, with a median aspect ratio of 7.5. For particles characterized as anthophyllite fibers, the median length and width were 1.45 μm and 0.13 μm, respectively, with a median aspect ratio of 9.5. Since the publication of this NIOSH document, some researchers have assumed that Gouverneur Talc Company mines contained particles that were mineralogically identified as asbestiform amphiboles (Hull et al., 2002).

However, the results of this analysis were subsequently challenged by Kelse and Thompson (1989), who suggested that rather than characterizing accessory minerals found in the Gouverneur Talc District using the mineralogical definition of asbestiform, NIOSH instead "applied its regulatory asbestos definition to bulk and airborne dust samples collected at this mine" (Kelse and Thompson 1989: p. 615). In other words, Kelse and Thompson (1989) contended that NIOSH assumed that particles with aspect ratios ≥3:1 and lengths ≥5 μm were asbestiform fibers (i.e., amphibole minerals in the asbestiform habit). Furthermore, Kelse and Thompson (1989) cited to commentary provided by a group of mineral scientists following an OSHA hearing indicating that for asbestos fibers ≥5 μm, aspect ratios typically ranged

Table 1. Timeline of epidemiology studies evaluating health effects associated with exposure to Upstate New York Talc.

Decade(s)	Year	Findings	Reference
1870s	1878	Talc mining operations began in St. Lawrence County, New York	St. Lawrence County Chamber of Commerce (2024)
1930s	1933	Observed pulmonary fibrosis among miners and millers. Average airborne dust exposures were as high as 1,440 mppcf	Dreessen (1933)
1940s	1943	Observed pulmonary fibrosis among miners and millers; no cases of fibrosis were observed in workers with less than 10 years of exposure. Airborne dust concentrations in the mines ranged from 6 to 5,000 mppcf, and in the mills from 46 to 163 mppcf. Engineering controls were subsequently implemented to reduce exposure to dust	Siegal et al. (1943)
	1948	The Gouverneur Talc Company began operations in St. Lawrence County, New York	
1950s	1955	First death from mesothelioma (pleural) in New York talc miners and millers was reported. The complete occupational history of the case was not provided	Kleinfeld et al. (1955)
1960s	1963	Reported that unlike asbestosis "pulmonary talcosis has not been associated with an increased incidence of pulmonary carcinoma."	Kleinfeld (1963)
	1964	Aside from several metrics of pulmonary function, no differences were observed in the health experience of workers exposed to fibrous talc (group A) versus granular talc (group B)	Kleinfeld et al. (1964)
	1967	First study to demonstrate an increased mortality from lung cancer in these talc workers, although owing to a lack of smoking data, the authors concluded that "one cannot assess the role played by smoking in the causation of the pulmonary carcinomas" in talc workers. Also reported one death due to peritoneal mesothelioma, which did not result in a statistically significant increase in cancer of the gastrointestinal tract and the peritoneum	Kleinfeld et al. (1967)
1970s	1973	Appears to be the first epidemiology study in which the asbestos minerals in talc were specifically referred to as "asbestiform." reported that "[t]here is at present no conclusive data that it is the fiber per se which is solely responsible for producing both the fibrotic and malignant changes" (p. 140). Kleinfeld et al. (1973) concluded that "[i]t is possible that commercial talc containing tremolite and anthophyllite as major fibrous constituents may be less fibrogenic than chrysotile or amosite at the degrees and duration of dust exposure present in this study" (p. 142)	Kleinfeld et al. (1973)
1980s	1980	Reported an increased risk of NMRD and lung cancer in miners and millers, although the authors did not control for smoking or previous occupational exposure. One case of mesothelioma was reported which was not attributed to work at the Gouverneur Talc Company (likely due to insufficient latency [16 years], and prior construction employment)	Brown and Wagoner (1980)
	1981	Reported an increased rate of mesothelioma in Jefferson County, although talc had not been mined in this county for over a century. An increased rate of mesothelioma was not reported for St. Lawrence county	Vianna et al. (1981)
	1982	Evaluated the same workers assessed by Brown and Wagoner (1980), but reported that NMRD and lung cancer were not statistically significantly elevated. The authors noted that the majority of lung cancer cases were in short-term workers, which was indicative of an "inverse dose response."	Stille and Tabershaw (1982)

(continued)

Table 1. (continued)

Decade(s)	Year	Findings	Reference
	1988	Compared the mortality experience of Gouverneur Talc Company to Vermont talc workers, noting that "[t]he upstate New York talc contains an elongated particulate not found in the Vermont talc." No difference was observed in lung cancer mortality. NMRD was only elevated in Vermont millers but not miners, and not in Gouverneur Talc Company miners or millers. The authors reported that the risk of lung cancer for both groups of workers was elevated for miners but not millers, despite higher exposures in millers, and confirmed that the excess in lung cancer was only present in short-term workers	Lamm and Starr (1988)
1980s (cont.)	1988	Reanalyzed the studies by Brown and Wagoner (1980) and Stille and Tabershaw (1982) and confirmed that lung cancer risk was limited to short-term workers, and therefore not related to talc work. Conversely, NMRD risk was only observed in workers with at least 1 year of employment. The authors observed one case of mesothelioma in Gouverneur Talc Company workers, which was not attributed to talc exposure likely due to insufficient latency	Lamm et al. (1988)
1990s	1990	Reported that NMRD was significantly increased in workers with >1 year employment, although lung cancer was not; rather, lung cancer was only elevated in short-term workers. Despite these findings, the authors concluded that the "magnitude of the risk for both lung cancer and non-malignant respiratory disease indicate that the workplace exposures at [Gouverneur Talc Company] are, in part, associated with these excesses in mortality."	Brown et al. (1990)
	1993	Found that risk of lung cancer did not increase significantly with increasing tenure and concluded that "[t]he lack of an exposure-response trend with talc tenure is contrary to the conventional wisdom and to the conclusion that workplace talc exposures account for the increased risk of lung cancer." rather, "[t]he time occurrence of lung cancer among these talc workers is more congruent with a smoking than a talc etiology."	Gamble (1993)
2000s	2002	Reported an increased risk of pulmonary fibrosis in the highest exposure group; conversely, the risk of lung cancer was inversely related to cumulative exposure, and as such the authors acknowledged that it was unlikely to be related to talc. The authors described one additional case of mesothelioma that worked at the facility from 1948 to 1949 as a draftsman during mill construction, and who was likely exposed to insulation materials at other employments. The authors concluded that this case was not related to talc work	Honda et al. (2002)
	2002	Documented five cases of mesothelioma that worked in various capacities in the talc industry, with tenures ranging from 2 to 25 years; complete occupational histories of the cases were not provided, and a risk estimate for mesothelioma was not reported	Hull et al. (2002)
2010s	2011	Mesothelioma mortality rates in Jefferson County and St. Lawrence County, New York from 1999 to 2005 were "similar to the overall U.S. mesothelioma death rates for this same period."	NIOSH (2011)
	2018	Reported that despite "long exposures and elevated [regulatory fiber] levels for [R.T. Vanderbilt] talc workers", the occurrence of pneumoconiosis was similar to that found among platy talc workers not exposed to regulatory fibers, as well as the general unexposed population	Kelse (2018)

