REVIEW

# Lung cancer risk and talc not containing asbestiform fibres: a review of the epidemiological evidence

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A literature search was done and all epidemiological cancer studies mentioning talc as a risk factor were selected. The talc exposed populations were divided into three groups: (1) populations in which no other occupational carcinogen was mentioned (only talc millers satisfied this criterion); (2) populations of talc miners exposed to talc, quartz, and/or radon; and (3) other industrial populations in which talc is associated with quartz, nitrosamines, and asbestos depending on the study. No excess lung cancer mortality was found for the populations of talc millers exposed to high levels of talc but without any other potential carcinogen (SMR = 0.92, 42 cases) while the summary of mortality of talc miners exposed to quartz and/or radon was in excess (fixed effect SMR = 1.20, random effect RR = 1.85, 40 cases). Six studies in other industrial settings were identified. All reported increased lung cancer mortality among talc exposed workers but the talc exposure was confounded with other carcinogens and only one study was able to adjust on them. In conclusion, no increased lung cancer mortality was observed among talc millers despite their high exposure experience. In populations in which talc was associated with other potential carcinogens, some lung cancer excesses were observed.

The talc mineral ($Mg_3Si_4\ O_{10}\ (OH)_2$), is a member of the silicate family but its physical and chemical properties are very different from those of asbestos minerals or of crystalline silica.[1–3] These differences are mainly linked to their crystalline structure. The talc mineral is characterised by its two dimensional structure in sheets separated by slight forces. This explains the platy shape of talc particles and its smoothness in touch (hardness 1 on the Mohs scale) for which it is valued in industrial applications. Talc is also characterised by its hydrophobic property and its very low solubility. When milled, some cleavage fragments within the talc powder meet the WHO definition of fibres, although in fact these particles are elongated talc platelets. These ''fibres'' have low aspect ratios (usually 3–10) and have been shown to make up to 1% of the powder.

Asbestos minerals can be separated in two silicate families. Tremolite-actinolite ($Ca_2\ (Mg,Fe)_5\ Si_8\ O_{22}\ (OH)_2$, anthophyllite ($(Mg,Fe)_7\ Si_8O_{22}\ (OH)_2$), amosite ($(Mg,Fe)_7\ Si_8O_{22}\ (OH)_2$), and crocidolite ($Na2\ Fe^{2+}_3\ Fe^{3+}_2\ Si_8O_{22}\ (OH)_2$) belong to the amphibole family characterised by a one dimensional chain structure. Chrysotile ($Mg_3Si_2O_5\ (OH)_4$) belongs, like talc, to the sheet silicate family but it is characterised by its very typical scrolled structure of the layers. The asbestos minerals exhibit a higher hardness (5–6 for amphibole asbestos, 2–4 for chrysotile). Quartz, the only form of crystalline silica possibly associated with talc ore, is characterised by a three dimensional structure with strong bonding explaining its high hardness (7 on the Mohs scale) and its great abrasiveness.

As talc mineral and asbestos minerals are composed of the same chemical elements (Si, Mg, Fe, and more or less Ca), they can be found in neighbouring geological environments. During the genesis of the deposits and depending of the pressure and temperature conditions, talc or asbestos could both grow but only exceptionally in the same deposit. For example, mineral talc is generated during the slow hydrothermal transformation of calcareo-magnesian rocks (dolomite, magnesite) or of ultramafic rocks (peridotite, amphibolite). In the first case talc is mainly associated with chlorite and calcite and exceptionally with tremolite. In the second case, talc is mainly associated with serpentine and chlorite and exceptionally with actinolite and anthophyllite.

The extracted talc ore never consists of a pure talc mineral. Thus the products marketed as talc are in fact mixtures of 50% to 90% talc and other minerals, depending on the deposit and its geological origin. An extreme case is the New York state talc which contains only about 25% of the talc mineral. The associated minerals in this deposit (tremolite, anthophyllite, and serpentine) have been described as existing at least partially as asbestiform fibres. The term asbestiform refers to the unusual crystallisation habit of a mineral in which the crystals are thin, hair-like (single dimensional) fibres with enhanced strength, flexibility, and durability.

