

Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment

Assessment of data on Talc (non-asbestiform): Discussion paper

Introduction

1. At the July 2025 meeting, HSE presented an introductory paper on the consideration of the carcinogenicity of talc ($(\text{Mg}_3\text{H}_2(\text{SiO}_3)_4)$, not containing asbestos and asbestiform fibres) under the GB Classification, Labelling and Packaging Regulation (GB CLP) to the Committee (CC/2025/03).
2. That paper (CC/2025/03) explained the process whereby HSE is required to consider an opinion on the classification of talc in the EU prepared by ECHA's Risk Assessment Committee (RAC). In accordance with GB CLP, HSE assesses the evidence that RAC used in forming its position on classification. HSE must then present its own proposal on classification within six months of the RAC opinion being published. The RAC opinion on talc was published in July 2025.
3. In the EU, harmonised classification and labelling (CLH) of talc was proposed for carcinogenicity and specific target organ toxicity upon repeated exposure (STOT-RE). RAC supported classification of talc for carcinogenicity in Category 1B (route of exposure not specified) and STOT-RE category 1 via inhalation (target organ: lungs). The basis of RAC's conclusion on classification for carcinogenicity is in section 3.5.3.2 of the opinion.
4. The International Agency for Research on Cancer (IARC) also recently assessed the carcinogenicity of talc (IARC 2025). RAC did not consider this in its assessment because it was not published at the time of RAC's deliberations. The data included in the IARC assessment are largely the same as the data considered

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by RAC. HSE's evaluation of the data will take into account both RAC's and IARC's assessments. Some of IARC's conclusions on the data are included in this paper for context.

5. The current paper focuses on the key data that underpin RAC's position on classification for carcinogenicity, alongside specific questions related to this evidence base in each section for which HSE is kindly seeking the views of the Committee.

Lung cancer

6. The initial CLH report provided information on animal and human studies by the inhalation route (CLH 2023; p91-102). RAC assessed in detail the study conducted by the National Toxicology Program (NTP), in which the carcinogenicity of talc (non-asbestiform) following inhalation exposure was investigated in rats and mice (NTP, 1993). The study design was similar to the OECD test guideline (OECD 453) and it was conducted in accordance with Good Laboratory Practice (GLP). RAC noted that the other available animal studies (in which the induction of lung tumours was not reported following inhalation exposure to talc) had major limitations which it considered to affect reliability, and were therefore not taken into account in the assessment. RAC also assessed occupational studies in predominantly talc miners/millers, in which an association between talc exposure and lung cancer was not found.

7. In NTP (1993), an increase in the incidence of lung tumours was reported at the end of the study in female rats, but not in male rats or mice. RAC based its conclusions on the potential for talc (non-asbestiform) to induce lung cancer primarily on the findings in female rats in this study.

Design and conduct of NTP (1993)

8. In the NTP (1993) study, F344 rats (50/sex/group) were exposed via whole-body inhalation to aerosolised, micronised talc for 6h/day, 5d/week at concentrations of 0, 6, or 18 mg/m³. The talc used in the study was grade MP 10-52, described as

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“high purity talc that has a top particle size of 10µm”; analysis of this material indicated it was virtually free of silica and without asbestiform minerals or tremolite.

9. To support selection of the applied concentrations, the study author referred to previous reports that talc produces its toxic effects after prolonged (stated by NTP to be one year) exposure; and that lung talc burden, not talc toxicity, would be the limiting factor for dose selection. For this reason, the NTP conducted a 4-week lung talc burden study in rats rather than the conventional 13-week study; this study indicated that the amount of talc retained in the lung was similar between sexes and proportional to exposure concentration. An accumulation of alveolar macrophages was observed only in the 18 mg/m³ group; the study authors predicted that concentrations above this would *“overwhelm lung clearance mechanisms, impair lung function and possibly shorten survival”*. Consequently, 6 and 18 mg/m³ were selected as the exposure concentrations for the main study.