from 20:1 to 100:1 or higher. As part of their analysis, air samples were obtained during work activities in the Gouverneur Talc Company mine and mill, which were analyzed by PCM, polarized light microscopy (PLM), scanning electron microscopy (SEM), computer-controlled SEM, and transmission electron microscopy (TEM). According to Kelse (1989), based on SEM, unlike asbestiform tremolite for which 40% of fibers have aspect ratios >10:1 and approximately one third have aspect ratios >20:1, only one tremolite particle from upstate New York talc had an aspect ratio >10:1 (0.1%) and none had an aspect ratio >20:1. Furthermore, all tremolite particles identified in upstate New York talc had widths >0.25 µm. Indeed, based on PCM and PLM analyses, while regulatory fibers were found, no asbestiform tremolite fibers were present. Nonetheless, in 1992, OSHA noted that the debate over the mineralogical content of the New York tremolitic talc ore was unresolved, but that the presence of asbestiform talc in the ore may have led to the identification of asbestiform tremolite and anthophyllite (OSHA 1992).

In 2000, a report from OSHA's Salt Lake Technical Center (Crane 2000) acknowledged that "tremolitic industrial talcs such as those found in New York present a difficult analytical problem," noting that New York talc ore contains "a high component of" nonasbestiform tremolite, "mostly" nonasbestiform anthophyllite, talc in both massive and asbestiform habits, and minor amounts of other minerals and mineraloids (p. 2). Furthermore, Crane (2000) suggested that, in some cases, cleavage fragments of nonasbestiform tremolite and anthophyllite in the talc ore and products may have been misidentified as asbestos fibers.

Epidemiology of New York State talc miners and millers. Numerous epidemiology studies have been performed on upstate New York talc mine and mill workers, including studies specifically on Gouverneur Talc Company miners and millers (Brown et al., 1990; Gamble 1993; Honda et al., 2002; Lamm et al., 1988; NIOSH 1980; Stille and Tabershaw 1982). An overview of the seminal studies is provided below, in chronological order, separated by the health endpoint evaluated.

Non-malignant respiratory disease and lung cancer. Dreessen (1933) was the first researcher to evaluate the health experience of talc miners and millers in the Gouverneur, New York area (NIOSH 1980). The talc mined by this population was described as "tremolite talc," and was noted to contain up to 45% tremolite with limited free silica (p. 65). Airborne dust concentrations measured in the talc mines during pneumatic jackhammer drilling were the highest of any measured activity, and averaged 1,440 million particles per cubic foot (mppcf). Airborne dust concentrations measured in the mills during talc crushing and milling activities averaged 52 mppcf. Dust concentrations in air collected outside of the talc mill during quarrier and yardmen work activities averaged 4 mppcf. Fifty-seven workers engaged in talc mining and milling underwent chest X-rays and were assessed for "first, second, or third stage … pneumoconiosis" based on the level of pulmonary fibrosis (p. 71). Sixty-seven percent of the workers (38 of 57) demonstrated evidence of increased pulmonary fibrosis above normal levels, while 26% (15 of 57 workers) demonstrated evidence of early or first stage pneumoconiosis. Only one worker, who was reportedly employed in the talc mining industry for over 40 years, demonstrated levels of pulmonary fibrosis consistent with stage two pneumoconiosis. It was found that all workers with at least 10 years of talc exposure (17 of 57 workers) had evidence of increased pulmonary fibrosis. Dreessen (1933) concluded that "[w]hile very dusty conditions prevail in certain departments… the resultant pneumoconiosis ha[d not] led to disability" (p. 78).

In the following decade, Siegal et al. (1943) evaluated the health experience of talc miners and millers in St. Lawrence County; the talc mined by this population was described to be "of the asbestine variety" (p. 28). Airborne dust concentrations measured in area mines in 1941 reportedly ranged from 16 to 5,000 mppcf during drilling, 760 and 4,000 mppcf during stopping, and from 6 to 50 mppcf during mucking. In the mills, average dust concentrations were reportedly lower, and ranged from 46 to 163 mppcf during various operations. According to the authors, based on a survey performed in 1940, 14.5% of workers (32 of 221) exhibited a "marked" degree of fibrosis (p. 20). No cases of fibrosis were observed in workers with less than 10 years of exposure. The reported incidence of fibrosis in men with 10 or more years of employment was 29.9%, and in those with 30 or more years of employment was 74%. In a later survey on this population, the authors excluded workers with prior exposure to "other types of siliceous dust"; following this exclusion 18 men with no prior exposures in a dusty industry were identified as having marked

fibrosis, which led the researchers to conclude that talc was the cause of the fibrosis. In addition, the authors noted observing "talc plaques" in 14 of 221 talc workers originally roentgenographed, which were found in the visceral pleura and occasionally the pericardium. Siegal et al. (1943) described that these plaques were not "necessarily associated with other pulmonary pathology" and that the "underlying lung tissue may or may not show fibrosis" (p. 24). The authors acknowledged that their findings of fibrosis were similar to those previously reported by Dreessen (1933) in "tremolit[ic] talc workers in the same geographic area", although the fibrosis presented in this analysis was seemingly "more severe" (p. 25). The authors suggested that given the lack of free silica in the talc mines and mills, and the fact that the "dust is largely fibrous in character", that this "particular physical characteristic" may be responsible for the fibrosis.

In 1955, Kleinfeld published an updated analysis that included an evaluation of the health status of New York talc miners and millers, and presented the results of air sampling that was conducted in the mines and mills after the implementation of engineering controls in 1943 (Kleinfeld et al., 1955). In the mines, average airborne dust concentrations were reduced to 3 mppcf and 4 mppcf during drilling and mucking, respectively. In the mills, average dust concentrations generally ranged from 11 to 63 mppcf during various operations. Of the 32 patients previously diagnosed with fibrosis, 19 had died, 4 of whom died as a result of talc pneumoconiosis. Regarding those who were not deceased, the authors noted that "although no statistically significant correlative data can be formulated between the duration of tremolite talc exposure and longevity, it is of interest that an above average life span may occur, following prolonged exposure to talc dust and associated with pulmonary dysfunction" (p. 67). Furthermore, the authors confirmed the previous findings that there was no correlation between symptomology and X-ray findings.