In its 1987 review, the International Agency for Research on Cancer (IARC)[3] separated the talcs containing and not containing asbestiform fibres. It concluded that there was sufficient evidence for the carcinogenicity to humans of talc containing asbestiform fibres based on a series of epidemiological studies conducted in the populations of talc workers in New York

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**Abbreviations:** IARC, International Agency for Research on Cancer; NMRD, non-malignant respiratory diseases

State, and that there was inadequate evidence for the talc not containing asbestiform fibres.

The latter assessment was based on four epidemiological studies among miners and millers of talc: Selevan,[4] Rubino,[5] Léophonte,[6] and Kastnelson.[7] The last three were considered not to be interpretable because of their non-standard methodology.

The purpose of this paper is to update the evidence as to the lung carcinogenicity of talc not containing asbestiform fibres in the light of a series of recently published epidemiological studies. It also updates the more recent (2000) unpublished 10th Report on Carcinogens of the US National Toxicology Program (10th RoC) which did however not reach a final conclusion with respect to talc.

## MATERIALS AND METHODS

A literature search was done in the online reference database PubMed of the National Library of Medicine, updating the references included in the IARC review. The last reference included in the IARC review was published in 1983, so the literature search was considered complete until this date. The keywords used in the database search were ''talc and lung cancer'' and ''talc and epidemiology''. The papers cited in the selected papers and in the background document of the 10th RoC on talc were also considered.

Included were all papers with original information (comments and editorials were excluded) giving information of the lung cancer mortality of populations exposed to talc. Excluded were studies mentioning fibrous talc or studying New York talc populations as well as papers concerned with the medical use of talc in the treatment of malignant tumours (talc pleurodesis). Some of the authors of the selected papers were contacted in order to obtain complementary information.

The study populations were classified into one of three groups:

1. Populations in which no other occupational carcinogen was mentioned (only talc millers satisfied this criterion).

2. Population of talc miners exposed to talc, quartz, and/or radon.

3. Other industrial populations in which talc is associated with quartz, nitrosamines, aromatic amines, and asbestos depending on the study.

A test of heterogeneity of standardised mortality ratios (SMRs) and a summary (fixed effect) SMR was performed as described in Breslow and Day[8] when only SMRs were combined. When significant heterogeneity was detected, a random effect estimate and corresponding confidence intervals were computed as described in Sutton *et al*.[9]

## RESULTS

Thirty nine papers were identified using keywords ''talc, lung cancer and epidemiology''. Two other relevant papers were identified when using ''talc and cancer'' or ''talc and epidemiology'' as keywords.

Out of these 41 papers, nine papers were published before 1983 and were thus covered by the IARC review. As mentioned in the introduction, the single paper among those nine considered relevant by the IARC and whose results will be included in the present review is the paper by Selevan.[4] Eleven further papers were about short term effects of talc pleurodesis, two were reviews or comments on results, one was a toxicology report on animals, two papers described case series, three papers showed updates of the New York talc studies, leaving 13 papers for closer scrutiny.

Stern *et al* gave the results of a PMR study of 12 873 deceased unionised construction plasterers and cement masons.[10] Given the inadequate methodology and the lack of a specific talc exposure, this paper was not considered further. McDonald *et al* compared the fibre types in the lung tissue of mesothelioma patients and in a series of referents.[11] They found no difference in the content of talc fibres between the two series. However, as this paper gives no direct estimate of a cancer risk in relation to talc exposure, it will not be further commented on.

The remaining papers described the mortality of cohorts of occupationally exposed workers: a cohort of pottery workers exposed to talc and silica,[12 13] a cohort study in a Chinese rubber factory in which talc was used,[14] a mortality and cancer morbidity follow up of Norwegian talc miners and millers,[15] a cohort of employees of a fibreglass manufacturing facility,[16] a cohort mortality study of German rubber workers exposed to talc and asbestos,[17 18] a mortality cohort of women in the Russian printing industry,[19] a cohort of women in the Norwegian pulp and paper industry,[20] a mortality cohort study of French and Austrian talc workers,[21] and a mortality cohort updating the Italian talc workers cohort.[22]