10. In the main study, exposure was continued beyond the standard two-year timeframe because of a report that *“80% of pulmonary neoplasms induced in rats by inhalation exposure to diesel exhaust occurred after 2 years”* (Mauderly et al., 1987). No further explanation was provided in the study report, but HSE notes that the primary difference between studies that have not demonstrated a carcinogenic response in animals to diesel exhaust and those that have provided evidence of an association was the duration of exposure: this was 24 months or less in the negative studies and up to 30 months in those that were positive (NIOSH, 1990). Mauderly was named as a contributor to the NTP report. As a result, rats were exposed until mortality in any group reached 80%; this was 113 weeks in male rats, and 122 weeks in female rats. After the end of the exposure period, rats were exposed to filtered air for 10/11 days, before necropsy and pathology evaluation; it is unclear why this step was carried out. Additional interim evaluations on rats (22/sex/group) were performed at 6, 11, 18 and 24 months for the assessment of lung talc burden, pulmonary function, lung biochemistry, cytology and phagocytosis measurements.

11. The median mass aerodynamic diameter (MMAD) of talc aerosols was 2.7 µm in the 6 mg/m³ chamber and 3.2 µm in the 18 mg/m³ chamber, both with geometric standard deviations of 1.9 µm. However, aerosol concentrations were not consistent

throughout the study. At week 11-18, the chamber concentration for the 18 mg/m³ group varied between approximately 30-40 mg/m³, owing to issues with the monitoring system. At week 70-82, difficulties in generating the aerosol led to substantially lower chamber concentrations across both treatment groups. The study authors stated that the “*problems with maintaining the target concentrations in the NTP study had no apparent substantive effect on lung talc burden*”.

Results of NTP (1993)

12. No clinical signs or exposure-related deaths were noted in male or female rats. Mean body weights of male and female rats exposed to 18 mg/m³ were lower than controls, particularly after week 65; terminal body weight was reduced in females (-14%), but only minimally in male rats compared with controls.

13. In the 18 mg/m³ group, there was a statistically significant increase in benign and malignant lung neoplasms (alveolar/bronchiolar adenomas and carcinomas) in the female rats compared with the concurrent control and historical control data (HCD) (Table 1). The incidence of alveolar/bronchiolar adenoma or carcinoma combined was also increased in this group. The HCD (which comprised chronic inhalation studies performed between 1985-1993; NTP, 1997) were obtained from studies of up to 105 weeks' duration, hindering a direct comparison with the incidences obtained in the NTP study.

14. Tumours developed late in life: the first incidence of adenoma was observed after 716 days (approximately 102 weeks) and the first incidence of carcinoma was observed after 828 days (approximately 118 weeks).

15. There was not an increase in lung tumours in the females of the 6 mg/m³ group nor in male rats of either exposure group. The study authors postulated that the difference in tumour incidence between males and females might have resulted from the longer exposure duration in females, or from qualitative or quantitative differences between the sexes.

Table 1: Overall incidences of lung neoplasms in rats in the lifetime inhalation talc study (NTP, 1993), with corresponding historical control data.

Tumour type	Sex	0 mg/m³	6 mg/m³	18 mg/m³	HCD (% mean \pm SD)
<i>Adenoma</i>	Male	0/49 (0%)	1/50 (2%)	1/50 (2%)	(1.7 \pm 2.4%)
<i>Carcinoma</i>	Male	0/49 (0%)	0/50 (0%)	1/50 (2%)	(0.8 \pm 1.2%)
<i>Adenoma or carcinoma</i>	Male	0/49 (0%)	1/50 (2%)	1/50 (2%)	(2.5 \pm 2.6%)
<i>Squamous cell carcinoma</i>	Male	0/49 (0%)	0/50 (0%)	0/50 (0%)	(0.4 \pm 0.8%)
<i>Adenoma</i>	Female	1/50 (2%)	0/48 (0%)	9/50 (18%)	(1.1 \pm 1.3%)
<i>Carcinoma</i>	Female	0/50 (0%)	0/48 (0%)	5/50 (10%)	(1.1 \pm 1.3%)
<i>Adenoma or carcinoma</i>	Female	1/50 (2%)	0/48 (0%)	13/50 (26%)	(1.3 \pm 1.5%)
<i>Squamous cell carcinoma</i>	Female	0/50 (0%)	0/48 (0%)	1/50 (2%)	(0.1 \pm 0.4%)

Source: Study data from NTP (1993). Historical control data from chronic inhalation studies performed by NTP between 1985-1993, cited as NTP (1997).