Over the next decade, Kleinfeld (1963) continued to report on cases of talc pneumoconiosis, including describing evidence of pleural plaques and thickening and "asbestos bodies" (p. 115). However, as described by Kleinfeld, while many of the findings were similar to those observed in cases of asbestosis, unlike asbestosis "pulmonary talcosis has not been associated with an increased incidence of pulmonary carcinoma" (p. 115). Kleinfeld et al. (1964) also evaluated clinical and roentgenologic data in a cohort of workers exposed to fibrous talc (Group A) versus a cohort exposed exclusively to granular talc (Group B). According to the authors, the two cohorts were no different in terms of the mean duration of talc exposure (A: 19.5 years; B: 17.9 years), the mean weighted level of dust exposure (A: 63.1 mppcf; B: 62.7 mppcf), nor the mean cumulative dust exposure (A: 1,248.8 mppcf-years; B:1,150.7 mppcf-years). No significant difference was found between the groups with respect to the frequency of dyspnea, abnormal lung findings or pulmonary infiltration, rather the only observed differences were in several metrics of pulmonary function. In a follow-up analysis, Kleinfeld et al. (1965) confirmed the previous findings that prolonged exposure to talc dust can produce (in some individuals) impaired pulmonary function; however, they noted that the "correlation between the degree of dust exposure and the various parameters of lung function was poor" (p. 16).

In 1967, Kleinfeld et al. performed a cohort mortality study that included all New York talc miners and millers (n = 220) employed in 1940 with 15 or more years of exposure to talc dust, as well as those who had achieved a minimum of 15 years of such exposure between 1940 and 1965. Airborne dust concentrations before 1945 averaged between 120 and 818 mppcf in the mines, and 69 to 1,227 mppcf in the mills. Between 1946 and 1965, airborne dust concentrations were considerably lower, and ranged from 5 to 9 mppcf in the mines, and 25 to 73 mppcf in the mills. Kleinfeld et al. (1967) reported 91 deaths in the cohort, of which 28 were due to pneumoconiosis or complications thereof, 9 deaths were from carcinomas of the lung, and 1 was a fibrosarcoma of the pleura. The authors noted that the overall mortality from lung and pleural cancer combined was roughly 4 times that expected; however, compared with asbestos insulators, the occurrence of these malignancies in talc workers appeared in older age groups. Kleinfeld et al. (1967) noted that all workers with carcinoma of the lung or pleura began their employment prior to the institution of wet drilling (which was associated with a marked decrease in airborne dust concentrations), although they concluded that "there is no evidence to indicate that there was a direct relationship between the duration of exposure prior to the onset of wet drilling and the occurrence of pulmonary carcinoma" (p. 666). Furthermore, Kleinfeld et al. (1967) noted that "[i]n the absence of adequate smoking data one cannot assess the role played by smoking in the causation of the pulmonary carcinomas in both" talc workers and asbestos insulators (p. 666). The authors concluded

that this was the first study to demonstrate an increased risk of mortality from carcinoma of the lung in these talc workers.

In a subsequent paper, Kleinfeld et al. (1973) evaluated the exposure and health experience of 39 workers, exposed for at least 10 years to "[a]sbestiform [m]inerals in [c]ommercial [t]alc [m]anufacture" (p. 132). This appears to be the first paper in which the asbestos minerals in talc were specifically referred to as "asbestiform" although no reference was cited that confirmed the mineralogical habit of the asbestos minerals present (p. 132). According to the authors, asbestiform tremolite and anthophyllite were "the major fibrous components" of the talc processed (p. 132). Air samples (duration: 10 min) were collected in the breathing zones of the miners and millers, as well as at various areas within the mine and mill (p. 133). In addition to assessing dust concentrations, to the best of our knowledge, this paper was the first to assess airborne fiber concentrations using PCM (fibers were defined as particles >5 µm in length with aspect ratios >3:1). These concentrations were then compared to a "[c]omparative plant" that was assessed in 1969 (p. 136). Mean dust concentrations measured from 1954 to 1970 during mining operations were highly variable and ranged from 2 to 140 mppcf; airborne fiber counts measured in 1970 ranged from 8 to 260 f/cc (>5 µm). During milling operations, mean dust concentrations measured from 1954 to 1970 ranged from 3 to 109 mppcf; airborne fiber counts measured in 1970 ranged from 8 to 33 f/cc (>5 µm). The authors indicated that the airborne fiber concentrations measured in this plant were substantially lower than those measured at the comparative plant, despite airborne dust concentrations being similar.

Kleinfeld et al. (1973) reported that compared to an unexposed control population, there was no significant differences in the prevalence of cough, lung crepitations, or clubbing, although the frequency of dyspnea was significantly increased in the talc workers. While the proportions of smokers in the talc cohort and the control group were not different, no comparative information was provided on the cumulative smoking history of both groups. Only one of the talc-exposed workers, who was employed as a janitor for 11 years, "showed a chest roentgenogram consistent with pneumoconiosis" (p. 136). In addition, Kleinfeld et al. (1973) reported that the prevalence of radiographic findings compatible with pneumoconiosis, dyspnea, and lung crepitations was significantly greater in the comparative plant versus the present plant, despite the fact that the proportions of smokers were not significantly different between the two groups. Once again, information was not provided regarding the cumulative smoking histories of both groups. The authors concluded that "[t]here is at present no conclusive data that it is the fiber per se which is solely responsible for producing both the fibrotic and malignant changes" (p. 140). Furthermore, the authors acknowledged that "[t]o date, no instances of malignancy have occurred in any of the workers exposed exclusively to commercial talc at the plant studied," although they noted that the "occurrence of malignancy requires a longer elapsed time from onset of exposure" (p. 141). Kleinfeld et al. (1973) concluded that "[i]t is possible that commercial talc containing tremolite and anthophyllite as major fibrous constituents may be less fibrogenic than chrysotile or amosite at the degrees and duration of dust exposure present in this study" (p. 142).

Shortly thereafter, Kleinfeld et al. (1974) published an updated analysis of all talc miners and millers (n = 260) employed in 1940 with 15 or more years of exposure to talc dust, as well as those who achieved a minimum of 15 years of such exposure between 1940 and 1969. The authors noted that the study participants represented the total workforce of the worker population under study. Average airborne dust concentrations reported by Kleinfeld et al. (1974) differed slightly from those previously published by Kleinfeld et al. (1967). Before 1945, airborne dust concentrations averaged between 120 and 818 mppcf in the mines (median: 30 to 413 mppcf), and between 1946 and 1965, the average airborne dust concentration was 5 mppcf (median: 3 to 5 mppcf). In the mills, prior to 1948 airborne dust concentrations averaged between 69 and 1,227 mppcf (median: 61 to 1,196 mppcf), and between 1948 and 1965, the average airborne dust concentration ranged from 25 to 73 mppcf (median: 13 to 63 mppcf). From 1966 to 1969 average dust concentrations during mining ranged from 9 to 19 mppcf (median 9 to 19 mppcf) and milling ranged from 28 to 43 mppcf (median: 20 to 25 mppcf). In 1972, in addition to dust counts, airborne fiber concentrations were also determined. According to Kleinfeld et al. (1974), in 1972 average dust counts during mining ranged from 3 to 7 mppcf (median: 3 to 7 mppcf), and fiber counts (>5 µm) ranged from 2 to 3 f/cc. During milling, average dust counts ranged from 7 to 36 mppcf (median: 7 to 28 mppcf), and fiber counts (>5 µm) ranged from 24 to 62 f/cc.

