TALC

Perineal use of talc-based body powder (Group 2B)
Inhaled talc not containing asbestos or asbestiform fibres (Group 3)

[The text of these Summaries and Evaluations may be edited for language and clarity during the checking of the main text of the Monographs.]

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5. Summary of Data Reported

5.1 Exposure data

The term ‘talc’ refers to both mineral talc and industrial products that contain mineral talc in proportions that range from about 35% to almost 100% and are marketed under the name talc. Mineral talc occurs naturally in many regions of the world where metamorphosed mafic and ultramafic rocks or magnesium carbonates occur. Mineral talc is usually platy but may also occur as asbestiform fibres. (Asbestiform refers to a habit, i.e. a pattern of mineral growth and not to the presence of other minerals. Asbestiform talc must not be confused with talc that contains asbestos.) Together with platy talc, asbestiform talc is found in the Gouverneur District of New York State, USA, and occasionally elsewhere; it may be associated with other minerals as observed by transmission electron microscopy.

Talc products vary in their particle size, associated minerals and talc content depending on their source and application. Minerals commonly found in talc products include chlorite and carbonate. Less commonly, talc products contain tremolite, anthophyllite and serpentine.

Mineral talc is valued for its softness, platyness, inertness and ability to absorb organic matter. It is used in agricultural products, ceramics, paint and other coatings, paper, plastics, roofing, rubber, cosmetics and pharmaceuticals and for waste treatment. Cosmetic talc, which contains more than 90% mineral talc, is present in many cosmetic products and is used for many purposes, including baby powders and feminine hygiene products. The type of talc that is currently used for cosmetic purposes in the USA does not contain detectable levels of amphibole, including asbestos. Based on information from Pakistan, it is not known whether this is true in other countries.

Workers are exposed to talc during its mining and milling. Reported exposure levels to respirable dust are typically in the range of 1–5 mg/m^3 (geometric mean). Workers may also be exposed in user industries, primarily in the rubber, pulp and paper and ceramic industries. Exposure in the user industries is difficult to assess because of the lack of data from such industries and concomitant exposure to many other particles. Consumer exposure by inhalation could occur during the use of loose powders that contain talc.

Accurate estimates of prevalence are not available, but the use for feminine hygiene of body powders, baby powders, talcum powders and deodorizing powders, most of which contain cosmetic talc in varying amounts, has been reported to be as high as 50% in some countries, based on the controls from the ovarian-cancer epidemiological studies. Perineal use for such purposes seems to be common practise in the USA, Canada, Australia and the United Kingdom. Based on information from Pakistan, the prevalence of use may be considerable in other countries as well.

5.2 Human carcinogenicity data

The carcinogenic effect of exposure to talc not contaminated by asbestiform fibres has been investigated in five independent but relatively small cohort studies of talc miners and millers in the USA, Norway, Italy, France and Austria. The miners and to a lesser extent the millers in these cohorts were also exposed to quartz. In the miners in the US study, an excess risk for lung cancer was found, which may have been due to exposure to radon daughters and quartz in the workplace. In all the other groups of workers studied, there was no increased risk for lung cancer. In the two studies from Norway and Italy, which included an estimate of cumulative exposure to talc dust, the risk for lung cancer in the highest category was found to be close to or below unity. In a case–control study nested in the combined cohorts of talc workers from France and Austria, there was no tendency of higher risks for lung cancer by increasing cumulative exposure of workers to talc dust. In four of five studies, it was explicitly stated that no case of mesothelioma was observed.

In female workers in the Norwegian pulp and paper industry there was an increased risk for ovarian cancer, which, however, was attributed to exposure to asbestos. A community-based case–control study did not find an increased risk for ovarian cancer associated with occupational exposure to talc, but prevalence of exposure was low.