16. Other effects observed in the respiratory system of rats included alveolar epithelial hyperplasia, interstitial fibrosis, and granulomatous inflammation. The incidence of alveolar epithelial hyperplasia increased with concentration for both sexes, and the severity increased with exposure duration. For interstitial fibrosis, incidence increased with concentration, and was on average more severe in females compared with males from the 18-month timepoint. Minimal to moderate granulomatous inflammation was recorded in almost all exposed rats throughout the interim evaluation time-points and the main study (RAC 2025, Table 2). Chronic inflammatory responses in the lungs of mice were also reported.

17. Consensus on whether or not the maximum tolerated dose (MTD) had been exceeded in female rats was not achieved amongst members of the NTP Technical Reports Review Subcommittee, which provided independent review of the draft study report (NTP 1993). One of the subcommittee's discussion points around the evidence for exceedance or otherwise of the MTD was the degree of chronic disease, manifested as lung fibrosis and inflammation.

18. Cytoplasmic alterations were observed in the nose of exposed rats, including hyperplasia of the respiratory epithelium of the nasal mucosa in males, with incidence increasing with concentration. Similar effects were observed in females, but lacked statistical significance. Accumulation of large focal and multifocal cytoplasmic, eosinophilic droplets in the nasal mucosal epithelium of both sexes were observed, with incidences occurring in a concentration dependent manner. RAC suggested that these findings indicated possible direct (primary) effects of talc, caused by talc-intrinsic properties inducing oxidative stress at the site of contact (RAC 2025, p23/Table 3).

19. Talc lung burdens in rats were generally proportional to the exposure concentration and increased progressively from 6 to 24 months for all exposed females and at 6 mg/m³ for male rats, both in absolute value and when normalised to control lung weight and/or exposure concentrations. The talc lung burden of males in the 18 mg/m³ group was similar at the 24-month evaluation to that at the 18-month timepoint (RAC 2025, Table 5). Additional parameters of lung clearance were measured, specifically, the viability and phagocytic activity of alveolar macrophages (AM) in the lungs of exposed animals. At final sacrifice, comparably low viability levels of AMs were observed between control and exposed males. Mean phagocytic activity was lower in exposed males, but lacked statistical significance and dose dependence. In exposed females, AM viability was dose-dependently but non-statistically-significantly reduced, with no effects on phagocytic activity in the 18 mg/m³ group and a non-statistically significant reduction in the 6mg/m³ group (RAC 2025, Table 6).

Lung overload/PSLT Hypothesis

20. One of the main considerations for assessing the rat data from NTP (1993) is the concept of ‘lung overload’, which refers to an impaired clearance of particles from the deep lung after inhalation of high concentrations of poorly soluble, low toxicity (PSLT) particles. This impairment is proposed to be caused by the physical loading of macrophages, leading to a loss of cell mobility.

21. Lung overload with PSLTs has been reported to result in lung cancer in chronic rat studies, although the relevance to humans is controversial. Lung particle overload is also often associated with pulmonary inflammation, epithelial hyperplasia and metaplasia, and fibrosis, which can precede the development of lung cancer but can also occur at exposure levels that do not cause cancer. Such findings were reported in the study in male and female rats. Some publications (e.g. Bevan *et al.*, 2018) refer to talc as a poorly soluble, low toxicity particle.

