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RESEARCH ARTICLE

Occupational exposures to cosmetic talc and risk of mesothelioma: an updated pooled cohort and statistical power analysis with consideration of latency period

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ABSTRACT

Objectives: We previously published a pooled statistical power analysis of mesothelioma incidence in the Italian, Norwegian, Austrian, and French cosmetic talc miner and miller cohorts. Soon thereafter, updates to the Italian and Norwegian cohorts were published, providing an additional 14,322 person-years of observation. In this study, we provide an updated power analysis using the newly available information.

Methods: We pooled the current results regarding pleural cancer/mesothelioma mortality or incidence in four cosmetic talc miner and miller cohorts in Italy, Norway, Austria, and France. We used the expected numbers of cases as reported by the authors and the power analysis was based on an *a priori* one-sided significance level of 0.05 and Poisson distribution probabilities.

Results: There was a pooled total of 113,344 person-years in the cohorts. Although 3.0 pleural cancers/mesotheliomas were expected, there were no reported pleural cancer or mesothelioma cases in any cohort. Our pooled analysis was associated with 79 and 62% power to detect a 3.0-fold and 2.5-fold or greater increase in pleural cancer/mesothelioma, respectively. These favorable power characteristics were effectively maintained when restricting the pooled cohort to workers with a latency period of 30 or more years (observation time from first employment).

Conclusions: The epidemiological evidence from the cosmetic talc miner/miller cohort studies does not support the hypothesis that exposure to cosmetic talc is associated with the development of pleural cancer/mesothelioma.

Abbreviations: ACGIH: American Conference of Governmental Industrial Hygienists; ATS: American Thoracic Society; ATSDR: Agency for Toxic Substances and Disease Registry; CI: Confidence interval; CPSC: U.S. Consumer Product Safety Commission; FDA: U.S. Food and Drug Administration; IARC: International Agency for Research on Cancer; ICD: International Classification of Diseases; NIOSH: National Institute for Occupational Safety and Health; NMRD: Non-malignant respiratory disease; OSHA: Occupational Safety and Health Administration; RR: Relative risk; SMR: Standardized mortality ratio; TSFE: Time since first employment; USEPA: U.S. Environmental Protection Agency; WHO: World Health Organization; XRD: X-ray diffraction

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Introduction

Cosmetic talc has primarily been used in a variety of consumer products, for example, adult and baby dusting powders, makeup, antiperspirants and deodorants, lotions, hair care products, etc., as well as in other pharmaceutical and food applications (Zazenski et al. 1995; IARC 2010). Mines containing relatively pure (>95%) platiform talc are sourced for cosmetic talc used in these applications (Drechsel et al. 2018); the term platiform or 'platy' refers to a general morphology in which the length and width of a particle are long and approximately equal, while its thickness (or height) is shorter, which contributes to the desired smooth and lubricating properties of cosmetic talc (Campbell et al. 1977; Zazenski et al. 1995). Historically, talc used for cosmetic purposes in the U.S. has comprised only a small percentage of the total talc consumed (Zazenski et al. 1995; Bolen 2018).

Currently, no governmental agency or scientific body regulates or designates pure talc as a carcinogen (USEPA 1992; ACGIH 2001; IARC 2010). However, it has been acknowledged that some geological talc deposits may, in fact, contain other silicates, such as the amphibole minerals tremolite and anthophyllite, both of which can exist in fibrous and non-fibrous forms (also referred to as 'asbestiform' and 'non-asbestiform' structures, respectively) (IARC 2010). While the non-asbestiform types of these minerals do not possess biological activity and are not regulated as 'asbestos' (CPSC 1988; ATS 1990; OSHA 1992; Vu 1993; ATSDR 2001; Addison and McConnell 2008; Gamble and Gibbs 2008; Mossman 2008; Williams et al. 2013; Mossman 2018), sufficient exposures to the asbestiform varieties can

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pose a risk of mesothelioma and other asbestos-related respiratory health effects (Finley et al. 2012). Clearly, if an amphibole mineral is present in a cosmetic talc mine, it is critical to understand whether it is asbestiform or non-asbestiform.

By the early 1970s, some of the major cosmetic talc source mines, including the Val Chisone mine in northern Italy, were shown to contain no detectable levels of asbestiform minerals (Lightfoot et al. 1972). However, in the mid-1970s, researchers at Mt. Sinai claimed to have measured elevated levels of asbestos mineral in numerous cosmetic talc products (Rohl et al. 1976). Following the publication of their initial study, Rohl et al. (1976) acknowledged that the method employed in their 1976 study (i.e. X-ray diffraction [XRD]) was not capable of distinguishing between asbestiform and non-asbestiform minerals (Rohl and Langer 1979). Recently, the International Agency for Research on Cancer (IARC) working group also concluded that the Rohl et al. (1976) analysis of cosmetic talc did not differentiate between asbestos and non-asbestiform minerals, and that because of potential interferences, 'little reliance' was placed on the results (IARC 2010, p. 304). Nonetheless, there continues to be some debate on this issue. For example, Gordon et al. (2014) recently claimed to have measured 0.004–0.9% by weight asbestos fiber in bulk samples of cosmetic talc. Using different analytical methods, Anderson et al. (2017) analyzed the same product and concluded there was no detectable asbestos fiber.

Even if trace levels of asbestos fiber were consistently found to be present in cosmetic talc products, one would still need to address the question of whether or not asbestos exposures during personal talc use would be sufficient to increase the risk of asbestos-related disease. To our knowledge, there are no published epidemiology studies of mesothelioma risk in cosmetic talc users. However, there are several published studies of disease incidence in miners and millers of cosmetic talc. If it is true that asbestos fibers are present in cosmetic talc at levels sufficient to pose a consumer health risk, then it is reasonable to expect that miners and millers of cosmetic talc would be at a high risk of asbestos-related disease due to the much greater and more prolonged occupational talc exposures (USEPA 1992).

As of 2016, there were several published epidemiology studies of miners and millers employed at cosmetic talc mines in Italy (Rubino et al. 1976; Rubino et al. 1979; Coggiola et al. 2003), Norway (Wergeland et al. 1990), Austria (Wild et al. 2002), and France (Wild et al. 2002). None of these studies reported a single death or incident case (only the Norwegian cohort was evaluated for incident cases; deaths and incident cases are referred to in this paper generically as 'cases') of mesothelioma or pleural cancer (mesothelioma is a specific form of pleural cancer and both diseases are referred to as 'mesothelioma' in this paper unless a specific reference to pleural cancer is warranted). In 2017, we published a pooled statistical power calculation of mesothelioma mortality/incidence in the aforementioned cohorts (Finley et al. 2017), and determined that 4.0 mesothelioma cases would have been expected from the combined 99,022 person-years of observation. This finding was associated with 84 and 67% statistical power to observe a 3.0-fold or greater and 2.5-fold or greater increase in pleural mesothelioma mortality, respectively. We concluded that these findings did not support a belief that cosmetic talc use was a risk factor for mesothelioma. Soon after our original analysis was published, Pira et al. (2017) and Wergeland et al. (2017) published updates to the Italian and Norwegian cohorts, respectively. In this article, we report an updated power analysis to the original Finley et al. (2017) pooled analysis using previously unavailable information from the updated Italian and Norwegian cohorts.

Materials and methods

Pooled analysis

Since the publication of Finley et al. (2017), we identified two updated studies for the Italian and Norwegian cohorts: Pira et al. (2017) provide an update to the Italian cohort, most recently described by Coggiola et al. (2003), while Wergeland et al. (2017) provide an update to the Norwegian cohort, previously described by Wergeland et al. (1990). In our original analysis, we estimated expected mesothelioma counts for each cohort. With the publication of Pira et al. (2017) and Wergeland et al. (2017), expected values (as calculated and reported by the study authors) now exist for each cohort. These expected values were used in this assessment to estimate the total number of expected mesotheliomas in the pooled cohort.

To evaluate the extent to which it was possible for the combined studies to detect important true elevations in mesothelioma risk, we updated our pooled statistical power analysis using the reported expected values. As in our original power analysis (Finley et al. 2017), because a reduced risk of mesothelioma resulting from exposure to cosmetic talc is an implausible event, our power analysis focused on detecting only elevated mesothelioma risks. Thus, we entered into our pooled analysis with the *a priori* alternative hypothesis (H_A) that the relative risk (RR; estimated using standardized mortality or incidence ratios) for mesothelioma among cosmetic talc miners and millers would be greater than that expected in the corresponding general reference populations (i.e. H_A: RR $>$ 1.0), and used a 5% one-sided significance test to test the null hypothesis (H_0) of no excess risk (i.e. H_0: RR $=$ 1.0). Power calculations were based on exact Poisson distribution probabilities as described by Breslow and Day (1987).

Latency analysis

Because mesothelioma has a latency of approximately 20–40 years (Mazurek et al. 2017), we sought to quantify the total number of expected mesotheliomas contributed by those individuals across the various cosmetic talc cohorts who had a latency period (calculated as the time since first employment [TSFE] until death or end of observation period) of at least 30 years. A latency analysis was performed for each

cohort using person-years data reported in or estimated from each cohort study, as well as age-specific pleural mesothelioma rates for males in each country (Italy, Norway, France, and Austria), as calculated from mortality and population data obtained from the World Health Organization (WHO) Mortality Database (accessed 24 April 2019) for all years available between 1980 and 2016. Until the 10th revision of the International Classification of Diseases (ICD-10), pleural mesothelioma was not assigned a specific code. As such, deaths attributed to pleural mesothelioma were coded as pleural cancer in earlier revisions of the ICD (e.g. ICD-9 and -8). We used combined pleural mesothelioma (ICD-10; C45.0) and pleural cancer (ICD-9 and -8; 163) deaths to calculate age-specific rates, and, as mentioned above, refer to these two outcomes as 'mesothelioma.'