According to Kleinfeld et al. (1974), a total of 108 workers had died, of which 29 were due to

pneumoconiosis, or complications thereof. In addition, 12 deaths were from carcinomas of the lung, and similar to their 1967 analysis, 1 death was a fibrosarcoma of the pleura (i.e., no additional deaths due to fibrosarcoma of the pleura were reported in the follow-up period). Consistent with their previous investigation, the proportional mortality due to lung and pleural cancer combined was roughly 4 times what was expected; however, compared with asbestos insulators, the occurrence of these malignancies appeared in older age groups. No information was provided regarding the smoking habits of any of the workers. The authors remarked that "[t]he improved mortality experience between 1960 and 1969 in the case of lung and pleural cancers is particularly pertinent since environmental controls have resulted in an appreciable reduction in the dust counts in the mines and mills, although the fiber counts still remain high" (p. 347).

In 1980, NIOSH prepared a technical report describing three studies that they conducted on Gouverneur Talc Company miners and millers: an industrial hygiene study (Dement and Zumwalde 1980), a cross sectional morbidity study (Gamble et al., 1980), and a mortality study (Brown and Wagoner 1980). According to the report, a talc mining company in this district maintained that the results of previous analyses performed on miners and millers in this district were not applicable to all talcs in the Gouverneur Talc District, citing that "talcs extracted from its original mine in the Gouverneur Talc District do not contain asbestiform minerals and that the talcs have been so certified" (p. 2). It was noted, however, that Kleinfeld et al. (1973) evaluated "the same operations" and concluded that asbestiform minerals were present; therefore, NIOSH sought to investigate this contradiction (NIOSH 1980: p. 2). The results of the industrial hygiene survey were discussed previously (see *Composition of New York State Talc*).

In the same year, Gamble et al. (1980) performed a cross sectional respiratory morbidity study on current Gouverneur Talc Company male miners and millers ($n = 121$), 35 of whom previously worked at other talc mines. The authors evaluated lung function, the prevalence of respiratory symptoms (e.g., cough, phlegm, hemoptysis, and dyspnea), and radiographic findings (e.g., pleural thickening, pleural calcifications, and irregular opacities) in the study population, which were then compared to a cohort of coal miners from the National Coal Study and a cohort of potash miners from the Study of the Effects of Diesel Exhaust in Non-Coal Miners. The prevalence of respiratory symptoms in talc miner and millers without prior occupational exposure to talc was not significantly different compared to the control subjects. The authors reported that most of the study population that reported respiratory symptoms were smokers or ex-smokers, which is associated with increased prevalence of cough, phlegm overproduction, hemoptysis, and dyspnea. Furthermore, talc miner and millers with at least 15 years of exposure had a higher prevalence of pleural thickening ($p < .05$) compared with the control subjects and it was noted that "nearly one out of every three talc worker[s]" had pleural thickening (p. 26). The authors ultimately reported that the prevalence of pleural thickening in the talc miners and millers was four times higher than that seen in chrysotile asbestos workers in Canada and recommended additional medical surveillance of the workforce.

In 1980, NIOSH conducted a retrospective cohort mortality of males initially employed sometime between January 1, 1947, and December 31, 1959 ($n = 398$) at Gouverneur Talc Company, who were followed through June 30, 1975. A total of 74 deaths were reported of which 8 were due to non-malignant respiratory disease (SMR: 280; $p < .05$), and 9 were due to lung cancer (SMR: 270; $p < .05$) (Brown and Wagoner 1980). Four of the 9 cases of lung cancer were short term (<1 year) workers, and only 1 case worked for greater than 5 years. The mortality experience was not reported separately for mine versus mill workers, and dose-response assessments were not performed. Furthermore, the authors did not control for smoking or previous occupational exposure.

Two years later, Stille and Tabershaw (1982) published a historical prospective cohort study on the same work force previously assessed by Brown and Wagoner (1980). The study population consisted of 655 white male talc workers employed at Gouverneur Talc Company between January 1, 1948, and December 31, 1977. Deaths from respiratory cancer, lung cancer, and non-malignant respiratory disease were not statistically significantly elevated when compared to the U.S. white male population. The authors noted that the SMR for respiratory cancer "is consistent with a smoking effect," and reported that among workers given a medical examination in 1979, 46% were current smokers and 25% were past smokers (p. 481). Furthermore, when stratified by prior employment, only 2 deaths due to lung cancer were observed in talc workers with no known work prior to their employment at the talc company (SMR: 76; $p > .05$), versus 9 due to respiratory cancer (SMR: 228; $p <$

.05) and 8 due to lung cancer (SMR: 21; $p > .05$) in those with prior employment. Stille and Tabershaw (1982) reported that 9 of the 12 lung cancer cases were in workers with less than 5 years of employment, which the authors noted was indicative of an "inverse dose response" (p. 483). The authors ultimately concluded that "previous work experience" may have been responsible for the lung cancer in this cohort (p. 480).

In a letter to the editor, Brown et al. (1983) subsequently challenged the findings of Stille and Tabershaw (1982), alleging that the "report fails to address adequately the question of whether or not there is an increased risk from lung cancer specifically associated with working at the … [Gouverneur Talc Company]" (referred to as TMX) (p. 179). They claimed that the Stille and Tabershaw (1982) analysis was limited because of the following: (1) they "performed no analysis of mortality by latency interval"; (2) "the distinction made … between previously employed and not previously employed workers overlooks several possibly confounding factors" resulting in "selection biases inherent in the definition of the subcohorts" (specifically, differences in the subcohorts by follow-up length and percentage of recent hires); and (3) it "does not calculate the relative risk of lung cancer by 'dose'" (p. 179). In their reply, Tabershaw and Thompson (1983) stated that Brown et al. (1983) "ignore[d]" their latency analysis, "which demonstrated the inconsistency" between the average latency of the lung cancer cases for the facility at-issue (19.9 years) and those of other studies (36.5 years) (p. 180). Tabershaw and Thompson (1983) also noted that unlike previous analyses performed by NIOSH on the respiratory health of other cohorts (e.g., Vermont talc workers and Homestake gold miners) in which a minimum employment duration of 1 year was specified, for their analysis of Gouverneur Talc Company workers, no minimum duration of employment was required. This is critical, as of the nine cases of lung cancer reported by Brown and Wagoner (1980), four were employed for less than 1 year, with one employed for 17 days and another 8 days. Tabershaw and Thompson (1983) then pointed out that excluding these short-term employees "would eliminate any significant increase in SMR with increasing latency" (p. 180). On the potential for selection basis by stratifying their analysis on prior employment status, Tabershaw and Thompson (1983) questioned the likelihood that "the cohort contains a higher percentage of more recently hired workers with no prior work experience" owing to a historical policy of preferentially hiring "experienced workers," noting that "the single largest infusion of new hires came in 1974" following acquisition of "a nearby talc mine" (p. 180). Tabershaw and Thompson (1983) emphasized that "their rationale for subdividing the cohort remains sounds" and added that even when the cohort is analyzed in its entirety, an increased risk of lung cancer is explainable "by a smoking effect" (p. 180). Lastly, regarding cancer risk by "dose," they reiterated the frequency of the cases with employment at the facility for less than 1 year and noted that "only one" lung cancer case was observed in a miller, despite the fact that "millers' dust exposure historically has been greater than that of miners" (p. 180).