Conclusions on the NTP (1993) lung tumour data

22. The occurrence of lung tumours in female rats in the NTP (1993) study was one of the key justifications for RAC’s conclusion on the carcinogenicity of talc. Regarding the absence of tumours in talc-exposed mice, RAC noted uncertainties regarding the study that “may have prevented/masked actual treatment-related effects”. The uncertainties related specifically to the high background incidences of lung tumours (tumour data in mice shown in RAC, 2025, Table 7). RAC noted that the differing outcomes in rats and mice did not contradict the relevance of the findings in rats.

23. RAC considered that no firm conclusion on overload conditions and the potential cessation of lung clearance in talc-exposed rats could be made (RAC 2025, Section 3.3.1.1.2). The committee considered that the data from this study were *“unsuitable for the development of generalised and informative assertions regarding the potential impact of talc accumulation in the rat lungs and on their lung clearance, and a hypothesised unspecific toxicity and carcinogenicity”*. RAC rejected the PSLT/particle-driven lung overload hypothesis, pointing to the induction of site-of-contact inflammatory effects by talc. As RAC concluded that these were intrinsic

toxic (inflammatory) properties, the committee considered that talc did not meet the definition of a PSLT. Overall, RAC concluded that the observed lung tumours in female rats were “unambiguously” caused by talc treatment, and that they could not be conclusively attributed to lung overload.

24. RAC stated that the lung-tumour findings in female rats were of relevance for humans. In presenting its classification position, RAC concluded that the animal data (specifically, the lung tumours in female rats) provided ‘limited evidence for carcinogenicity’ of talc. Therefore, RAC’s inclusion of lung tumours in its justification for a carcinogenicity classification hinged on the NTP (1993) study.

25. IARC (2025) noted that NTP (1993) ‘was a well-conducted GLP study that covered most of the lifespan, used an adequate number of animals per group, both sexes, two doses, and an adequate duration of exposure and observation.’ IARC did not comment on the possible PSLT status of talc or the potential for lung-overload to have occurred. Owing to the occurrence of tumours in this one study (lung and adrenal (see below) tumours), IARC concluded that there was sufficient evidence in experimental animals for the carcinogenicity of talc.

26. Because NTP (1993) was the only study conducted in animals in which inhalation exposure of talc resulted in an increased incidence of lung tumours and thus because of its importance to developing a position on classification, HSE has focused on the interpretation of the lung-tumour data from this study.

27. Some of the key considerations that will impact how HSE interprets the lung-tumour data from this study are:

- a potential impact of lung overload. The authors of the 4-week range-finding study predicted that concentrations of talc above 18 mg/m³ would have overwhelmed lung clearance. It is possible that with the increase in exposure duration, clearance was impacted and the MTD was exceeded in the study. Furthermore, an issue with the aerosol generation system (weeks 11-18) resulted in the 18 mg/m³ group being exposed to concentrations of ~30-40mg/m³ for several weeks; this may have had a considerable impact on lung burden.

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- study design, namely the duration of the study. In standard carcinogenicity studies, rats are typically exposed to the test material for two years (104 weeks). In the NTP (1993) study, female rats were exposed for up to 122 weeks. Noting that the tumours developed late in life, the additional 18 weeks/4.5 months of exposure might have led to increased susceptibility for tumour development, particularly if the MTD was achieved or exceeded.

Questions on which the views of the Committee are sought - lung cancer

28. Members are invited to consider the following questions on NTP (1993):

- i) The methodology of NTP (1993) differed from a normal OECD guideline carcinogenicity study. Does the Committee have any comments on the study design and its impact on the occurrence of lung tumours and their interpretation?
- ii) Does the Committee have a view regarding the impact on the findings of the difficulties with aerosol control observed in Week 11-18?
- iii) Does the Committee consider that the maximum tolerated dose (MTD) was met or exceeded within NTP (1993)?
- iv) Does the Committee have any information which could explain the observed differences in tumour incidence between male and female rats?
- v) With respect to the latest scientific evidence, guidelines, and definitions, does the Committee have a view as to whether talc is a 'poorly soluble, low toxicity' (PSLT) particle?
- vi) Does the Committee have a view on whether lung overload occurred within NTP (1993)?