Table 1 summarises the main study population characteristics of the papers describing the mortality of talc producing companies. The mortality of talc workers from Vermont,[4] Norway,[15] Austria, France,[21] and Italy[22] was compared to local or national rates. Within these studies, miners usually have a co-exposure to silica and/or radon with the possible exception of the Norwegian miners. On the other hand, no co-exposure to other carcinogens is mentioned among talc millers. A somewhat special situation occurred among Austrian talc workers as one of the sites (D) was not exposed to talc but to a mineral (leucophylite) containing 33% quartz. However, the mortality of talc workers not exposed to quartz (sites B and D) can be obtained from an unpublished report (Haidinger G, Wild P, Leodolter K, *et al*. Mortality patterns among French and Austrian talc workers. 2000) In order to compare the exposure levels, a conversion of mppcf (million particles per cubic foot) used in the past in Italy is necessary. Such a conversion is controversial as it depends on the fraction collected and the particle size distribution within the fraction. A tentative conversion factor of 15 mppcf $= 2$ mg/m$^3$ for particles $<5$ μm has been proposed by the American Conference of Governmental Industrial Hygienists (ACGIH) in 1981. For the Italian workers one could rely on the fourfold decrease in number of particles measured among millers between 1960 and 1975 and assume that the exposure was stable until the first gravimetric determinations in the early 1990s. Thus one can safely assume that the exposure levels in the 1960s were at least four times higher than 1.23 mg/m$^3$ measured in 1993. Applying such rules, one can consider that the French talc millers were by far the most exposed group followed by the Austrian, Norwegian, and Vermont miners, with the Italian millers appearing to be the least exposed ones. In any case, the exposure in all the studies has been higher (and sometimes considerably so) than the present threshold limit values.

Additional smoking information could be obtained for the Italian talc workers (personal communication of Dr Coggiola), for the Austrian talc workers (Pfeiffer K, Schmidt H. Cross sectional Studie bei 38 Arbeitnehmern der Talkmühle Oberfeistritz. 1989) and for the French talc workers.[23] Smoking prevalence was high and higher than in the reference populations when the data were available.

Table 2 summarises the main study population characteristics of the papers describing the mortality of talc exposed populations in other industries. Zhang *et al*[14] and Straif *et al*[17 18] describe populations of rubber workers in which talc has been used. While Zhang *et al* do not identify any exposure to potential carcinogens likely to occur in rubber factories, Straif *et al* developed an internal job exposure matrix with semiquantitative levels for all major exposures. Chiazze *et al* report talc exposure in a glass fibre facility along with other

**Table 1** Summary characteristics of talc exposed populations in talc producing companies

| Study | Cohort definition | Talc exposure | Other | Smoking |
|---|---|---|---|---|
| Selevan *et al*, talc miners[4] | All male talc miners radiographed in annual surveys of workers in dusty trade in Vermont (US), from five companies with at least one year employment between 1940 and 1969, followed up from 1940–75 | No information<br>Levels >20 mppcf not uncommon | Radon (up to 1.2 WL = 240 pCi/l), possibly tremolite | No information |
| Selevan *et al*, talc millers[4] | All male talc millers radiographed in annual surveys of workers in dusty trade in Vermont (US), from five companies with at least one year employment between 1940 and 1969, followed up from 1940–75 | No information<br>Levels >20 mppcf not uncommon | None,<br>quartz <0.25% | No information |
| Wergeland *et al*, talc miners[15] | All male employees from a Norwegian mine with at least one year employment between 1944 and 1972 followed up from 1953–87 | In 1980:<br>0.94–97.35 mg/m$^3$<br>peak at 319 mg/m$^3$<br>0.2–0.9 f/ml | 3.5 pCi/l radon | 76% smokers in 1981 |
| Wergeland *et al*, talc millers[15] | All male employees from a Norwegian talc mill with at least two years employment between 1935 and 1972 followed up from 1953–87 | In 1980:<br>1.4–54.1 mg/m$^3$ peak at 109 mg/m$^3$<br>0.2–0.9 f/ml | None | No information |
| Wild *et al*, French talc millers[21] | All male employees from a French talc mill (site A) with at least one year employment between 1945 and 1994 followed up from 1968–95 | >30 mg/m$^3$ in production until the 1970s, 5–30 mg/m$^3$ until 1990, <5 mg/m$^3$ since except some dusty jobs | None,<br>quartz <3%. Some workers had past quartz exposure in former jobs | 59% present smokers in 1989; 39% in a French population survey in 1986 |
| Wild *et al*, Austrian talc millers and miners[21] | All male workers of an Austrian talc producing company having been employed at least one year in three mines (site B to D) and mills or in the head office (site E) between 1972 and 1995 followed up from 1972–95. | >30 mg/m$^3$ in sites B and C before 1960 and for millers in D 1970–80, 5–30 for millers 1960–80, <5 since 1980 | Quartz (and no talc) in site D and in miners of site B until 1960<br>Elsewhere quartz <3% | 42% smokers in 1988; 16% ex-smokers in site B |
| Coggiola *et al*, Italian talc miners[22] | All male employees from Italian talc mine with at least one year employment between 1946 and 1995 followed up from 1946–95 | Decreased from more than 200 mppcf in 1950 to less than 5 mppcf in 1965 (Rubino 1979) | High quartz in the past.<br>Radon in 1992, 500 Bq/m$^3$ = 13.5 pCi/l | 47% smokers in 1993; 34% in an adult Italian population survey in 1994 |
| Coggiola *et al*, Italian talc millers[22] | All male employees from Italian talc mill with at least one year employment between 1946 and 1995 followed up from 1946–95 | Decreased from about 20 mppcf until 1960 to about 5 mppcf in 1975 (Rubino 1979). In 1993 1.3 mg/m$^3$ (personal communication) | None<br>Quartz <1% | 44% smokers in 1993; 34% in an adult Italian population survey in 1994 |