For the purposes of our analysis, we assumed that each individual began employment at age 20–29, and so would have accrued 30 or more years of employment (TSFE/latency) when they reached age 50–59. Thus, the age distribution of cohort members in the longer TSFE/latency period categories would be older and associated with much higher rates of mesothelioma than those in the shorter TSFE/latency period categories (Moolgavkar et al. 2009, 2017; Boffetta et al. 2018). In fact, Moolgavkar et al. (2009; 2017) show that the age-specific incidence rates of pleural mesothelioma increase continuously with age and that every doubling of age increases the risk of pleural mesothelioma approximately 30-fold. Thus, mesothelioma rates increase in an exponential fashion with age, being very low and relatively constant up to about age 50 when they begin to increase dramatically and continue to increase throughout life.

Results

Pooled analysis

Following the publication of Finley et al. (2017), both the Italian and Norwegian cosmetic talc cohorts were updated to include an additional 14,322 person-years of observation. Specifically, the Italian cohort follow-up period was extended 19 years (Pira et al. 2017) and the Norwegian cohort was extended 24 years (Wergeland et al. 2017). Pira et al. (2017) reported that almost 20,000 person-years in the Italian cohort came from individuals who had at least 30 years since first employment. For the two updated cohorts, the authors specifically stated that none of the study subjects developed a pleural cancer of any type and, for the first time, an expected value for pleural cancers (or mesothelioma) was presented for each study (Table 1). Pira et al. (2017) did identify two deaths from peritoneal cancers, but specifically noted that these were neoplasms other than mesothelioma. Both Pira et al. (2017) and Wild et al. (2002) used regional rates as the default standard population for calculating expected numbers of pleural cancer or mesothelioma deaths, respectively, using national rates only for earlier time periods when regional rates were unavailable (regional

Table 1. Updated and original cohort studies included in a pooled analysis of pleural cancers/mesotheliomas associated with employment as a cosmetic talc miner or miller.

Study	Employment	Follow-up period	Additional years of follow-up	Location	Sample size	ICD version	Person-years	Reference population for expected deaths or incident cases	Observed mesotheliomas	Expected mesotheliomas reported by authors	Observed pleural cancers	Expected pleural cancers reported by author	Combined expected cancers reported
Pira et al. (2017)[a]	1946–1995	1 January 1946 to 31 March 2013	19 years	Italy	Miners = 1166 Millers = 556	9	59,339	Regional and National[b]	0	NA	0	2.0	2.0
Wergeland et al. (2017)[c]	1944–1972	1 January 1953 to 31 December 2011	24 years	Norway	Miners = 94 Millers = 296	7	15,687	National[d]	0	NA	0	0.6	0.6
Wild et al. (2002)	1945–1994	1 January 1945 to 31 December 1996	Not updated	France	Miners and millers = 1070	8 and 9	28,849	Regional and National[e]	0	0.3	NA	NA	0.3
	1972–1995	1 January 1973 to 31 December 1995	Not updated	Austria	Miners and millers = 542	8 and 9	9469	Regional[f]	0	0.1	NA	NA	0.1

[a]Previous analysis of the Italian cohort by Coggiola et al. (2003) included 1795 miners and millers, comprising 50,701 person-years, followed from 1 January 1946 to 31 December 1995.
[b]Regional rates were used for the period 1970 to 2013; national death rates were used for the period 1950 to 1969. Rates were not available for the period 1946 to 1949, for which 1950 to 1954 national rates were used.
[c]Previous analysis of the Norwegian cohort by Wergeland et al. (1990) included 94 miners, employed starting in 1944, and 295 millers, employed starting in 1935, comprising 10,003 person-years total, followed from 1 January 1953 to 31 December 1987.
[d]National rates were used, as these were recorded in the same national cancer registry used to identify pleural cancer incident cases.
[e]Local (département de l'Ariège) and national mortality rates were used. Local mortality rates were only available since 1968.
[f]Regional rates of the federal state of Styria were exclusively used.
NA: Not applicable.

Table 2. Statistical power analysis based on the minimum detectable relative risk and expected mesothelioma counts (at one-tailed 0.05 significance level).

Expected mesothelioma cases (rounded)	Minimum detectable relative risk (SMR > 1.0)			
	1.5	2.0	2.5	3.0
1	0.07	0.14	0.24	0.35
2	0.08	0.21	0.38	0.55
3	0.17	0.39	0.62	0.79
4	0.15	0.41	0.67	0.84

rates were used exclusively by Wild et al. (2002) for the Austrian cohort). Wergeland et al. (2017) used only national incidence rates to compute expected pleural cancer cases, as these were recorded in the same national cancer registry used to identify pleural cancer cases.

Using the reported expected values for pleural cancer, as well as the Wild et al. (2002) estimate of expected mesothelioma deaths, we would expect to have observed 3.0 pleural cancers/mesotheliomas in the updated analysis (Table 1). We note that Wild et al. (2002) reported expected counts specifically for mesothelioma. Thus, our pooled expected number of pleural cancers of 3.0 is the lower limit of expected cancers for this analysis because mesothelioma is a subcategory of pleural cancers.

Table 2 shows the results of our statistical power analysis for expected numbers of mesothelioma cases ranging from 1 to 4, and minimum detectable relative risks (expressed as standardized mortality ratios [SMRs]) ranging from 1.5 to 3.0. Using the pooled collection of original and updated studies (with 3.0 expected cases), we now have 79 and 62% power to detect a 3.0-fold or 2.5-fold or greater increase in mesothelioma, respectively. These results are not materially different from our previous findings based on 4.0 expected cases (84 and 67%, respectively) (Finley et al. 2017).

For the sake of clarity, we note that Table 2 includes a counterintuitive finding where statistical power does not increase monotonically with increasing expected cases for a minimum detectable relative risk of 1.5 (3.0 expected cases, power = 17%; 4.0 expected cases, power = 15%). This seemingly discrepant pattern in Table 2 (Table 3 in Finley et al. (2017)) stems from the use of the discrete Poisson probability distribution to calculate exact statistical power values. That is, statistical power is found by summing discrete Poisson probability values rather than finding the corresponding area under a smooth curve, such as the normal distribution, which approximates exact Poisson probabilities when the expected number of events is sufficiently large. Especially with small expected numbers, such as 3.0 or 4.0, relatively larger jumps occur in the probability values between discrete counts of events, which can lead to this non-monotonic pattern in statistical power values. For 3.0 expected events, Figure 1 illustrates this area discrepancy when attempting to find the critical value corresponding to a right tail area or p value of 0.05 (5.8 for normal distribution and 7 for the Poisson [the largest tail area under the Poisson distribution that does not exceed 0.05 is 0.0335]).

We also note that with 3.0 expected mesotheliomas, 7 or more mesotheliomas (or an SMR of $7/3 = 2.33$ or greater) would need to be observed across the three pooled cohort studies to reject at the 0.05 significance level the null hypothesis of no association (i.e. SMR = 1.0) between exposure to cosmetic talc and mesothelioma. This result is illustrated in Figure 2(A) along with the associated statistical power to detect a 1.5-fold or greater increase in risk, corresponding to $3 \times 1.5 = 4.5$ expected cases (Figure 2(B)) using the same critical value (X = 7) used in Figure 2(A). As in Figure 1, the sum of the tail probabilities in Figure 2(A) (0.0335) is the p value associated with 7 or more observed events and 3.0 expected events, and Figure 2(B) shows the corresponding statistical power based on 4.5 expected events (as in Table 2 or 17%). For 4.0 expected events, a similar analysis (not shown) yields a critical value of 9 or more observed events and statistical power of 15% to detect a 1.5-fold increase in risk, corresponding to $4 \times 1.5 = 6.0$ expected cases (Table 2).

Latency analysis

The results of our latency (TSFE) analysis are summarized here and in Table 3. Details of the cohort-specific TSFE analyses are provided in the Appendix. Overall, the percent of total person-years (113,345) observed across all cohorts comprised by those individuals with TSFE of at least 30 years are 33, 85, 22, and 20%, for the Italian, Norwegian, French, and Austrian cohorts, respectively. Remarkably, although cohort members with TSFE of at least 30 years contributed only 41,133 or 36.3% of the total person-years of observation, these workers were at a much greater risk of developing mesothelioma due to their older ages (50+ years). Specifically, Table 3 shows that mesothelioma rates among miners and millers aged 50+ years were approximately 37 (Austria) to 124 (France) times greater than the rates among workers aged less than 50 years. Because of this pattern, 2.77 or 97.9% of the 2.82 total expected mesotheliomas occurred among workers with TSFE of at least 30 years (TSFE 30+). We note that the total number of expected mesotheliomas in Table 3 (2.82) differs only slightly from that reported in Table 1 (3.0) due to our use of different standard rates to estimate expected deaths. Proportionally, using 3.0 expected mesotheliomas, 2.94 would have been expected among workers with TSFE 30+.

The latency analysis shows that our reported statistical power of 79 and 62% to detect a respective 3.0-fold or 2.5-fold or greater increase in mesothelioma among the overall pooled cohort of talc miners and millers is effectively maintained within the pooled subcohort of workers with TSFE 30+.

Discussion

Importance of the Italian and Norwegian cohort updates

To our knowledge, the initial pooled analysis (Finley et al. 2017) of the cosmetic talc cohort studies was the first attempt to quantitatively address the concern of insufficient statistical power in the four individual cohorts. Another

Table 3. Expected number of pleural mesotheliomas by age group (aged 20–49 *vs.* 50+ or TSFE <10–29 *vs.* 30+) in cosmetic talc cohorts.