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Pheochromocytomas

Data summary

29. In addition to the lung tumours, a statistically significant trend towards increased incidence of adrenal pheochromocytomas was observed in both male and female rats in the NTP (1993) study. The incidences in the exposed groups exceeded HCD ranges (Table 2). However, the background incidences in the concurrent control animals were high and also exceeded the HCD.

30. RAC also assessed the pheochromocytoma incidence using a 'combined' approach (i.e. benign, malignant, or complex tumour incidence), based on a previous report by Huff *et al.* (1989). The combined tumour incidences in both the exposed and control groups were also high, exceeding HCD. As noted above, the HCD were obtained from studies of up to 105 weeks' duration, hindering a direct comparison with data from NTP (1993).

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Table 2: Adrenal pheochromocytoma incidences in NTP (1993), with corresponding historical control data

Tumour type	Sex	0 mg/m³	6 mg/m³	18 mg/m³	HCD (% mean ± SD)
<i>Benign</i>	Male	25/49 (51%)	30/48 (63%)	36/47 (77%)	(30.4 ± 10.4%)
<i>Malignant</i>	Male	3/49 (6%)	3/48 (6%)	7/47 (15%)	(1.9 ± 2.1%)
<i>Complex</i>	Male	0/49 (0%)	2/48 (4%)	1/47 (2%)	(0.3 ± 0.7%)
<i>Combined (benign, malignant or complex)</i>	Male	26/49 (53%)	32/48 (67%)	37/47 (79%)	(31.6 ± 10.0%)
<i>Benign</i>	Female	13/48 (27%)	14/47 (30%)	18/49 (37%)	(5.2 ± 3.8%)
<i>Malignant</i>	Female	0/48 (0%)	1/47 (2%)	10/49 (20%)	(0.5 ± 1.1%)
<i>Complex</i>	Female	0/48 (0%)	0/47 (0%)	0/49 (0%)	(0.5 ± 1.1%)
<i>Combined (benign malignant or complex)</i>	Female	13/48 (27%)	14/47 (30%)	23/49 (47%)	(6.2 ± 3.5%)

Source: Study data from NTP (1993). Historical control data from chronic inhalation studies performed by NTP between 1985-1993, cited as NTP (1997).

31. Adrenal pheochromocytomas were not observed in the NTP (1993) mouse study.

Conclusions on the NTP (1993) adrenal pheochromocytoma data

32. RAC acknowledged that the concurrent controls showed a high background incidence that exceeded the HCD, therefore preventing a firm conclusion on the relevance of the pheochromocytomas (RAC 2025, section 3.5.2).

33. RAC also noted that in a previous systematic analysis of chronic inhalation studies, there was a possible correlation between marked hypoxic conditions in the lungs and the occurrence of pheochromocytomas in rats (Ozaki *et al.*, 2002; Greim *et al.*, 2009). The committee considered that, as there were no conclusive data regarding the induction of stress or hypoxia in talc-exposed rats in the NTP study, it was difficult to assess whether hypoxia was the main and only mode of action in the development of pheochromocytomas (RAC 2025, section 3.3.3).

34. RAC concluded that the limitations of the data hampered assessment, but assumed that the tumour type and its potential underlying mode of action was relevant to humans, even if tumorigenesis in rats were secondary to pulmonary inflammation and fibrosis. In its weight-of-evidence assessment, RAC placed less weight on the pheochromocytomas and considered them to be of limited relevance for classification.

35. As noted above, IARC considered NTP (1993) to be a well-conducted study. Although IARC noted that the occurrence of adrenal tumours in the study was 'unusual', the occurrence of lung and adrenal tumours in this one study formed the basis of IARC's conclusion that there was sufficient evidence in experimental animals for the carcinogenicity of talc. IARC did not discuss a possible impact of hypoxia.

36. Some of the key considerations that will impact how HSE interprets the pheochromocytoma data from this study are outlined below.

