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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).

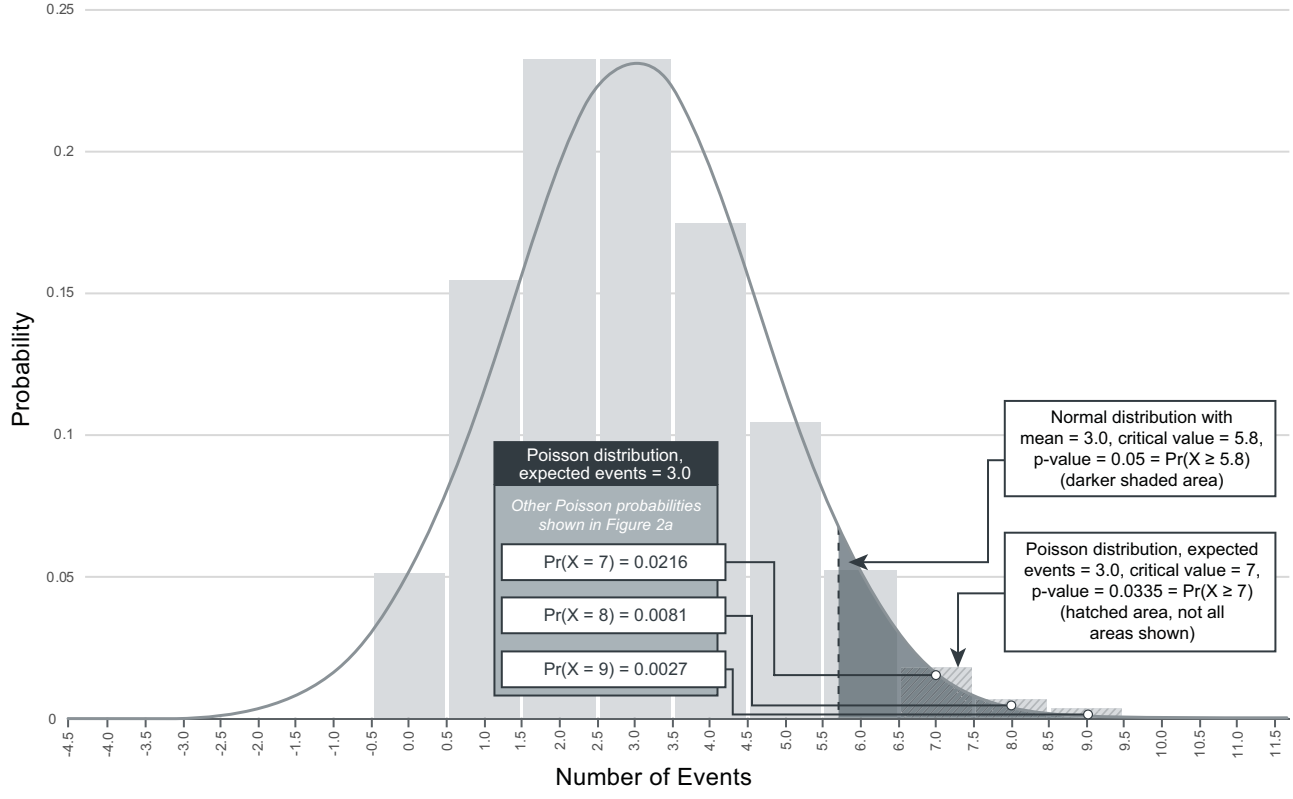

Figure 1. Discrepancy between *p* values using normal and Poisson distribution.

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

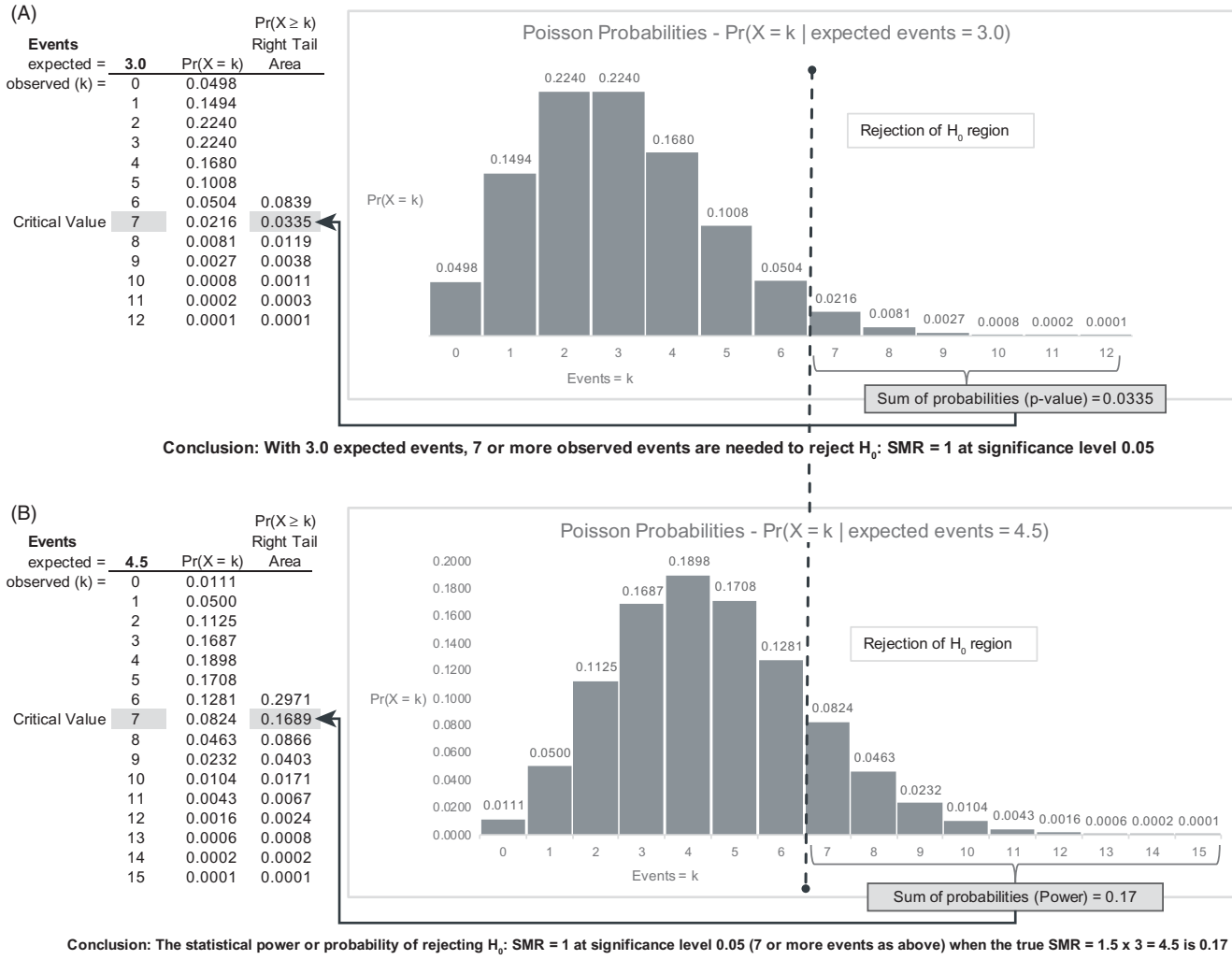

Figure 2. Poisson probability distributions with number of expected events = 3.0 and 4.5.

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.