Cohort	Total person-years	Percent (%) person-years with TSFE 30+[e]	Person-years by TSFE		Age-specific pleural mesothelioma rates for males[f]		Expected mesotheliomas		Total expected mesotheliomas
			TSFE <10–29	TSFE 30+	TSFE <10–29	TSFE 30+	TSFE <10–29	TSFE 30+	
Italy[a]	59,340[d]	33	39,782	19,558	0.0974	9.27	0.0387	1.81	1.85
Norway[b]	15,687	85	2353	13,334	0.105	4.36	0.00246	0.581	0.584
France[c]	28,849	22	22,502	6347	0.0360	4.47	0.00811	0.284	0.292
Austria[c]	9469	20	7575	1894	0.124	4.61	0.00936	0.0874	0.0967
Total	113,345	37	72,212	41,133	–	–	0.0587	2.77	2.82

TSFE: Time since first employment until death or end of observation period.
[a]Pira et al. (2017).
[b]Wergeland et al. (2017).
[c]Wild et al. (2002).
[d]The authors reported that their Italian cohort members contributed 59,339 total person-years of observation. However, the person-years in Table 4 of their paper sum to 59,340. The numbers as reported in Table 4 of Pira et al. (2017) were used, as the difference of 1 person-year is not expected to have any significant impact on our latency analysis.
[e]Provided by authors or estimated from available data in each study.
[f]Based on mortality and population data obtained from the WHO Mortality Database (per 100,000 population).

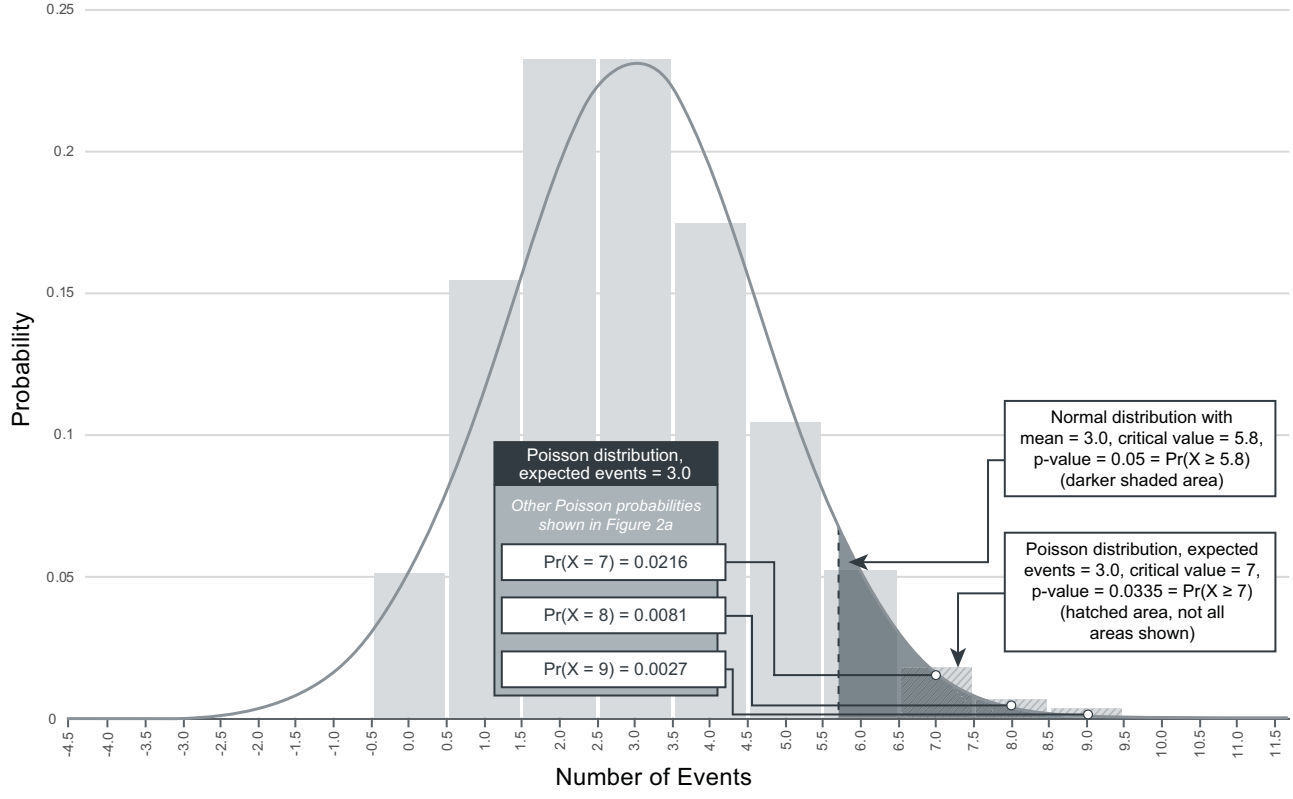

Figure 1. Discrepancy between *p* values using normal and Poisson distribution.

concern that we addressed and discuss below in this article was insufficient latency period for the development of mesothelioma. With the publication of the two new updates of the Italian and Norwegian cohorts, these cohorts now comprise approximately 80% of the total person-years accrued by workers with 30 or more years from first employment (latency period; Table 3). Specifically, Pira et al. (2017) reported that '[t]he very long TSFE in the present analysis (over 9000 person-years of observation, or 16% of the total, had more than 40 years since first employment) excludes the possibility that the lack of cases of mesothelioma is a consequence of insufficient latency' (Pira et al. 2017, p. 663). Regarding the Norwegian cohort, Wergeland et al. (1990) noted that '85% of all subjects in the present study have a follow-up TSFE of 20 years or more' (Wergeland et al. 1990, p. 510). In the 2017 update, the Norwegian cohort follow-up was extended an additional 24 years (Table 1), so we can now conclude that 85% of this cohort has a follow-up TSFE of at least 40 years. Therefore, the increased latency of the Italian and Norwegian cohorts is a major strength of our current pooled analysis.

Specific issues related to the Italian cohort

Our current findings are further reenforced by an evaluation of workers excluded from the Pira et al. (2017) analysis. Pira et al. (2017) censored participants who were 85 years of age or older at the time of their death. We agree with the

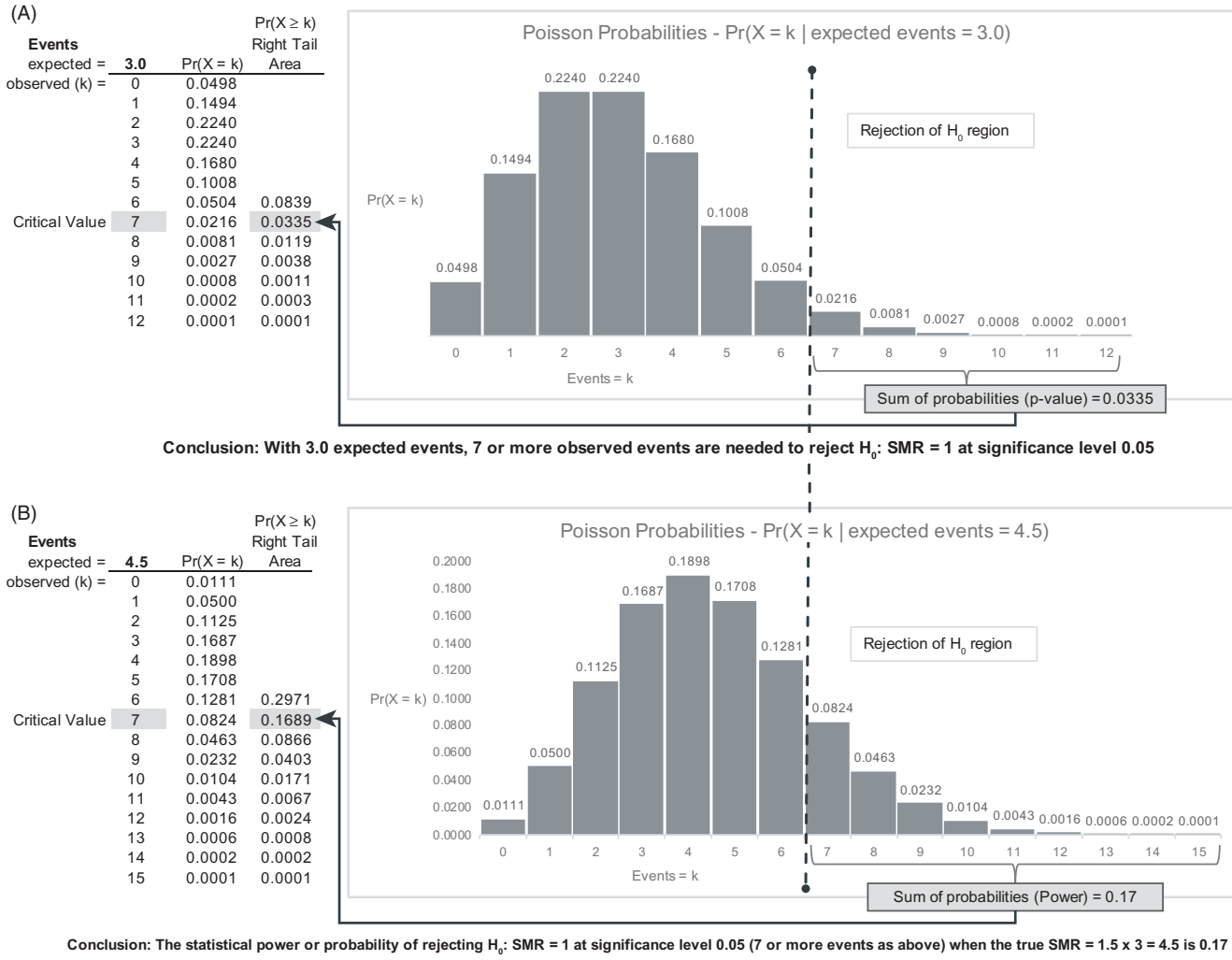

Figure 2. Poisson probability distributions with number of expected events = 3.0 and 4.5.

authors' decision to exclude these individuals from their study, as it has been shown that the accuracy of mesothelioma diagnoses made *via* death certificates decreases as age increases (Selikoff 1992). Yet, it is well known that the risk of mesothelioma increases exponentially with age (Moolgavkar et al. 2017), so it is possible that death(s) due to mesothelioma could have occurred in one or more of the censored individuals. We requested data from the authors regarding the number of individuals who were censored and their respective causes of death. We were able to ascertain the cause of death for the 115 individuals who were excluded from Pira et al. (2017). None of these participants experienced a death due to mesothelioma (Pira et al. 2018, Personal Communication). If we were to include all censored individuals (those still alive, and those who died within the follow-up period), the person-time observed for the Italian cohort, as well as the expected number of mesotheliomas (and associated statistical power), would increase.