Lamm and Starr (1988) compared the standardized mortality ratios for lung cancer and non-malignant respiratory disease for talc miners and millers with at least 1 year of employment at the Gouverneur Talc Company versus Vermont; this analysis was presented at the VIIth International Pneumoconioses Conference. According to Lamm and Starr (1988), "[t]he upstate New York talc contains an elongated particulate not found in the Vermont talc that is considered by scientists at [NIOSH] as tremolitic asbestos and by scientists at the Bureau of Mines and at the company that owns the plant as true talc particulates and as prismatic non-asbestiform tremolite" (p. 1576). Furthermore, the authors indicated that NIOSH refers to the New York State talc as "asbestiform talc" and the Vermont talc as "non-asbestiform talc" (p. 1576). The SMRs for lung cancer for both New York and Vermont were elevated for miners but not millers, yet as noted by the authors, "[t]he exposures of millers generally exceed that of miners by a factor of two to six" (p. 1577). As described by the authors, both cohorts lacked information on smoking history, although "most" of the lung cancer cases occurred in smokers (p. 1581). Nonetheless, there was no indication that miners and millers differed in their smoking habits, thus it was "unlikely" that the differences observed were due to smoking (p. 1581). No difference was observed in the lung cancer mortality of miners or millers when comparing Gouverneur Talc Company versus Vermont workers. The SMR for non-malignant respiratory disease was only statistically elevated for Vermont millers, but not miners, and was not elevated for Gouverneur Talc Company miners or millers. Additional analyses were performed on the Gouverneur Talc Company cohort to assess the effects of duration of employment. The authors observed a statistically significant excess in lung cancer in

workers employed for less than 1 year (SMR: 316; $p < .05$); when stratified by miners versus millers with less than 1 year of employment, this excess was only apparent for miners (SMR: 701; $p < .05$).

Lamm et al. (1988) subsequently published a re-analysis of the NIOSH study by Brown and Wagoner (1980) and the Stille and Tabershaw (1982) evaluation of Gouverneur Talc Company workers. When stratifying workers employed at the company for at least 1 year ($n = 425$) compared to workers employed for less than 1 year ($n = 280$), excess lung cancer mortality risk was only observed in workers with less than 1 year of employment (SMR: 317; $p < .05$). The authors attributed the increased lung cancer mortality risk in short-term workers to several possibilities, including greater exposures for those with short periods of employment, differences in smoking habits, and prior employment in industrial jobs. After evaluating the workers' prior exposure histories, the authors reported that lung cancer mortality risk "predominate[d] in those who had potential lung cancer risk exposure prior to their talc employment" (p. 1204). Importantly, increased mortality from noninfectious, nonneoplastic respiratory disease was only observed in workers with at least 1 year of employment (SMR: 370; $p < .05$). According to the authors, "[i]f the talc exposure experienced by workers at this plant is believed to be both fibrogenic and carcinogenic, one would expect a similar exposure-related mortality pattern for both lung cancer deaths and noninfectious, nonneoplastic respiratory disease" (p. 1208). They concluded that, since lung cancer mortality risk decreased with increasing employment duration, while mortality risk from noninfectious, nonneoplastic respiratory disease increased with increasing employment duration, "the sources of these risks are different" (p. 1208).

At the request of R.T. Vanderbilt, NIOSH conducted a Health Hazard Evaluation to update their 1980 study on their employees at Gouverneur Talc Company (Brown et al., 1990). NIOSH acknowledged that to date four cohort mortality studies have been conducted on this cohort, and that "[t]he interpretation of the epidemiologic findings of these studies; and the controversy about the mineralogical composition of the talc and its contaminants at this mine has been the subject of numerous publications" (p. 2). The cohort evaluated by Brown et al. (1990) included all white males who worked at least 1 day at the Gouverneur Talc Company between the beginning of operation in 1947 through December 31, 1978 ($n = 710$); vital status was determined as of December 31, 1983. The authors reported a statistically significant excess in lung cancer (SMR: 207; 95% CI: 120-331) mortality and in "other non-malignant respiratory disease" (SMR: 296; 95% CI: 130-594). When stratified by tenure, lung cancer and NMRD were not statistically significantly increased in workers with <1 year employment. Conversely, NMRD was statistically significantly increased in workers with >1 year employment (SMR: 289; 95% CI: 145–518), although lung cancer was not statistically significantly elevated. When stratified by both tenure and latency, an excess lung cancer risk was only observed in very short-term workers with <1 year tenure, and with 20 to 36 years since their date of hire. No information was provided regarding the smoking histories of study participants. The authors noted that as many as half of the lung cancer cases worked in other talc mining operations and stated that "there may have been exposure to other lung carcinogens from employment previous to [Gouverneur Talc Company]" (p. 5). Despite these findings, the authors concluded that the "magnitude of the risk for both lung cancer and non-malignant respiratory disease indicate that the workplace exposures at [Gouverneur Talc Company] are, in part, associated with these excesses in mortality" (p. 1).

The New York State Department of Health conducted a "descriptive study" of radiographic chest abnormalities in residents of St. Lawrence and Jefferson counties (Fitzgerald et al., 1991: p. 153). The motivation for this was "a cluster of parenchymal fibroses and pleural changes suggestive of exposure to asbestiform minerals" reportedly identified by "a local radiologist … as a result of his review of routine chest radiographs of 'general' hospital patients" (p. 152). Cases were identified using hospital-based radiological records of patients who had a radiograph between April 1, 1982 and March 31, 1983, and were at ≥40 years of age and residents of either St. Lawrence or Jefferson counties. The local radiologist whose work prompted this study initially evaluated chest films for parenchymal fibrosis and pleural changes and then any that "he deemed positive" were provided to a "B-reader" for subsequent evaluation (p. 152). Also, cases (B-reader confirmed) or their next-of-kin were interviewed to collect data on occupational history, and the occupational distribution of male cases were compared with that of U.S. Census data from 1960 for these counties. Of the 9,442 patients that first met the inclusion criteria, 355 (8%) "had a radiographic chest abnormality consistent with dust exposure"; 246 (2.6%) "[had] pleural thickening or calcification

without parenchymal involvement"; and 109 (1.2%) were "diagnosed … as having parenchymal disorders with or without pleural findings" (p. 152). Interview data were collected for 306 cases; talc mining and milling (n = 111, 36.3%) and construction (n = 76, 24.8%) were the most frequently recorded types of occupations in which cases had been employed for at least 1 year. Similarly, when the case data were analyzed by usual occupation or industry, talc mining and milling and construction were the most frequently recorded, which contrasted with the Census data distributions (15.5% vs. 2.4% and 13.4% and 6.5%, respectively). The authors concluded that "there was no evidence of widespread radiographic abnormalities resulting from ambient [talc] dust exposure", but that "[t]he data … support[ed] earlier studies that indicate that talc miners and millers experience excess parenchymal fibrosis and pleural changes" (p. 151).