exposures.[16] Four different levels (in f/ml) were estimated from an internal job-time period exposure matrix. The job history of each study member was converted in a cumulative exposure in days×f/l which was used to estimate risk in nested case control studies of lung cancer and non-malignant respiratory diseases. A conversion from f/ml to mg/m$^3$ is impossible as the type of talc used is not specified. Of particular interest is the mortality study of Thomas[12 13] among ceramic workers exposed to quartz and non-fibrous talc. Unfortunately no quantitative estimate of either exposure is available and no quartz free group could be identified. Langseth *et al*[20] and Bulbulyan *et al*[19] mention talc exposure as part of the paper dust exposure, talc being sometimes used as filler in paper production.

**Table 2** Summary characteristics of talc exposed populations in other industries

| | Cohort definition | Talc exposure | Other | Smoking |
|---|---|---|---|---|
| Thomas *et al*, pottery workers[12 13] | All employees of three US ceramic factories with one year employment 1939–66 followed up from 1955–81 | No, non-fibrous, fibrous | Quartz high/low | No information |
| Zhang *et al*, rubber workers[14] | Employees (male and female) of a Shanghai rubber factory who entered a screening program for heart disease in 1972 followed up from 1972–84 | Exposure during curing.<br>No precision as to whether fibrous or not fibrous | Curing agents, condensed volatiles, gases nitrosamines | Available for everybody, controlled in the analysis |
| Chiazze *et al*, fibreglass workers[16] | Production and maintenance workers employed at least one year in a Ohio fibreglass plant from 1940–62, followed up until 1982 | Expressed in estimated f/ml.<br>No precision as to whether fibrous or not fibrous | Asbestos, silica, formaldehyde, | Available for everybody, controlled in the analysis |
| Straif *et al*, rubber workers[17 18] | All male employees from five German rubber plants with at least one year employment retired or active in 1981 followed up from 1981–91 | Low/medium/high<br>Non-fibrous talc | Asbestos, nitrosamines, carbon black | No information |
| Langseth and Andersen, paper workers[20] | All female employees of a pulp and paper mill working at least one year between 1920–93 followed up for cancer incidence from 1953–93 | As a constituent of paper dust in the paper departments | Paper dust, sulphur dioxide, hydrogen sulphide, chlorine, chlorine dioxide | No information |
| Bulbulyan *et al*, printing workers[19] | All female employees of two printing plants working at least two year between 1978–93 followed up for cancer incidence from 1979–93 | As a constituent of paper dust in the book binding department and among press operators | Paper dust, benzene, solvents, aromatic hydrocarbons, carbon black | No information |