It was recently suggested that a case of pleural mesothelioma occurred in a 'maintenance worker' who was previously employed at the Italian mine (Mirabelli 2017, 2018). However, Pira et al. (2018) were not able to identify this individual in their cohort roster and, as such, they concluded that '[t]he number of observed deaths from pleural mesothelioma in [their] cohort therefore remains zero' (Pira et al. 2018, p. e73). Mirabelli acknowledged that even if this 'mesothelioma' had been included in the original analysis, Pira et al.'s (2017) 'finding of no excess risk of mortality from pleural cancer would not have changed' (Mirabelli 2018, p. e72).

It is worth noting that Pira et al. (2017) reported that the number of observed deaths in their cohort attributed to pneumoconiosis was significantly higher than expected, yielding an SMR for pneumoconiosis of 26.62 (95% CI = 20.71–33.69), a larger excess than reported for non-neoplastic 'respiratory tract diseases' in the previous cohort update (SMR = 22.82 [95% CI = 19.02–27.15]) (Coggiola et al. 2003, p. 65). Notably, the number of expected deaths in the Pira et al. (2017) cohort due to pneumoconiosis ($n = 2.6$) was similar to that of mesothelioma ($n = 2.0$), yet the authors observed 69 deaths due to pneumoconiosis and 0 deaths due to mesothelioma. As we previously noted (Finley et al. 2017), the excess risk of pneumoconiosis in the Italian cohort is important because it indicates that these workers were exposed to very high levels of cosmetic talc, levels well beyond those ever encountered by cosmetic talc consumers.

If cosmetic talc exposures were associated with an increased risk of mesothelioma, it would likely be observed in these workers who experienced very high exposures. However, not one case of mesothelioma was observed.

Pira et al. (2017) used regional (Piedmont) mesothelioma rates to estimate the expected number of mesothelioma deaths in the Italian cohort. Because there were several active asbestos industries in Piedmont, it has been claimed that the use of regional mesothelioma rates may lead to an overestimate of expected deaths for the Italian cohort (Finkelstein 2017; Mirabelli 2017). Marinaccio et al. (2018) specifically reported that among women in the Piedmont region, 'both environmental and familial exposures contribute to the female mesothelioma clusters, attributable to large asbestos cement plants' (Marinaccio et al. 2018, p. 260). In addition, there are numerous ongoing sources of non-occupational asbestos exposures throughout the region, including: (1) naturally-occurring tremolite outcroppings located near the Val Chisone cosmetic talc mine (Mirabelli and Cadum 2002), (2) asbestos cement sheeting that was used for roofing material in the Italian Western Alps (Frassy et al. 2014), and (3) asbestos waste material, such as the powdered *polverino*, which was used as thermal attic insulation, garden amendment, and roadbed fill (Coggiola and Graziadei 2013). These sources of asbestos should be considered when discussing non-occupational exposures that may occur in this region.

There is strong evidence that these non-occupational asbestos exposures in the Piedmont region were sufficient to increase mesothelioma risk. For example, Piedmont has the highest proportion of mesothelioma cases attributed to non-occupational exposures in all of Italy (24.4%, as reported in Marinaccio et al. (2015)), which is consistent with the fact that the rate of mesothelioma for women in the Piedmont region (3.18 per 100,000) is higher than any other region across Italy and is almost three times the female national rate (1.25 per 100,000) (Marinaccio et al. 2012).

If non-occupational asbestos exposures are a significant risk factor for mesothelioma in the Italian cosmetic talc miners and millers, then use of national rates or rates from other regions would almost certainly lead to an underestimation of expected mesotheliomas for this cohort. As described in the Magnani et al. (2008) analysis of cement workers in the Piedmont region: '[m]ortality in the cohort was compared to regional rates, which are more appropriate because of the wide regional differences in respiratory cancer mortality in Italy. As regards pleural cancer, comparison with the regional rather than the national population is also more appropriate because mortality from pleural cancer is higher in Piedmont, and in general varies widely among Italian regions' (Magnani et al. 2008, p. 168).

Regarding the alleged presence of asbestos in the Italian cosmetic talc mines, Mirabelli (2017) stated that 'low-level exposure to airborne asbestos fibers was indeed reported by Rubino et al. (1976)' (Mirabelli 2017, p. 341). However, Rubino et al. (1976) did not report the presence of airborne asbestos fibers at the mine, nor did they claim there was any 'exposure' to such fibers. On the contrary, Rubino et al. (1976) consistently emphasized the purity of the Italian talc: 'This particular talc has been mined for many decades and has continued to be recognized to be of the highest standard of purity' and 'our conclusions support the thesis of no cancerogenic effect attributable to pure talc' (Rubino et al. 1976, p. 186, 192). The authors referenced a report authored by Dr. Pooley and colleagues in which samples from the Val Chisone mines and mills, as well as historical samples of talcum powders produced from these mines/mills, were analyzed by optical and electron microscopy, in addition to X-ray diffraction (Lightfoot et al. 1972). In their report, the investigators identified tremolite and actinolite mineral in the footwall contact rocks and rock inclusions, but noted that this amphibole mineral was 'hardly fibrous,' and that '[n]o amphibole or chrysotile mineral was detected in any of the numerous powders examined' (Lightfoot et al. 1972). Any trace amphibole mineral present in the mines is likely not of any biological significance (i.e. non-asbestiform), which is supported by the lack of mesotheliomas in the pooled cohort (Pira et al. 2017).

Latency analysis

As hypothesized, the total number of expected mesotheliomas among the cosmetic talc cohorts assessed herein was driven primarily by the older age groups in each respective cohort; these individuals had longer latency (TSFE) periods and considerably higher rates of pleural mesothelioma/cancer. Indeed, we found that while cohort members with TSFE 30+ years contributed only 36.3% of the total person-years of observation in the pooled cohort, they generated nearly all (97.9%) of the total expected mesotheliomas, rendering our statistical power values for the total cohort effectively unchanged for the subcohort of workers with TSFE 30+. A limitation of our latency analysis was the need to estimate the numbers of person-years in the Norwegian, French, and Austrian cohorts among workers with TSFE 30+ because these were not reported directly by the authors. However, as we note in the Appendix, any bias in our estimates would lead to conservative underestimates of person-years for workers with TSFE 30+, resulting in fewer expected deaths and lower statistical power (Table 2). Our latency analysis for the Italian cohort, which comprised the majority (59,340 or 52%; Table 3) of person-years accrued by the pooled cohort, were exact, as the number of workers with TSFE 30+ was reported by the authors (Pira et al. 2017).

Additionally, the age-specific pleural mesothelioma rates as calculated from the WHO Mortality Database represent national rates rather than regional rates. As we noted above, the use of national rates would likely lead to an underestimation of expected mesotheliomas for the cosmetic talc miner and miller cohorts, especially with regard to the Italian cohort, which is evidenced by the 2.82 total expected mesotheliomas calculated in the latency analysis *vs.* 3.0 expected mesotheliomas as reported in the original studies. However, age-specific regional mesothelioma rates were

unavailable for these cohorts; as such, national rates were used as the best available alternative. Furthermore, it was not our intent to use exact rates to derive absolute numbers for total expected mesotheliomas for each cohort. Rather, our goal with the latency analysis was to estimate the relative number of expected mesotheliomas in the TSFE 30+ group in order to help demonstrate that the majority of expected mesotheliomas would occur in this older age group. If we applied an adjustment factor to the national rates to reflect regional rates, we would have expected 2.94 total mesotheliomas (97.9%) in the TSFE 30+ group.

Finally, our latency analysis assumed that all cohort members were hired at age 20–29. Any bias or overestimation of expected mesotheliomas from workers actually entering employment before age 20 could have been more than offset by the underestimation of expected mesotheliomas from workers actually entering employment after age 29, as the latter group would have reached the 30+ TSFE/latency in relatively older age groups associated with even higher mesothelioma rates (Moolgavkar et al. 2009, 2017; Boffetta et al. 2018).

The Vermont cohort

In 1979, Selevan et al. reported on the health effects observed in a cohort of miners and millers at Vermont cosmetic talc facilities (Selevan et al. 1979). We chose not to include the Vermont cohort in our pooled analysis because, although the authors did not report any cases of mesothelioma, they also did not explicitly state that they assessed mesothelioma as a disease endpoint. For the purposes of a sensitivity analysis, we calculated the expected number of mesotheliomas in the Vermont cohort, following the power analysis methodology described above. The Vermont cohort contributed an additional 7682.6 person-years to our analysis (Selevan et al. 1979). Based on U.S. national and state-specific age-adjusted background mesothelioma rates as reported by Henley et al. (2013), the expected number of mesotheliomas for the Vermont talc cohort would be less than 0.16, which would minimally affect our expected number of mesotheliomas of 3.0 and statistical power calculations from the pooled cohort studies of Italian, Norwegian, Austrian, and French miners and millers. As such, we maintain that 3.0 is the lower limit of expected mesotheliomas for our pooled analysis.