NIOSH subsequently performed a case-control study nested in the Brown et al. (1990) cohort to investigate "the confounding potential of non-[Gouverneur Talc Company] risk factors and exposure-response relationships while controlling for these risk factors and using tenure as a surrogate for exposure" (Gamble 1993: p. 449). All persons with lung cancer certified as the underlying cause of death on the death certificate were defined as cases, and each case was assigned three controls matched with respect to date of birth and date of hire. To control for possible confounding due to non-talc exposure, a panel of nine epidemiologists and industrial hygienists rated the risk of lung cancer associated with non-talc jobs on a scale of zero to three; this score combined with occupational tenure was used to assess whether non-talc exposure was a risk factor for lung cancer. All of the lung cancer cases (n = 22) were smokers (91%) or ex-smokers (9%); of the controls 64% were smokers and 9% were ex-smokers. The risk of lung cancer in smokers was nearly six times that of non-smokers and ex-smokers (combined). According to Gamble (1993), non-talc exposure was not a significant risk factor for lung cancer, nor was non-Gouverneur Talc Company talc exposure. The risk of lung cancer did not increase significantly with increasing tenure at the Gouverneur Talc Company. Indeed, when considering only smokers with ≥20 years latency, risk of lung cancer decreased with increasing tenure. Gamble (1993) concluded that "[t]he lack of an exposure-response trend with talc tenure is contrary to the conventional wisdom and to the conclusion that workplace talc exposures account for the increased risk of lung cancer" (p. 454). Rather, "[t]he time occurrence of lung cancer among these talc workers is more congruent with a smoking than a talc etiology" (p. 455).

In 2002, Honda et al. reported results from the most recent follow-up of the Gouverneur Talc Company cohort, for which cancer mortality was assessed from 1950 to 1989 (n = 809), and non-cancer mortality from 1960 to 1989 (n = 782) (Honda et al., 2002). Study participants were white males that worked for at least 1 day from 1948 until the end of 1989. SMRs were determined for the cohort compared to the general population living in the county in which the Gouverneur Talc Company is located, as well as the 5 surrounding counties; additional analyses were carried out to determine relative risks (RR) using an internal referent group. Mortality was assessed separately based on work area, years since hire, tenure and estimated cumulative exposure to respirable dust. The overall SMRs for "other" NMRD (SMR: 297; 95% CI: 173–475) and lung cancer (SMR: 232; 95% CI: 157–329) were statistically significantly elevated (p. 578). The observed excess in NMRD and lung cancer mortality was confined to subjects hired prior to 1955.

When accounting for latency, SMRs for "other" NMRD and lung cancer were not significantly increased in workers with less than 20 years since hire, regardless of the duration of employment. In workers with less than 5 years of employment and greater than 20 years since hire, statistically significantly elevated SMRs for "other" NMRD (SMR: 271: 95% CI: 109–558) and lung cancer (SMR: 33; 95% CI: 199–516) were observed; however, when compared to the internal referent group, the RRs were not statistically significantly elevated (Honda et al., 2002). However, for longer term employees (those with five or more years of employment) and 20 or more years since hire, the SMR was statistically significantly elevated for "other" NMRD (SMR: 302, 95% CI 111–657), but not lung cancer, and none of the RRs were statistically significantly elevated.

The SMRs for "other" NMRD were statistically significantly elevated for both miners and millers, however, the SMR for lung cancer was only statistically significantly increased for miners, but not millers. However, when compared to an internal referent group, the RRs for "other" NMRD and lung cancer were not statistically significantly increased for miners or millers. The risk of "other" NMRD increased with increasing cumulative dust exposure, although the risk estimates for the second and third tertiles of exposure were not significantly elevated when compared to the

first tertile. However, there was a statistically significant increased risk of pulmonary fibrosis in the highest exposure group (RR: 11.8; 95% CI: 3.1–44.9). Conversely, the risk of lung cancer was inversely related to cumulative exposure (i.e., risk decreased with increasing exposure). In addition, according to the authors, the "estimated cumulative exposure [to respirable dust] was 33% lower for lung cancer decedents and over seven times higher for decedents with pulmonary fibrosis than for the overall group of decedents" (p. 580). Based on several findings, such as the lack of a dose-response relationship, the authors concluded "several observations from the present study indicate that exposure to talc at the facility may not have been responsible for the excess" in lung cancer mortality. Furthermore, the authors noted that "[t]he association may be due, in part, to confounding by smoking and by other unidentified risk factors. It is unlikely to be related to respirable talc ore dust per se" (p. 584). Smoking was not controlled for in these analyses, and the authors noted that of 25 of the 28 cases of NMRD for which employment records were available, 20 had worked at other mining operations prior to their employment at the Gouverneur Talc Company.

As part of the first Monticello Conference, Kelse (2018) presented the more recent data on pneumoconiosis in employees of R.T. Vanderbilt. The study population consisted of all male workers actively employed at the mine or mill for any period between 1978 and 2008, who had undergone at least one chest radiograph. Despite "long exposures and elevated [regulatory fiber] levels for [R.T. Vanderbilt] talc workers," the occurrence of pneumoconiosis was reportedly similar to that found among platy talc workers not exposed to regulatory fibers, as well as the general unexposed population (p. 1). Pleural plaques were reportedly observed in some but not all talc workers, although little to no functional impairment was also noted. As noted by Kelse (2018) "the total [regulatory fiber] airborne exposure for the talc workers exceeded the asbestos permissible fiber exposure standard by a factor of 15 to 20" (p. 1). Particles meeting the definition of a regulatory fiber found in New York talc consisted of elongated amphibole cleavage fragments and fibrous/asbestiform talc, each of which "separately exceeded this standard by a factor of 7 to 10 (averaged over a span of decades)" (p. 1).

In summary, while an increased risk of NMRD has been observed in some studies of New York talc miners and millers, particularly in workers with the highest levels and longest duration of exposure, this has not been observed for lung cancer. Indeed, an inverse dose-response has been reported for lung cancer, which supports that exposure to upstate New York talc, including that mined and milled by the Gouverneur Talc Company, is not associated with the development of lung cancer. This is despite the fact that airborne concentrations of "regulatory fibers" often exceeded 20 f/cc, which exceeds that reported for insulators in the 1960s (Nicholson 1975).

Mesothelioma. Very few mesothelioma cases have been reported among upstate New York talc miners and millers, including Gouverneur Talc Company workers, and none of the cohort mortality studies on these workers have reported an association between talc exposure and the development of mesothelioma. The first death from mesothelioma in New York talc miners and millers was reported by Kleinfeld et al. (1955). This death was reportedly due to "mesothelioma of the pleura – pneumoconiosis (bilateral)"; no information was provided regarding this worker's occupational history, including the talc mine or mill at which they worked, their length of employment at the talc mines and/or mills nor their age, and the authors did not attribute the mesothelioma to talc exposure (p. 67). Kleinfeld et al. (1967, 1974) subsequently reported one death due to peritoneal mesothelioma, although unlike the asbestos insulator comparison cohort used in their analysis, no statistically significant increase was observed in cancer of the gastrointestinal tract and the peritoneum.