- Spontaneous pheochromocytomas arise frequently in the ageing rat, as demonstrated by the HCD presented in Table 2. The high background tumour incidence in control rats in NTP (1993) means that it is challenging to determine if there was a specific substance-related effect. Furthermore, since

ageing of rats is a key factor in the occurrence of spontaneous tumours of the adrenal medulla, which is illustrated in the higher background incidences in controls of the NTP study compared with the HCD, the findings of the NTP study are not directly comparable with the HCD.

- Talc is insoluble and toxicokinetic information indicates that it is not systemically available following inhalation exposure; the biological plausibility of these tumours being directly attributable to talc administered by inhalation is therefore questionable.
- An indirect mode of action by which particles might induce pheochromocytomas is systemic hypoxia caused by space-occupying lung pathologies (Ozaki *et al.*, 2002). Inflammation and fibrosis were reported in both male and female rats, whilst decreases in lung capacity and carbon monoxide diffusion were observed in both exposed groups of both sexes from 11 months onwards (RAC 2025, Table 13). The NTP study authors reported that 'in exposed male and female rats there was a concentration-related impairment of respiratory function which increased in severity with increasing exposure duration.' One of the characteristics of this impairment was reduced gas exchange efficiency.
- Ozaki *et al.* (2002) investigated a possible correlation between non-neoplastic chronic pulmonary lesions and adrenal pheochromocytoma in nine NTP particulate inhalation studies in male F344 rats. NTP (1993) was one of the studies included in this analysis. Whilst noting that chemically-related increased pheochromocytoma occurred in both males and females, Ozaki *et al.* only evaluated the statistical associations in male rats, since the same pattern of pulmonary damage and severity was recorded in females. The authors concluded that there was a significant ($p < 0.01$) association between the occurrence of pheochromocytoma and the severity of inflammation and fibrosis in each of the studies (which included talc) in which there was a chemical-related increase in the incidence of pheochromocytoma. The authors stated that 'The hypoxemic condition, which may follow chronic pulmonary inflammation and fibrosis, may be implicated in the induction of

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pheochromocytoma in these studies.’ On the basis of Ozaki *et al.*, pheochromocytomas induced in male rats that are secondary to hypoxemia and occur following inhalation to particulates are considered not to be relevant to humans (ECHA, 2024, section 3.6.2.3.2.)

37. Because of these factors, HSE’s current thinking is that these tumours should be disregarded in its assessment.

Questions on which the views of the Committee are sought - adrenal pheochromocytomas

- i) HSE considers that the reported increase in pheochromocytomas in rats in the NTP study should be disregarded in its assessment. Does the Committee agree with this conclusion?

Ovarian cancer

Data summary

38. RAC evaluated several epidemiological studies on ovarian cancer, comprising cohort and case-control studies (RAC 2025, section 3.3.5). These individual studies have also been considered as part of meta-analyses.

39. Four prospective cohort studies were available, referred to in the literature as the NHS-I study, the NHS-II study, the Sister study, and the WHI-OS study. In these individual studies, a positive association between ‘ever use’ of talc and ovarian cancer was not observed. However, in a meta-analysis/pooled cohort analysis of these individual studies (O’Brien *et al.* 2020), the subgroup of women with ‘patent reproductive tract’ and specifically without prior tubal ligation resulted in a slight but statistically significant association between ever use of talc in the genital area and ovarian cancer risk. In considering the cohort studies, RAC proposed that the meta-analysis by O’Brien *et al.* (2020) take precedence over the individual studies.

40. RAC hypothesised that this subgroup had a higher risk because of anticipated ‘retrograde translocation of talc particles’. The basis of the hypothesis was that

genital/perineal talc use resulted in retrograde translocation to the ovaries with consequent inflammatory-mediated ovarian cancer. Tubal ligation was suggested to prevent translocation from the vagina to the ovaries. RAC considered this hypothesis to be supported by the presence of talc in ovarian cancer tissue from human studies as well as from experimental studies in animals (RAC 2025, section 3.3.6).