**Table 3** Lung cancer and mortality from all causes in the talc producing companies

| | | Lung cancer | | | Mortality, all causes |
|---|---|---|---|---|---|
| | n | Type of RR | RR (cases) | 95% CI | SMR (cases) |
| Talc millers | | | | | |
| Vermont [4] | 225 | SMR US rates | 1.02 (2) | 0.09–3.69 | 1.18 (44) |
| Norway [15] | 295 | SIR Norwegian rates | 0.77 (4) | 0.21–1.96 | 0.74 (90) |
| Italy [22] | 551 | SMR regional rates | 0.69 (11) | 0.34–1.23 | 1.08 (290) |
| France [21] | 945 | SMR regional rates | 1.24 (21) | 0.76–1.89 | 0.93 (294) |
| Austria, site B | | SMR regional rates | 0.69 (3) | 0.14–2.01 | 0.70 (40) |
| Austria, site C | | SMR regional rates | 1.11 (1) | 0.01–6.19 | 0.97 (11) |
| All talc millers—fixed effect | | | 0.92 (42) | 0.67–1.25 | 0.95 (769) |
| Talc miners | | | | | |
| Vermont [4] | 163 | SMR US rates | 4.35 (5) | 1.40–10.2 | 1.28 (34) |
| Norway [15] | 94 | SIR Norwegian rates | 1.58 (2) | 0.18–5.69 | 0.82 (27) |
| Italy [22] | 1244 | SMR regional rates | 1.07 (33) | 0.74–1.50 | 1.26 (590) |
| All talc miners—fixed effect | | | 1.20 (40) | 0.86–1.63 | 1.24 (651) |
| All talc miners—random effect | | | 1.85 (40) | 0.68–5.05 | 1.10 (651) |

RR, relative risk; SIR, standardised incidence ratio; SMR, standardised mortality ratio.

It must be noted that neither Zhang *et al*, nor Bulbulyan *et al*, nor Chiazze *et al* mention whether or not the talc used contained asbestiform fibres. The talc used in the Norwegian paper mill can be supposed to be free of asbestiform fibres assuming that this producer used European talc paralleling a similar argument used by Straif *et al*.[17]

Table 3 gives the summary mortality results of the talc millers and miners. Among millers, in which no other carcinogen is mentioned, only one RR (in the French cohort) was above unity but not significantly so. Moreover in this population, an internal case control study showed no increasing trend with cumulative exposure. Overall the SMR among millers is equal to 0.92 (95% CI 0.65 to 1.25) and below the SMR for all causes and no heterogeneity between the studies was detected ($\chi^2 = 3.21$, 5 df, $p = 0.67$).

If we rank the observed SMRs by increasing global exposure based on the fragmentary exposure information available as given in the preceding section, we observe a slight non-significant increase from the SMR of the Italian millers (0.67 presumed to have the lowest exposure) to the SMR of the French millers (1.24) presumed to have the highest exposure. Of somewhat better precision is the dose-response relation explored in a nested case control study in the French and Austrian cohort.[21] The odds ratios decreased with increasing cumulative talc exposure, the odds ratios with respect to non-talc exposed subjects exposed from 400–800 years×mg/m$^3$ was 0.60 and for subjects above 800 years×mg/m$^3$ it was 0.73. The latter subjects correspond to a job held for more than 20 years in the highest exposure category (>30 mg/m$^3$). Note also that the mortality from lung cancer does not increase by duration of employment among Italian millers and miners.[22]

Among miners for whom exposures to quartz and radon are mentioned, the only significant increase is in the Vermont talc miners. Overall the SMR among miners is 1.20 (95% CI 0.86 to 1.63) and is close to the SMR for all causes. However a significant heterogeneity was detected, owing to the very large risk among Vermont miners ($\chi^2 = 10.1$, $df = 2$, $p = 0.006$). The random effect summary estimate is therefore larger with a wider confidence interval (RR = 1.85, 95% CI 0.68 to 5.05).

Table 4 summarises the relative risks with respect to talc exposures in other industries. Overall all relative risks are above unity but only in the study of Chiazze *et al*[16] was the talc exposure adjusted on the major confounders. The highest risks are seen in the US ceramic industry in which the SMRs increased with increasing duration to non-fibrous talc exposure but not with silica. No combined estimate was computed as the studies differ too much in the exposure circumstances.

## DISCUSSION

The preceding analyses show that in the populations of talc millers in which talc was (nearly) the single exposure, lung