Body powder has been used by women on the perineum (or genital area) and on sanitary napkins. In total, data from one prospective cohort study and 19 case–control studies were reviewed to evaluate the association of use of talc-based body powder and risk for ovarian cancer. The information collected on perineal use varied substantially by study (e.g. ever use versus regular use, whether information on mode of application, frequency or duration of use was available).

The cohort study was conducted among nurses in the USA and included 307 cases of ovarian cancer that occurred over 900 000 person–years of observation and a maximum of 14 years of follow-up. Information was collected on frequency but not duration of regular use. Perineal use of talc-based body powder was not associated with risk for ovarian cancer.

The 19 case–control studies were conducted in the USA, Canada, the United Kingdom, Australia, Greece, Israel and China and included between 77 and 824 cases and between 46 and 1105 controls. Five were hospital-based designs and the others were population-based studies. The Working Group selected a subset of these studies as being more informative based on the following characteristics: whether the study was population-based, was of a reasonable size, had acceptable participation rates and included information to allow control for potentially important confounders.

Eight population-based case–control studies from Australia, Canada (Ontario) and the USA (two non-overlapping studies in Boston, and one each in eastern Massachusetts and New Hampshire, California, Delaware Valley and Washington State) were thereby identified as being more informative. The selected studies included at least 188 cases and had participation rates generally ranging from 60 to 75%. Among these eight studies, the prevalence of perineal use of talc-based body powder among controls ranged from 16 to 52%; however information on exposure was not collected in a comparable manner across studies. In addition, frequency and duration of use or total lifetime applications were reported in several studies as well as consideration of prior tubal ligation or hysterectomy. Only sparse data were available on whether women had used body powder prior to or after the mid-1970s.

The relative risks for ovarian cancer among body powder users (versus non-users) were homogenous across this relatively diverse set of eight studies, each of which indicated a 30–60% increase in risk. Among the other 11 case–control studies, most also reported relative risks of this magnitude or higher. The subset of studies that assessed use of talc on a diaphragm was relatively uninformative due to low precision.

Results on exposure–response relationships were presented in the cohort study and in seven of the more informative case–control studies. In the cohort study, no exposure–response trend was apparent. Positive exposure–response trends were apparent in the two Boston-based studies, which presented the most comprehensive analysis. In the remaining five studies, consistent trends were not observed.

The cohort study and four of the eight more informative case–control studies presented results on histological type of ovarian cancer. When the analysis of the cohort study was restricted to the 160 serous invasive cases, a statistically significant increase in risk of about 40% was observed. The risk increased with increasing frequency of body powder use. Relative risks for serous ovarian cancer were somewhat greater than those for other histological types in two of the four case–control studies that presented results on histological type. Results for other histological types were inconclusive.

The Working Group carefully weighed the various limitations and biases that could have influenced these findings. Non-differential misclassification of talc use, given the relatively crude definitions available, would have attenuated any true association. Although the available information on potential confounders varied by study, most investigators accounted for age, oral contraceptive use and parity. In most studies, only the adjusted relative risks were presented; however, in the three studies in which both age-adjusted and fully adjusted estimates were provided, relative risks did not differ materially, suggesting minimal residual confounding by these factors.

It is possible that confounding by unrecognised risk factors may have distorted the results. One or more such factors, if they are causes of ovarian cancer and also associated in the population with perineal use of talc, could induce the appearance of an association between the use of talc and ovarian cancer where there is none. In order for such an unrecognised risk factor to induce the consistent pattern of excess risks in all the case–control studies, it would be necessary for the factor to be associated with perineal talc use across different countries and different decades. While the range of countries and decades covered by the more informative case–control studies is not very broad, it provides some diversity of social and cultural context and thereby reduces the likelihood of a hidden confounder.