Within their cohort study, Brown and Wagoner (1980) reported one case of mesothelioma among the Gouverneur Talc Company workers, who was diagnosed 16 years after beginning his employment; this case worked for 11 years in construction prior to his employment, and the authors did not attribute this case to work at the Gouverneur Talc Company. In addition, Lamm and Star (1988) noted observing one case of mesothelioma each in both the Gouverneur Talc Company and Vermont talc mining and milling cohorts, described previously. The Gouverneur Talc Company case was diagnosed 15 years after hire, which "followed 28 years in mining and construction" (p. 1577); the authors did not attribute this case to talc exposure, likely due to insufficient latency. No information was provided regarding the Vermont case. Honda et al. (2002) described two cases of mesothelioma in the Gouverneur Talc Company cohort, which they noted were "difficult to interpret" (p. 583).

The first case, which appears to be the same case initially documented by Lamm and Starr (1988), died 15 years after starting employment at the Gouverneur Talc Company, and had previously worked as a carpenter and millwright for 16 years, as a lead miner for 8 years, and as a repairman in a milk plant for 5 years. The other case worked only briefly at the facility from 1948 to 1949 as a draftsman during mill construction. He previously worked during the construction of another talc mine, after which he installed and repaired heating systems, which may have exposed him to insulating materials. Honda et al. (2002) concluded that "because of the short amount of time between first exposure and death of the first case and the low exposure of the second case, it is unlikely that either of the two mesotheliomas was due to talc ore dust" (p. 583).

In an additional paper, Hull et al. (2002) documented five cases of mesothelioma occurring in workers at "[a]sbestiform [f]iber-bearing [t]alc [m]ines in New York State," of which three were histologically and immunohistochemically confirmed (p. 132). The five cases reported by Hull et al. (2002) worked in a variety of capacities in the talc industry, some of which worked at more than one mine, with tenures ranging from 2 to 25 years. No information was provided regarding the remainder of the occupational histories of the cases. The authors also presented the results of lung fiber burden analyses from two of the mesothelioma cases (Case 1: 22 years in talc mining, Case 2: 4 years in talc mining) and eight non-mesothelioma cases (range: 2 to 30 years in talc mining); for fibers >1 μm in length, dimensions (length and width) and chemistry were determined. Both mesothelioma cases, and 6 of the 8 non-mesothelioma cases were diagnosed with both asbestosis and talcosis. Of the 6 non-mesothelioma cases, 2 were diagnosed with lung cancer and several were diagnosed with pleural plaques and silicosis.

The authors reported that, with the exception of mesothelioma Case 2, the concentrations of each fiber type within the lungs of mesothelioma and non-mesothelioma cases were similar, and there was no significant difference between the dimensions of the tremolite and talc fibers observed. Nonetheless, the results of the fiber burden analyses are difficult to interpret. For example, the tremolite/actinolite and anthophyllite fiber burdens reported for all cases have very little correlation with occupational tenure (the only metric of exposure evaluated). Furthermore, the observed ratios between the various fiber types are inconsistent. Likewise, the fiber burden results specifically reported for the two mesothelioma cases, suggest that the exposure profiles of the cases were substantially different. For instance, the tremolite/actinolite concentration in the case with the 4-year tenure (Case (2) was over 500 times that of the case with the 22-year tenure (Case 1). Also, despite the relatively high level of tremolite/actinolite reported, anthophyllite was not detected in the tissue from Case 2, while the anthophyllite burden for Case 1 exceeded that case's tremolite lung fiber burden by over two-fold.

These results presented by Hull et al. (2002) have been extensively criticized by others for reasons that include but are not limited to the following (Addison and McConnell 2008; Gamble and Gibbs 2008; Nolan et al., 2006; Price 2010):

- The occupational histories of the mesothelioma cases, as well as the non-mesothelioma cases are incomplete.
- The specific mine(s) at which the mesothelioma cases and non-mesothelioma cases were not reported.
- Immunological markers used for confirming the diagnoses of the three mesothelioma cases were so limited that diagnoses other than mesothelioma could not reasonably be excluded.
- The analytical technique used to identify the fibers (SEM) was insufficient to differentiate between minerals of similar chemical composition, but different crystal structures.
- The dimensions of the anthophyllite and tremolite "fibers" reported by Hull et al. (2002) are not consistent with those found for New York talc (NIOSH 1980; Siegrist and Wylie 1980).
- Fibers identified as anthophyllite in earlier lung content analyses of the cases reported by Hull et al. (2002) were later reported as talc fibers.
- Hull et al. (2002) inconsistently reported that the concentration of tremolite/actinolite experienced by Case 1 was at least one order of magnitude higher than previously reported by Abraham et al. (1990) for that case (identified by Abraham 1990 as Case 7) (Nolan et al., 2006).

Furthermore, Hull et al. (2002) did not compare the reported number of mesothelioma cases to an "expected" value, even though it is generally accepted that mesothelioma occurs in the general population in the absence of asbestos exposure; thus, this paper cannot be used to infer anything about mesothelioma risk among talc miners and millers (Attanoos et al., 2018; Moolgavkar et al., 2009; Price and Ware 2004; Teta

et al., 2008). As described by Finley et al. (2012), "[t]he numerous shortcomings and pitfalls associated with attempts to assess causation through the simplistic tallying of reported cases have been discussed at length" (FDA 2009; Feinstein 1988; Goodman et al., 2004; Greer et al., 2000; Huncharek et al., 1989; Husgafvel-Pursiainen et al., 1999; Sinks et al., 1994; Spirtas et al., 1985) (p. 113).

Hull et al. (2002) also described two studies that have previously reported an increased rate of mesothelioma in Jefferson County, New York (Enterline and Henderson 1987; Vianna et al., 1981). Vianna et al. (1981) evaluated the incidence of mesothelioma in New York state counties from 1973 through 1978. The authors reported that six "generally rural" counties (Seneca, Livingston, Steuben, Jefferson, Schoharie, and Schuyler), which were dispersed throughout the state, had mesothelioma incidence rates that were at least 2 times higher than that for the entire state of New York (p. 737). According to the authors, based on their review of death certificates, only 39.4% of the cases throughout the state were employed in occupations with known asbestos exposure. A total of 31 cases were reported in the six counties. Of these cases a "potential source of asbestos exposure" was reported for 24 cases (p. 737). Among the 24 cases, 4 males historically worked in talc mines, and 2 females were "talc workers" (p. 737). Vianna et al. (1981) discussed that "[c]ertain talc mines, particularly those located in St. Lawrence County, contain as much as 50% or more tremolite"; however, despite this observation, Vianna et al. (1981) offered no explanation as to why a similar increase in mesothelioma was not observed in St. Lawrence County. Furthermore, as of 2008, talc had not been mined in Jefferson County for over a century (Gamble and Gibbs 2008).