**Table 4** Lung cancer relative risks in relation to talc exposure in other industries

| | | Lung cancer | | |
|---|---|---|---|---|
| | n | Type of relative risk | RR (exposed cases) | 95% CI |
| Ceramic industry, US[12 13] | 2055 | SMR ever exposed to non-fibrous talc and high silica (US rates)—unadjusted | 2.54 (21) | 1.57–3.88 |
| | | SMR exposed to 15+ years non-fibrous talc and high silica (US rates)—unadjusted | 3.64 (8) | 1.57–7.17 |
| Rubber industry, China[14] | 1624 | Mantel-Haenszel RR (rubber curing adjusted on smoking) | Males 3.3 (7)<br>Females 4.6 (2) | 1.3–8.2<br>0.8–28.0 |
| Rubber industry, Germany[17 18] | 8933 | Internal RR (high talc exposure unadjusted) | 2.4 (13) | 1.2–4.9 |
| | | Internal RR (high talc or asbestos exposure adjusted on smoking and other exposures) | 2.0 (13) | 0.9–4.1 |
| Glass fibre production, US[16] | 144 cases, 280 controls | OR (high talc exposure adjusted on smoking and other exposures) | 1.36 (10) | 0.41–4.52 |
| Printing industry, Russia[19] | 1795 | SMR (in press operators and in bookbinders exposed to paper dust potentially containing talc) | 1.0 (6) | 0.35–2.18 |
| Pulp and paper mill, Norway[20] | | SIR (all workers with more than three years employment, at least 44% of which have been exposed to paper dust potentially containing talc) | 1.4 (14) | 0.70–2.16 |

OR, odds ratio; RR, relative risk; SIR, standardised incidence ratio; SMR, standardised mortality ratio.

cancer risk was not increased; the upper limit of the confidence limit being 1.25. On the other hand, in the presence of other carcinogens, in talc miners and in other settings, some excesses appeared.

Are the latter risks attributable to non-fibrous talc? In all these populations other potential occupational carcinogens co-exist with talc, thus all unadjusted relative risks are confounded to some degree. The study of Zhang *et al*[14] appears difficult to interpret as a study of talc exposure as it considered only working in the curing workshop as a risk factor. Curing rubber involves other possibly carcinogenic exposures especially exposure to nitrosamines. A later follow up of the same population (Li *et al*[23]) privileged this hypothesis. Furthermore it is not possible to tell whether the talc used contained asbestiform fibres. A similar feature occurs with the German rubber workers (Straif *et al*[17 18]). While the unadjusted relative risks with talc alone are increased and significant in this paper and some confounding with nitrosamines and asbestos is likely, the adjusted risks are only given for a combined asbestos and talc exposure. Thus the relative effect of these two exposures cannot be distinguished. The odds ratio of 1.36 after adjustment for smoking and a series of occupational exposure computed by Chiazze[16] is a rather weak evidence, especially as the unadjusted risk was below unity. The papers by Bulbulyan[19] and Langseth[20] mention a talc exposure as a component of paper dust. Following the recent worldwide multicentric IARC study in the pulp and paper industry, a number of nationwide mortality studies have been published (for example, see Szymczak *et al*, Sivo *et al*, Wild *et al*, and Matanoski *et al*[25–28]) most of which do not mention talc exposure. However the subpopulations of these studies involved in paper production could be considered to be talc exposed. Moreover, in the unpublished final report of the IARC multicentric study, the lung cancer mortality of subjects in the pulp and paper industry ever exposed to talc (286 observed cases *v* 295 expected) or ever highly exposed to talc (59 cases *v* 61.6 expected) was not in excess. However significantly increased lung cancer SMRs are observed in the subset of talc exposed women in the same report. Stronger evidence as to a possible carcinogenic effect of talc is provided by the paper of Thomas and Stewart[12] as a increasing trend with duration of non-fibrous talc exposure was observed, which was not observed for silica. However no quartz free talc exposure group could be identified in this cohort and the authors ''do not rule out the effect of silica as a cofactor''. Moreover the authors acknowledge that talc containing fibres had also been in use. In the light of these very different features a pooled risk estimate did not seem relevant.

Can the absence of lung cancer risk among talc millers be explained by healthy worker effect or by lack of control for smoking? As shown in table 3, the combined SMR for all causes is close to unity and is higher than the SMR for lung cancer. Thus a decreased SMR because of a healthy worker effect and/or inappropriate reference rates is highly unlikely. For four out of five studies some smoking data are available and, with the possible exception of the Austrian millers, the available data point towards a smoking prevalence which is higher than in the reference population. This is not unexpected among blue collar workers. Thus it is highly unlikely that the absence of information on smoking in the mortality studies could have hidden a risk due to talc. On the other hand, most of the talc worker cohorts include all employees of the mills and mines, so that it is likely that a number of unexposed subjects were included. This has probably lowered some of the SMRs but the impact of this necessarily small population on the cited SMRs should be virtually negligible.