Similar to the alleged Italian mesothelioma mentioned above, a case of mesothelioma in 'one Vermont talc man' from the Selevan et al. (1979) cohort was referenced in a published National Institute for Occupational Health and Safety (NIOSH) conference proceeding from 1990 (Lamm and Starr 1990, p. 1577). The authors did not provide any further information pertaining to this claimed Vermont mesothelioma case, and the case has never been verified. Regardless, even if both of the claimed mesotheliomas from the Italian and Vermont cohorts are regarded as 'confirmed' mesothelioma cases and included in the pooled analysis, we still calculate an SMR that is below the expected value (2 observed/3.0 expected, SMR = 0.66 [95% CI = 0.08–2.41]).

Relevance to cosmetic talc users

The ongoing debate regarding the potential absence/presence of trace levels of asbestos fibers in cosmetic talc appears to be largely irrelevant to the question of whether personal cosmetic talc use poses a risk of mesothelioma. Specifically, irrespective of whether trace fiber levels are or are not present in cosmetic talc, the fact is that the epidemiological evidence indicates that even significant occupational exposures to cosmetic-grade talc do not increase the risk of mesothelioma. Therefore, it can be concluded that the far lower cumulative exposures associated with brief and intermittent personal use are unlikely to pose a health risk (Burns et al. 2019). This conclusion is consistent with the U.S. Food and Drug Administration's (FDA) decision in the mid-1980s not to require an asbestos warning hazard on cosmetic talc products (Swanson 1986). Underlying that decision was FDA's hypothetical exposure and health risk assessment, which concluded that even if trace levels (<0.1%) of asbestiform mineral were present in cosmetic talc products, the cumulative asbestos inhalation exposure would be too low to increase the consumer risk of mesothelioma (Brown 1985; Swanson 1986).

Conclusion

Data pooling is a conventional, well-recognized statistical method that imposes a common data analysis strategy across studies allowing new associations to be identified that may be unrecognized within individual cohort studies that may lack statistical power (Checkoway et al. 2004). The cosmetic talc miner and miller cohort studies represent a good example of a collection of studies that can be pooled based on similar epidemiological designs (historical cohort) and occupational exposures (cosmetic talc) in order to elucidate potential risk of disease. The results of the current pooled power analysis, which accounts for a total of 113,344 person-years of observation from the Italian, Norwegian, French, and Austrian cohorts, has 79% power to detect a 3.0-fold or greater increase in pleural cancers and 62% power to detect a 2.5-fold or greater increase in pleural cancers. These power characteristics were effectively maintained when restricting the pooled cohort to workers with 30 or more years from first employment. No mesotheliomas have been confirmed in any of these cohorts, and we determined that 7 or more mesotheliomas would need to be observed across the pooled cohort studies to conclude that there might be an association between cosmetic talc exposure and mesothelioma. We conclude that the current epidemiological evidence does not support a hypothesis that exposure to cosmetic talc is associated with the development of pleural mesothelioma.

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Disclosure statement

All of the authors are employed by Cardno ChemRisk, a consulting firm that provides scientific advice to the government, corporations, law firms, and various scientific/professional organizations. GMM is also Professor of Biostatistics and Director and Founder, Center for Occupational Biostatistics and Epidemiology at the University of Pittsburgh, Graduate School of Public Health. This manuscript was prepared and written exclusively by the authors. No organizations other than Cardno ChemRisk were aware of the preparation of this manuscript, and no other organizations other than Cardno ChemRisk reviewed any part of this manuscript prior to its submission for publication. Two of the authors (BLF, GMM) have served as defense experts in cosmetic talc-related litigation.

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Appendix: Cohort-specific latency (TSFE) analysis

Italy

For the Italian cohort, Pira et al. (2017) tabulated in their Table 4 the specific number of person-years associated with four TSFE groups: <20 years = 26,206 person-years; 20–29 years = 13,576 person-years; 30–39 years = 10,206 person-years; and 40+ years = 9352 person-years. As such, cohort members with TSFE 30+ years and TSFE <10–29 contributed 19,558 (33%) and 39,782 person-years (67%), respectively. The average age-specific pleural mesothelioma mortality rates (per 100,000) from 2006 to 2015 for Italian males aged 20–49 (TSFE <10–29) and 50+ (TSFE 30+) were 0.0974 and 9.27, respectively. Therefore, the expected number of mesotheliomas in the TSFE <10–29 group was 0.0387 and that of the TSFE 30+ group was 1.81, totaling 1.85 mesotheliomas. This value is approximately equal to the 2.0 expected mesotheliomas value as reported by Pira et al. (2017).

Norway

Wergeland et al. (2017) did not provide a breakdown of person-years by TSFE groups. However, in their 1990 paper, the authors reported that 85% of all subjects had a follow-up time since first employment of 20 years or more (Wergeland et al. 1990). The Norwegian cohort was extended 24 years from the 1990 paper to the 2017 update. Therefore, we assumed that 85% of this cohort had a TSFE of at least 40 years. Overall, the cohort contributed a total of 15,687 person-years of observation. For the purposes of our analysis, we conservatively assumed that 85% of the cohort had a TSFE of at least 30 years; thus, cohort members aged 50+ (TSFE 30+) contributed 13,334 person-years (85%) of observation, while those aged 20–49 (TSFE <10–29) contributed 2353 person-years (15%). Average age-specific pleural mesothelioma mortality rates (per 100,000) from 1986 to 2015 for Norwegian males were 0.105 for those aged 20–49 (TSFE <10–29) and 4.36 for those aged 50+ (TSFE 30+). Therefore, the expected number of mesotheliomas in the TSFE <10–29 group was 0.00246 and that of the TSFE 30+ group was 0.581, totaling 0.584 mesotheliomas. This value is approximately equal to the 0.6 expected mesotheliomas value as reported by Wergeland et al. (2017).

France and Austria

In terms of TSFE information, the French and Austrian cohorts (Wild et al. 2002) had the least available data. The French cohort members contributed a total 28,849 person-years of observation. The average age-specific pleural mesothelioma mortality rate (per 100,000) from 2005 to 2014 for French males aged 20–49 (TSFE <10–29) was 0.0360 and for those aged 50+ (TSFE 30+) was 4.47. We assumed that 22% of the total person-years were contributed by those with TSFE 30+ in order to calculate the number of expected mesotheliomas close to the

total reported by the authors for this cohort (0.3). Therefore, the expected numbers of mesotheliomas in the TSFE <10–29 group was 0.00811 and that of the TSFE 30+ group was 0.284, totaling 0.292 mesotheliomas.

In the Austrian cohort (the smallest cohort of all the studies), there were a total of 9469 person-years of observation. The average age-specific pleural mesothelioma mortality rate (per 100,000) from 1991 to 1998 and from 2002 to 2016 for Austrian males aged 20–49 (TSFE <10–29) was 0.124 and for those aged 50+ (TSFE 30+) was 4.61. We assumed that 20% of the total person-years were contributed by those with TSFE 30+ in order to calculate the number of expected mesotheliomas close to the total of 0.1 reported by the authors for this cohort. Therefore, the expected numbers of mesotheliomas in the TSFE <10–29 group was 0.00936 and that of the TSFE 30+ group was 0.0874, totaling 0.0967 mesotheliomas.

Although Wild et al. (2002) did not provide TSFE information in a similar manner as the other two cohort studies, the authors did provide latency information for two nested case–control studies for non-malignant respiratory disease (NMRD) and lung cancer in Tables 2 and 4, respectively, of their paper. In the NMRD study, 38% of the cases had a latency of 15–66+ years, 41% had a latency of 1–65 years, and 21% had a latency of 1–45 years; while in the lung cancer study, 22% of the cases had a latency of 5–56+ years, 52% had a latency of 1–45 years, and 26% had a latency of 1–35 years. Based on this latency information, we believe our 22 and 20% assumptions for the French and Austrian cohorts, respectively, are conservative.

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Letter concerning: Occupational exposures to cosmetic talc and risk of mesothelioma: an updated pooled cohort and statistical power analysis with consideration of latency period by Gary M. Marsh et al. (Inhal Toxicol. 2019 Aug 5:1–11. doi:10.1080/08958378.2019.1645768)

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LETTER TO THE EDITOR

Letter concerning: Occupational exposures to cosmetic talc and risk of mesothelioma: an updated pooled cohort and statistical power analysis with consideration of latency period by Gary M. Marsh et al. (Inhal Toxicol. 2019 Aug 5:1–11. doi:10.1080/08958378.2019.1645768)

Dear Editor,

Marsh and colleagues have recently updated their pooled cohort analysis of mesothelioma incidence in Italian, Norwegian, Austrian, and French cosmetic talc miner and miller cohorts and concluded that the epidemiological evidence from these cohort studies does not support the hypothesis that exposure to cosmetic talc is associated with the development of pleural cancer/mesothelioma. Unfortunately, there are a number of errors in the paper and some statements made by the authors are worthy of further discussion. The purpose of this Letter is to draw these issues to the attention of your readers.

In the Introduction to their paper, the authors state that 'in the mid-1970s, researchers at Mt. Sinai claimed to have measured elevated levels of asbestos mineral in numerous cosmetic talc products (Rohl et al. 1976). Following the publication of their initial study, Rohl et al. (1976) acknowledged that the method employed in their 1976 study (i.e., X-ray diffraction [XRD]) was not capable of distinguishing between asbestiform and non-asbestiform minerals (Rohl and Langer 1979).' This statement by Marsh and colleagues is misleading and incomplete. In their 1979 paper, Rohl and Langer do write: 'The major limitation of x-ray diffraction analysis is its inability to distinguish between different morphological habits of the same mineral. For example, short tremolite fragments and long fibers of asbestiform tremolite give virtually identical x-ray patterns.' Marsh and colleagues fail to mention the next sentences and paragraph written by Rohl and Langer: 'To distinguish between different habits or shapes of the same mineral, including asbestos minerals, requires microscopic techniques. Transmission electron microscopy, used in conjunction with selected area electron diffraction (SAED), provides the resolution capability to visualize all particles and, in many cases, to identify them.' 'In a paper published in 1976, we reported a mineral and chemical characterization of 20 consumer talcums and powders obtained in New York city during the e period 1971–1975 (Rohl et al. 1976). Of the twenty products, 10 contained either tremolite or anthophyllite or both. The proportions, determined by step-scan x-ray diffraction ranged from 0.1% to over 14%, by weight. No attempt was made to *distinguish proportions* of fibrous and non-fibrous morphological phases, although every sample contained fiber. The presence of these minerals in fibrous form was verified by electron beam techniques (Figures 1,2).' The next pages of Rohl and Langer (1979) show electron micrographs of amphibole fibers in commercial cosmetic talcs. Marsh and colleagues are thus in error in suggesting that Rohl and Langer did not find amphibole asbestos fibers in the samples of commercial cosmetic talcs that they analyzed.