There was a distinct pattern of excess risk discernible in all of the more informative case–control studies when users were compared with non-users; however, methodological factors need to be considered. First, while chance cannot be ruled out as an explanation, it seems very unlikely to be responsible for the consistent pattern of excess risks. A second possible explanation would be recall bias, to which case–control studies may be particularly susceptible. This may have resulted if there had been widespread publicity about the possible association between use of body powder and cancer. Namely, in such circumstances, it is possible that women who had ovarian cancer would more likely report use of talc than women who did not have ovarian cancer. There was a flurry of publicity in the USA in the mid-1970s concerning the possible risks for cancer posed by the use of talc-based body powders, in response to which the industry decided to market talc powders without asbestos contamination (levels below the detection limit). It is the opinion of the Working Group that there has not been widespread public concern about this issue, at least until very recently. The Working Group therefore considers it unlikely that such a bias could explain the set of consistent findings that stretch over two decades. Another source of recall bias could result from the fact that women with a cancer may be more likely to remember or over-report a habit, such as body powder use, if they thought that it may have played a role in their illness. The Working Group believes this source of bias is a possibility inherent in the case–control studies and cannot be ruled out. The Working Group also considered publication and selection biases and these were not judged to have substantially influenced the pattern of findings.

The Working Group searched for documentation on the presence of known hazardous minerals in talc-based body powders. There are strong indications that these products contained quartz in the mid-1970s and still do. There are indications that occasional small concentrations of asbestos were present in these products before the mid-1970s, but the available information is sparse, sampling methods and detection limits were not described, and the range of locations where data are available is extremely limited. As a result, the Working Group found it difficult to identify a date before which talc-based body powders contained other hazardous minerals and after which they did not, or to have confidence that this would be applicable worldwide. In addition, the epidemiological studies generally do not provide information about the years when the female subjects were exposed. Consequently, the Working Group could not identify studies where an uncontaminated form of talc was the only one used by study subjects. Nonetheless, the Working Group noted that even in the most recent studies in the USA, where exposure histories are less likely to have been affected by hazardous contaminants of talc, the risk estimates were not different from those of the early studies where the possibility of such exposure was more likely.

In order to evaluate the evidence on whether perineal use of talc causes an increased risk for ovarian cancer, the Working Group noted the following:

- The eight more informative case–control studies, as well as most of the less informative ones, provided overall estimates of excess risk that were remarkably consistent; seven of these eight case–control studies examined exposure–response relationships: two provided evidence supporting such a relationship and five did not.

- The cohort study neither supports nor strongly refutes the evidence from the case–control studies;

- Case–control studies were susceptible to recall biases, which could tend to inflate risk estimates but to an unknown degree;

- All studies were susceptible to other potential biases, which could increase or decrease the association;

- All studies involved some degree of non-differential misclassification of exposure that would tend to underestimate any true underlying association.

5.3 Animal carcinogenicity data

Talc of different grades was tested for carcinogenicity in mice by inhalation exposure, subcutaneous, intraperitoneal and intrathoracic injection, in rats by oral administration, inhalation exposure, intraperitoneal injection, intrathoracic injection and intrapleural and ovarian implantation, and in hamsters by inhalation exposure and intratracheal injection.

Male and female rats and male and female mice were exposed by inhalation to a well-defined talc. The incidences of alveolar/bronchiolar carcinoma, and of adenoma and carcinoma combined, were significantly increased in female rats. Incidences of pheochromocytomas of the adrenal medulla (benign, malignant and complex combined) showed a significant positive trend and the incidences in high-dose male and female rats were significantly greater than those in controls. The incidence of malignant pheochromocytomas was also increased in high-dose female rats. The Working Group did not consider it probable that the increased incidence of pheochromocytomas was causally related to talc, but based on the experimental data available, neither can talc-related effects be excluded. Tumour incidence was not increased in mice of either sex in this study.

In one study in rats and two studies in mice of intraperitoneal administration of talc, no increase in the incidence of mesotheliomas was observed. Two other studies of intraperitoneal administration, one in rats and one in mice, were found to be inadequate for evaluation. One study in rats and one study in mice by intrathoracic administration were found to be inadequate for evaluation. In one study by intrapleural injection of talc in rats and in another study by intrapleural implantation of various talcs in rats, tumour incidence was not increased. A single subcutaneous injection of talc in mice did not produce local tumours. No tumour was produced in rats in one study of administration of talc in the diet or in another study by implantation of talc onto the ovary. Tumour incidence was not increased following administration of talc to hamsters by inhalation or intratracheal administration.