What is the strength of this evidence? The weight of this (negative) evidence is to a large extent dependent on the overall exposure and its characterisation. Unfortunately in most studies only very sketchy exposure information is given and only SMRs are given without any attempt to estimate possible exposure-response relations. However, it can be safely assumed that the exposure was high and sometimes extremely so in most populations of talc millers. This high exposure is documented by the fact that in all studied talc exposed populations cases of pneumoconiosis were observed. Although no miller died of non-malignant respiratory diseases (NMRD) in the Norwegian population and only one in the Austrian population, the past prevalence of pneumoconiosis was high in both populations. This contrasted with a high mortality from NMRD among Vermont millers[4] (SMR = 4.1, seven cases). In Italy[22] and France[21] the mortality from NMRD was slightly above the expected (SMR = 1.04 and 1.06 respectively) but in the latter population a significantly increasing trend could be shown: in the two highest exposure categories for which the lung cancer odds ratios were below unity (see results section) the ORs for NMRD increased significantly at respectively 1.97 and 2.53, thus validating the high talc exposure in these categories. The overall evidence of this absence of risk is further strengthened by the fact that no heterogeneity between the lung cancer SMRs among talc millers could be observed. However the main weakness of these data is the paucity of reliable studies of a possible dose-response effect.

What is the influence of a possible publication bias? It is unlikely that a cohort study conducted among talc workers would have gone completely unpublished if it showed an increased lung cancer risk. There has been a public awareness of a possible carcinogenic risk with respect to talc since the publication of the study by Kleinfeld *et al*[29] and the number of talc producing sites in quite limited. On the other hand the description of small cohorts may go unpublished if no risk is shown—for example, the site by site description among Austrian miners could not be published. Note that the mortality of the Norwegian talc workers is currently being updated (personal communication of Dr Wergeland).

A publication bias is more likely for the studies carried out in other industrial settings. Given the widespread use of talc in many industrial applications (paper, paints, plastics, rubber, ceramics, and so on) it is surprising that only six studies considered talc exposure as a potential carcinogen. One cannot exclude that negative results—that is, studies in which talc could not be shown to increase the lung cancer risk—were not included in necessarily condensed published papers.

The epidemiological evidence concerning a possible lung cancer relation must be considered in the light of the evidence from other human and animal studies. Talc has been suspected to be a human carcinogen based on the fact that talc powders contain a significant number of particles which meet the WHO definition of a fibre, and that these particles are very biopersistent and that persistent fibres have shown tumorigenic effects. This hypothesis does not seem to be supported by the available animal and vitro studies. The lung cancer excesses observed in a large chronic rat inhalation assay conducted by the NTP are interpretable as being the result of inflammation causing secondary genotoxicity on the basis of the well recognised phenomenon of lung overload in rats by poorly soluble low toxicity particles (Oberdörster *et al*,[30] Knaapen *et al*[31]). Thus this study does not give any indication as to a specific carcinogenicity of talc. Other studies using intrapleural instillation of high doses of talc (Wagner,[32] Stanton[33]) did not show any carcinogenic effect. This is consistent with results of a recent in vitro study by Nasreen[34] who describes how a talc sample at low doses

**Main message**

- There is no evidence of an increased lung cancer risk among workers exposed to talc not containing asbestiform fibres in the absence of other potential carcinogens.

(6 μg/cm$^2$) was able to cause apoptosis of malignant but not normal mesothelial cells. This selective apoptotic effect may also be the reason why humans who were treated with massive amounts of talc (5–10 g) for pleurodesis did not show chronic complications such as mesothelioma or lung cancer in the single follow up study of treated patients.[35]

Finally, a large literature exists on the potential relation between talc exposure and ovarian cancer. A recent meta-analysis[36] found a significantly increased summary relative risk, RR = 1.33 (95% CI 1.16 to 1.45). However the authors stated that ''the data showed a lack of clear dose-response relationship making the RRs of questionable validity''. It can also be remarked that some of the cosmetic talc powders in the US had been shown to contain asbestiform fibres in the past.

## CONCLUSION

No increased lung cancer mortality was observed among talc millers despite their high exposure experience. However few studies provide adequate exposure information. Further studies of possible quantitative exposure-response relations are needed. In populations in which talc was associated with other potential carcinogens, some lung cancer excesses were observed.

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