Marsh and colleagues go on to say 'Nonetheless, there continues to be some debate on this issue. For example, Gordon et al. (2014) recently claimed to have measured 0.004–0.9% by weight asbestos fiber in bulk samples of cosmetic talc. Using different analytical methods, Anderson et al. (2017) analyzed the same product and concluded there was no detectable asbestos fiber.' Marsh and colleagues fail to mention that Anderson and colleagues hired Dr. Mark Floyd of Forensic Analytical Laboratories to perform the microscopic analysis, and that he identified and classified fibers of anthophyllite in his initial report on the bulk samples. One of the Anderson et al. authors, Patrick Sheehan, who is not a microscopist, directed Floyd to alter the report and add the qualification that '… this classification was inconclusive due to the small number counted' (Egilman and Steffen 2018).

Further on in their report Marsh and colleagues discuss specific issues related to the Italian cohort and comment on deaths attributed to pneumoconiosis. They write: 'It is worth noting that Pira et al. (2017) reported that the number of observed deaths in their cohort attributed to pneumoconiosis was significantly higher than expected, yielding an SMR for pneumoconiosis of 26.62. Notably, the number of expected deaths in the Pira et al. (2017) cohort due to pneumoconiosis (n = 2.6) was similar to that of mesothelioma (n = 2.0), yet the authors observed 69 deaths due to pneumoconiosis and 0 deaths due to mesothelioma.' This statement with respect to expected deaths due to pneumoconiosis and to mesothelioma illustrates a problem with the use of the regional reference population in the Italian study. Pneumoconiosis is an occupational lung disease caused by inhaling large amounts of fibrosis-inducing dusts such as silica or asbestos. Individuals do not develop these diseases without inhaling these dusts. Therefore, the expected number of cases of pneumoconiosis in a general population without industrial exposures should be 0. Indeed, Marsh and colleagues write that Pira et al. (2017) used regional (Piedmont) mesothelioma rates to estimate the expected number of mesothelioma deaths in the Italian cohort. Because there were several active asbestos industries in Piedmont, it has been claimed that the use of regional mesothelioma rates may lead to an overestimate of expected deaths for the Italian cohort (Finkelstein 2017; Mirabelli

2017). Marinaccio et al. (2018) specifically reported that among women in the Piedmont region, 'both environmental and familial exposures contribute to the female mesothelioma clusters, attributable to large asbestos cement plants'. In using regional rates to compute their expected number of cases of mesothelioma in the talc mining cohort, Marsh and colleagues have essentially asked the question: How do mesothelioma rates in the mining cohort compare to the average rate in a region where many cases of mesothelioma are caused by exposures arising from the asbestos cement and other industries in Piedmont? In order to address the important question of how many cases of mesothelioma one might expect in a population without these known asbestos exposures, one would need rates in an unexposed reference population. Unfortunately, these are not available because the reference population cannot be divided among exposed and unexposed individuals.

With respect to pneumoconiosis, Marsh and colleagues go on to write: 'As we previously noted (Finley et al. 2017), the excess risk of pneumoconiosis in the Italian cohort is important because it indicates that these workers were exposed to very high levels of cosmetic talc, levels well beyond those ever encountered by cosmetic talc consumers.' This statement is false. The occurrence of pneumoconiosis *does not* indicate that the workers were exposed to very high levels of cosmetic talc; rather it indicates that they were exposed to very high levels of silica. The 1976 study of Rubino et al. tabulated 65 deaths from silicosis (62 in miners and 3 in millers) and there was a dose-response relationship with cumulative dust exposure. Rubino writes: 'Table 13 shows a remarkable difference of free silica amount in air dust respectively in the mines and in the mills and within the mines jobs between drilling and other operations. This is due to the high content of quartz in footwall rocks and inclusions as opposed to the absence of free silica in talc minerals. The small amount of free silica in mills operations is due, as above mentioned, to the actual incomplete screening of talc inclusions.'

Concerning the presence of asbestos in the Italian mines, Marsh and colleagues write 'Regarding the alleged presence of asbestos in the Italian cosmetic talc mines, Mirabelli (2017) stated that "low-level exposure to airborne asbestos fibers was indeed reported by Rubino et al. (1976)." However, Rubino et al. (1976) did not report the presence of airborne asbestos fibers at the mine, nor did they claim there was any "exposure" to such fibers.' *This is false*. Rubino et al. wrote: 'Table 13 shows a remarkable difference of free silica amount in air dust respectively in the mines and in the mills and within the mines jobs between drilling and other operations. This is due to the high content of quartz in footwall rocks and inclusions as opposed to the absence of free silica in talc minerals. The small amount of free silica in mills operations is due, as above mentioned, to the actual incomplete screening of talc inclusions. *The same explanation could be given for the very small number of fibers in air, caused by possible microinclusions of rock containing little amount of tremolite.*'

Marsh and colleagues comment on a case of mesothelioma in the Vermont talc cohort studied by Selevan et al. (1979). They computed 7682 person-years at risk and an expectation of 0.16 based upon US national and state-specific rates. Calculation of an SMR has the same caveats as discussed concerning reference rates in the Italian study.

Marsh and colleagues concluded that 'The epidemiological evidence from the cosmetic talc miner/miller cohort studies does not support the hypothesis that exposure to cosmetic talc is associated with the development of pleural cancer/mesothelioma. In a previous analysis (Finkelstein 2017) I commented that it is not possible to find a reference population purged of subjects with occupational exposures and I proposed a "thought experiment" in which the cosmetic talc miners are compared to the chrysotile miners of Quebec, Canada. Mcdonald and Mcdonald (1997) reported on mesothelioma mortality in Quebec miners and millers. They found 33 deaths from mesothelioma in a cohort of 9072 men (132,000 person-years). The mesothelioma mortality rates were 33.7 per 100,000 person-years among miners and millers in the Thetford Region and were 13.2 per 100,000 in the Asbestos Region. The average across the 2 regions was 25 deaths per 100,000 person-years. The pooled cohorts of the updated Marsh study comprised 113,344 person-years of observation.

Now, for the purposes of analysis, let us make two assumptions about the asbestos dust concentrations experienced by the cosmetic talc miners. Assumption (a) is that asbestos dust exposures in talc mining were 10% of the levels in Quebec chrysotile mining (high assumption), or, assumption (b) that asbestos dust exposures in talc mining were 1% of the asbestos dust exposures experienced by the Quebec miners and millers. How many mesothelioma deaths would be expected in the pooled cohort under these exposure conditions? In situation (a) we would expect the rate to be 10% of the Quebec rate of 25 per 100,000. In situation (b) we would expect the rate to be 1% of 25 per 100,000. Given that there were 113,000 person-years in the pooled cohort, we would then expect to see 2.5 cases of mesothelioma for situation (a) in which *asbestos exposure levels* were 10% of those in Quebec, and to see 0.25 cases in situation (b) where exposure levels were 1% of those in Quebec.

Now, there were no cases of mesothelioma observed in the three pooled cohorts. According to the Poisson distribution, used to compute confidence intervals for count data:

1. There is an *8% chance of observing no cases* when 2.5 were expected (situation A where the cosmetic talc miners asbestos exposure was 10% of the Quebec chrysotile miners exposure); and
2. There is a *78% probability of observing no cases* when 0.25 were expected (situation B where the cosmetic talc miners asbestos exposure was 1% of the Quebec chrysotile miners exposure).

The exposure at which there is a 50/50 chance of observing either no case, or, of observing one or more cases of

mesothelioma, corresponds to an asbestos exposure of about 3% of that experienced by the chrysotile miners and millers in Quebec.

I conclude that, given the size of the pooled cosmetic talc cohort, even at risk levels corresponding to asbestos exposures as high as 3% of those of the Quebec miners and millers, one is as likely to observe no cases of mesothelioma as one in likely to see one or more cases. Thus, despite the pooling of four cohorts and the accumulation of 113,000 person-years of observation, the epidemiologic evidence is too weak to draw conclusions about the risk associated with the low levels of asbestos exposure experienced by talc miners. Observation of a much larger cohort would be required to have confidence in a conclusion that there is no risk associated with these exposures. In the meantime, the best evidence concerning risk is derived from analyses of the mineral content of samples of cosmetic talc and of the analyses of the lung content of cosmetic talc users.

Disclosure statement

The author has served as a consultant for American attorneys involved in legal proceedings concerning cosmetic talc.