5.4 Mechanistic considerations and other relevant data

Different mechanisms are probably operative for the effects of talc on the lung and pleura depending on the method of exposure. (General particle characteristics and host factors that are considered to affect deposition and retention patterns of inhaled, poorly soluble particles such as talc are summarized in the monograph on carbon black.)

In humans, deposition, retention and clearance of talc have been insufficiently studied. Talc particles have been found at autopsy in the lungs of talc workers.

In humans and experimental animals, the effects of talc are dependent on the route of exposure, the dose and the properties of the talc. Talc pneumoconiosis is somewhat more

prevalent and severe among miners exposed to talc containing asbestiform minerals and/or asbestos than among those exposed to talc without such contaminants. The role of quartz and asbestos in the observed pneumoconiosis could not be ruled out. Inadvertent exposure to talc in intravenous drug users results in microembolization in a variety of organs and alterations in pulmonary function.

In animal studies, inhaled talc has been shown to cause granulomas and mild inflammation. Observations of effects in lungs of rats exposed by inhalation to talc suggest that there may be similar mechanisms operative as identified for carbon black. No teratological effects were observed in hamsters, rats, mice or rabbits following oral administration of talc. Talc is known to cause the release of cytokines, chemokines and growth factors from pleural mesothelial cells.

In humans, intrapleural administration of talc as a therapeutic modality results in pleural inflammation leading to pleural fibrosis and symphysis. Pleural fibrosis is the intended effect of intrapleural administration of talc in patients with malignant pleural effusions or pneumothorax. Talc has been shown to cause apoptosis of malignant human mesothelioma cells *in vitro*. Animal studies suggest that extrapulmonary transport of talc following pleurodesis increases with decreasing particle size and increasing administered dose.

Perineal exposure to cosmetic talc in women is of concern because of its possible association with ovarian cancer. A number of studies have been conducted to assess potential retrograde movement of particles through the reproductive tract to the ovaries. These studies have been conducted in women about to undergo gynaecological surgery, most of whom had diseases or complications of the reproductive tract and organs that required surgery. The findings reported in these studies may be confounded by the various levels of dysfunction in the female reproductive tract due to underlying pathologies. In addition, most of the studies had little or no further information on the use of talc products for perineal hygiene or changes in habits that may have preceded surgery. On balance, the Working Group considered that the evidence for retrograde transport of talc to the ovaries in healthy women is weak. In women with a gynaecological condition, there is some evidence of retrograde transport. Studies in animals (rodents, lagomorphs and non-human primates) showed no evidence of retrograde transport of talc to the ovaries. Conflicting data exist on the systemic distribution of talc in experimental animals.

There is evidence that the presence of anti-MUC1 antibodies is inversely associated with ovarian cancer risk. In a study among >700 women, anti-MUC1 antibodies were found in a significantly higher percentage of women who reported no perineal use of talc than in those who regularly used talc.

No data were available on the genotoxic effects to humans of exposure to talc. The results of the few in-vitro studies available on the genetic toxicology of talc were negative.

6. Evaluation

There is *limited evidence* in humans for the carcinogenicity of perineal use of talc-based body powder.

There is *inadequate evidence* in humans for the carcinogenicity of inhaled talc not containing asbestos or asbestiform fibres.

There is *limited evidence* in experimental animals for the carcinogenicity of talc not containing asbestos or asbestiform fibres.

Overall evaluation

Perineal use of talc-based body powder is *possibly carcinogenic to humans (Group 2B).*

Inhaled talc not containing asbestos or asbestiform fibres is *not classifiable as to its carcinogenicity to humans (Group 3).*

Rationale

To follow

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