41. The case-control studies covered different geographical regions, patient settings (hospital vs population) and sample sizes (RAC 2025, section 5.4). In many individual case control studies, a statistically significant positive association between use of talc in the perineal area and increased risk for ovarian cancer was indicated. Some studies reported a positive association without reaching or reporting statistical significance. One of the studies reported no association between perineal talc use and ovarian cancer risk (Tzonou *et al.* 1993), although this study had a limited number of cases of perineal talc users (6 cases, 7 controls). None of the studies that indicated a positive association yielded an odds ratio of < 1.2 , with the majority having an increased relative risk of 20-60%.

42. An additional four case-control studies also reported no association between talc use and ovarian cancer risk, but with positive association to other subgroups (RAC 2025, section 3.3.5.7).

43. Relevant case-control studies were included in three pooled meta-analyses: Berge *et al.* (2018), Penninkilampi *et al.* (2018) and Taher *et al.* (2019). Each meta-analysis assessed 'ever use' versus 'never use' of perineal/genital talc. In these three independent meta-analyses, each calculated an overall odds ratio (OR) of 1.2-1.3 when assessing the case-control and cohort studies. This was statistically significant and with narrow confidence intervals, indicating a 20-30% increased risk of ovarian cancer with perineal/genital talc use. The three meta-analyses presented a pattern of statistically significant positive associations, when assessing the included case control studies only. However, when considering the individual study design, cohort studies did not have the same positive association.

44. Only Berge *et al.* (2018) appeared to assess potential exposure to asbestos in their meta-analysis, by comparing early talc use (pre-1970/80s) to later use (after

1970/80s). The relative risks for 'early use' and 'later use' were 1.18 and 1.31, respectively.

Study limitations

45. The studies are subject to various limitations, including bias, sample size and statistical power, as well as confounding variables such as asbestos contamination.

46. In all studies, exposure to talc was determined by self-reported measures of use, often occurring years in the past. Recall bias might have resulted in (non-differential) misclassification of exposure. In patients with habitual use, it is more likely that this was recalled more accurately, but it is difficult to determine the impact of bias on the results across the varying user profiles. Individual study questionnaires might have defined different classifications of usage; for example, in the follow up of the initial NHS-I cohort study, participants were collapsed into either 'more than once/week' or 'less than once/week', of which the latter would have included 'never' users (Gates *et al.*, 2010).

47. In a quantitative analysis of recall bias by Goodman *et al.* (2024), data from the largest case-control study (Cramer *et al.* 2016) were used alongside recall sensitivity and specificity information reported by O'Brien *et al.* (2023) to address the potential impact of recall bias on risk estimates. Seven scenarios with varying recall sensitivity and specificity were modelled. All but two scenarios resulted in OR confidence intervals / simulation intervals that spanned null. Of the two remaining scenarios, one resulted in an OR < 1, whilst in the other the OR remained > 1. The latter scenario modelled ranges of recall sensitivity and specificity of 95–100% for both cases and controls, which the study authors considered to be less realistic than the other scenarios. Overall, Goodman *et al.* concluded that recall bias can have a large impact on risk estimates.

48. The presence of confounding variables which were, in some cases, unadjusted for, might have impacted the study outcomes. Asbestos impurities were reported as 'common' within talc products until the introduction of 'cosmetic talc' in the mid-1970s. Information on asbestos contamination within talc products is difficult to find, both around the 1970s to the present day; however, an analysis of talc-

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containing cosmetic products by the FDA as recently as 2019 found asbestos contamination (FDA, 2020). This leaves uncertainties with regards to the role of asbestos as a confounding variable within products, even in more modern studies. Several analytical methods are used for the quantification of asbestos within talc, each with varying limits of detection. This further complicates assessment of 'pure uncontaminated talc' (IARC, 2025).