Finkelstein (2012) published a commentary in which he described the identification of at least five new cases of mesothelioma that occurred in the cohort evaluated by Honda et al. (2002) since the truncation of follow-up in 1989. The new cases were identified from information contained within public responses to a draft NIOSH Bulletin on asbestos and other EMPs, which was subsequently published in final form (NIOSH 2011). Five men (Cases 1–5) with variable occupational histories (two of which had known or suspected exposure to asbestos on Navy ships or in a Navy Yard), including prior to employment with Gouverneur Talc Company, were reportedly diagnosed with mesothelioma "at biopsy, surgery, or autopsy" (p. 3). There was a sixth man (Case 6) suspected of having mesothelioma, but a diagnosis of adenocarcinoma could not be excluded. These men died between 1994 and 2007 and at ages ranging from 64 to 86 years. A statistically significant increase in the incidence of mesothelioma relative to that of U.S. white men was reported (IRRs: 5 [95% CI: 1.6–11.7] to 6 [95% CI: 2.2–13.0]). Finkelstein noted that because he did not actually follow the Honda et al. cohort and, in turn, the true number of person-years was unknown to him, he made the "conservative assumption" that none of the men presumed to be alive at the end of follow-up in 1989 had died between January 1, 1990, and 2007, resulting in an "underestimation" of the rate of mesothelioma (p. 3, 6). To reinforce his position, Finkelstein hypothesized that "some cases of mesothelioma in the cohort have been missed" (p. 5-6). However, this claim by Finkelstein is merely speculative and without adequate justification.

Nolan et al. (2013) challenged the commentary by Finkelstein (2012), characterizing his reported IRRs as "only crude approximations" and the "occupational exposure histories" of these six cases as "incomplete," noting the potential for exposure to commercial asbestos in the prior occupational histories as possibly etiologically relevant (p. 1116-1117). Nolan and colleagues revealed that the website sourced by Finkelstein provided additional information indicating that the New York State tremolitic talc mesothelioma cases occurred in non-miners, even though the description provided by Finkelstein for Case 4 "suggested mine work" (p. 1117). In addition, they noted that "[i]f there were a fibrous carcinogen present in the workplace, one would expect the excess of mesotheliomas to occur in the same work area as the excess lung cancers" (p. 1117). However, the findings, which were almost entirely based on mill workers, were at-odds with the evidence in Honda et al. (2002), indicating that there was an excess of lung cancer in the miners, not millers. Nolan and colleagues noted that the only exception to their reasoning was Case 4, a miner; however, they countered with the evidence "he also worked in a naval yard for 1 year (prior to becoming a miner), a workplace well known to be associated with an increased risk of mesothelioma" (p. 1117). Finkelstein (2013) subsequently responded to these (and other) points that were raised by Nolan et al. (2013), in which he largely reiterated his alleged conservatively estimated IRRs and disputed alternative exposures.

In 1987, Enterline and Henderson evaluated the geographic patterns for pleural mesothelioma in the

United States from 1968 through 1981. The authors reported that Jefferson County, New York had the sixth highest mortality rate of pleural mesothelioma for males (7 cases) and the second highest mortality rate for females (4 cases). Notably, the authors relied on the ICD-9 code for "malignant neoplasms of the pleura, mediastinum, and unspecified sites" (i.e., ICD 163) as a proxy for mesothelioma, which has previously been shown to include cases of non-mesothelioma pleural malignancies (Davis et al., 1992; Enterline and Henderson 1987: p. 31). Hull et al. (2002) reported that there was a "continued trend of increased mesothelioma mortality at 5–10 times the background rate in Jefferson County from 1982 to 1997" after reportedly identifying a total of five new male cases and three new female cases (p. 134). However, according to Price (2010), Hull et al. (2002) "mischaracterized the trend" in mesothelioma mortality in Jefferson County (Price 2010: p. 524). In fact, Price (2010) reported that data from the New York State (NYS) Cancer Registry indicated that rates of mesothelioma were decreasing for males and remained constant for females, noting that "[a] mesothelioma rate that is constant over time suggests that the disease was not caused by asbestos (Price and Ware, 2004) and certainly not caused by talc exposure" (p. 522). Unlike Hull et al. (2002), more recent findings by Bang et al. (2006), which evaluated malignant mesothelioma mortality in the U.S. from 1999 to 2001, did not identify Jefferson County, New York as being among the 20 U.S. counties with the highest age-adjusted malignant mesothelioma mortality rates (Bang et al., 2006).

Beginning in 1999, NIOSH's National Occupational Respiratory Mortality System (NORMS) tracked U.S. deaths due to malignant mesothelioma over a 7-year period following the introduction of a specific International Classification of Disease (ICD) code for mesothelioma. According to NIOSH, when using the new mesothelioma ICD code, age-adjusted mesothelioma mortality rates in Jefferson County and St. Lawrence County, New York from 1999 to 2005 were "similar to the overall U.S. mesothelioma death rates for this same period" (NIOSH 2011: p. 21).

In summary, while several cases of mesothelioma have been reported in individuals potentially exposed to New York talc, many had very short occupational tenures or insufficient latency, and none of the epidemiology studies of these workers have reported an association between talc exposure and the development of mesothelioma. This is despite the fact that an increased risk of NMRD has been observed in highly exposed New York talc miners and millers. The lack of mesothelioma risk in New York talc miners and millers is consistent with what has been observed in other talc miner and miller cohorts (Finley et al., 2017; Fordyce et al., 2019; Ierardi and Marsh 2020; Pira et al., 2017; Wergeland et al., 2017), as well as other cohorts exposed to amphibole cleavage fragments (Gamble and Gibbs 2008; Garabrant and Pastula 2018).

Conclusions

Our findings demonstrate that inhaled cleavage fragments associated with talc do not pose a mesothelioma hazard, driven principally by the dimensional and structural differences between cleavage fragments and their asbestiform analogs. Specifically, cleavage fragments are typically less than 8 μm in length, with diameters much larger than asbestos fibers of the same length (at least 0.3 μm); thus, many are too thick to reach the pulmonary region of the lungs (>0.7 μm). Of the fraction of cleavage fragments that may be respirable, their morphology allows for rapid clearance from the lungs by alveolar macrophages, and few if any cleavage fragments greater than 5 μm in length will be thin enough (<0.1–0.4 μm) to translocate to the pleura. A review of the animal studies evaluating the toxicology of tremolite cleavage fragments in talc indicated that, even those meeting dimensional criteria of a fiber, generally do not produce mesothelioma in excess of background following injection or implantation. These observations are consistent with the lack of association between talc exposure and the development of mesothelioma in epidemiology studies of cohorts exposed to cleavage fragments, including that of the New York industrial talc miner and miller cohorts. Given all of these observations, the weight of the evidence does not support that exposure to talc-associated amphibole minerals is associated with the development of mesothelioma.

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