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LETTER TO THE EDITOR

Response to Marsh, G. M., Ierardi, A. M., Benson, S. M., & Finley, B. L. (2019). Occupational exposures to cosmetic talc and risk of mesothelioma: an updated pooled cohort and statistical power analysis with consideration of latency period. Inhalation toxicology, 31(6), 213–223

Sir

Marsh et al. (2019) recently published an article in your journal providing an updated pooled analysis of four talc miner and miller cohorts. The power calculations reported by Marsh et al. (2019) overstate the actual power. The authors use reported "expected cancers" from the four component studies as the basis for their calculations. The Marsh et al. (2019) background incidence rate of mesothelioma is 2.64 cases per 100,000 person years. However, this rate derives from national and regional registries that include both asbestos-exposed and asbestos-unexposed individuals. To detect whether working in the industry increased the risk of mesothelioma, the expected cancer numbers should reflect *unexposed* incidence rates. Otherwise, the study is merely comparing mesothelioma rates in two exposed cohorts, which can only determine if the risk in the talc workers is higher than the risk in the other exposed population. The correct background rate for the power calculations is the incidence rate in an unexposed population. Several authors have estimated the unexposed rate and suggest a rate of 1–2 cases per 1,000,000 person years (McDonald 1985; Teta et al. 2008). Teta et al. (2008) utilized SEER data through 2002. We extended their analysis through 2016 producing an estimated unexposed rate of 2.1 per 1,000,000 (code available from the first author).

Furthermore, asbestos was used in over 3000 products and the 'cosmetic talc' manufacturers admit that talc used in cosmetics before 1976 contained asbestos (Steffen et al. 2017). In addition, the FDA found asbestos in cosmetic talc both before and after 1976 (Stuart 1974; Crane 2019). Few if any medical histories ask about exposures to most of these sources of exposure, thus estimates of 'unexposed' rates *over*estimate the true 'idiopathic' or 'natural' rate if one exists (Mark and Yokoi 1991; Strauchen 2011). We note that Hillerdal (1999) suggested that the 'natural level' is 'probably much lower' than 1 per 1,000,000.

Marsh et al. (2019) reported the power to detect a 3-fold and 2.5-fold increased risk as 79% and 62%, respectively. Using a more appropriate unexposed rate of 2.1 per 1,000,000, the one-sided power to detect a 3-fold and 2.5-fold increased risk is 18% and 14% respectively. The table below shows power at various risks (Newman 2001).

Assumed true risk ratio	Power (%)
2	11
2.5	14
3	18
4	25

We note that Marsh et al. (2019) is, in a statistical sense, internally inconsistent. If in fact the rate in the pooled cohorts is 2.64 per 100,000 person years, and assuming no effect of exposure, the probability of observing no cases is less than 5%. Using a rate of 2 per 1,000,000 person years, the corresponding probability of observing no cases is 80%. Even allowing for a four-fold increased risk, the corresponding probability of observing no cases (which is what has been reported) is 40%. Furthermore, for the individual cohorts, Marsh et al. (2019) assumed background rates vary from 3.8 per 100,000 in Italy to 1.0 per 100,000 in both France and Austria. The authors provide no explanation for why the background rate could vary by a factor of almost four across contiguous countries.

Disclosure statement

The first three authors have served as expert witnesses in asbestos litigation at the request of injured people. Lawyers did not provide financial support for or input into this research.

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Response to letters regarding "Occupational exposures to cosmetic talc and risk of mesothelioma: an updated pooled cohort and statistical power analysis with consideration of latency period"

Gary M. Marsh, A. Michael Ierardi, Stacey M. Benson & Brent L. Finley

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LETTER TO THE EDITOR

Response to letters regarding "Occupational exposures to cosmetic talc and risk of mesothelioma: an updated pooled cohort and statistical power analysis with consideration of latency period"

Sir,

We have reviewed the letters submitted by Finkelstein (2019) and Madigan et al. (2019) regarding our updated pooled analysis of mesothelioma risk following occupational exposures to cosmetic talc in the Italian, Norwegian, Austrian, and French miner and miller cohorts (Marsh et al. 2019).

First, we appreciate Dr. Finkelstein's various remarks on the analytical issues surrounding the potential presence of asbestos in cosmetic talc, as they highlight the very essence of our Introduction, namely that this is a hotly debated topic. Nonetheless, we do not find any of Dr. Finkelstein's arguments to be novel or convincing, and many of the points he raises have, in fact, already been addressed in our original text (Marsh et al. 2019) and in our responses (Finley et al. 2018) to a previous, nearly identical letter to the editor by Finkelstein (2017a). We maintain that the cosmetic talc analytical studies published in the 1960s and 1970s lack scientific rigor and are thus unreliable, which is a conclusion that has been drawn previously by individuals representing various other scientific bodies and organizations, including the International Agency for Research on Cancer (IARC) working group (as noted in Marsh et al. (2019)), the U.S. Food and Drug Administration (FDA), the Colorado School of Mines Research Institute, as well as the Mt. Sinai Medical Center (Chalmers, 1976; IARC, 2010; Krause, 1977; Swanson, 1986).

Indeed, in 1986, H. W. Swanson, the Acting Associate Commissioner for Regulatory Affairs at FDA, noted that '[d]uring the early 1970s, FDA became concerned about the possibility that cosmetic talc did contain significant amounts of [asbestiform minerals]. The agency received several reports about such contamination. However, at that time, the analytical procedures for determining asbestos in talc were not fully developed, and most of the analytical work was conducted without scientific agreement as to which methods were well-suited for the identification of asbestiform minerals in talc. Consequently, FDA considered all analytical results to be of questionable reliability. This assessment proved to be correct because many questions were subsequently raised about results reported in the literature in the early 1970s' (Swanson, 1986, p. 1).

We disagree with the authors' claim of the widespread presence of asbestos in cosmetic talc mines and thus in cosmetic talcum powder products, and believe that this claim is based on a misinterpretation of older studies that generally used imprecise language and methodologies to describe their analytical findings. Specifically regarding the claimed presence of tremolite asbestos by Rubino et al. (1976), as we noted in Marsh et al. (2019), Rubino et al. (1976) consistently emphasized the purity of the Italian talc: 'This particular talc has been mined for many decades and has continued to be recognized to be of the highest standard of purity' and 'our conclusions support the thesis of no cancerogenic effect attributable to pure talc' (Rubino et al. 1976, p. 186, 192). The authors referenced a report authored by Dr. Pooley and colleagues in which samples from the Val Chisone mines and mills, as well as historical samples of talcum powders produced from these mines/mills, were analyzed by optical and electron microscopy, in addition to X-ray diffraction (Lightfoot et al. 1972). In their report, the investigators identified tremolite and actinolite mineral in the footwall contact rocks and rock inclusions, but noted that this amphibole mineral was 'hardly fibrous,' and that '[n]o amphibole or chrysotile mineral was detected in any of the numerous powders examined' (Lightfoot et al. 1972, p. 122). Indeed, in a letter to FDA in March of 1976, Dr. Pooley confirmed that samples his group examined from the Italian mine 'have not been found to contain any asbestos minerals' (Pooley, 1976).

To our understanding, other more recent findings of asbestos in cosmetic talcum powder products are currently being investigated. Additionally, regarding Anderson et al. (2017), we do not have any independent knowledge regarding the concerns surrounding the microscopy analysis that Dr. Finkelstein raised in his letter. Our understanding of this issue is derived solely from the interpretation of the underlying documentation by Egilman and Steffen (2018), which they described in a letter to the editor. That being said, the reported finding of four anthophyllite asbestos fibers still does not account for the vast discrepancy between Gordon et al. (2014) and Anderson et al. (2017), which makes the interpretation of the results from both of these studies difficult.

Regardless of the potential presence of trace asbestos in cosmetic talc, it has been repeatedly demonstrated that even if one were to assume up to a 0.1% asbestos content for a cosmetic talcum powder product as a 'worst-case' scenario, potential asbestos exposures and associated health risk at this level are 'orders of magnitude below upper-bound estimates of cumulative asbestos exposure and risk at ambient levels, which have not been associated with increased incidence of asbestos-related disease' (Brown, 1985; Swanson, 1986; Burns et al. 2019, p. 2272). We acknowledge that the upper-bound bulk estimate (0.9%) as reported by Gordon

et al. (2014) exceeds this <0.1% assumption. However, as we previously noted (Finley et al. 2018), it is our understanding that Gordon et al.'s methods have been described as 'self-designed variations of scientifically accepted methodologies; a mishmash of scientifically acceptable methodologies' that are 'inherently unscientific' deviations from generally accepted methodologies; as a result, the Gordon et al. (2014) analysis has been routinely excluded from various courtrooms over the past several years (Memorandum Opinion in Brandt, 2017; Order in Hanson, 2018; Memorandum Opinion in Jackson, 2019).

Using essentially similar arguments, both Finkelstein (2019) and Madigan et al. (2019) questioned our use of regional (Piedmont) mesothelioma rates to estimate the expected number of mesothelioma cases in cosmetic talc miners and millers employed in the western Piedmont region of Italy. Dr. Finkelstein's arguments regarding the use of regional rates for the Italian cohort were nearly identical to those presented in his earlier letter to the editor (Finkelstein, 2017a) regarding Finley et al. (2017), and our responses that follow parallel those we used in our response to his earlier letter, and also included in the Discussion section of Marsh et al. (2019). Specifically, Finkelstein (2019) and Madigan et al. (2019) suggested that, because there were several active asbestos industries in Piedmont, use of regional mesothelioma rates may lead to an overestimate of expected cases due to risk factors that presumably are not relevant to the cosmetic talc miners. We disagree. First, it cannot be ruled out that at least some fraction of the cosmetic talc cohort was employed in a high-risk industry (e.g. cement manufacture) at some point in their occupational lifetime. Second, and more importantly, there are numerous ongoing sources of non-occupational asbestos exposures throughout the region, including areas near the Val Chisone cosmetic talc mine. These include: (1) naturally-occurring tremolite outcroppings located near the talc mine (Mirabelli and Cadum, 2002), (2) asbestos cement sheeting that was used for roofing material in the Italian Western Alps (Frassy et al. 2014), and (3) asbestos waste material, such as the powdered *polverino*, which was used as thermal attic insulation, garden amendment, and roadbed fill (Coggiola and Graziadei 2013). As noted in Marsh et al. (2019), '[t]hese sources of asbestos should be considered when discussing non-occupational exposures that may occur in this region,' i.e. the Piedmont region of Italy (Marsh et al. 2019, p. 219).