49. The link between asbestos exposure and ovarian cancer has been explored in various studies. IARC (2012) stated that asbestos causes cancer of the ovary, noting that the biological plausibility for an association between asbestos and ovarian cancer derived in part from the finding of asbestos fibres in the ovaries of women with potential for (non-occupational) exposure to asbestos. The IARC Working Group also noted that the histopathological diagnosis of ovarian carcinoma is difficult. This was also stated in a recent systematic review and meta-analysis of ovarian cancer in women with occupational exposure to asbestos (Turati *et al.*, 2023). Whilst reporting an increased risk of ovarian cancer in these women, the study authors noted one of the limitations to be potential misclassification, as peritoneal mesothelioma which colonises the ovary might be classified as ovarian cancer. Older studies could have been subject to different pathology criteria, as new techniques became available over time.

Conclusions on the human ovarian cancer data

50. RAC included ovarian tumours in its justification for the carcinogenicity classification because of the epidemiological evidence for positive associations between the genital/perineal use of talc and the risk of ovarian cancer. RAC considered that there was consistent, replicated evidence overall. They also suggested that this causal relationship was credible, but "bias and confounding could not be completely ruled out with reasonable confidence". RAC suggested that owing to the increase in relative risk for 'ever' users compared with 'never' users, relative risk for those who regularly use talc were actually underestimated.

51. IARC (2025) concluded that the overall human data were "limited", but noted that "positive associations have been observed between exposure to talc and cancer

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of the ovary". IARC (2025) provided an additional quantitative bias analysis on the human studies to address impacts of exposure misclassification for ovarian cancer. This analysis used the data from four cohort studies and a representative sample of eleven case control studies. This resulted in a calculated effect range of 1.04-1.18, compared with the initial pooled estimates of 1.0-1.3.

52. Regarding retrograde transport of talc to the ovaries, in its earlier evaluation IARC considered the evidence for this in women without diseases or complications of the reproductive tract and organs to be weak (IARC, 2010). Some evidence of retrograde transport in women with impaired clearance function was reported, whilst the Working Group noted that there was no evidence of retrograde transport of talc to the ovaries in animal studies. In the 2025 evaluation, IARC stated again that in most animal studies no translocation from the perineal region to the ovaries was reported (IARC, 2025). The 2025 Working Group did not present an overall conclusion on the evidence for retrograde transport of talc to the ovaries of women from perineal use.

53. Some of the key considerations that will impact how HSE interprets the data on ovarian cancer from epidemiology studies are:

- the various limitations described above, which potentially had a large impact on the risk estimates provided. This is especially true for the meta-analyses, as although their statistical power is higher than for individual studies, it is unclear how the summation of 'limited' studies impacts on the overall risk estimates;
- the potential impact of asbestos contamination of talc products. Taking into account the difficulties with the analysis of asbestos within talc products, and the lack of detailed exposure characterisation in individual studies, it is possible that asbestos is a key confounding variable that should not be understated.

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Question on which the views of the Committee are sought- human ovarian cancer:

- i) With respect to the human ovarian cancer studies, does the Committee consider potential asbestos contamination is a major confounding variable?
- ii) Does the Committee agree with RAC's approach to assessing the human data/meta-analyses, particularly when considering the individual study weaknesses?
- iii) How plausible does the Committee consider the 'retrograde translocation' hypothesis for exposure to talc after perineal/genital use to be?

**Health and Safety Executive
November 2025**

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List of Abbreviations and Technical terms

AM	Alveolar Macrophage
CLH	Harmonised Classification and Labelling
ECHA	European Chemicals Agency
EU	European Union
FDA	Food and Drug Administration
GB	Great Britain
GB CLP	GB Classification, Labelling and Packaging Regulation
GLP	Good Laboratory Practice
HCD	Historical Control Data
HSE	Health and Safety Executive
IARC	International Agency for Research on Cancer
MMAD	Mass Median Aerodynamic Diameter
MP	Micronised Powder
MTD	Maximum Tolerated Dose
NHS-I / NHS-II	Nurse's Health Study (I/II)
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
OR	Odds Ratio
PSLT	Poorly Soluble Low Toxicity
RAC	Risk Assessment Committee
STOT-RE	Specific Target Organ Toxicity – Repeated Exposure
US	United States
WHI-OS	Women's Health Initiative Observational Study

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