There is strong evidence that the non-occupational asbestos exposures in the Piedmont region were sufficient to increase mesothelioma risk. For example, Piedmont has the highest proportion of mesothelioma cases attributed to non-occupational exposures in all of Italy (24.4%, as reported in Marinaccio et al. (2015)), which is consistent with the fact that the rate of mesothelioma for women in the Piedmont region (3.18 per 100,000) is higher than any other region across Italy and is almost three times the female national rate (1.25 per 100,000) (Marinaccio et al. 2012). Marinaccio et al. (2012) reported elevated mesothelioma rates in the areas near the Val Chisone mines (Figure 1 in the Marinaccio et al. (2012) paper) and a majority of the mesotheliomas near this area (e.g. in Collegno and Torino) were classified as 'environmental,' i.e. they were not due to occupational exposure, nor were they due to living with an asbestos worker (Marinaccio et al. 2015). Hence, it is clear that non-occupational asbestos exposures are a significant risk factor for mesothelioma in the cosmetic talc miners and millers and, therefore, use of national rates or rates from other regions would almost certainly lead to an underestimation of expected mesotheliomas (particularly mesotheliomas related to non-occupational exposures) for this cohort. In fact, this underestimation is evidenced by the 2.82 expected mesotheliomas calculated in our latency analysis using national age-specific pleural mesothelioma rates from the World Health Organization (WHO) Mortality Database vs. 3.0 expected mesotheliomas as reported in the original studies (Marsh et al. 2019; WHO Mortality Database, 2019).

We also note that our use of regional reference rates for mesothelioma is supported in principle by authoritative books on occupational epidemiology and in application by Italian and other investigators. For example, in their book, Checkoway et al. (2004) explain that the use of the national population as an external reference group 'may not always be a suitable choice when, for example, there is considerable geographic heterogeneity of disease rates within a country. In that situation, comparisons of the disease rates for a worker cohort located in a particular region with national rates would be confounded by factors that caused geographic disease rate variability'; Checkoway and colleagues continue, '[a]n advantage of using regional rates for external comparisons is that they should better represent the experience of the source population for the cohort than would rates for the national population' (Checkoway et al. 2004, p. 151–152).

In actual applications, many Italian investigators have emphasized the importance of using regional rates for epidemiologic research conducted in Italy. For instance, in a mortality study conducted in an asbestos cement factory in Naples, Italy, Menegozzo et al. (2011) reported that the '[r]egional population was chosen as reference because national rate is a weighted average of heterogeneous Italian regional rates, while local mortality rates are not stable enough to assume the absence of random error' (Menegozzo et al. 2011, p. 302). Fazzo et al. (2014) used regional and municipal reference rates to calculate age standardized incidence ratios for mesothelioma incidence in an Italian neighborhood where an asbestos cement plant was located. Additionally, and as cited in Marsh et al. (2019), Magnani et al. (2008), in their analysis of cement workers in the Piedmont region of Italy stated that '[m]ortality in the cohort was compared to regional rates, which are more appropriate because of the wide regional differences in respiratory cancer mortality in Italy. As regards pleural cancer, comparison with the regional rather than the national population is also more appropriate because mortality from pleural cancer is higher in Piedmont, and in general varies widely among Italian regions' (Magnani et al. 2008, p. 168). In summary, we believe our use of Piedmont

regional rates was consistent with standard epidemiological principles and practices for assessing mesothelioma risk in Italian cohorts, and was the proper choice for evaluating mesothelioma risk in cosmetic talc miners and millers in this region.

Similarly, Finkelstein (2019) suggests that our estimate of 0.16 as the expected number of mesothelioma cases in our evaluation (Marsh et al. 2019) of the Vermont cohort (Selevan et al. 1979) was inflated due to the use of US national and state-specific (regional) rates. Because we considered both national and regional rates to calculate a hypothetical expected number of mesothelioma cases for the Vermont cohort (and ultimately relied on the national reference rate), it is thus unclear to us what Dr. Finkelstein would recommend as an appropriate reference rate to rely on when calculating Standardized Mortality Ratios (SMR). Nevertheless, we note that in a recent update of the Vermont cohort, Fordyce et al. (2019) estimated 0.60 expected mesothelioma cases, rendering our estimate of 0.16 based on national reference rates as conservative in relation to statistical power calculations.

Madigan et al. (2019) additionally challenged our use of background rates to calculate the expected number of mesotheliomas, which they claimed varied from 3.8/100,000 in Italy to 1.0/100,000 in France and Austria. First, it is unclear to us how Madigan et al. (2019) calculated these rates, as we did not report or calculate any such numbers in the original Marsh et al. (2019) analysis. Second, Madigan et al. (2019) note an apparent discrepancy (i.e. the background rate varies 'by a factor of almost four across contiguous countries'); however, this finding is not in any way a discrepancy, as Marinaccio et al. (2012) demonstrated that the rate of mesothelioma in Italian men ranges from 0.29 to 14.13 per 100,000, depending on region. Again, this highlights the importance of using region-specific rates when evaluating mesothelioma rates in Italy. Finally, we believe that there is no reason to challenge the validity of the background rates we used in our paper (Marsh et al. 2019), as the rates were either those reported by the original authors (for the power analysis) or those based on mortality and population data we obtained from the WHO Mortality Database (for the latency analysis), as referenced in our article (Marsh et al. 2019; WHO Mortality Database, 2019).

Finkelstein (2019) also challenged our interpretation of the excess risk of pneumoconiosis observed in the Italian cohort; however, the cause(s) of pneumoconiosis is not as straightforward as Dr. Finkelstein suggests. To this point, many of the cases of nonmalignant respiratory disease (NMRD) reported by Rubino et al. (1976) in the Italian miners ($n = 62$) and millers ($n = 3$) were in fact labeled as 'silicosis,' and an excess risk of disease was reported for miners only. Yet, Coggiola et al. (2003), in a follow-up evaluation of this cohort, explained the role of mixed dust exposures in the development of NMRD among individuals in the Italian cohort: 'A significant excess mortality from nonmalignant respiratory diseases was found in miners only. This observation has already been made by Rubino et al. (1979, 1976) in previous follow-up of the same cohort, and was attributed to the high frequency of silicosis as a cause of death in this cohort. This can be explained by the mixed exposure (including a certain amount of inhalable silica particles) that took place in the past, when rock drilling activity was frequent and technical prevention means had not yet been introduced' (Coggiola et al. 2003, p. 67). Indeed, Gibbs et al. (1992) noted that talc pneumoconiosis or "talcosis' frequently represents disease associated with a variety of minerals and talc is [sic] a common denominator' (Gibbs et al. 1992, p. 1353). Today, many medical professionals capitalize on the capability of talc to elicit a fibrogenic response and currently recommend this mineral as the treatment method of choice for pleural effusion (Baiu et al. 2019).

It is also interesting to note that in the most recent update of the Italian cohort, Pira et al. (2017) for the first time reported a significantly increased SMR of 6.23 (95% CI = 2.29–13.58) for pneumoconiosis among millers, whereas in previous evaluations, an excess risk of pneumoconiosis was only identified in miners (Coggiola et al. 2003; Rubino et al. 1979; Rubino et al. 1976). This finding, therefore, is suggestive of a high level of mixed dust/talc exposure among both Italian miners and millers, as the levels of free silica in the mills specifically were historically less than or equal to 2% (Rubino et al. 1976). Thus, the cases of pneumoconiosis initially identified by Rubino et al. (1976) could very well have represented cases of talcosis caused by mixed dust exposures experienced in the talc mining/milling environments. We therefore used this knowledge of a mixed dust environment, along with measured dust (talc) exposure levels reported for the Italian cohort (Coggiola et al. 2003; Pira et al. 2017; Rubino et al. 1979; Rubino et al. 1976), to point out that cosmetic talc exposures among workers would be well above those ever encountered by cosmetic talc consumers.

Regarding the 'thought experiment' once again offered by Finkelstein (2019), we note that this is similar to the 'experiment' contained in his criticism of Finley et al. (2017) (Finkelstein, 2017a) and Pira et al. (2017) (Finkelstein, 2017b). As we stated in our response (Finley et al. 2018) to Finkelstein (2017a), we believe this hypothetical is deeply flawed and we agree with the response from Pira et al. (2018) that Dr. Finkelstein's analysis is 'purely speculative, given the lack of support to the hypothesis of 3% asbestos exposure (or any other value different from zero) compared with Quebec miners' (Pira et al. 2018, p. e73).

In closing, we would like to reiterate that the current letters to the editor authored by Finkelstein (2019) and Madigan et al. (2019) do not contain any novel arguments that we have not previously considered or addressed in prior publications. We would also like to note that the majority of the 'contributions' that the authors, in particular Drs. Finkelstein and Egilman, have made to the scientific literature over the past several years consist mainly of letters to the editor, which are not original contributions and do not undergo the same rigorous review process as peer-reviewed publications. We would therefore invite the authors to publish their original research in the peer-

reviewed literature so that we may consider any newly presented evidence in future updates to our publications.

Disclosure statement

All of the authors are employed by Cardno ChemRisk, a consulting firm that provides scientific advice to the government, corporations, law firms, and various scientific/professional organizations. GMM is also Professor of Biostatistics and Director, Center for Occupational Biostatistics and Epidemiology at the University of Pittsburgh, Graduate School of Public Health. This response was prepared and written exclusively by the authors. No organizations other than Cardno ChemRisk were aware of the preparation of this response, and no other organizations other than Cardno ChemRisk reviewed any part of this response prior to its submission for publication. Two of the authors (BLF, GMM) have served as defense experts in cosmetic talc-related litigation.

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